Title	A systematic review of proton pump inhibitors for the treatment of adult patients with symptomatic gastroesophageal reflux disease or peptic ulcer disease.
Review Question(s) Requested	**Requested by PSD** 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 (duodenal and gastric) ulcer? 3. What are the comparative safety and adverse events of different proton pump inhibitors in patients being treated for symptoms of gastroesophageal reflux disease and peptic ulcer? 4. 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?
Drug	The following five proton pump inhibitors (PPI) drugs will be reviewed 1. Esomeprazole (Nexium® and its generic equivalent) 2. Lansoprazole (Prevacid® and its generic equivalent) 3. Omeprazole* (Losec® and its generic equivalent) 4. Pantoprazole* sodium and magnesium (Pantoloc®, Panto IV and their generic equivalent and Tecta® 5. Rabeprazole* (Pariet® and its generic equivalent) Note: *Omeprazole, Pantoprazole and Rabeprazole have been identified as reference drugs by PSD. Esomeprazole and Lansoprazole will be compared to these three reference drugs.

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ABBREVIATIONS

AE	Adverse Event
BD	Twice Daily
BMI	Body Mass Index
CI	Confidence Interval
DERP	Drug Effectiveness Review Project
DB	Double-Blind
DU	Duodenal Ulcer
EE	Erosive Esophagitis
ENRD	Endoscopy-Negative Reflux Disease
FDA	Food and Drug Administration
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
GDU	Gastro-Duodenal Ulcer
GU	Gastric Ulcer
H. pylori	*Helicobacter pylori*
H2RA	Histamine H2-Receptor Antagonist
ITT	Intention-to-Treat Population
IV	Intravenous
kg	kilogram
mg	milligram
mg/d	milligram/day
NA	Not Applicable
NERD	Non-Erosive Reflux Disease
NR	Not Reported
NSAID	Non-Steroidal Anti-Inflammatory Drug
NUD	Non-Ulcer Dyspepsia
OD	Once daily
PSD	Pharmaceutical Services Division
PPI	Proton Pump Inhibitor
PSUR	Periodic Safety Update Report
PUD	Peptic Ulcer Disease
QoL	Quality of Life
RCT	Randomized Controlled Trial
RoB	Risk of Bias
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the mean
SoF	Summary of Findings
TDS	Three times daily
UBT	Urea Breath Test

US	United States
WD	Withdrawal
WDAE	Withdrawal Due to Adverse Event

Drug Name Abbreviations

L	Lansoprazole
E	Esomeprazole
P	Pantoprazole
R	Rabeprazole
O	Omeprazole
A	Amoxicillin
C	Clarithromycin
T	Tinidazole
M	Metronidazole

1 EXECUTIVE SUMMARY

1.1 Background

Gastroesophageal reflux disease (GERD) refers to symptoms and/or complications that result from an excessive reflux of gastric contents into the esophagus, oropharynx or lungs. Reflux may cause inflammation (*erosive esophagitis*) and complications such as the development of an ulcer, bleeding or stricture. Chronic esophagitis can further evolve through attempted repair into metaplastic columnar epithelium (*Barrett's esophagus*) and the development of esophageal adenocarcinoma. However, about 55–80% of GERD patients do not have erosive disease on endoscopy and is termed as *non-erosive reflux disease* (NERD). Mild symptoms of GERD do not interfere with daily activity and are usually of low intensity, short in duration, not nocturnal, infrequent (<3 times weekly) and without major complications. However, severe symptoms regularly interfere with daily activities and are usually of high intensity, persistent (>6 months), nocturnal, frequent and often associated with complications. (Canadian consensus 2004) Peptic ulcer disease (PUD) includes both gastric and duodenal ulcer. Eradication of *Helicobacter pylori* is an important indicator of the long-term outcome of treatment (reduces the risk of ulcers and ulcer complications).

The goal of therapy for both GERD and PUD is quick relief of symptoms (heart burn; acid regurgitation; epigastric pain) 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.

Pharmaceutical Services Division (PSD) has requested an update of the Drug Effectiveness Review Project (DERP) 2009 report on the class review of proton pump inhibitors (PPIs) for the treatment of adult patients with symptomatic GERD or PUD.

1.2 Research Questions (according to Cochrane 'PICOS' format)

1. Based on head to head randomized controlled trials, does Esomeprazole or Lansoprazole provide a therapeutic advantage (includes benefit and harm) as compared to other proton pump inhibitors (Omeprazole, Pantoprazole or Rabeprazole) in adult patients with symptomatic GERD?
2. Based on head to head randomized controlled trials, does Esomeprazole or Lansoprazole provide a therapeutic advantage (includes benefit and harm) as compared to other proton pump inhibitors (Omeprazole, Pantoprazole or Rabeprazole) in adult patients with symptomatic PUD?
3. Based on head to head randomized controlled trials, are there subgroups of patients based on demographics, other medications or co-morbidities (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 in adult patients with symptomatic GERD and PUD?

4. Based on large, long term (6 months or more), select comparative observational studies (cohort and nested case control) what is the safety and adverse events profile of different proton pump inhibitors in adult patients with symptomatic GERD and PUD?

1.3 Method

An updated search of the DERP 2009 report was performed in the following databases: MEDLINE (2009 - March 2014), MEDLINE-in-process, EMBASE (2009 - March 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (2009 - March 2014), and the Cochrane Database of Systematic Reviews (until March 2014). English language reports of randomized controlled trials (RCTs) comparing specified PPIs were included if they were at least 4 weeks in duration in patients with symptomatic GERD or 1 week in duration in patients with PUD.

1.4 Results

Results are presented according to hierarchy of outcome measures based on specific comparisons in patients with symptomatic GERD and PUD.

Esomeprazole versus other PPIs (Omeprazole, Pantoprazole and Rabeprazole) in patients with GERD

26 RCTs (23 double-blind and 3 open-label) compared Esomeprazole to other PPIs in 23,789 adult patients with symptomatic GERD. Ten RCTs compared Esomeprazole to Omeprazole in 9638 patients; twelve RCTs compared Esomeprazole to Pantoprazole in 10,503 patients; and five RCTs compared Esomeprazole and Rabeprazole in 3716 patients. One RCT had multiple treatment arms. These studies were conducted in centres across USA, Canada, Australia, Europe, Singapore, India, Brazil, Taiwan and China. Patients were randomized to receive Esomeprazole 20 mg or 40 mg OD; Omeprazole 20 mg OD; or Pantoprazole 20 to 40 mg OD; or Rabeprazole 10 to 50 mg OD.

The mean age ranged from 35 to 59 years; 56 to 61% patients were men and 39 to 44% were women. The baseline characteristics of randomized patients was not reported uniformly across studies and very few studies reported on race, BMI, smoking, alcohol consumption, *H. pylori* status and severity of the esophagitis at baseline. Data on patients completing the study was available in 15 of the 26 RCTs and total randomized patients completing the study in these RCTs ranged from 89 to 94%.

Efficacy based on hierarchy of outcome measures, presented as [# RCTs; RR with 95% CI]: (Refer to Summary of Findings table 1, 2 and 3 in Appendix 8)

1. Total symptomatic relief of symptoms was not reported in RCTs comparing Esomeprazole to Omeprazole or Rabeprazole. Pantoprazole was significantly better in providing complete symptomatic relief at 4 weeks compared to Esomeprazole [5 RCTs; 0.94 (0.90, 0.98)]; graded as very low quality evidence].
2. Relief of heart burn data was not provided in RCTs comparing Esomeprazole to Pantoprazole. Esomeprazole was significantly better in providing relief of heart burn at 4 weeks compared to Omeprazole [8 RCTs; 1.08 (1.05, 1.12); graded as very low quality of evidence] and was not significantly different from Rabeprazole [3 RCTs; 1.03 (0.96, 1.11); graded as low quality evidence].

3. Time to first resolution of symptoms was not significantly different between Esomeprazole compared to Omeprazole (median days ranged from 1 to 4 days); compared to Pantoprazole (median of 2 days); and Rabeprazole (median of 8.5 to 9 days for heart burn and 6 to 7.5 days for acid regurgitation). Similarly, no significant difference in time to sustained resolution of symptoms was observed between Esomeprazole and any of the 3 PPI comparators.
4. Healing of esophagitis did not differ significantly between Esomeprazole and Rabeprazole [3 RCTs; 0.97(0.92, 1.02) at 4 to 8 weeks; graded as low quality evidence]. Esomeprazole was significantly better in providing endoscopic healing of esophagitis at 4 to 8 weeks compared to Omeprazole [6 RCTs; 1.07 (1.05, 1.09); graded as low quality of evidence] and at 4 to 12 weeks compared to Pantoprazole group [6 RCTs; 1.02(1.00, 1.04); graded as very low quality of evidence].
5. Quality of life scores were not report in any of the 26 RCTs meeting the inclusion criteria.
6. Remission rate reported in 1 RCT was not significant different between Esomeprazole and Pantoprazole group at 6 months [1 RCT, 1.01 (0.97, 1.06)).
7. Based on very limited data from 12 of the 26 RCTs meeting the inclusion criteria, Esomeprazole was not significantly different from Omeprazole, Pantoprazole or Rabeprazole in harm outcomes mortality; serious adverse events, withdrawal due to adverse events; patients with at least one adverse event). Specific adverse events were also not significantly different except for headache (significantly greater in Esomeprazole group compared to Omeprazole [5 RCTs; 1.29 (1.08, 1.54); graded as low quality of evidence].

Lansoprazole versus other PPI (Omeprazole, Pantoprazole and Rabeprazole) in patients with GERD

13 RCTs (8 double-blind and 5 open-label) compared Lansoprazole to other PPIs (5 RCTs had multiple treatment arms) in 7532 adult patients with symptomatic GERD. Twelve RCTs compared Lansoprazole to Omeprazole in 6648 patients; five RCTs compared Lansoprazole to Pantoprazole in 1089 patients; and two RCTs compared Lansoprazole to Rabeprazole in 215 patients. These studies were conducted in centres across USA, Canada, China, Japan, Scandinavia, Germany, Italy France and Netherlands. Patients were randomized to treatment with Lansoprazole 30 to 60 mg/day or Omeprazole 20 to 40 mg/day or Pantoprazole 40 to 80 mg/day or Rabeprazole 20 mg/day. The mean duration of study ranged from 4 to 8 weeks except for one study Carling 1998 which was 48 weeks in duration.

The mean age range across these studies was 46 to 78 years; 48 to 63% patients were men and 37 to 52% were women. The baseline characteristics of randomized patients was not reported uniformly across studies and very few studies reported on race, BMI, smoking, alcohol consumption, *H. pylori* status and severity of the esophagitis at baseline. The number *H. pylori* positive patients ranged from 28% to 80%. Data on patients completing the study was available in 12 of the 13 RCTs and total randomized patients completing the study ranged from 85 to 94%.

Efficacy based on hierarchy of outcome measures, presented as [# RCTs; RR with 95% CI]: (Refer to Summary of Findings table 4, 5 and 6 in Appendix 8)

1. Total symptomatic relief of symptoms was not reported in RCTs comparing Lansoprazole to Omeprazole or Rabeprazole. Lansoprazole did not differ from Pantoprazole in providing

complete symptomatic relief at 4 weeks [2 RCTs; 0.96 (0.91, 1.02)]; graded as low quality evidence].

2. Relief of heart burn data was provided for all comparisons. Lansoprazole did not differ significantly from Omeprazole in providing relief of heart burn at 4 weeks [4 RCTs; 1.01(0.98, 1.03); graded as low quality evidence]. Pantoprazole was significantly better in providing relief of heart burn at 4 to 8 weeks compared to Lansoprazole [3 RCTs; 0.95 (0.90, 0.99); graded as very low quality of evidence] and Rabeprazole was significantly better at providing relief of heart burn at 8 weeks compared to Lansoprazole [1 RCT; 0.83(0.75, 0.92); graded as very low quality evidence].
3. Relief of acid regurgitation data was provided for all comparisons. Omeprazole was significantly better compared to Lansoprazole at 4 to 8 weeks [3 RCTs; 0.83(0.75, 0.93); graded as very low quality evidence]. Pantoprazole was significantly better at 4 to 8 weeks compared to Lansoprazole [2 RCTs; 0.94 (0.89, 1.00); graded as very low quality of evidence] and Rabeprazole was significantly better at 8 weeks compared to Lansoprazole [1 RCT; 0.83(0.72, 0.96); graded as very low quality evidence].
4. Relief of epigastric pain was provided for all comparisons. Both Omeprazole and Pantoprazole was significantly better at 8 weeks compared to Lansoprazole [1 RCT; 0.87 (0.78, 0.97); graded as very low quality of evidence] and Rabeprazole was significantly better at 8 weeks compared to Lansoprazole [1 RCT; 0.83(0.75, 0.92); graded as very low quality evidence].
5. Relief of dysphagia was provided for all comparisons. Lansoprazole did not differ from Omeprazole in relief of dysphagia at 4 to 8 weeks [2 RCTs; 0.98(0.94, 1.03); graded as very low quality evidence] or from Pantoprazole at 4 to 8 weeks [1 RCT; 1.00 (0.97, 1.03); graded as low quality of evidence] or Rabeprazole at 8 weeks [1 RCT; 1.00 (0.98, 1.02); graded as very low quality evidence].
6. Time to first resolution of symptoms was not reported in any of the 13 RCTs meeting the inclusion criteria. Time to sustained resolution of symptoms was reported in 1 RCT. The time to first episode of 3 consecutive days free of heartburn (median 3 days) and for retrosternal pain (median 4 days) was similar between Lansoprazole and Omeprazole groups.
7. Endoscopic healing of esophagitis at week 4 to 8 of treatment did not differ significantly between Lansoprazole and Omeprazole [7 RCTs; 1.00 (0.96, 1.04); graded as low quality evidence] or Pantoprazole [3 RCTs; 0.96 (0.91, 1.01); graded as low quality of evidence] or Rabeprazole [2 RCTs; 0.90(0.80, 1.01); graded as very low quality of evidence].
8. Quality of life scores were not reported in any of the 13 RCTs meeting the inclusion criteria.
9. Recurrence or relapse of symptoms was reported for two comparisons. Lansoprazole did not differ significantly from Omeprazole at 48 weeks [1 RCT; 0.48 (0.04, 5.27) or Pantoprazole at 4 weeks [1 RCT; 1.00 (0.49, 2.05); graded as very low quality evidence].
10. Based on selectively reported data from 7 of the 12 RCTs meeting the inclusion criteria, Lansoprazole was not significantly different from Omeprazole in harm outcomes mortality; serious adverse events, withdrawal due to adverse events; patients with at least one adverse event). Specific adverse event were also not significantly different except for diarrhea

(significantly greater in Lansoprazole group compared to Omeprazole [5 RCTs; 1.23 (1.02, 1.48); graded as low quality of evidence].

11. Based on selectively reported data from 2 of the 5 RCTs meeting the inclusion criteria, Lansoprazole was not significantly different from Pantoprazole in harm outcomes mortality; serious adverse events, withdrawal due to adverse events; and specific adverse events. Patients with at least one adverse event were significantly less in Lansoprazole group compared to Pantoprazole [2 RCTs; 0.60 (0.42, 0.852); graded as very low quality of evidence].
12. Harm outcomes mortality, serious adverse events, withdrawal due to adverse events were not reported in the 2 RCTs comparing Lansoprazole to Rabeprazole. No significant difference in patients with at least 1 adverse event [1RCT; 1.00 (0.06, 15.71); graded as very low quality evidence] or for any specific adverse event.

Esomeprazole versus other PPI (Omeprazole, Pantoprazole and Rabeprazole) in patients with PUD

A total of 6 RCTS in 1753 patients (3 were double blind; 1 RCT outcome assessor was blinded; and 2 were open label RCTs) compared Esomeprazole to other PPIs. No RCT met the inclusion criteria comparing Esomeprazole to Rabeprazole. Five RCTs compared Esomeprazole to Omeprazole in 1553 patients and one RCT compared Esomeprazole to Pantoprazole in 200 adult patients with peptic ulcer or gastritis who were *H. pylori* positive. These RCTs were conducted in Europe, Canada, Czech Republic, Hungary, Poland, Germany and Taiwan. 1691(96%) randomized patients completed the study. Patients were randomized to treatment with Esomeprazole 20mg BD or 40mg BD or Omeprazole 20 mg BD or Pantoprazole 40 mg BD in addition to antibiotics (Clarithromycin 500mg BD plus Amoxicillin 1g BD; Metronidazole, 400mg BD or 500 mg BD, and Clarithromycin 250 mg BD) for duration of 1 week. The duration of follow up in studies ranged from 4 to 8 weeks.

Of the 1753 patients 969 (55%) were men and 784 (45% women with mean age ranging from 42 to 59 years. BMI data was not provided in any trial. One study comparing Esomeprazole to Omeprazole, Van Zanten 2003 with 379 patients included 354 (93%) Caucasian patients; 124 patients (33%) were smokers; and 228 (60%) consumed alcohol. One study (Hsu 2005) comparing Esomeprazole to Pantoprazole in 200 patients provided baseline characteristics of patients - 27% were smokers; 14% ingested coffee; 25% ingested tea; 24% had underlying diseases; 12% consumed alcohol; and 41% had history of peptic ulcer. The primary efficacy variable was *H. pylori* eradication determined by follow-up endoscopy with histology and culture and/or rapid urease test. Eradication was defined differently in trials. Trials comparing Esomeprazole to Omeprazole defined it as only patients with a negative urea breath test result at both follow-up visits were considered to be *H. pylori*-negative. Trials comparing Esomeprazole to Pantoprazole defined it as (1) negative results of both rapid urease test and histology, or (2) a negative result of urea breath test

Efficacy based on hierarchy of outcome measures, presented as [# RCTs; RR with 95% CI]: (Refer to Summary of Findings table 7 and 8 in Appendix 8)

1. Total symptomatic relief of symptoms was not reported in the 6 RCTs meeting the inclusion criteria.

2. Relief of heart burn at 4 weeks was not provided in RCTs comparing Esomeprazole to Pantoprazole. Esomeprazole did not significantly differ compared to Omeprazole [2 RCTs; 0.97 (0.70, 1.35); graded as very low quality of evidence].
3. Relief of epigastric pain at 4 weeks was not provided in RCTs comparing Esomeprazole to Pantoprazole. Esomeprazole did not significantly differ compared to Omeprazole [2 RCTs; 0.84 (0.56, 1.26; graded as very low quality of evidence].
4. Time to first resolution of symptoms was not reported in the 6 RCTs meeting the inclusion criteria.
5. Healing of ulcer did not differ significantly in Esomeprazole compared to Omeprazole [1 RCT; 0.99 (0.93, 1.05); graded as very low quality evidence] or to Pantoprazole [1 RCT; 1.07 (0.91, 1.25); graded as very low quality evidence].
6. *H. pylori* eradication at 6 to 8 weeks did not differ significantly in Esomeprazole compared to Omeprazole group [5 RCTs; 1.03 (0.98, 1.07); graded as very low quality evidence]. Esomeprazole significantly increased *H. pylori* eradication as compared to Pantoprazole [1 RCT; 1.15 (1.03, 1.27); graded as very low quality evidence].
7. Quality of life scores were not report in any of the 26 RCTs meeting the inclusion criteria.
8. Recurrence or relapse of symptoms was not reported in any of the 6 RCTs meeting the inclusion criteria.
9. Based on very limited data from 3 of the 5 RCTs meeting the inclusion criteria, Esomeprazole was not significantly different from Omeprazole in harm outcomes mortality [1 RCT; no deaths]; serious adverse events [3 RCTs; 0.20 (0.02, 1.73); graded as very low quality evidence], withdrawal due to adverse events[1 RCT; 1.01 (0.33, 3.11); graded as very low quality evidence]; patients with at least one adverse event [5 RCTS; 1.00 (0.90, 1.11); graded as very low quality evidence]or any specific adverse event.
10. One RCT meeting the inclusion criteria reported limited data on harm outcomes comparing Esomeprazole to Pantoprazole. Mortality and serious adverse events were not reported. Esomeprazole did not significantly different from Pantoprazole in withdrawal due to adverse events [1 RCT; 0.50 (0.09, 2.67); graded as very low quality evidence]; patients with at least one adverse event [1 RCT; 0.62 (0.35, 1.12); graded as very low quality evidence] or any specific adverse event.

Lansoprazole versus other PPIs in patients with PUD

A total of 19 RCTs (4 were double blind; 4 were single blind with blinding of outcome assessor and 11 were open label RCTs) in 3649 patients compared Lansoprazole to other PPIs. No RCT met the inclusion criteria comparing Lansoprazole to Pantoprazole. Fifteen RCTs compared Lansoprazole to Omeprazole in 2265 patients and seven RCTs compared Lansoprazole to Rabeprazole in 1574 adult patients with endoscopically confirmed peptic ulcer and who are *H. pylori* positive. Three of these RCTs had multiple treatment arms. These RCTs were conducted in Sweden, Italy, Japan and Taiwan. Patients were randomized to treatment with PPI- Lansoprazole (30mg OD or 30mg BD) or to Omeprazole (20mg OD or 40mg OD, or 20mg BD) or to Rabeprazole 10mg BD or 20 mg BD in addition to antibiotics (Clarithromycin 500mg BD or 200mg BD or TDS or 400mg BD) or (Metronidazole 250 mg BD or 400mg

BD) plus (Amoxicillin 200mg BD OR 250 mg TDS or 750 mg BD or 1000mg BD or 500mg TDS) or Tinidazole (500mg BD) for duration of 1 week in most trials and up to 6-8 weeks in Carpuso 1995 and Florent 1994. The duration of follow up in studies ranged from 4 to 16 weeks in most trials and up to a year in Fanti 2001 study. Treatment was considered successful if the results of both endoscopy and/or rapid urease test were negative. In one study (Murakami 2008) treatment success was considered when rapid urease test, culture, histologic examination, and the urea breath test (UBT) were all negative. Fifteen RCTs reported on number of patients completing the study and 82 to 97% patients included in these RCTs completed the study.

Of the 3839 patients included in 22 RCTs comparing Lansoprazole to Omeprazole or Rabeprazole, 71% were men and 29% were women; mean age ranged from 46 to 56 years; BMI data was provided in only 2 trials; race was provided 5 trials and included Japanese and Taiwanese patients; smoking was reported in 11 trials and 20% randomized patients were smokers; alcohol consumption was reported in 8 trials and 13% randomized patients consumed alcohol.

Efficacy based on hierarchy of outcome measures, presented as [# RCTs; RR with 95% CI]: (Refer to Summary of Findings table 9 and 10 in Appendix 8)

1. Total symptomatic relief of symptoms was not reported in 19 RCTs meeting the inclusion criteria.
2. Day time and night time relief of ulcer pain at 4 weeks was provided in one RCT comparing Lansoprazole to Omeprazole. Lansoprazole was significantly better compared to Omeprazole in relieving day time pain [1 RCT; 1.43 (1.15, 1.78); graded as very low quality of evidence] and night time pain [1 RCT; 1.43 (1.22, 1.68); graded as very low quality of evidence].
3. Time to first resolution of symptoms was not reported in the 19 RCTs meeting the inclusion criteria.
4. Healing of ulcer was not provided in trials comparing Lansoprazole to Rabeprazole. Lansoprazole significantly improved healing of ulcer at 4 to 8 weeks compared to Omeprazole [8 RCTs; 1.04 (1.01, 1.07); graded as low quality evidence].
5. *H. pylori* eradication in the Lansoprazole group did not differ significantly from the Omeprazole group at 1 to 8 weeks [12 RCTs; 1.03 (0.97, 1.08); graded as low quality evidence] or from Rabeprazole group at 1 to 16 weeks [7 RCTs; 0.97 (0.93, 1.01); graded as low quality evidence].
6. Quality of life scores were not report in any of the 19 RCTs meeting the inclusion criteria.
7. Recurrence or relapse of symptoms was not reported in any of the 13 RCTs meeting the inclusion criteria.
8. Based on very limited data from 5 of the 15 RCTs meeting the inclusion criteria, Lansoprazole was not significantly different from Omeprazole in harm outcomes mortality [5 RCTs; 0.37(0.02, 8.82); graded as low quality evidence]; serious adverse events [4 RCTs; RR was not estimable; graded as low quality evidence]; withdrawal due to adverse events [4 RCT; 0.45 (0.16, 1.27); graded as low quality evidence] ; patients with at least one adverse event [5 RCTS; 0.89 (0.75, 1.07); graded as low quality evidence]or any specific adverse event.
9. Mortality and serious adverse events were not reported in any RCT comparing Lansoprazole to Rabeprazole. Based on very limited data from 4 of the 7 RCTs meeting the inclusion criteria,

Lansoprazole was not significantly different from Rabeprazole in harm outcomes withdrawal due to adverse events [2 RCTs; 1.02 (0.23, 4.47); graded as very low quality evidence]; patients with at least one adverse event [4 RCTS; 0.94 (0.75, 1.18); graded as low quality evidence]; or any specific adverse event except for diarrhea Lansoprazole had significantly fewer adverse events [3 RCTs; 0.51 (0.30, 0.86); graded as low quality evidence].

Summary of subgroup analysis from RCTs

The data in subgroup of patients in trials meeting the inclusion criteria was presented based on severity of GERD at baseline, severity of peptic ulcer at baseline, or presence or absence of *H. pylori* infection at baseline or at end of treatment. Analyses of subgroups from included RCTs for both GERD and PUD are based on a very small subset of total randomized patients. For GERD, four out of 10 trials comparing Esomeprazole to Omeprazole; two out of 12 RCTs comparing Esomeprazole to Pantoprazole; and two out of 5 RCTs comparing Esomeprazole to Rabeprazole provided data on endoscopic healing of esophagitis in a subgroup of patients based on severity of GERD at baseline. For Lansoprazole compared to other PPIs, of a total of 19 RCTS meeting the inclusion criteria, only one RCT provided data for each of the comparisons for healing of esophagitis. Subgroup analysis for remission rate was provided in 1 RCT based on status of *H. pylori* at baseline. Of the 25 trials meeting the inclusion criteria for PUD for various comparisons, subgroup analyses was selectively reported in 5 RCTs based on type of metabolizer and sensitivity or resistance to specific antibiotics.

Based on the limited data provided, Esomeprazole showed a significant greater endoscopic healing of esophagitis compared to both Omeprazole and Pantoprazole if LA grade of GERD at baseline was severe (B, C and D grade), but is not different from Rabeprazole in Grade C or D patients. Lansoprazole showed a significantly greater endoscopic healing of esophagitis compared to Omeprazole in patients with symptomatic GERD who were cured of *H. pylori* infection at end of 8 week treatment but significantly lower healing rate in Savary-Miller classification Grade III-IV GERD patients. These results are subjected to high risk of selective reporting bias. The results are hypothesis generating that need to be tested in future properly designed randomized controlled trials in particular subgroup of patients with long-term follow-up period. Therefore, no conclusions can be drawn from subgroup analysis in patients with GERD or PUD.

Summary of safety:

DERP 2009 report concluded there was very limited comparative evidence on long term adverse effects of PPIs. There was no long-term, head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects. An updated search from 2009 until March 2014 did not result in any additional observational studies meeting the inclusion criteria on comparative effectiveness of PPIs. Overall, long term adverse effects of PPI are known to be associated with risk of fracture, hypomagnesemia, iron deficiency, vitamin B12 deficiency, enteric infection, pneumonia, acid rebound, acute renal injury and neoplasia (gastric polyps, gastric cancer, carcinoids, and colon cancer). For the majority of the potential adverse effects of PPI therapy, a reasonable biological hypothesis exists. Most of the information is based on retrospective observational studies and some of the associations

observed are most likely not causal but due to bias, confounding or chance. Summary of studies regarding adverse effects showed significant heterogeneity and inconsistent results between observational studies, inadequate control for potential confounding and a lack of data on a dose-response or temporal relationship. The best evidence supports a relevant risk of increase in enteric infections, in particular C. difficile infections in hospitalized patients with significant co-morbidity; and increased risk of community and hospital acquired pneumonia. Specific adverse effects with long term PPI use needs to be studied in high quality, prospective well designed long-term observational studies incorporating data on dosage and duration of treatment with extended follow up.

1.5 Strengths of review

This review provides the most comprehensive evidence for comparative efficacy and harm outcomes of specific PPI comparisons (Esomeprazole or Lansoprazole compared to Omeprazole or Pantoprazole or Rabeprazole) in patients with GERD or PUD. We followed the rigorous gold standard systematic review methodology of the Cochrane Collaboration and included all published randomized controlled trials comparing PPIs of interest in this review. We evaluated the risk of bias of each included study using the Risk of Bias tool of the Cochrane collaboration. We used the Cochrane review Manager 5.2 software to meta-analyze data when appropriate. Also evidence for each specific efficacy or harm outcome is reported according to the hierarchy of outcomes stated in the protocol and it was graded as high, moderate, low or very low quality of evidence using the GRADE pro software and presented as Summary of Findings table (SoF Table 1 to 10 in Appendix 8).

1.6 Limitations of review

Although the review included randomized controlled trials of comparative effectiveness, the highest level study design as the inclusion criteria, critical appraisal of included studies showed varying quality. The factors evaluating selection bias, performance and detection bias, attrition bias, selective reporting bias and source of funding bias resulted in judgement of most studies as unclear or high risk of bias in several categories. Studies used varying definition for some of the outcome measures (total symptomatic relief or individual symptomatic relief or methods to determine criteria used for H. pylori eradication).

Not all outcomes of interest were reported in trials meeting the inclusion criteria. Data has been reported in a subset of trials meeting the inclusion criteria for each comparison and a high risk of selective reporting bias between and within trials was observed. We did not contact authors of these studies to obtain missing information due to time constraints. Mortality, serious adverse events and details of these events, withdrawal due to adverse events and reasons for withdrawals were not reported in over half the trials meeting the inclusion criteria and limited our ability to draw definitive conclusions. No new randomized trials or observational studies for comparative safety of PPI were identified in this updated review. Since many trials did not report on how many patients discontinued the study and how they were accounted in data analysis, we performed an intention-to-treat analysis using conservative analysis (patients who withdrew from the study were deemed as not to have experienced a positive response).

Publication bias was assessed in comparisons for which at least 10 trials met the inclusion criteria. The funnel plot for the outcomes heartburn relief (Esomeprazole vs Omeprazole) and total symptomatic relief (Esomeprazole vs Pantoprazole comparison) in patients with symptomatic GERD showed evidence of publication bias. In patients with PUD, funnel plot for the outcome *H. pylori* eradication (Lansoprazole compared to Omeprazole) showed the presence of publication bias.

Very limited data was provided in subgroup of patients included in RCTs meeting the inclusion criteria. Subgroup analyses for all comparisons based on age, gender, race, BMI, smoking, alcohol consumption, genotype of CYP3A4 liver enzyme, associated co-morbidity (liver disease); and concomitant medications could not be performed. Subgroup analysis was limited to nine of the 38 trials meeting inclusion in patients with GERD and in five of the 25 trials meeting the inclusion criteria in patients with PUD.

As most studies were performed as multinational, multicentre trials in Europe, USA, Japan and Taiwan including some studies that were performed in multi centres in Canada generalizability to the Canadian health care system may be feasible but limited. In addition, the generalizability issues associated with randomized controlled trials, where patients are carefully monitored need to be considered.

Applicability of trial results to community/clinical practice was difficult to determine. The studies generally excluded patients with bleeding disorder or signs of GI bleeding within 3 days prior to randomization; history of gastric or esophageal surgery; evidence of Zollinger-Ellison syndrome; primary motility disorder; esophageal stricture; Barrett's esophagus; upper GI malignancy; severe concomitant disease (liver cirrhosis, COPD, diabetes, renal failure, congestive heart failure, anemia); pregnant or lactating; patients taking PPI or H2RA on a daily basis 2 weeks prior endoscopy; patients taking diazepam, quinidine, dilantin, warfarin, anticholinergic, prostaglandin, sucralfate, corticosteroids or anti-coagulants, hypersensitive to Omeprazole or aluminium/magnesium hydroxide; patients with history of drug abuse, chronic alcoholism or other conditions with poor compliance; patients on NSAID, COX-2 inhibitors, aspirin, PPI or H_2RA use in last 10 days prior to study entry. This pre-selection of patients may have resulted in a group of patients whose disease was less severe in comparison to patients who were not enrolled or are generally treated in clinical practice.

Another concern was that most trials were either funded by the manufacturer or source of funding was not reported which is known to lead to high risk of bias by either overestimating or underestimating the effect size of a particular PPI.

In the maintenance trials, patients were enrolled on the basis of successful treatment with acute PPI treatment. This pre-selection may have resulted in a patient population that was adherent to treatment and could tolerate adverse effects of the PPI previously used in the acute phase.

1.7 Overall Summary of findings

1. Based on 26 randomized trials in 23,789 adult patients with symptomatic GERD comparing Esomeprazole to other PPIs (Omeprazole, Pantoprazole and Rabeprazole), Esomeprazole was not significantly different than other PPIs for most outcome measures - time to first resolution of symptoms; mortality; serious adverse events, withdrawal due to adverse events; and patients

with at least one adverse event. Quality of life scores were not reported in any RCT. A few significant differences in outcome measures stated below are based on low to very low quality evidence and the effect size may very likely change in future research.

- Pantoprazole was significantly better in providing complete symptomatic relief at 4 weeks compared to Esomeprazole [5 RCTs; 0.94 (0.90, 0.98)]; graded as very low quality evidence; no RCT comparing Esomeprazole to Omeprazole or Rabeprazole reported this outcome.
- Esomeprazole was significantly better compared to Omeprazole in providing relief of heartburn at 4 weeks [8 RCTs; 1.08 (1.05, 1.12); graded as very low quality of evidence] but not different from Pantoprazole or Rabeprazole.
- Esomeprazole was significantly better compared to Pantoprazole at endoscopic healing of esophagitis at 4 to 12 weeks [6 RCTs; 1.02(1.00, 1.04); graded as very low quality of evidence], and to Omeprazole at 4 to 8 weeks [6 RCTs; 1.07 (1.05, 1.09); graded as low quality of evidence]. Esomeprazole was not different from Rabeprazole in this outcome.
- The only specific adverse event significantly different between treatment groups was headache (significantly greater in Esomeprazole group compared to Omeprazole [5 RCTs; 1.29 (1.08, 1.54); graded as low quality of evidence].

2. Based on 13 randomized trials in 7,532 adult patients with symptomatic GERD comparing Lansoprazole to other PPIs (Omeprazole, Pantoprazole and Rabeprazole), Lansoprazole was not significantly different than other PPIs for most outcome measures – total relief of symptoms; relief of retrosternal pain; relief of dysphagia; time to first resolution of symptoms; endoscopic healing of esophagitis; recurrence or relapse of symptoms; mortality; serious adverse events, withdrawal due to adverse events; and patients with at least one adverse event. Quality of life scores were not reported in any RCT. A few significant differences in outcome measures stated below are based on low to very low quality evidence and the effect size may very likely change in future research.
    - Both Pantoprazole and Rabeprazole compared to Lansoprazole were significantly better in providing relief of heartburn at 4 to 8 weeks [3 RCTs; 0.95 (0.90, 0.99); graded as very low quality of evidence] and at 8 weeks [1 RCT; 0.83(0.75, 0.92); graded as very low quality evidence], respectively. Omeprazole and Lansoprazole were not different in providing heartburn relief at 4 to 8 weeks.
    - Omeprazole and Pantoprazole was significantly better in providing relief of acid regurgitation at 4 to 8 weeks compared to Lansoprazole [3 RCTs; 0.83 (0.75, 0.93); graded as very low quality evidence] and [2 RCTs; 0.94 (0.89, 1.00); graded as very low quality of evidence] respectively; and Rabeprazole was also significantly better in providing relief of acid regurgitation at 8 weeks compared to Lansoprazole [1 RCT; 0.83(0.72, 0.96); graded as very low quality evidence].
    - Omeprazole and Pantoprazole was significantly better in providing relief of epigastric pain at 8 weeks compared to Lansoprazole [1 RCT for each comparison; 0.87 (0.78, 0.97); graded as very low quality of evidence for both comparisons]. Rabeprazole was

also significantly better in providing relief of epigastric pain at 8 weeks compared to Lansoprazole [1 RCT; 0.83 (0.75, 0.92); graded as very low quality evidence].

- Patients with at least one adverse event were significantly less in Lansoprazole group compared to Pantoprazole [2 RCTs; 0.60 (0.42, 0.85); graded as very low quality of evidence].
- The only specific adverse event significantly different between treatment groups was diarrhea (significantly greater in Lansoprazole group compared to Omeprazole [5 RCTs; 1.23 (1.02, 1.48); graded as low quality of evidence].

3. No RCT met the inclusion criteria comparing Esomeprazole to Rabeprazole in adult patients with peptic ulcer disease. Based on 6 randomized trials in 1,753 patients comparing Esomeprazole to other PPIs (Omeprazole and Pantoprazole), Esomeprazole was not significantly different than other PPIs for most outcome measures – relief of heartburn; relief of epigastric pain;; endoscopic healing of ulcer; mortality; serious adverse events, withdrawal due to adverse events; patients with at least one adverse event; or any specific adverse event. *H. pylori* eradication at 6 to 8 weeks did not differ significantly in Esomeprazole compared to Omeprazole group [5 RCTs; 1.03(0.98, 1.07); graded as very low quality evidence]. Total symptomatic relief; time to first resolution of symptoms; recurrence or relapse of symptoms; and quality of life scores were not reported in any RCT. The only significant difference was Esomeprazole significantly increased *H. pylori* eradication as compared to Pantoprazole [1 RCT; 1.15 (1.03, 1.05); graded as very low quality evidence] and the effect size may very likely to change in future research.
4. No RCT was identified that compared Lansoprazole to Pantoprazole. Based on 19 randomized trials in 3,649 adult patients with peptic ulcer disease comparing Lansoprazole to other PPIs (Omeprazole and Rabeprazole), Lansoprazole was not significantly different than other PPIs for most outcome measures – *H. pylori* eradication; mortality; serious adverse events, withdrawal due to adverse events; and patients with at least one adverse event. Total symptomatic relief; time to first resolution of symptoms; recurrence or relapse of symptoms; and quality of life scores were not reported in any RCT. A few significant differences in outcome measures stated below are based on low to very low quality evidence and the effect size may very likely to change in future research.
    - Lansoprazole was significantly better compared to Omeprazole at week 4 in day time relief of ulcer pain [1 RCT; 1.43 (1.15, 1.78); graded as very low quality of evidence] and night time relief of ulcer pain [1 RCT; 1.43 (122, 1.68); graded as very low quality of evidence].
    - Lansoprazole significantly improved healing of ulcer compared to Omeprazole at 4 to 8 weeks [8 RCTs; 1.04 (1.01, 1.07); graded as low quality evidence] and data was not provided for Lansoprazole compared to Rabeprazole.
    - The only specific adverse event significantly different between treatment groups was diarrhea (significantly lower in Lansoprazole group compared to Rabeprazole [3 RCTs; 0.51(0.30, 0.86); graded as low quality evidence].

5. No definitive conclusions could be drawn on subgroup analysis based on severity of GERD at baseline, severity of peptic ulcer at baseline, or presence or absence of *H. pylori* infection at baseline or at end of treatment. The results are subjected to high risk of selective reporting bias and presented in a very small subset of total randomized patients. Subgroup analyses results are hypothesis generating that need to be tested in future properly designed randomized controlled trials with long term follow up period.
6. DERP 2009 report concluded there was very limited comparative evidence on long term adverse effects of PPIs. There was no long-term, head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects. An updated search from 2009 until May 2014 did not result in any additional observational studies meeting the inclusion criteria on comparative effectiveness of PPIs.
7. Overall, long term adverse effects of PPI are known to be associated with risk of fracture, hypomagnesemia, iron deficiency, vitamin B12 deficiency, enteric infection, pneumonia, acid rebound, acute renal injury and neoplasia (gastric polyps, gastric cancer, carcinoids, and colon cancer). The best evidence supports a relevant risk of increase in enteric infections, in particular C. difficile infections in hospitalized patients with significant co-morbidity; and increased risk of community and hospital acquired pneumonia.

1.8 Conclusions

Implications for Practice

Due to the paucity of high-quality data, the results presented in this review provide weak/poor evidence of the comparative efficacy and harm of different PPIs. For outcomes graded as low quality - future research is very likely to have an important impact on our confidence in the estimate and may change the estimate. For outcomes graded as very low quality - we are very uncertain about the estimate.

Implications for Research

Adequately powered randomized controlled trials comparing different PPIs are needed to evaluate long term benefits and harm of PPI therapy and should report on all outcome measures specified in the hierarchy of health outcomes in this review.

Trials in specific subgroups based on baseline characteristics (age, gender, race, BMI, smoking, alcohol consumption, genotype of CYP2C19 and CYP3A4 liver enzyme, associated co-morbidity; concomitant medications, severity of grade of GERD; and presence of *H. pylori* infection) are required to determine if differences in efficacy exist between different PPIs.

Specific adverse effects associated with long-term therapy using different PPIs need to be studied in high quality, prospective well designed long term observational studies incorporating data on dosage and duration of treatment with extended follow up.

A systematic review of the comparative effectiveness of proton pump inhibitors for the treatment of adult patients with gastroesophageal reflux disease or peptic ulcer disease

2 INTRODUCTION

2.1 Disease Prevalence and Incidence

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. (Fennerty B et al 1996) The symptoms include primarily heartburn, regurgitation, hyper salivation or non-cardiac chest pain. Several extra esophageal syndromes associated with GERD, include chronic cough, asthma, laryngitis, hoarseness, dysphonia, oropharyngeal ulceration and dental erosions. Diagnosis of GERD can usually be established on the basis of a careful history and physical examination. Further investigation is generally not required. (Canadian Consensus Guideline 2009)

GERD is believed to be caused by a combination of conditions that increase the presence of gastric content in the esophagus. These conditions include frequent and prolonged transient lower esophageal sphincter relaxation, decreased lower esophageal sphincter tone, impaired esophageal clearance, delayed gastric emptying, and decreased salivation. Smoking, large meals, fatty foods, caffeine, pregnancy, obesity, body position, drugs, and hormones may all exacerbate GERD. Complications may result from an excessive reflux of gastric contents into the esophagus, oropharynx or lungs. Reflux may cause inflammation (*erosive esophagitis*) and complications such as the development of an ulcer, bleeding or stricture. Chronic esophagitis can further evolve through attempted repair into metaplastic columnar epithelium (*Barrett's esophagus*) and the development of esophageal adenocarcinoma. However, about 55–80% of GERD patients have no erosive disease on endoscopy. GERD with no demonstrable esophageal disease is termed *non-erosive reflux disease* (NERD).

In a population survey, approximately 17% of Canadians reported heart burn in the preceding 3 months and 13% reported moderate to severe symptoms occurring at least weekly. (Tougas G et al 1999) The prevalence of esophagitis is probably between one third to two-thirds among patients with reflux symptoms (Shaheen N et al 2003) suggesting prevalence of 5% to 12% in the general population. (Veneables TL et al 1997) Although disease related mortality is low, health-related quality of life is worse in patients with GERD than in patients with diabetes, hypertension, mild heart failure or arthritis. (Revicki D et al 1998) GERD is associated with loss of time from work and decreased productivity. 41% of the 102 patients surveyed reported some loss of work productivity because of their disease (Henke C et al 2000) Mild GERD symptoms do not interfere with daily activity and are usually of low intensity, short in duration, not nocturnal, infrequent (<3 times weekly) and without major complications. Severe GERD symptoms regularly interfere with daily activities and are usually of high intensity, persistent (>6 months), nocturnal, frequent and often associated with complications. However, severity of symptoms is not a reliable indicator of esophagitis. Alarm features in the presence of GERD symptoms include

persistent vomiting, bleeding, anemia, involuntary weight loss, dysphagia, odynophagia or chest pain. (Canadian Consensus Guideline 2009)

Peptic ulcer disease (PUD) is a chronic, inflammatory condition of the stomach or duodenum. It includes both gastric and duodenal ulcer. One-year point prevalence is estimated as 1.8% and lifetime prevalence is approximately 10%. (Fantry G 2007) Prevalence has shifted from predominance in males to similar occurrences for both sexes with the lifetime prevalence for males at approximately 11-14% versus 8-11% for women. Trends also reflect complex changes in risk factors for PUD, including age-cohort phenomena with the prevalence of *H. pylori* infection and the use of NSAIDs in older populations.

Since the discovery that *H. pylori* cause many peptic ulcers, eradication of *H. 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. Although the goal of therapy for ulcer disease is quick relief of symptoms (heart burn) 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 (strictures, bleeding, and columnar metaplasia).

Pharmaceutical Services Division has requested an update of the Drug Effectiveness Review Project (DERP) 2009 report on the class review of proton pump inhibitors (PPIs) for the treatment of adult patients with symptomatic gastroesophageal reflux disease (GERD) and peptic ulcer. The specific request from PSD is to limit the update to systematically reviewing comparative effectiveness of PPIs in adult patients with GERD or peptic ulcer disease.

2.2 Standard of Therapy

Non-pharmacological therapy includes

- Lifestyle modifications such as elevating the head of the bed and avoiding recumbence shortly after feeds can be helpful
- Dietary modifications (avoid chocolate, caffeine, citrus juices, large fatty meals)
- Weight loss if BMI > 30kg/m^2 or experienced recent weight gain
- Avoid eating 3 hours before bedtime
- Elevate legs by 10 to 20cm particularly if nocturnal symptoms are present and
- Stop smoking and avoid tight clothing
- Eliminate drugs that impair esophageal motility and lower esophageal sphincter tone (e.g., anticholinergic agents, beta-blockers, calcium channel blockers, theophylline, and tricyclic antidepressants)

Pharmacological options include:

- In **mild cases** symptomatic relief is obtained by antacids, alginates or histamine H_2 receptor antagonists (H_2RA) – cimetidine; famotidine, nizatidine and ranitidine.
- In **moderate to severe cases**, antacids or H_2RAs alone are generally not effective. An effective approach is an 8-week course of a proton pump inhibitor (PPI) to effectively raise the gastric pH above 4. PPIs include Omeprazole, Esomeprazole, Pantoprazole, Rabeprazole; Dexlansoprazole and Lansoprazole.

2.3 Drug

2.3.1 Drug characteristics:

The PPIs included in this review are Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole magnesium, Pantoprazole sodium and Rabeprazole.

Table 2-1 Drugs Key Characteristics (e CPS product monograph)

	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Mechanism of action	PPIs are pro-drugs requiring proton pump activation for optimal efficacy; hence they are best administered 30–60 minutes before a meal. PPIs effectively block acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase (the proton pump) on the apical surface of the parietal cell membrane of the stomach.				
Indication(s)	Reflux esophagitis, maintenance treatment of patients with reflux esophagitis, symptomatic GERD; Non-erosive GERD; Symptomatic relief and healing of peptic ulcer (duodenal and gastric); Healing of NSAID associated gastric ulcers; Reduction of risk of NSAID associated gastric ulcers; Treatment of pathological hyper secretory conditions including Zollinger-Ellison syndrome. PPIs in combination with clarithromycin and amoxicillin are indicated for the treatment of patients with duodenal ulcer associated with *H. pylori* infection to eradicate the *H. pylori* and heal ulcers.				
Route of administration	Oral capsule, and oral suspension	Oral tablet, oral capsule, and oral suspension	Oral tablet, oral capsule, and oral suspension	Oral tablet, oral capsule, and oral suspension	Oral tablet
Recommended dose Patients should use the lowest dose and shortest duration of PPI therapy	20-40 mg once daily po ½ h before food.	15–30 mg once daily po ½ h before food	20-40 mg once daily po ½ h before food	Sodium: 20-40 mg once daily po ½ h before food Magnesium 40mg once daily po ½ h before food	10-20 mg once daily po ½ h before food
Dose range	10 to 40mg	15 to 60mg	10 to 40mg	20 to 80mg	10 to 40mg
Recommended therapy	***Initial therapy*** is once a day before breakfast for 4 to 8 weeks. In those with ***partial response*** consider twice a day dosing. In patients with Zollinger-Ellison syndrome consider highest dose twice a day. Once symptomatic relief is obtained with full strength PPIs, gradually decrease the intensity of acid suppression in NERD until breakthrough symptoms occur. Use PPI at the lowest dose that provides symptom relief. Half of the healing PPI dose may suffice. Some patients can transition to H_2RAs once symptomatic relief has been achieved with PPIs, without adversely affecting quality of life.				

Table 2-1 Drugs Key Characteristics (e CPS product monograph)					
	Esomeprazole	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
	Maintenance therapy is long term and is important in severe esophagitis and Barrett's esophagus. Dose and frequency is tailored to keep symptom free. ***On-demand therapy*** is an alternative to a continuous maintenance regimen particularly in those with NERD in whom symptom control is paramount. On-demand therapy is contraindicated in erosive esophagitis. PPI is used for a period of time sufficient to achieve resolution of the reflux symptoms at which time the patient discontinues the drug with a subsequent drug-free remission which may last months. In patients with *H. pylori*, the recommended dose is low dose of PPI, amoxicillin 1000mg and clarithromycin 500mg, all administered twice a day for 7 days.				
Serious side effects/safety warnings	Potential concerns with long term PPI therapy relate to the development of nosocomial pneumonia, enteric infections like *C. difficile*, osteoporosis causing fractures of the hip, wrist or spine and rarely magnesium deficiency. Other 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), colorectal cancer, malabsorption syndromes, and diarrhea.				
Other risks	1. Acid rebound occurs with their discontinuation and may be a factor in gastrointestinal symptoms recurring after PPIs are withdrawn. 2. The patients most likely at risk of complications are those who have a genetic deficiency of the active enzyme (CYP 2C19) responsible for metabolizing Omeprazole (about 5% of Caucasians and 20% of Orientals). These individuals, who can only be identified in a research setting, are exposed to plasma concentrations of Omeprazole which are >10 times higher than other patients taking Omeprazole. (Horai Y 1989; Andersson T 1990) 3. Concomitant use of PPIs with Clopidogrel following acute coronary syndrome in a cohort study in 8,000 patients showed increased risk of death or rehospitalisation with OR 1.25(1.11 to 1.41). (Ho PM 2009) 4. Concomitant use of PPIs with Clopidogrel following acute myocardial infarction increased the risk of readmission for recurrent MI with 30 days OR 1.27(1.03, 1.57) based on a small nested case control study of 734 cases and 2057 controls. (Jurrlink DN 2009)				

2.4 Goals of Therapy

Although the immediate goal is symptomatic relief, the long term goal is preventing recurrence or relapse and future complications that affect patient's quality of life.

2.5 Guidelines

Several guidelines recommendations have been published for the management of patients with GERD or peptic ulcer disease and are discussed below:

Guidelines for patients with GERD

a. **BC Guidelines 2009 recommendations** http://www.bcguidelines.ca/pdf/gastro.pdf
    1. ***The initial management of GERD*** in the absence of alarm features should consist of diet and lifestyle modifications, antacids, alginates or histamine$_2$ receptor antagonists (H_2 RA). Under these circumstances barium X-rays and endoscopy results are frequently normal and are generally not recommended. Antacids and alginates may be effective in patients with intermittent or sporadic symptoms.
    2. In the absence of improvement with the above management strategy, ***for management of severe symptoms or poor response*** H_2RA or PPIs may be tried for duration of 4-8 weeks to see a response.
    3. ***Absence of response*** to the above regimens justifies specialist consultation and/or further investigation. Endoscopy is the investigation of choice. Endoscopy is not necessary or universally effective in making a diagnosis of GERD, but is considered the investigation of choice to identify esophagitis, assess its severity and rule out complications including strictures and Barrett's esophagus. Barium studies are not adequate to assess the mucosa or diagnose reflux disease.
    4. Patients with ***complicated GERD*** (Barrett's esophagus, ulceration, bleeding, or peptic stricture) may require long-term PPI therapy. The efficacy of prokinetic agents (domperidone and metaclopramide) has not been established. Anti-reflux surgery could be considered in patients who respond well to PPI therapy, but who are intolerant or reluctant to take medications. Outcomes are highly dependent on individual factors.

b. **The Canadian guideline 2009** has been adapted from the Canadian consensus conference on the management of patients with GERD and the Montreal definition and classification of GERD. The recommendations contained in this guideline do not apply to pregnant or lactating women or patients under 18 years of age. (Canadian Guideline 2009)
    Treatments recommended are:
    1. Lifestyle modification includes weight control; reduction of alcohol, caffeine intake and tobacco; avoid lying down until 2 hours after eating; avoid spices, peppermint, chocolate or citrus juice. It has limited effectiveness for GERD and is usually ineffective in severe GERD symptoms.
    2. Over-the-counter antacid or H_2RA are useful for mild or infrequent symptoms.
    3. If patient fails to respond to lifestyle modification and/or over-the-counter medication add PPI once daily for 4- 8 weeks.
    4. If symptoms are not resolved by treatment or if symptoms recur consider extending therapy to 16 weeks after careful review to determine diagnostic accuracy; *or* consider BID PPI for 4 weeks; or if previous treatment did not use PPI then, PPI is recommended for 4-8 weeks.

Patients should be followed-up at 2 to 4 weeks to review the diagnosis and reassess management.

5. Failure to respond to 16 weeks of PPI therapy warrants a careful reassessment of diagnosis and further investigation by endoscopy.
6. Patients whose symptoms require ongoing use of acid suppression medication for many years should have an endoscopy by 10 years into their condition to search for Barrett's esophagus.

c. **American Guideline by Katz P et al 2013 recommend the following for management of GERD** (*Katz P et al* 2013; 108:308 – 328; doi: 10.1038/ajg.2012.444; published online 19 February 2013)

1. Weight loss for GERD patients who are overweight or have had recent weight gain. (Conditional recommendation, moderate level of evidence)
2. Head of bed elevation and avoidance of meals 2 – 3 h before bedtime for patients with nocturnal GERD. (Conditional recommendation, low level of evidence)
3. Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and / or spicy foods) is **NOT** recommended in the treatment of GERD. (Conditional recommendation, low level of evidence)
4. An ***8-week course of PPIs*** is the therapy of choice for symptom relief and ***healing of erosive esophagitis***. There are no major differences in efficacy between the different PPIs. (Strong recommendation, high level of evidence)
5. ***Traditional delayed release PPIs*** should be administered 30-60 minutes before meal for maximal pH control. (Strong recommendation, moderate level of evidence). Newer PPIs may offer dosing flexibility relative to meal timing. (Conditional recommendation, moderate level of evidence)
6. PPI therapy should be initiated at once a day dosing, before the first meal of the day. (Strong recommendation, moderate level of evidence).
7. For patients with ***partial response*** to once daily therapy, tailored therapy with ***adjustment of dose timing and/or twice daily dosing*** should be considered in patients with night-time symptoms, variable schedules, and/or sleep disturbance. (Strong recommendation, low level of evidence).
8. ***Non-responders to PPI*** should be referred for evaluation. (Conditional recommendation, low level of evidence, see refractory GERD section).
9. In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. (Conditional recommendation, low level evidence).
10. ***Maintenance PPI therapy*** should be administered for GERD patients who continue to have symptoms after PPI is discontinued and in patients with complications including erosive esophagitis and Barrett's esophagus. (Strong recommendation, moderate level of evidence).
11. For patients who require ***long-term PPI therapy***, it should be administered in the ***lowest effective dose***, including on demand or intermittent therapy. (Conditional recommendation, low level of evidence)

12. H_2 -receptor antagonist (H_2RA) therapy can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. (Conditional recommendation, moderate level of evidence).
13. Bedtime H_2RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but may be associated with the development of tachyphylaxis after several weeks of use. (Conditional recommendation, low level of evidence)
14. Therapy for GERD other than acid suppression, including prokinetic therapy and/or baclofen, should **NOT** be used in GERD patients without diagnostic evaluation. (Conditional recommendation, moderate level of evidence).
15. There is **NO** role for sucralfate in the non-pregnant GERD patient. (Conditional recommendation, moderate level of evidence)

Peptic ulcer disease (http://www.bcguidelines.ca/guideline_dyspepsia.html)

d) **BC guidelines for dyspepsia** with or without *H. pylori* infection recommends managing patients with mild or infrequent symptoms without further investigations using non-prescription acid reducing agents. Since many medications can cause dyspeptic symptoms drug history including non-prescription medication is recommended.

In patients with more persistent symptoms two approaches can be followed:

1. Test for *H. pylori* infection in patients who have not been previously screened and who have high risk for *H. pylori* infection. Individuals with dyspepsia who currently have an endoscopically or radiographically confirmed duodenal or gastric ulcer, or have had one within the past five years, should be tested for *H. pylori* infection.
2. In patients who are unlikely to have *H. pylori* infection or who have previously tested negative a 4-8 week course of PPI or H_2 receptor antagonist may be prescribed.

Patients with chronic non-progressive symptoms previously investigated with negative results and no alarm symptoms have functional dyspepsia, a benign but chronic relapsing condition and do not require further investigation. It has not been established that long term pharmacotherapy improves outcomes for dyspepsia and its use should be reassessed periodically. Education, reassurance and support are the foundations of care.

For ***patients tested positive with H. pylori infection*** treatment of 1 week duration with PPI bid, amoxicillin 1000mg bid and clarithromycin 500mg bid or PPI bid, metronidazole 500mg bid and clarithromycin 250 mg bid or PPI bid, bismuth subsulfate 2 tabs QID, metronidazole 250mg QID and tetracycline 500mg QID is recommended. PPI recommended are Rabeprazole 20 mg, Lansoprazole 30 mg, Omeprazole 20 mg, Pantoprazole 40 mg, or Esomeprazole 20 mg.

Patients with alarm features that require prompt investigation include: gastrointestinal blood loss, weight loss, early satiety, dysphagia, persistent vomiting, or symptom onset after the age of 55 years.

This group requires prompt investigation and endoscopy to identify gastric or duodenal ulcer as well as esophageal and gastric cancers is recommended. Gastric ulcers are potentially malignant and require endoscopic biopsy. There is evidence that *H. pylori* infection is associated with adenocarcinoma of the stomach (Isaacson P 1993).

The duration of treatment for *H. pylori* is somewhat controversial. While a seven day treatment is most often recommended, a fourteen day treatment is thought to yield a 5% increase in eradication success rates. This increase must be weighed against added cost and risk of adverse events which include Clostridium difficile colitis, allergic reactions, and increased antibiotic resistance.

e) **Canadian *H. pylori* guideline 2009**

The Canadian *H. pylori* guideline 2009 update also recommends eradication regimens with a proton pump inhibitor (PPI) plus two antibiotics as choices to eradicate *H. pylori*. Successful eradication requires clarithromycin as one of the 2 antibiotics in these protocols. These protocols continue to perform well in Canada with over 80% cure rates. Extending the duration of treatment beyond 7 days is unlikely to be beneficial.

3 OBJECTIVES AND METHODS:

3.1 Objectives requested (PICOS format)

1. To determine from head to head randomized controlled comparative trials if proton pump inhibitors (Esomeprazole or Lansoprazole) provide a therapeutic advantage (includes benefit and harm) as compared to other proton pump inhibitors (Omeprazole, Pantoprazole or Rabeprazole) in adult patients with symptomatic gastroesophageal reflux disease.
2. To determine from head to head randomized controlled comparative trials if proton pump inhibitors (Esomeprazole or Lansoprazole) provide a therapeutic advantage (includes benefit and harm) as compared to other proton pump inhibitors (Omeprazole, Pantoprazole or Rabeprazole) in adult patients with peptic ulcer (includes gastric and duodenal ulcer).
3. To determine from head to head randomized controlled comparative trials if there are subgroups of patients based on demographics, other medications or co-morbidities (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 in adult patients with symptomatic gastroesophageal reflux disease and peptic ulcer.
4. To determine based on large, long term (6 months or more), select comparative observational studies (cohort and nested case control) the safety and adverse events profile of different proton pump inhibitors in adult patients with symptomatic gastroesophageal reflux disease and peptic ulcer.

3.2 Methods:

3.2.1 Eligibility Criteria

Studies were selected for inclusion in the systematic review based on the PICOS selection criteria presented in Table 3-1.

Table 3-1 Inclusion Criteria for the Systematic Review	
Patient Population	Adult out patients with symptoms of GERD or peptic ulcer disease. Note: patients with stress ulcers, iatrogenic ulcers or drug induced ulcers were excluded.
Intervention	PPIs: Esomeprazole or Lansoprazole (at any dose or dosing regimen)
Comparator	Other PPIs: Omeprazole, Pantoprazole or Rabeprazole (at any dose or dosing regimen)
Outcomes (Hierarchy)	Since the diagnosis of GERD and peptic ulcer is based on symptoms, mortality rate is very low and non-fatal serious adverse events such as stricture formation, bleeding, perforation of ulcer, and adenocarcinoma occur after disease becomes chronic and lasts for several years, this systematic review will present outcomes according to the following hierarchy: 1. Symptomatic relief (heart burn, regurgitation of acid or bile, hyper-salivation, non-cardiac chest pain) 2. Time to first resolution of symptoms 3. Healing of esophagitis (endoscopic healing) in GERD and healing of ulcer in peptic ulcer disease 4. Quality of life (using validated scores) 5. Recurrences or relapse 6. Eradication of *H. pylori* in peptic ulcer disease 7. Non-fatal serious adverse events (includes stricture formation, bleeding, perforation of ulcer) 8. All-cause mortality (including fatal bleeding, cancer) 9. Specific adverse events include the following: a. *Short term adverse effects include* - rebound acid secretion, headache, nausea, diarrhea, abdominal pain, fatigue and dizziness. b. *Infrequent adverse effects include* - rash, flatulence, anxiety, depression, pancreatitis, erythema multiforme, Stevens-Johnson syndrome, thrombocytopenia and acute interstitial nephritis. c. *Long term adverse effects include* - Vitamin B_{12} deficiency, C. difficile associated diarrhea, community acquired pneumonia; bone fractures; increased enteric infections (salmonella, campylobacter and shigella); gastric- carcinoid tumor, hypomagnesaemia, hypocalcaemia and hypokalemia. d. *Adverse effects due to drug-drug interaction* - increased risk of myocardial infarction, stroke and cardiovascular death when PPI is used with Clopidogrel.
Study design	To evaluate efficacy we included randomized active comparator trials at least 4 weeks' duration for patients with GERD and treatment duration of 1 week for patients with peptic ulcer disease. For safety evaluation, besides RCTs, we have also included long term observational studies (cohort and nested case-control studies) at least 6 months duration.

3.2.2 Search strategy and findings

The updated search strategy of the DERP 2009 report was created with the help of an information specialist. (Refer to Appendix 1: Literature Search Strategy)

The following electronic databases were searched: MEDLINE (2009 -March 2014), MEDLINE-in-process, EMBASE (2009 - March 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (2009 - March 2014), and the Cochrane Database of Systematic Reviews (until March 2014). English language reports of randomized comparative controlled trials in adult patients with symptomatic GERD comparing two different PPIs at least 4 weeks in duration were included. For Peptic ulcer disease English language reports of randomized comparative controlled trials in adult patients with symptomatic PUD comparing two different PPIs at least 1 week in duration were included. Also existing systematic reviews and health technology evidence reports that are published since 2009 DERP report are reviewed and bibliography is cross checked to confirm all trials meeting the inclusion criteria are included.

This systematic review and meta-analysis will include all RCTs meeting the inclusion criteria in the DERP 2009 report (Update 5) as well as additional new RCTs identified. In addition harm data will be summarized from the DERP report and specific select observational studies (cohort and nested case control studies) at least 6 months in duration identified in updated search until March 2014 which compare safety between different PPIs are included.

3.2.3 Study selection

Selection eligibility criteria were applied to each title and abstract identified in the literature search by two independent review authors in a standardized manner. Citations based on reading titles and abstract and those that were clearly irrelevant are excluded. Full text articles of all citations considered potentially relevant by one reviewer were retrieved. The reviewers were not blinded to study authors or centre of publication prior to study selection. Two reviewers independently made the final selection of studies to be included in the review, and any differences were resolved through discussion with the third reviewer. Lists of included (Refer to section 3.2.2) and excluded studies (Refer to Appendix 2) are listed in the report.

3.2.4 Data extraction and synthesis

Data abstraction was performed using standardized data abstraction form. (Refer to Appendix 3 for Data extraction template). All extracted data were checked for accuracy by two independent review authors. The original, primary publication for each unique study included was used for data extraction.

The following data was extracted from included studies and are presented in a table format:

1. Characteristics of included studies
    a. Study design; location; number randomized patients; dose, duration and mode of administration of interventions and comparators; and outcomes
    b. Inclusion and exclusion criteria
    c. Baseline characteristics of trial participants (sex; mean age; BMI; race; smoking; alcohol consumption; type of ulcer ; and *H. pylori* status)
    d. Patient disposition (including total withdrawals; and reasons for withdrawals)

2. Efficacy outcomes (refer to item 1-5 in hierarchy of health outcomes)
3. Safety outcomes (refer to item 6-9 in hierarchy of health outcomes)

Detail of each included studies are classified according to patient population (GERD or PUD) and also presented according to the following specific comparisons (See Appendix 6):

GERD comparisons 1 to 6

GERD Comparison 1: Esomeprazole vs. Omeprazole – Table I [A] to Table I [E]
GERD Comparison 2: Esomeprazole vs. Pantoprazole – Table II [A] to Table II [E]
GERD Comparison 3: Esomeprazole vs. Rabeprazole – Table III [A] to Table III [E]
GERD Comparison 4: Lansoprazole vs. Omeprazole – Table IV [A] to Table IV [E]
GERD Comparison 5: Lansoprazole vs. Pantoprazole – Table V [A] to Table V [E]
GERD Comparison 6: Lansoprazole vs. Rabeprazole – Table VI[A] to Table VI[E]

PUD comparisons 7 to 12

PUD Comparison 7: Esomeprazole vs. Omeprazole – Table VII [A] to Table VII [E]
PUD Comparison 8: Esomeprazole vs. Pantoprazole – Table VIII [A] to Table VIII [E]
PUD Comparison 9: Esomeprazole vs. Rabeprazole (no RCT)
PUD Comparison 10: Lansoprazole vs. Omeprazole – Table X [A] to Table X [E]
PUD Comparison 11: Lansoprazole vs. Pantoprazole (No RCT)
PUD Comparison 12: Lansoprazole vs. Rabeprazole – Table XII [A] to Table XII [E]

3.2.5 Quality Assessment:

3.2.5.1 Risk of Bias in individual studies:

The quality of each included study meeting the inclusion criteria was objectively assessed using Cochrane collaboration's tool for assessing Risk of Bias (Chapter 8 Cochrane Handbook for intervention reviews) and presented using Review Manager 5.2 software of the Cochrane Collaboration.
The Risk of Bias evaluation at the study level includes the following 7 factors for a randomized controlled trial (RCT): random sequence generation (selection bias); allocation concealment (selection bias); blinding of participant and personnel (performance bias); blinding of outcome assessor (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and source of funding bias (other bias).
Each of these factors will be assessed based on the information provided in the published report and will be judged as:

- Low risk of bias – if bias is of insufficient magnitude to have a notable impact on the results.
- High risk of bias – if bias is of sufficient magnitude to have a notable impact on the results.
- Unclear risk of bias – if insufficient details are reported and risk of bias is unknown.

Cochrane recommends using unclear risk of bias judgment as high risk of bias during study outcome data interpretation. (Refer to Appendix 4 for details).

The Risk of bias summary: review authors' judgements about each risk of bias item for each included study summary figure generated by Review Manager 5.2 are provided. Refer to Section 4.5.1 for summary of critical appraisal of all included studies meeting the inclusion criteria.

3.2.5.2 Risk of Bias across studies:

To grade the quality of the overall effect size in individual forest plots, outcome specific risk of bias across all studies contributing data to the meta-analysis was assessed.

3.2.6 Data synthesis

Data has been synthesized using Review Manager 5.2 program of the Cochrane collaboration. For dichotomous outcomes (e.g. such as number of patients with symptomatic relief; number of patients with healed esophagitis; number of patients with recurrence or relapse of symptoms; mortality; serious adverse events; withdrawal due to adverse events; total adverse events; and specific adverse events) relative risk with 95% confidence interval (RR with 95% CI) using Mantel-Haenszel method and fixed effects model are presented. Intention to treat (ITT) analysis was applied to all dichotomous analysis.

For continuous outcomes (e.g. such as time to first resolution of symptoms; and quality of life scores), mean difference with 95% confidence interval using inverse variance method and fixed effects model was planned to be presented. Data was not provided for any of these outcome measures in this systematic review.

Heterogeneity was assessed between studies using I^2 statistics for meta-analysis of each comparison. We also used random effects model in cases when significant heterogeneity was present. We tried to investigate reasons for heterogeneity If value of I^2 was 50 % or greater between trials.

3.2.7 Assessment of Publication bias

Publication bias was assessed using funnel plots for the primary outcome measure (if 10 or more studies met the inclusion criteria for a specific comparison). This was possible for 2 comparisons in patients with GERD (Esomeprazole versus Omeprazole) and (Esomeprazole versus Pantoprazole) and for only one comparison (Lansoprazole versus Omeprazole) in patients with PUD. An asymmetrical plot would imply publication bias, as in the absence of bias the plot should resemble an inverted funnel.

3.2.8 Additional analyses

If data was available, subgroup analyses based on age, gender, race, BMI, smoking, alcohol consumption, genotype of CYP2C19 and CYP3A4 liver enzyme, associated co-morbidity (liver disease); and concomitant medications was planned to be performed. However, due to lack of data being reported in most of the pre-specified subgroups, we were not able to conduct these analyses. Only one RCT provided data on *H. Pylori* eradication rates based on genotype of CYP2C19 in patients with PUD (Refer section 4.6.2.1.10)

3.2.1 Sensitivity analyses

If relevant heterogeneity was present, sensitivity analysis was conducted based on aspects of the PICO statement and study methodology to explore reasons for heterogeneity.

RESULTS

This section provides the results of the literature review, critical appraisal of the studies identified, and comparability of the studies.

3.3 Findings from the Literature

Search findings results are presented in Table 4-1 and 4-2. The prisma Flow diagram detailing the flow of studies is given in Figure 4-1 and 4-2.

RCT search for GERD: Updated literature search from June 2009 until March 2014 identified 1571 new citations from Medline, EMBASE and Cochrane Central Register of Controlled Trials, and 47 from other sources (previous systematic reviews and DERP report). De-duplication resulted in 1361 records, which were screened, of which 1282 were excluded on initial screening. Seventy-nine full text articles were retrieved to check for eligibility criteria, of which 39 were excluded (refer Appendix 2 for reasons for exclusion). Of the remaining citations, 38 RCTs were identified that met the inclusion criteria and were included in this review.

RCT search for PUD: Updated literature search from June 2009 until March 2014 identified 1379 new citations from Medline, EMBASE and Cochrane Central Register of Controlled Trials, and 25 from other sources (previous systematic reviews and DERP report). De-duplication resulted in 1202 records, which were screened, of which 1146 were excluded on initial screening. Fifty-six full text articles were retrieved to check for eligibility criteria, of which 31 were excluded (refer Appendix 2 for reasons for exclusion). Of the remaining citations, 25 RCTs were identified that met the inclusion criteria and were included in this review. Records excluded on initial screen in GERD and PUD citations were mainly due to some of the following reasons: Review articles; drug induced ulcers; stress ulcers; PPI compared to placebo; same PPIs compared at different doses; wrong comparator; same PPI dose but different antibiotics used in treatment arms; and high dose PPI versus low dose PPI comparison of same PPI; or PPI vs H_2RA.

Updated search for observational studies for both GERD and PUD from June 2009 until March 2014 identified 2326 new citations from Medline, EMBASE and Cochrane Central Register of Controlled Trials, and 16 from other sources (previous systematic reviews and DERP report). De-duplication resulted in 2094 records, which were screened, of which 2025 were excluded on initial screening. A total of 69 full text articles were retrieved to check for eligibility criteria, of which all were excluded as comparative safety of PPIs was not provided. We have summarized recent general safety issues of long term use of PPIs as a class.

Gastroesophageal reflux disease (N = 38 RCTs* met inclusion criteria)

*Note: 5 RCTs had multiple comparative treatment arms

Table 0-1 Search findings for GERD		
Comparison number	**Comparators**	**Number of trials meeting inclusion criteria**
GERD Comparison 1	Esomeprazole vs. Omeprazole	10 RCTs (1 article reported 3 RCTs)
GERD Comparison 2	Esomeprazole vs. Pantoprazole	12 RCTs
GERD Comparison 3	Esomeprazole vs. Rabeprazole	5 RCTs (1 article reported 2 RCTs)
GERD Comparison 4	Lansoprazole vs. Omeprazole	12 RCTs
GERD Comparison 5	Lansoprazole vs. Pantoprazole	5 RCTS
GERD Comparison 6	Lansoprazole vs. Rabeprazole	2 RCTs
Total for all comparisons		46 RCTs of which 3 RCTs are counted twice, 1 RCT counted 3 times and 1 RCT counted 4 times making unique individual RCT count = 38

Peptic Ulcer Disease (N = 25 RCTs* met inclusion criteria)

* Note 3 RCTs had multiple comparative treatment arms

Table 0-2 Search findings for PUD		
Comparison number	**Comparators**	**Number of trials meeting inclusion criteria**
Comparison number	Comparators	Number of trials meeting inclusion criteria
PUD Comparison 7	Esomeprazole vs. Omeprazole	5 RCTs
PUD Comparison 8	Esomeprazole vs. Pantoprazole	1 RCT
PUD Comparison 9	Esomeprazole vs. Rabeprazole	0 RCT
PUD Comparison 10	Lansoprazole vs. Omeprazole	15 RCTs
PUD Comparison 11	Lansoprazole vs. Pantoprazole	0 RCT
PUD Comparison 12	Lansoprazole vs. Rabeprazole	7 RCTs
Total for all comparisons		28 RCTS of which 3 RCTs are counted 2 times = 25 RCTs

Figure 0-1 PRISMA Flow Diagram Detailing Flow of Studies (GERD – RCTs)

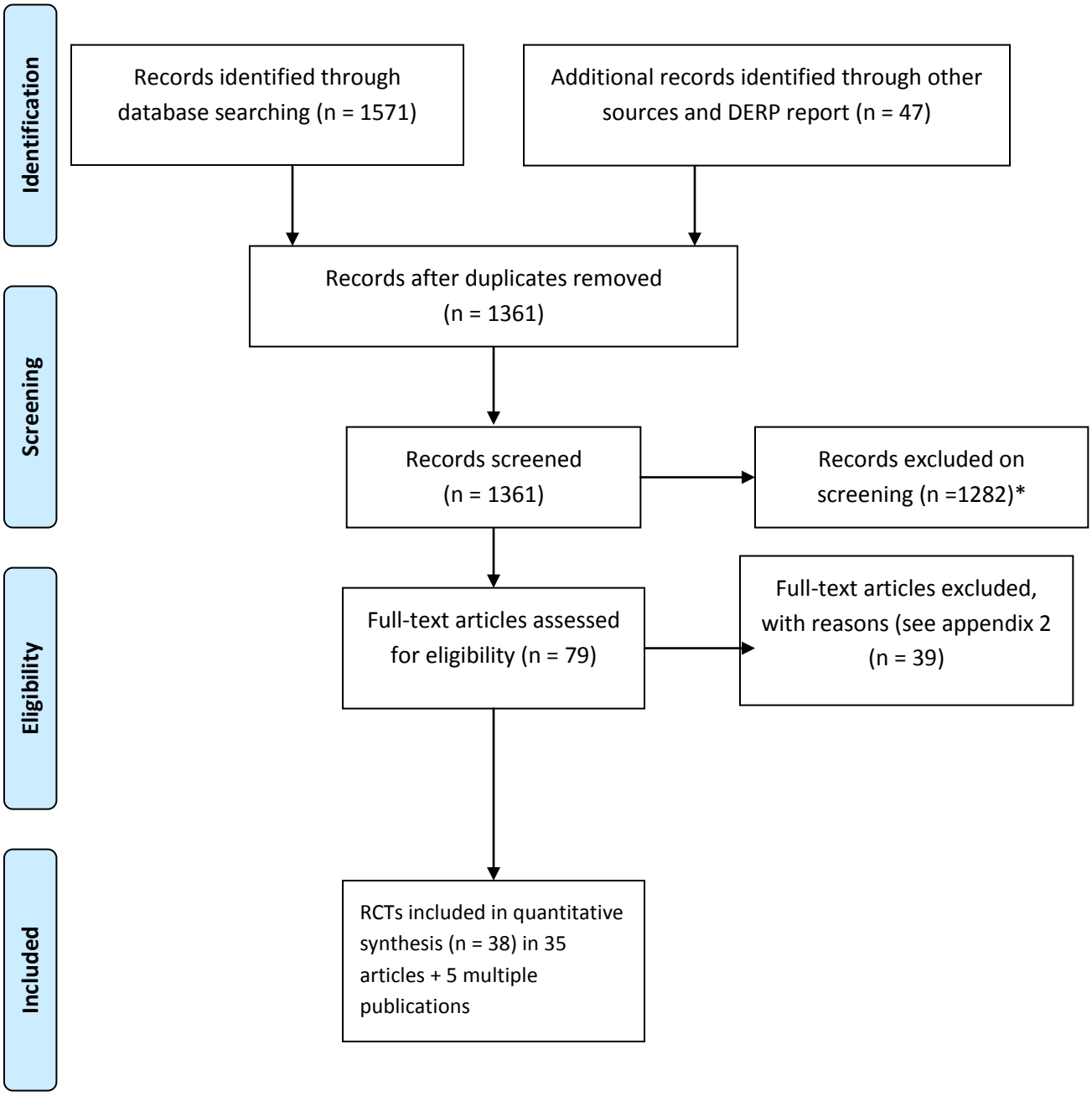


Figure 0-2 PRISMA Flow Diagram Detailing Flow of Studies (PUD – RCTs)

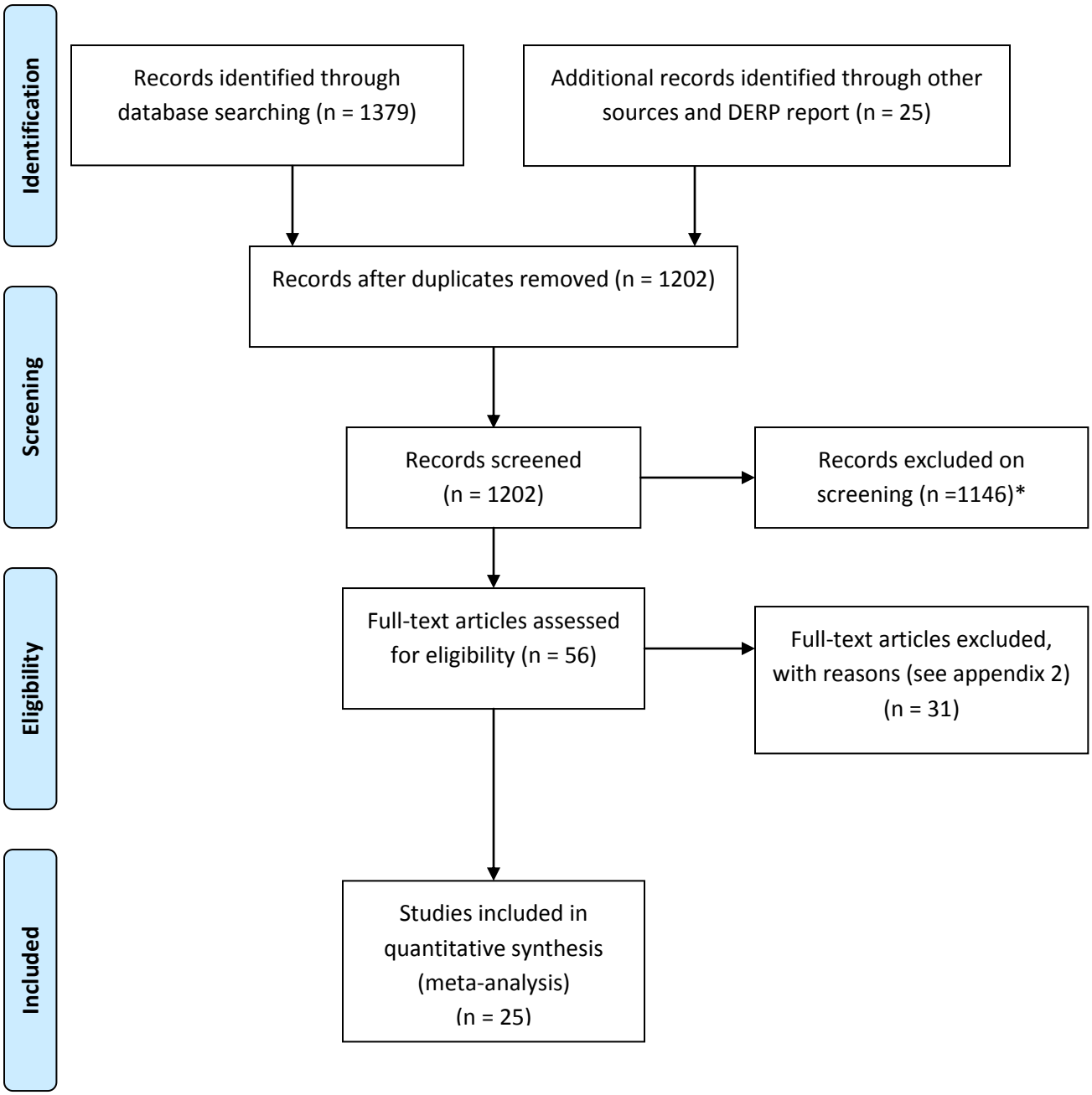
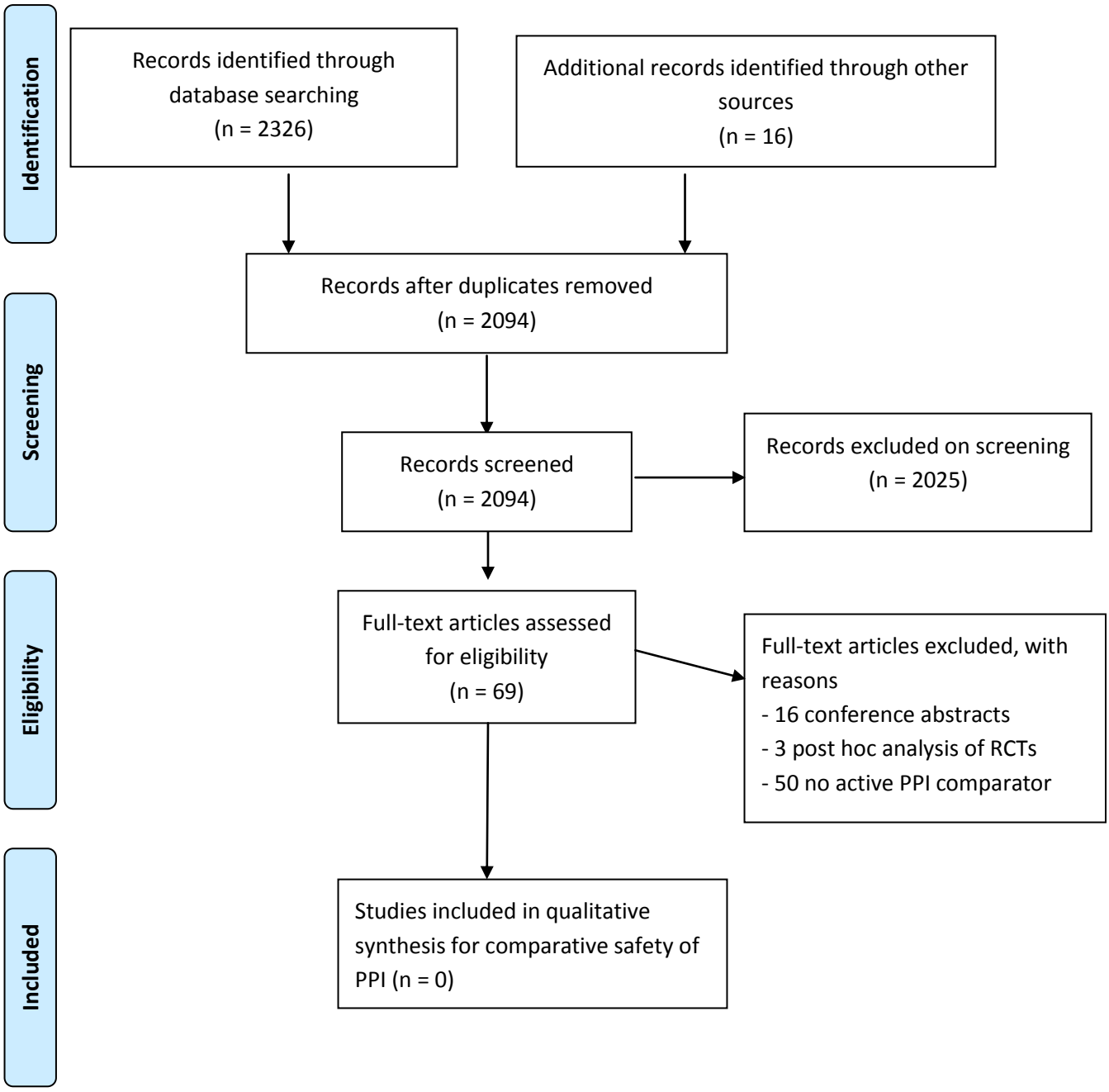


Figure 0-3 PRISMA Flow Diagram Detailing Flow of Studies (GERD and PUD – Observational Studies)



3.4 Trials meeting inclusion criteria are listed according to specific comparisons

Gastroesophageal reflux disease (N = 36 RCTs)

GERD comparison 1: Esomeprazole vs. Omeprazole (10 RCTS)

1) Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared with Omeprazole in reflux esophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Alimentary Pharmacology & Therapeutics. CR 2000; 14(10):1249-1258.
2) Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of Esomeprazole compared with Omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. American Journal of Gastroenterology. 2001a; 96(3):656-665.
3) Kao AW, Sheu BS, Sheu MJ, et al. On-demand therapy for Los Angeles grade A and B reflux esophagitis: Esomeprazole versus Omeprazole. Journal of the Formosan Medical Association. 2003;102(9):607-612
4) Armstrong D, Talley NJ, Lauritsen K, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with Esomeprazole or Omeprazole. Alimentary pharmacology & therapeutics. 2004; 20(4):413-421. (STUDY A)
5) Armstrong D, Talley NJ, Lauritsen K, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with Esomeprazole or Omeprazole. Alimentary pharmacology & therapeutics. 2004; 20(4):413-421. (STUDY B)
6) Armstrong D, Talley NJ, Lauritsen K, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with Esomeprazole or Omeprazole. Alimentary pharmacology & therapeutics. 2004; 20(4):413-421. (STUDY C)
7) Chen C-Y, Lu C-L, Luo J-C, Chang F-Y, Lee S-D, Lai Y-L. Esomeprazole tablet vs Omeprazole capsule in treating erosive esophagitis. World Journal of Gastroenterology. May 28 2005; 11(20):3112-3117.
8) Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of Esomeprazole (40 mg) and Omeprazole (20 mg) for the treatment of erosive esophagitis. Digestive Diseases & Sciences. May 2006; 51(5):844-850.
9) Lightdale C, Schmitt C, Hwang C, Hamelin B. A Multicenter, Randomized, Double-Blind, 8-Week Comparative Trial of Low-Dose Esomeprazole (20 mg) and Standard dose Omeprazole (20 mg) in Patients with Erosive Esophagitis. Dig Dis Sci. 2006:1-6.
10) Zheng RN: Comparative study of Omeprazole, Lansoprazole, Pantoprazole and Esomeprazole for symptom relief in patients with reflux esophagitis. World J Gastroenterol 2009; 15:990-995.

GERD comparison 2: Esomeprazole vs. Pantoprazole (12 RCTs)

1) Scholten T, Gatz G, Hole U. Once-daily Pantoprazole 40 mg and Esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. Alimentary Pharmacology & Therapeutics. 2003; 18(6):587-594.
2) Gillessen A, Beil W, Modlin IM, Gatz G, Hole U. 40 mg Pantoprazole and 40 mg Esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux disease-related symptoms. Journal of Clinical Gastroenterology. 2004; 38(4):332-340.
3) Labenz J, Armstrong D, Lauritsen K, et al. A randomized comparative study of Esomeprazole 40 mg versus Pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Alimentary Pharmacology & Therapeutics. 2005; 21(6):739-746.
4) Labenz J, Armstrong D, Lauritsen K, et al. Esomeprazole 20 mg vs. Pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. Alimentary Pharmacology & Therapeutics. Nov 1 2005; 22(9):803-811.
    - Labenz JA: A randomized comparative study of Esomeprazole 40 mg versus Pantoprazole 40 mg for healing erosive oesophagitis: The EXPO study. Alimentary Pharmacology and Therapeutics 2005; 21:739-746.
    - Labenz J, Armstrong D, Zetterstrand S, Eklund S, Leodolter A: Clinical trial: factors associated with freedom from relapse of heartburn in patients with healed reflux oesophagitis--results from the maintenance phase of the EXPO study. Aliment Pharmacol Ther 2009; 29:1165-1171.
    - Labenz JA: Clinical trial: Factors associated with resolution of heartburn in patients with reflux oesophagitis - Results from the EXPO study. Alimentary Pharmacology and Therapeutics 2009; 29:959-966.
    - Ormeci NC: Cost-effectiveness of Esomeprazole versus Pantoprazole in acute and maintenance treatments of reflux esophagitis in Turkey. Value in Health 2011; Conference: A392.
5) Monnikes H, Pfaffenberger B, Gatz G, Hein J, Bardhan KD. Novel measurement of rapid treatment success with ReQuest: first and sustained symptom relief as outcome parameters in patients with endoscopy-negative GERD receiving 20 mg Pantoprazole or 20 mg Esomeprazole. Digestion. 2005; 71(3):152-158.
    - Monnikes H, Pfaffenberger B, Gatz G, Hein J, Bardhan KD. Novel measurement of rapid treatment success with ReQuest: first and sustained symptom relief as outcome parameters in patients with endoscopy-negative GERD receiving 20 mg Pantoprazole or 20 mg Esomeprazole. Digestion. 2007; 75 Suppl 1:62-68.
6) Glatzel D, Abdel-Qader M, Gatz G, Pfaffenberger B. Pantoprazole 40 mg is as effective as Esomeprazole 40 mg to relieve symptoms of gastroesophageal reflux disease after 4 weeks of treatment and superior regarding the prevention of symptomatic relapse. Digestion. 2006;74(3-4):145-154
7) Vcev A, Begic I, Ostojic R, et al. Esomeprazole versus Pantoprazole for healing erosive oesophagitis. Collegium Antropologicum. Sep 2006; 30(3):519-522.

8) Bardhan KD, Achim A, Riddermann T, Pfaffenberger B. A clinical trial comparing Pantoprazole and Esomeprazole to explore the concept of achieving 'complete remission' in gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics. Jun 15 2007; 25(12):1461-1469.
9) Goh K-L, Benamouzig R, Sander P, Schwan T, Emancipate. Efficacy of Pantoprazole 20 mg daily compared with Esomeprazole 20 mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial – the EMANCIPATE study. European Journal of Gastroenterology & Hepatology. Mar 2007; 19(3):205-211.
10) Scholten T, Teutsch I, Bohuschke M, Gatz G. Pantoprazole on-demand effectively treats symptoms in patients with gastro-oesophageal reflux disease. Clinical Drug Investigation. 2007; 27(4):287-296.
11) Zheng RN: Comparative study of Omeprazole, Lansoprazole, Pantoprazole and Esomeprazole for symptom relief in patients with reflux esophagitis. World J Gastroenterol 2009; 15:990-995.
12) Moraes-Filho JPP: Randomised clinical trial: Daily Pantoprazole magnesium 40 mg vs. Esomeprazole 40 mg for gastro-oesophageal reflux disease, assessed by endoscopy and symptoms. Alimentary Pharmacology and Therapeutics 2014; 39:47-56.

GERD comparison 3: Esomeprazole vs. Rabeprazole (5 RCTs)

1) Fock KM, Teo EK, Ang TL, Chua TS, Ng TM, Tan YL. Rabeprazole vs Esomeprazole in non-erosive gastro-esophageal reflux disease: a randomized, double-blind study in urban Asia. World journal of gastroenterology: WJG. 2005;11(20):3091-3098
2) Eggleston A, Katelaris PH, Nandurkar S, Thorpe P, Holtmann G, Treat Study Group: Clinical trial: the treatment of gastro-oesophageal reflux disease in primary care--prospective randomized comparison of Rabeprazole 20 mg with Esomeprazole 20 and 40 mg. Aliment Pharmacol Ther 2009;29:967-978.
3) Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C, Rossiter G, Lu Y: Randomised clinical trial: a novel Rabeprazole extended release 50 mg formulation vs. Esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33:203-212. (STUDY 1)
4) Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C, Rossiter G, Lu Y: Randomised clinical trial: a novel Rabeprazole extended release 50 mg formulation vs. Esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33:203-212. (STUDY 2)
5) Maiti R, Jaida J, Israel PLJ, Koyagura N, Mukkisa S, Palani A: Rabeprazole and Esomeprazole in mild-to-moderate erosive gastroesophageal reflux disease: A comparative study of efficacy and safety. J Pharmacol Pharmacother 2011;2:150-157

GERD comparison 4: Lansoprazole vs. Omeprazole (12 RCTs)

1) Hatlebakk JG, Berstad A, Carling L, et al. Lansoprazole versus Omeprazole in short-term treatment of reflux oesophagitis. Results of a Scandinavian multicentre trial. Scandinavian Journal of Gastroenterology. 1993; 28(3):224-228.
2) Castell DO, Richter JE, Robinson M, Sontag SJ, Haber MM. Efficacy and safety of Lansoprazole in the treatment of erosive reflux esophagitis. American Journal of Gastroenterology. 1996; 91(9):1749-1757.
3) Mee AS, Rowley JL. Rapid symptom relief in reflux oesophagitis: a comparison of Lansoprazole and Omeprazole. Alimentary Pharmacology & Therapeutics. 1996; 10(5):757-763.
4) Mulder CJ, Dekker W, Gerretsen M. Lansoprazole 30 mg versus Omeprazole 40 mg in the treatment of reflux esophagitis grade II, III and IVa (a Dutch multicentre trial). Dutch Study Group. European Journal of Gastroenterology & Hepatology. 1996; 8(11):1101-1106.
5) Carling L, Axelsson CK, Forssell H, et al. Lansoprazole and Omeprazole in the prevention of relapse of reflux esophagitis: a long-term comparative study. Alimentary Pharmacology & Therapeutics. 1998;12(10):985-990
6) Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E. A comparison of Omeprazole, Lansoprazole and Pantoprazole in the maintenance treatment of severe reflux esophagitis. Alimentary Pharmacology & Therapeutics. 1998;12:49-52
7) Fass RM: Omeprazole 40 mg once a day is equally effective as Lansoprazole 30 mg twice a day in symptom control of patients with gastro-oesophageal reflux disease (GERD) who are resistant to conventional-dose Lansoprazole therapy - A prospective, randomized, multi-centre study. Alimentary Pharmacology and Therapeutics 2000; 14:1595-1603.
8) Richter JE, Kahrilas PJ, Sontag SJ, Kovacs TO, Huang B, Pencyla JL. Comparing Lansoprazole and Omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. [Comment]. American Journal of Gastroenterology. 2001b; 96(11):3089-3098.
9) Mulder CJ, Westerveld BD, Smit JM, et al. A double-blind, randomized comparison of Omeprazole Multiple Unit Pellet System (MUPS) 20 mg, Lansoprazole 30 mg and Pantoprazole 40 mg in symptomatic reflux esophagitis followed by 3 months of Omeprazole MUPS maintenance treatment: a Dutch multicentre trial. European Journal of Gastroenterology & Hepatology. 2002; 14(6):649-656.
10) Adachi K, Hashimoto T, Hamamoto N, et al. Symptom relief in patients with reflux esophagitis: comparative study of Omeprazole, Lansoprazole, and Rabeprazole. Journal of Gastroenterology & Hepatology. 2003; 18(12):1392-1398.
11) Zheng RN: Comparative study of Omeprazole, Lansoprazole, Pantoprazole and Esomeprazole for symptom relief in patients with reflux esophagitis. World J Gastroenterol 2009; 15:990-995.
12) Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients. World Journal of Gastroenterology. Sep 7 2007; 13(33):4467-4472.

GERD comparison 5: Lansoprazole vs. Pantoprazole (5 RCTS)

1) Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E. A comparison of Omeprazole, Lansoprazole and Pantoprazole in the maintenance treatment of severe reflux oesophagitis. Alimentary Pharmacology & Therapeutics. 1998; 12:49-52.
2) Dupas JL, Houcke P, Samoyeau R, French Collaborative Pantaprazole Study G. Pantoprazole versus Lansoprazole in French patients with reflux esophagitis. Gastroenterologie Clinique et Biologique. 2001; 25(3):245-250.
3) Mulder CJ, Westerveld BD, Smit JM, et al. A double-blind, randomized comparison of Omeprazole Multiple Unit Pellet System (MUPS) 20 mg, Lansoprazole 30 mg and Pantoprazole 40 mg in symptomatic reflux esophagitis followed by 3 months of Omeprazole MUPS maintenance treatment: a Dutch multicentre trial. European Journal of Gastroenterology & Hepatology. 2002; 14(6):649-656.
4) Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients. World Journal of Gastroenterology. Sep 7 2007; 13(33):4467-4472.
5) Zheng RN: Comparative study of Omeprazole, Lansoprazole, Pantoprazole and Esomeprazole for symptom relief in patients with reflux esophagitis. World J Gastroenterol 2009; 15:990-995.

GERD comparison 6: Lansoprazole vs. Rabeprazole (2 RCTs)

1) Adachi K, Hashimoto T, Hamamoto N, et al. Symptom relief in patients with reflux esophagitis: comparative study of Omeprazole, Lansoprazole, and Rabeprazole. Journal of Gastroenterology & Hepatology. 2003; 18(12):1392-1398.
2) Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients. World Journal of Gastroenterology. Sep 7 2007; 13(33):4467-4472.

<u>Peptic ulcer disease</u> (total = 25 RCTs)

PUD comparison 7: Esomeprazole vs. Omeprazole (5 RCTs)

1) Veldhuyzen van Zanten SJ, Lauritsen K, Delchier JC, et al. One week triple therapy with Esomeprazole provides effective eradication of *Helicobacter pylori* in duodenal ulcer disease. Aliment Pharmacol Ther 2000; 14: 1605–11.
2) Tulassay Z, Kryszewski A, Dite P, et al. One week of treatment with Esomeprazole-based triple therapy eradicates *Helicobacter pylori* and heals patients with duodenal ulcer disease. European Journal of Gastroenterology & Hepatology. 2001; 13(12):1457-1465.
3) Miehlke S, Schneider-Brachert W, Bastlein E, Ebert S, Kirsch C, Haferland C, Buchner M, Neumeyer M, Vieth M, Stolte M, Lehn N, Bayerdorffer E: Esomeprazole-based one-week triple therapy with clarithromycin and metronidazole is effective in eradicating *Helicobacter pylori* in the absence of antimicrobial resistance. Aliment Pharmacol Ther 2003; 18:799–804.

4) Veldhuyzen Van Zanten S, Machado S, Lee J: One-week triple therapy with Esomeprazole, clarithromycin and metronidazole provides effective eradication of *Helicobacter pylori* infection. Aliment Pharmacol Ther 2003; 17:1381–1387.
5) Sheu BS, Kao AW, Cheng HC, Hunag SF, Chen TW, Lu CC, Wu JJ: Esomeprazole 40 mg twice daily in triple therapy and the efficacy of *Helicobacter pylori* eradication related to CYP2C19 metabolism. Aliment Pharmacol Ther 2005; 21: 283–288.

PUD comparison 8: Esomeprazole vs. Pantoprazole (1 RCT)

1) Hsu PI, Lai KH, Lin CK, Chen WC, Yu HC, Cheng JS, Tsay FW, Wu CJ, Lo CC, Tseng HH, Yamaoka Y, Chen JL, Lo GH: A prospective randomized trial of Esomeprazole vs. Pantoprazole-based triple therapy for *Helicobacter pylori* eradication. Am J Gastroenterol 2005; 100:2387–2392.

PUD comparison 9: Esomeprazole vs. Rabeprazole (No RCT)

PUD comparison 10: Lansoprazole vs. Omeprazole (15 RCTs)

1) Ekstrom P, Carling L, Unge P, Anker-Hansen O, Sjostedt S, Sellstrom H. Lansoprazole versus Omeprazole in active duodenal ulcer. A double-blind, randomized, comparative study. Scandinavian Journal of Gastroenterology. 1995; 30(3):210-215.
2) Florent C, Audigier JC, Boyer J, et al. Efficacy and safety of Lansoprazole in the treatment of gastric ulcer: A multicentre study. Eur J Gastroenterol Hepatol. 1994; 6(12):1135-1139.
3) Capurso L, Di Pietro C, Bordi C, et al. Lansoprazole in the treatment of peptic ulcer disease: A multicentre double-blind study. Gastroenterology International. 1996; 8(3):125-132.
4) Chang FY, Chiang CY, Tam TN, Ng WW, Lee SD. Comparison of Lansoprazole and Omeprazole in the short-term management of duodenal ulcers in Taiwan. Journal of Gastroenterology & Hepatology. 1995; 10(5):595-601.
5) Chang FY, Lee CT, Chiang CY, Lee SD. Effect of Omeprazole and Lansoprazole on serum pepsinogen a levels in patients with duodenal ulcer. Current Therapeutic Research, Clinical & Experimental. 1995; 56(9):887-893.
6) Misiewicz JJ, Harris AW, Bardhan KD, et al. One week triple therapy for *Helicobacter pylori*: a multicentre comparative study. Lansoprazole Helicobacter Study Group. Gut 1997; 41: 735–9.
7) Spinzi GC, Bierti L, Bortoli A, et al. Comparison of Omeprazole and Lansoprazole in short-term triple therapy for *Helicobacter pylori* infection. Aliment Pharmacol Ther 1998; 12: 433–8.
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11) Eralp Y, Dobrucali A, Bagatur N, et al. A comparison of Lansoprazole and Omeprazole based triple combinations for the treatment of *Helicobacter pylori* associated gastritis and peptic ulcer. Turkish Journal of Gastroenterology. 2000; 11(1):25-29.
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13) Ungan M, Kulacoglu H, Kayhan B. Cure rates obtained with five different *Helicobacter pylori* eradication protocols in patients with duodenal ulcer: A prospective, open-label, randomized study in a primary care setting in Turkey. Current Therapeutic Research, Clinical & Experimental. 2001; 62(6):462-472. (3 treatment arms have wrong comparators)
14) Inaba T, Mizuno M, Kawai K, et al. Randomized open trial for comparison of proton pump inhibitors in triple therapy for *Helicobacter pylori* infection in relation to CYP2C19 genotype. Journal of Gastroenterology & Hepatology. 2002; 17(7):748-753.
15) Murakami K, Okimoto T, Kodama M, Sato R, Watanabe K, Fujioka T. Evaluation of three different proton pump inhibitors with amoxicillin and metronidazole in retreatment for *Helicobacter pylori* infection. Journal of Clinical Gastroenterology. Feb 2008; 42(2):139-142.

PUD comparison 11: Lansoprazole vs. Pantoprazole (No RCT)

PUD comparison 12: Lansoprazole vs. Rabeprazole (7 RCTs)

1) Miwa H, Ohkura R, Murai T, et al. Impact of Rabeprazole, a new proton-pump inhibitor, in triple therapy for *Helicobacter pylori* infection-comparison with Omeprazole and Lansoprazole. Aliment Pharmacol Ther 1999; 13: 741–6.
2) Miwa H, Yamada T, Sato K, et al. Efficacy of reduced dosage of Rabeprazole in PPI/AC therapy for *Helicobacter pylori* infection comparison of 20 and 40 mg Rabeprazole with 60 mg Lansoprazole. Digestive Diseases & Sciences. 2000; 45: 77-82.
3) Inaba T, Mizuno M, Kawai K, et al. Randomized open trial for comparison of proton pump inhibitors in triple therapy for *Helicobacter pylori* infection in relation to CYP2C19 genotype. Journal of Gastroenterology & Hepatology. 2002; 17(7):748-753.
4) Murakami K, Sato R, Okimoto T, et al. Eradication rates of clarithromycin-resistant *Helicobacter pylori* using either Rabeprazole or Lansoprazole plus amoxicillin and clarithromycin. Alimentary Pharmacology & Therapeutics. 2002; 16(11):1933-1938.
    - Murakami K, Nasu M, Fujioka T, et al. Evaluation of the eradication effect for *Helicobacter pylori* against clarithromycin sensitive strains and clarithromycin resistant strains in triple therapy with Rabeprazole, amoxycillin and clarithromycin: randomized comparison with triple therapy using Lansoprazole. Gut 2002; 51 A99 (Abstract).
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3.4.1 Description of studies

Study design; sample size of randomized patients; population; intervention and comparator including dose and duration of treatment and outcome measured in the study have been described in detail characteristics of included studies in Appendix 6 in Tables I[A] to VI [A] for GERD and in Tables VII[A], VIII[A], X[A] and XII[A]for PUD.

3.4.1.1 GERD Comparison 1: Esomeprazole vs. Omeprazole (10 RCTs)

Ten RCTs, one with multiple PPI treatment arms in 9638 adult patients, age 18 and older, with GERD met the inclusion criteria. These RCTs were conducted in USA, Canada, Europe, Taiwan and China. Eight of the 10 RCTs were double-blind RCT (Kahrilas 2000; Ritcher 2001a; Armstrong 2004 a, b and c; Chen 2005; Lightdale 2006; Schmitt 2006).

3.4.1.2 GERD Comparison 2: Esomeprazole vs. Pantoprazole (12 RCTs)

Twelve RCTs examined the effect of PPI in 10,503 patients with GERD met the inclusion criteria. Nine RCTs were acute studies and 3 RCTs were maintenance studies. These RCTs were conducted mostly in Germany, but also in various other European countries, China and Brazil. Ten of the included RCTs were double blind (Scholten 2003; Gilessen 2004; Labenz 2005a; Monnikes 2005; Glatzel 2006; Bardhan 2007; Moraes- fiho 2014; Labenz 2005b; Goh 2007 and Scholten 2007) and 2 were not blinded.

3.4.1.3 GERD Comparison 3: Esomeprazole vs. Rabeprazole (5 RCTs)

Five RCTs, published in 4 publications, comparing Esomeprazole and Rabeprazole met the inclusion criteria. These RCTs, conducted in more than 200 centres in over 21 countries including Canada, US, Australia, Singapore and India, randomized 3716 patients with GERD. Four out of 5 RCTs were double blind (Fock 2005; Eggleston 2009; Laine 2011 Study 1; and Laine 2011 Study 2).

3.4.1.4 GERD Comparison 4: Lansoprazole vs. Omeprazole (12 RCTs)

Twelve RCTs in 6648 adult patients with GERD met the inclusion criteria. These RCTs were conducted in centres across USA, Canada, China, Japan, Scandivania, and the European Union. Seven of the 12 RCTs were double-blind (Mee 1996; Mulder 1996; Carling 1998; Hatlebakk 2003; Castell 1996; Richter 2001b; and Mulder 2002).

3.4.1.5 GERD Comparison 5: Lansoprazole vs. Pantoprazole (5 RCTs)

Five RCTs in 1089 adult patients with GERD met the inclusion criteria. These RCTs were conducted in Germany (Jaspersen 1998), China (Zheng 2009), Italy (Pilotto 2007), 72 centres in France (Dupas 2001) and 31 centres in Netherlands (Mulder 2002). Out of the 5 RCTs, 2 were double-blind (Dupas 2001 and Mulder 2002 and 3 were open-label.

3.4.1.6 GERD Comparison 6: Lansoprazole vs. Rabeprazole (2 RCTs)

Two open label RCTs in 215 GERD patients met the inclusion criteria. These RCTs were conducted in Japan and Italy.

3.4.1.7 PUD Comparison 7: Esomeprazole vs. Omeprazole (5 RCTs)

Five RCTs in 1553 adult patients with peptic ulcer who were *H. pylori* positive met the inclusion criteria. These RCTs were conducted in 94 centres in Europe and Canada; 28 centres in the Czech Republic, Hungary and Poland; University hospitals, community hospitals and gastroenterologists in private practice in Germany; and in Taiwan. At baseline 69% of the patients had PUD and 7% had gastritis or dyspepsia. Three out of 5 RCTs were double blind (Van Zanten 2003; Tulassay 2001; and Van Zanten 2000).

3.4.1.8 PUD Comparison 8: Esomeprazole vs. Pantoprazole (1 RCT)

One open label RCT in 200 adult patients with peptic ulcer or gastritis who were *H. pylori* positive met the inclusion criteria and was conducted in Taiwan.

3.4.1.9 PUD Comparison 9: Esomeprazole vs. Rabeprazole (0 RCT)

No RCT met the inclusion criteria.

3.4.1.10 PUD Comparison 10: Lansoprazole vs. Omeprazole (15 RCTs)

15 RCTs in 2265 adult patients with endoscopically confirmed peptic ulcer and *H. pylori* positive (10 RCTs) or in those *H. pylori* status was not determined (5 RCTs) met the inclusion criteria. Four RCTs were double blind (Ekstrom 1994; Florent 1994; Capurso 1995; and Dobrilla 1999); three were single blind (Chiang and Chang 1995; Chang and lee 1995; and Misiewicz 1997) and remaining 8 were open label. 1117 patients were randomized to Lansoprazole and 1148 to Omeprazole. These RCTs were conducted in Sweden, Italy, Japan and Taiwan.

3.4.1.11 PUD Comparison 11: Lansoprazole vs. Pantoprazole (0 RCT)

No RCT met the inclusion criteria.

3.4.1.12 PUD Comparison 12: Lansoprazole vs. Rabeprazole (7 RCTs)

Seven open label RCTs in 1574 adult patients with peptic ulcer who were *H. pylori* positive met the inclusion criteria. At baseline 96% of the patients had PUD and 4% had gastritis. Of the 7 RCTS, six were conducted in Japan and one in Taiwan. These RCTs were conducted in Japan and Taiwan.

3.4.2 Population

Tables I [B] to VI [B] in Appendix 6 describe inclusion/exclusion criteria of included GERD RCTs. Baseline characteristics of their randomized patients are provided Tables I[C] to VII[C].

Tables VII [B], VIII [B], X [B] and XII [B] in Appendix 6 describe inclusion/exclusion criteria of included PUD RCTs. Baseline characteristics of their randomized patients are provided in VII[C], VIII[C], X[C] and XII [C].

3.4.2.1 GERD Comparison 1: Esomeprazole vs. Omeprazole (10 RCTs)

Of the ten RCTs in 9638 adult patients, 56% of the study participants were men and 44% were women with mean age ranging between 45 to 59 years. Over 90% of the participants in the 3 RCTs that reported race are Caucasians. One study (Kao 2003) reported the participants had mean BMI of 23.1 and Chen 2005 reported that the participants in their trial had a mean weight 69 kg and mean height of 168 cm. Kao 2003 reported that 30% of participants were smokers and 24% consumed alcohol. Richter 2001a, Lightdale 2006 and Schmitt 2006 included about 10% patients with *H. pylori* positive status. Armstrong 2004 (a, b and c) (>60%), Chen 2005 (>40%), Zheng 2009 (>80%) included larger portion of patient who are *H. pylori* positive. Nine RCTs reported the LA grade of esophagitis at baseline, 34.3% (2396/6989) of patients were grade A, 38.9% (2721/6989) of patients were grade B, 20.1% (1410/6989) of patients were grade C, and 6.6% (462/6989) of patients were grade D.

3.4.2.2 GERD Comparison 2: Esomeprazole vs. Pantoprazole (12 RCTs)

Of the 10, 503 patients randomized in 12 RCTs, 61.0% were men and 39% were women with mean age ranging between 42 to 58 years and mean BMI ranging from 26 to 27 Kg/m^2. Seven RCTs reported race of patients, and more than 80% of randomized patients were Caucasian. Four RCTs reported that on average about 20% of patients were smokers. Only 2 RCTs reported that less than 10% of participants consumed alcohol. Eleven RCTs reported that on average 22 to 50% of patients were *H. pylori* positive. Ten RCTs reported the disease severity by LA grade at baseline, which 3526/9641 (36.6%) of patients were grade A, 4198/9641 (43.5%) were grade B, 1555/9641 (16.1%) were grade C and 362/9641 (3.8%) were grade D.

3.4.2.3 GERD Comparison 3: Esomeprazole vs. Rabeprazole (5 RCTs)

Of the 5 RCTs in 3716 patients, 60% patients were men and 40% women with mean age ranging between 35 to 51 years. One study, Fock 2005, randomised 134 non-erosive GERD (NERD) patients which included 80% Chinese, 9% smokers, 16% alcohol users. The severity of GERD was not reported in Eggleston 2009 which included patients with GERD associated heartburn (97% Caucasian; 66% smokers; 28% alcohol users). Maiti 2011 was conducted in India included Grade A and B patients while Laine 2011 included only Grade C and D patients according to the LA classification (88% white; smoker and alcohol user not provided). BMI data was provided only in Laine 2011 (57% with BMI<30kg/m2) and Eggleston (mean BMI of 29 kg/m2). *H. pylori* status was provided in 3 studies: Maiti 2011 (43% positive); Fock 2005 (45% positive); and Laine 2011 (<1% positive).

3.4.2.4 GERD Comparison 4: Lansoprazole vs. Omeprazole (12 RCTs)

Of the 12 RCTs in 6648 patients, 61% were men and 39% were women. Baseline BMI was only reported in one study. The mean age of patients ranged between 46 to 60 years except in 2 Pilotto 2007 (mean age: 78 years) and Adachi 2003 (mean age: 66 years). Five RCTs reported baseline *H. pylori* status of the randomized patients; the percentage of *H. pylori* positive patients ranged from 28 to 43% in 4 RCTs and from 68% to 80% in Pilotto 2007. Approximately one-quarter of the patients were smokers (reported only in 6 studies) and about half are alcohol users (reported in 4 studies). Ethnicity was reported in only 3 RCTS: Castell 1996 (White 85%); Richter 2001b (White 88%); and Fass (Caucasian 72.7%).

3.4.2.5 GERD Comparison 5: Lansoprazole vs. Pantoprazole (5 RCTs)

Of the 5 RCTs in 1089 patients 63% were men and 37% women. Baseline data on ethnicity, smokers and alcohol users were not reported in any of the studies except for Dupas 2001 which included 22% smokers and 20% with daily alcohol consumption. Their mean age ranged between 50 to 62 years except for PIlotto 2007 which included only elderly patients (mean age 77 years). BMI data was only reported in Mulder 2002 (mean BMI of 27).

3.4.2.6 GERD Comparison 6: Lansoprazole vs. Rabeprazole (2 RCTs)

Of the 2 RCTs in 215 patients, 48% were male and 52% female with mean age ranging between 65 to 78 years. The baseline data on BMI, ethnicity, smoking habits and alcohol consumption were not reported in any of the studies. Adachi 2003 is conducted in Italy and included patients with baseline esophagitis Grade A to D (A: 20%; B: 53%; C: 25%; D: 2%) and 40% *H. pylori* positive patients. Pilotto 2007 was conducted in Japan and included patients with baseline esophagitis severity Grade I to IV (I: 79%; II: 47%; III-IV: 24%) and 73% Pylori positive patients.

3.4.2.7 PUD Comparison 7: Esomeprazole vs. Omeprazole (5 RCTs)

Of the 1553 adult patients with peptic ulcer in five RCTs who were *H. pylori* positive 54% of the participants were men and 46% women with mean age ranging between 42 to 59 years. BMI data was not provided in any trial. One study Van Zanten 2003 with 379 patients included 354 (93%) Caucasian patients; 124(33%) were smokers; and 228(60%) consumed alcohol.

3.4.2.8 PUD Comparison 8: Esomeprazole vs. Pantoprazole (1 RCT)

Based on 200 patients in one open label RCT Hsu 2005, 45% of the patients had PUD and 55% had gastritis at baseline. Study included 67% male patients and 33% female patients; mean age ranged from 56 years. BMI data was not provided; 27% were smokers; 14% ingested coffee; 25% ingested tea; 24% had underlying diseases; 12% consumed alcohol; and 41% had history of peptic ulcer.

3.4.2.9 PUD Comparison 9: Esomeprazole vs. Rabeprazole (0 RCT)

No RCT met the inclusion criteria

3.4.2.10 PUD Comparison 10: Lansoprazole vs. Omeprazole (15 RCTs)

Of the 2265 patients included in 15 RCTs, 75% were men and 25% were women with mean age ranging between 46 to 56 years. BMI data was not provided in 13/15 trials. Two trials provided data on mean

BMI ± SD was 23 ± 3.0 and race (Taiwanese patients) in Chang and Chiang 1995 and Chang and Lee 1995. Two trials included Japanese patients (Inaba 2002 and Murakami 2008). Race is not reported in 11/15 trials. Smoking was reported in 8 of 15 RCTs (Ekstrom 1994; Florent 1994; Chang and Chiang 1995; Chang and Lee 1995; Dobrilla 1995; Fanti 2001; Ungan 2001 and Inaba 2002) and 442(19.5%) of total randomized patients in these RCTs were reported as smokers. Alcohol consumption was reported in 6 RCTs (Ekstrom 1994; Florent 1994; Chang and Chiang 1995; Dobrilla 1999; Fanti 2001; and Ungan 2001) and 309(13.6%) of randomized patients in these RCTs consumed alcohol.

3.4.2.11 PUD Comparison 11: Lansoprazole vs. Pantoprazole (0 RCT)

No RCT met the inclusion criteria.

3.4.2.12 PUD Comparison 12: Lansoprazole vs. Rabeprazole (7 RCTs)

Of the 1574 patients in 7 RCTS, 66% were men and 44% women with mean age ranging between 48 to 52 years. BMI data was not provided in any trial. Three studies included Japanese patients (Inaba 2002; Kwabata 2003; and Murakami 2008). Smoking was reported in 4 out of 7 RCTs (Miwa 2000; Inaba 2002; Kwabata 2003; and Liu 2013) and 318(20.2%) of randomized patients in these RCTs were smokers. Alcohol consumption was reported in 2 RCTs (Miwa 2000 and Liu 2013) and 205 (13%) of randomized patients in these RCTs consumed alcohol.

3.4.3 Interventions

Tables I [A] to VI [A] in Appendix 6 describe dose and duration of treatment of included GERD studies. Tables VII [A], VIII [A], X [A] and XII [A] in Appendix 6 describe dose and duration of treatment of included PUD studies.

3.4.3.1 GERD Comparison 1: Esomeprazole vs. Omeprazole (10 RCTs)

Patients were randomized to receive Esomeprazole 20mg or 40mg OD compared to Omeprazole 20mg OD for 4 to 8 weeks.

3.4.3.2 GERD Comparison 2: Esomeprazole vs. Pantoprazole (12 RCTs)

Patients were randomized to Esomeprazole 20mg to 40mg per day compared to Pantoprazole 20mg to 40mg per day for 4 week to 6 months of duration. Three studies that lasted 6 months examined the rate of remission after 6 months.

3.4.3.3 GERD Comparison 3: Esomeprazole vs. Rabeprazole (5 RCTs)

Patients were randomized to treatment with Esomeprazole 20mg to 40mg OD or Rabeprazole 10mg to 50mg per day. The duration of studies was 4 weeks except for Laiti 2011 which included an additional 4 weeks treatment for patients with unhealed esophagitis at week 4.

3.4.3.4 GERD Comparison 4: Lansoprazole vs. Omeprazole (12 RCTs)

Patients were randomized to treatment with Lansoprazole 30mg OD or BD or to Omeprazole 20mg to 40mg OD. The mean duration of study ranged from 4 to 8 weeks except for Carling 1998 which is 48 weeks in durations.

3.4.3.5 GERD Comparison 5: Lansoprazole vs. Pantoprazole (5 RCTs)

Patients were randomized to treatment with Lansoprazole 30mg OD or BD or to Pantoprazole 40mg OD or BD (N=538). The mean duration of studies ranged from 4 to 8 weeks. Dupas 2001 included 83% patients with Grade II/III esophagitis at baseline, Mulder 2002 with 60% Grade I and 28% Grade II patients, Pilotto 2007 included 29% Grade I and 47% Grade II patients; Zheng 2009 included 29% Grade A, 39% Grade B and 30% Grade C patients.

3.4.3.6 GERD Comparison 6: Lansoprazole vs. Rabeprazole (2 RCTs)

Patients were randomized to treatment with Lansoprazole 30mg OD and Rabeprazole 20mg OD. Both studies were 8 weeks in duration.

3.4.3.7 PUD Comparison 7: Esomeprazole vs. Omeprazole (5 RCTs)

Patients were randomized to treatment with Esomeprazole 20mg BD or 40mg BD or to Omeprazole 20mg BD in addition to antibiotics (Clarithromycin 500mg BD plus Amoxicillin 1g BD; Metronidazole, 400mg BD or 500 mg BD, and Clarithromycin 250 mg BD) for duration of 1 week. The duration of follow up in studies ranged from 4 to 8 weeks. Only 1 study Van Zanten 2003 after 1 week of treatment with PPI and antibiotics continued patients randomized to Omeprazole 20mg BD for additional 3 weeks of treatment and administered placebo BD to patients randomized to Esomeprazole treatment group.

3.4.3.8 PUD Comparison 8: Esomeprazole vs. Pantoprazole (1 RCT)

Patients were randomized to treatment with PPI- Esomeprazole 40mg BD or to Pantoprazole 40mg BD in addition to antibiotics (Clarithromycin 500mg BD plus Amoxicillin 1g BD for duration of 1 week. Patients with peptic ulcers in initial endoscopy received an additional 3 weeks of monotherapy with Pantoprazole 40 mg orally once daily, while patients with gastritis only took 3 weeks of antacid following eradication therapy. The duration of follow up was 8 weeks after eradication therapy.

3.4.3.9 PUD Comparison 9: Esomeprazole vs. Rabeprazole (No RCT met the inclusion criteria)

3.4.3.10 PUD Comparison 10: Lansoprazole vs. Omeprazole (15 RCTs)

Patients were randomized to treatment with PPI- Lansoprazole (30mg OD or 30mg BD) or to Omeprazole (20mg OD or 40mg OD, or 20mg BD) in addition to antibiotics (Clarithromycin 500mg BD or 200mg TDS) or Metronidazole 400mg BD plus Amoxicillin (200mg BD OR 250 mg TDS or 1000mg BD or 500mg TDS) or Tinidazole (500mg BD) for duration of 1 week. The duration of follow up in studies ranged from 4 to 8 weeks in most trials and up to a year in Fanti 2001 study. Two studies Florent 1994 and Murakami 2008 allowed half dose of H_2RA was continued until eradication was assessed. In one study Eralp 2000 both treatment groups received maintenance therapy of famotidine 40 mg OD for six weeks, followed by endoscopic examination.

3.4.3.11 PUD Comparison 11: Lansoprazole vs. Pantoprazole (No RCT met the inclusion criteria)

3.4.3.12 PUD Comparison 12: Lansoprazole vs. Rabeprazole (7 RCTs)

Patients were randomized to treatment with PPI- Lansoprazole 30mg BD or to Rabeprazole 10mg BD or 20mg BD in addition to antibiotics (Clarithromycin 200mg BD or 200mg TDS or 400mg BD) or Metronidazole 250mg BD plus Amoxicillin (750mg BD or 500mg TDS) for duration of 1 week. The duration of follow up in studies ranged from 4 to 16 weeks. In 1 study Murakami and Sato 2003, half dose of H_2RA was continued until eradication was assessed.

3.4.4 Outcomes (primary and other outcomes)

3.4.4.1 GERD Comparison 1: Esomeprazole vs. Omeprazole (10 RCTs)

The primary efficacy outcomes were endoscopic confirmed healing of reflux esophagitis in 5 studies (Kahrilas 2000; Richter 2001a; Chen 2005; Lightdale 2006; and Schmitt 2006) sustained symptomatic relief in 1 study (Kao 2003); Complete relief of heart burn in 3 studies (Armstrong 2004a; 2004b and 2004 c study)

3.4.4.2 GERD Comparison 2: Esomeprazole vs. Pantoprazole (12 RCTs)

The primary efficacy outcomes for 9 acute studies were usually symptom score or rate of endoscopically confirmed healing. The primary outcomes for the 3 remission studies were healing or symptom remission at 6 months.

3.4.4.3 GERD Comparison 3: Esomeprazole vs. Rabeprazole (5 RCTs)

The primary efficacy outcomes were symptomatic relief in Fock 2005 and Eggleston 2009, endoscopic healing in Laine 2011 and both outcomes as efficacy endpoints in Maiti 2011.

3.4.4.4 GERD Comparison 4: Lansoprazole vs. Omeprazole (12 RCTs)

The primary efficacy outcomes were symptomatic relief or endoscopic healing in 10 of RCTs. In 2 other RCTS (Carling 1998 and Jaspersen 1998) it was symptomatic and/or endoscopic relapse or remission.

3.4.4.5 GERD Comparison 5: Lansoprazole vs. Pantoprazole (5 RCTs)

The primary efficacy outcomes were endoscopy healing in 2 studies (Pilotto 2007 and Dupas 2001) and symptomatic relief in 2 studies (Mulder 2002 and Zheng 2009). Jasperson 1998 is a 4 weeks maintenance study in 30 patients who had achieved esophagitis healing and symptom relief following therapy with Omeprazole. In this study, the primary outcome is the maintenance of remission at week 4, defined as the absence of esophagitis and symptoms.

3.4.4.6 GERD Comparison 6: Lansoprazole vs. Rabeprazole (2 RCTs)

The primary efficacy outcomes were esophagitis healing rates at week 8 (Pilotto 2007) and rapid symptom relief in the first week of drug administration (Adachi 2003).

3.4.4.7 Comparison 7: Esomeprazole vs. Omeprazole (5 RCTs)

The primary efficacy outcome was *H. pylori* eradication determined by follow-up endoscopy with histology and culture and/or rapid urease test. Only patients with a negative UBT result at both follow-up visits were considered to be *H. pylori*-negative.

3.4.4.8 Comparison 8: Esomeprazole vs. Pantoprazole (1 RCT)

The primary efficacy outcome was *H. pylori* eradication determined by follow-up endoscopy with histology and culture and/or rapid urease test. Eradication was defined as (1) negative results of both rapid urease test and histology, or (2) a negative result of urea breath test

3.4.4.9 Comparison 9: Esomeprazole vs. Rabeprazole (0 RCT)

No RCT was identified.

3.4.4.10 Comparison 10: Lansoprazole vs. Omeprazole (15 RCTs)

The primary efficacy outcomes were *H. pylori* eradication determined by follow-up endoscopy with histology and culture and/or rapid urease test and healing of ulcer. Treatment was considered successful if the results of both endoscopy and/or rapid urease test were negative. In one study (Murakami 2008) treatment success was considered when rapid urease test, culture, histologic examination, and the urea breath test (UBT) were all negative.

3.4.4.11 Comparison 11: Lansoprazole vs. Pantoprazole (0 RCT)

No RCT was identified.

3.4.4.12 Comparison 12: Lansoprazole vs. Rabeprazole (7 RCTs)

The primary efficacy outcome was *H. pylori* eradication determined by follow-up endoscopy with histology and culture and/or rapid urease test. Treatment was considered successful if the results of the rapid urease test were negative. In one study (Murakami 2008) treatment success was considered when rapid urease test, culture, histologic examination, and the urea breath test (UBT) were all negative.

3.4.5 Statistical Analysis

Data analyses were conducted using Cochrane Review Manager 5.2 software. Forest plots for efficacy and safety outcomes are provided in section 4.6

3.5 Patient Disposition

Tables I [D] to VI [D] in Appendix 6 describe summary of patient disposition of included GERD studies. Tables VII [D], VIII [D], X [D] and XII [D] in Appendix 6 describe summary of patient disposition of included PUD studies.

3.5.1.1 GERD Comparison 1: Esomeprazole vs. Omeprazole (10 RCTs)

Of the 10 included RCTs (N=9638), only 5 RCTs in 6857 patients reported on the total number of patients completing the studies. Of the 6857 patients, 6437 (94%) patients completed the study and 420 (6%) patients discontinued early.

3.5.1.2 GERD Comparison 2: Esomeprazole vs. Pantoprazole (12 RCTs)

Of the 12 included RCTs (N=10503), only 6 RCTs in 6090 patients reported the total of number of patients completing the study. Of the 6090 patients, 5413 (88.9%) patients completed the study and 677 (11.1%) discontinued early.

3.5.1.3 GERD Comparison 3: Esomeprazole vs. Rabeprazole (5 RCTs)

Of the 5 included RCTs (N=3716), 4 RCTs in 3582 patients reported the total of number of patients completing the study. Of the 3582 patients, only 3572 received treatments and 3202 (89.6%) patients completed the study and 380 (10.6%) discontinued early.

3.5.1.4 GERD Comparison 4: Lansoprazole vs. Omeprazole (12 RCTs)

Of the 12 included RCTs (N=6648), only 7 RCTs in 4441 patients reported the total of number of patients completing the study. A total of4246 (95.6%) patients completed the study and 195 (4.4%) discontinued early.

3.5.1.5 GERD Comparison 5: Lansoprazole vs. Pantoprazole (5 RCTs)

Of the 5 included RCTs (N=1089), 4 RCTs in 628 patients reported the total of number of patients completing the study. Of the 628 patients, 604 (96.2%) patients completed the study and 24 (3.8%) discontinued early.

3.5.1.6 GERD Comparison 6: Lansoprazole vs. Rabeprazole (2 RCTs)

Of the 2 included RCTs (N=215), 1 RCT in 160 patients reported the total of number of patients completing the study. Of the 160 patients, 150 (93.8%) patients completed the study and 10 (6.2%) discontinued early.

3.5.1.7 PUD Comparison 7: Esomeprazole vs. Omeprazole (5 RCTs)

Five RCTS randomized 1553 patients of which 1479 (96%) completed the study and 61(4%) discontinued.

3.5.1.8 PUD Comparison 8: Esomeprazole vs. Pantoprazole (1 RCT)

One RCT randomized 200 patients of which 194(97%) completed the study and 6 (2%) discontinued.

3.5.1.9 PUD Comparison 9: Esomeprazole vs. Rabeprazole (0 RCT)

No RCT was identified that met the inclusion criteria.

3.5.1.10 PUD Comparison 10: Lansoprazole vs. Omeprazole (15 RCTs)

Of the 2265 patients included in 15 RCTs, 5 RCTs in 754 patients did not report on how many patients completed the study. Of the remaining 1511 patients from 10 RCTS, 1238 completed the study (82%) and 273 (18%) discontinued.

3.5.1.11 PUD Comparison 11: Lansoprazole vs. Pantoprazole (0 RCT)

No RCT was identified that met the inclusion criteria.

3.5.1.12 PUD Comparison 12: Lansoprazole vs. Rabeprazole (7 RCTs)

Of the 1574 patients in 7 RCTs, 2 RCTs in 333 patients did not report on how many patients completed the study. Based on 5 RCTs in 1231 patients, 1196 (97%) completed the study and 35 (3%) discontinued.

3.6 Exposure to treatment

3.6.1 Investigational products

Evidence was available for the following interventions - Esomeprazole and Lansoprazole at specified doses mentioned below as compared to other PPIs (Omeprazole, Pantoprazole and Rabeprazole). The dosage used in GERD and PUD studies ranged from 20, 40mg or 80 mg per day for Esomeprazole and 15, 25, 30 or 60 mg per day for Lansoprazole. The duration of treatment for GERD was 4 to 8 weeks in most trials and up to 6 months in maintenance therapy RCTs. The duration of treatment for PUD was 1 week for most trials and ranged up to 8 weeks; follow-up ranged from of 4-16 weeks in most trial and up to 1 year in one trial.

Table 0-3 Dosage of Esomeprazole and Lansoprazole used in included RCTs

Treatment evaluated	Dose specification per day	Number of studies GERD 38 RCTs	Number of studies PUD 25 RCTs
Esomeprazole	20 mg OD	10	-
	40 mg OD (or 20mg BD)	15	2
	80 mg (40mg BD)	-	4
Lansoprazole	15mg OD	1	-
	30mg OD	10	8
	60mg (30mg BD)	2	11

3.6.2 Concomitant Medications

Concomitant medications allowed in RCTs are described in Tables I [B] to VI [B] in Appendix 6 for GERD studies and in Tables VII [B], VIII [B], X [B] and XII [B] for PUD studies.

Of the 38 RCTs included for GERD, a total of 15 RCTs allowed the use of antacids, 6 RCTS allowed ASA intake up to 150-163mg/day and 16 other RCTs did not report on the concomitant medications used. In Pilotto 2007, *H. pylori* positive patients were treated with additional two antibiotics i.e., amoxicillin 1g twice daily and clarithromycin 250 mg twice daily or metronidazole 250 mg four times daily for 7 day.

Of the 25 RCTs included for PUD, two RCTs (Chang and Chiang 1994; Change and Lee 1995) allowed concomitant use of antacids. Three studies (Florent 1994; Murakami and Sato 2003; and Murakami 2008) allowed half dose of H_2RA was continued until eradication was assessed. The other 20 RCTs did not report on whether any specific concomitant medications were allowed.

3.7 Critical Appraisal

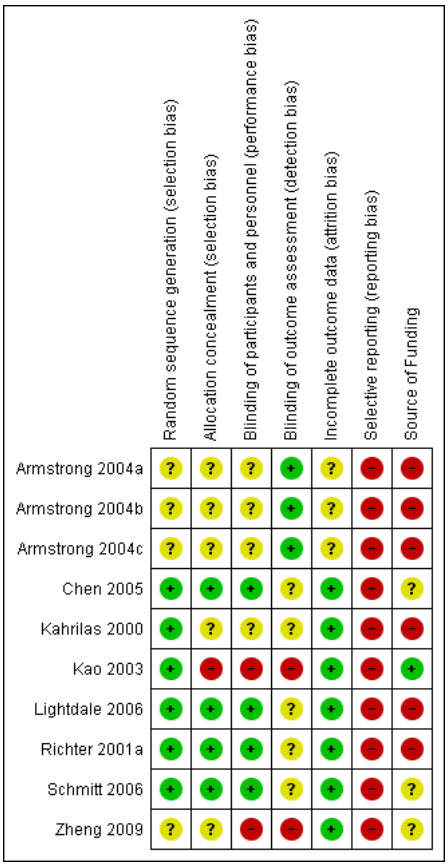
3.7.1 Internal Validity

3.7.1.1 GERD comparison 1: Esomeprazole vs Omeprazole

Included in this comparison were 10 RCTs examining Esomeprazole with Omeprazole in 9,638 patients with GERD. This comparison has overall high risk of selection bias (randomization was unclear in 4 studies; allocation concealment was unclear in 5 studies and was judged as high risk of bias in 1 study). This comparison has overall high risk of reporting bias because all the studies have some level of selective reporting. The outcome that was most often not reported was serious adverse event. None of the studies reported any information regarding serious adverse event. In addition, withdrawal due to adverse effect, which is an important harm outcome for short term studies, was only reported in half of the studies containing about 2/3 of the patients. Selectively reporting of such important outcome raised concern about the quality of the studies.

Many of the studies did not report any information regard the procedure to protect integrity of blinding. This made the assessment on the risk of detection bias difficult. Many studies were rated as unclear risk meaning that there was simply not enough information to judge in this category. Six of the ten studies were funded by the manufacturer.

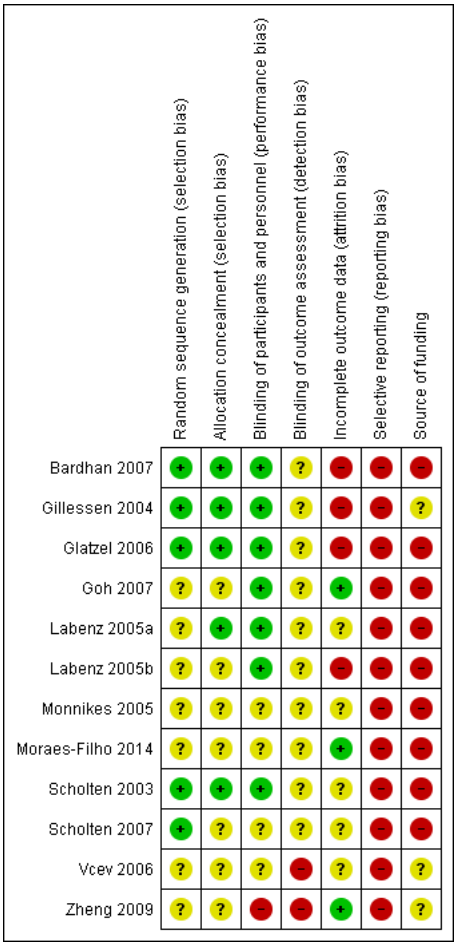
Figure 0-4 Risk of Bias Summary (GERD: E vs O)



3.7.1.2 GERD comparison 2: Esomeprazole vs Pantoprazole

Included in this comparison were 12 RCTs examining Esomeprazole with Pantoprazole in 10,503 patients with GERD. This comparison has overall high risk of selection bias (randomization was unclear in 7 studies and allocation concealment was also unclear in 7 studies). This comparison has overall high risk of reporting bias because all the studies have some level of selective reporting. Five of the 12 RCTs did not report on how many patients discontinued the study. Eight out of 12 studies did not report on withdrawal due to adverse events. Three studies did not report on serious adverse events. Selectively reporting of such important outcome raised concern about the quality of the studies. Blinding of participants and personnel was low risk of bias in 7 studies and unclear in 5 Studies. Blinding of the outcome assessor was high in 2 studies and unclear in the remaining 10 studies. Nine of the 12 studies were funded by the manufacturer.

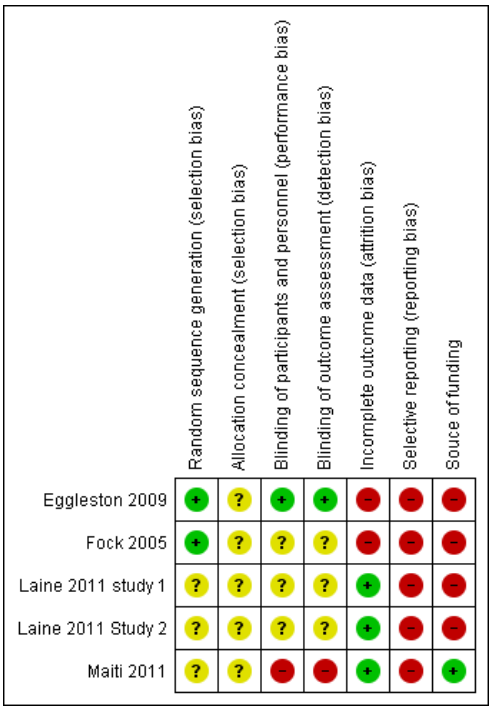
Figure 0-5 Risk of Bias Summary (GERD: E vs P)



3.7.1.3 GERD comparison 3: Esomeprazole vs Rabeprazole

Included in this comparison were 5 RCTs examining Esomeprazole with Rabeprazole in 3,716 patients with GERD. This comparison has overall high risk of selection bias (randomization was unclear in 3 studies and allocation concealment unclear in all 5 studies). There was an unclear to high risk of reporting bias - One of the 5 RCTs did not report on how many patients discontinued the study. Four of the 5 RCTS did not reported on mortality. One study did not report on serious adverse events. Blinding of participants and personnel and outcome assessor was assessed as low risk of bias in 1 study, high risk of bias in 1 study and unclear in the remaining 3 studies. Four of the 5 studies were funded by the manufacturer.

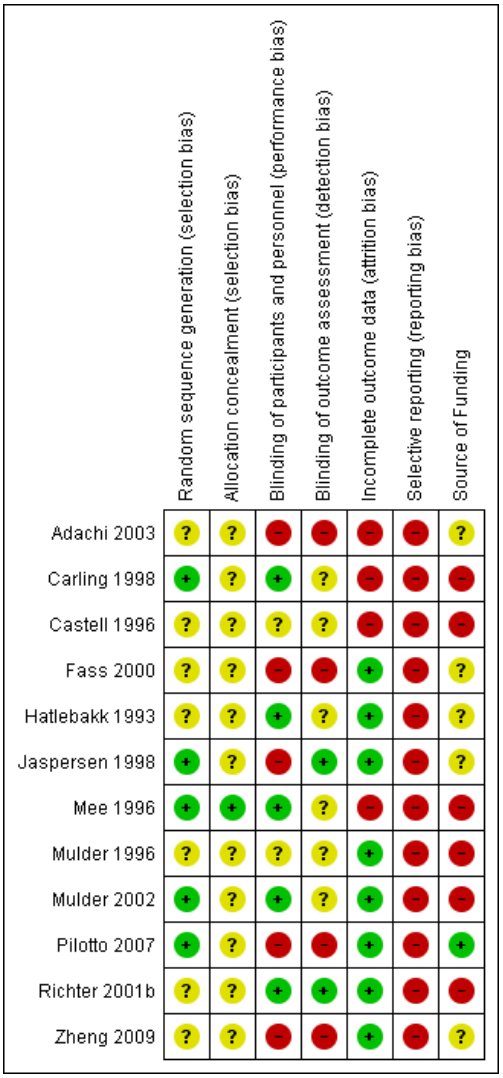
Figure 0-6 Risk of Bias Summary (GERD: E vs O)



3.7.1.4 GERD comparison 4: Lansoprazole vs Omeprazole

Included in this comparison were 12 RCTs examining Lansoprazole with Omeprazole in 6,648 patients with GERD. This comparison has overall high risk of selection bias (randomization was unclear in 7 studies and allocation concealment was unclear in 11 studies). Performance bias was judged as high due to open label study design in 5 studies and unclear risk in 2 RCTs. There was high risk of attrition bias in 4 studies. Selective reporting bias was high in all 12 studies primarily due to inadequate reporting of mortality, SAEs and other safety outcomes. Six of the 12 studies were funded by the manufacturer.

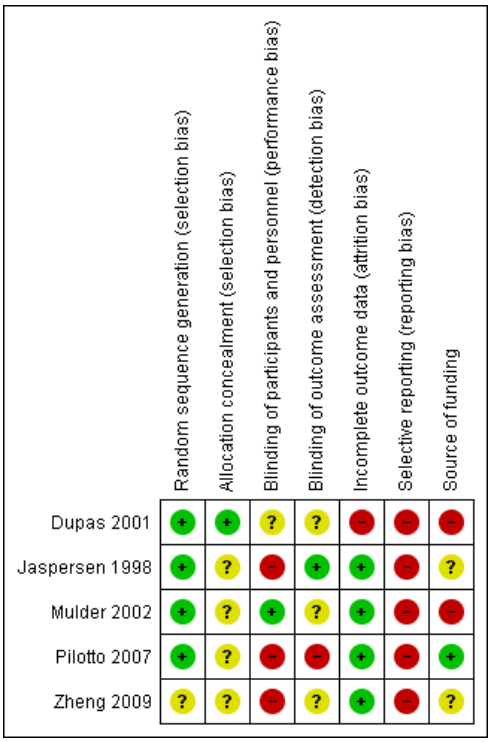
Figure 0-7 Risk of Bias Summary (GERD: L vs O)



3.7.1.5 GERD comparison 5: Lansoprazole vs Pantoprazole

Included in this comparison were 5 RCTs examining Lansoprazole with Pantoprazole in 1,089 patients with GERD. This comparison has overall high risk of selection bias (randomization as unclear in 1 study and allocation concealment was unclear in 4 of the 5 studies). Performance bias was judged as high due to open label study design in 3 studies and unclear risk in 1 RCT. Due to lack of blinding of outcome assessor, detection bias was high in 1 study and unclear in 3 studies. There was high risk of attrition bias in 1 study. Selective reporting bias was judged as high in all 5 RCTs. Mortality was not reported in 2 studies. Withdrawal due to adverse event was reported only in 1 study. Two studies provided overall withdrawals but did not report how many in each treatment group. Two studies did not report on total adverse events. Two of the five studies were sponsored by the manufacturer.

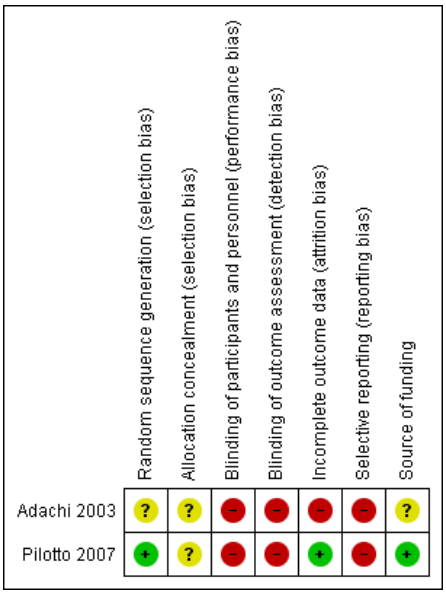
Figure 0-8 Risk of Bias Summary (GERD: L vs P)



3.7.1.6 GERD comparison 6: Lansoprazole vs Rabeprazole

Included in this comparison were 2 RCTs examining Lansoprazole with Rabeprazole in 215 patients with GERD. This comparison has overall high risk of selection bias (randomization unclear in 1 study and allocation concealment was unclear in both studies). Due to lack of blinding of participant, physician and outcome assessor both performance and detection bias was judged as high. There was high risk of attrition bias in 1 study. Selective reporting bias was judged as high in both RCTs. Mortality, serious adverse events, withdrawal due to adverse events was not reported in both studies.

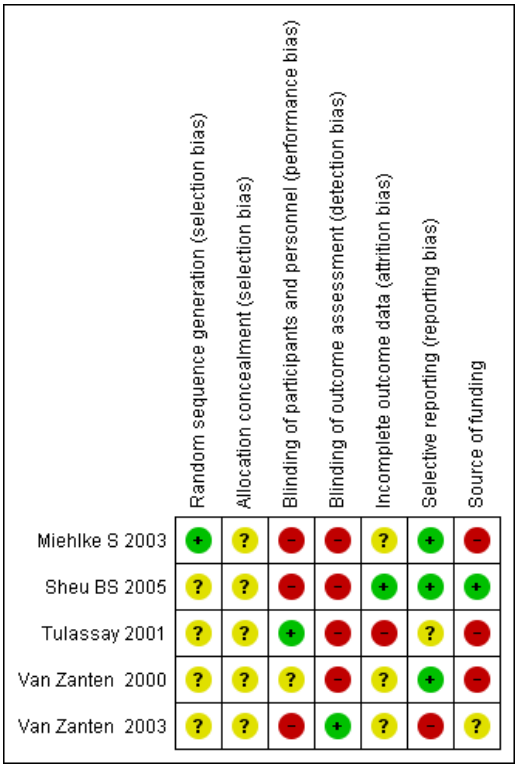
Figure 0-9 Risk of Bias Summary (GERD: L vs R)



3.7.1.7 PUD comparison 7: Esomeprazole vs Omeprazole

Included in this comparison were 5 RCTs examining Esomeprazole with Omeprazole in 1553 patients with PUD. This comparison has overall high risk of selection bias (randomization unclear in 4 studies and allocation concealment was unclear in all 5 studies). Due to lack of blinding of participant, physician in 3 studies and outcome assessor in 4 studies, both performance and detection bias was judged as high. There was high risk of attrition bias in 1 study and unclear in 3 studies. Selective reporting bias was judged as high in 1 RCT. Three of the 5 Studies were sponsored by the manufacturer.

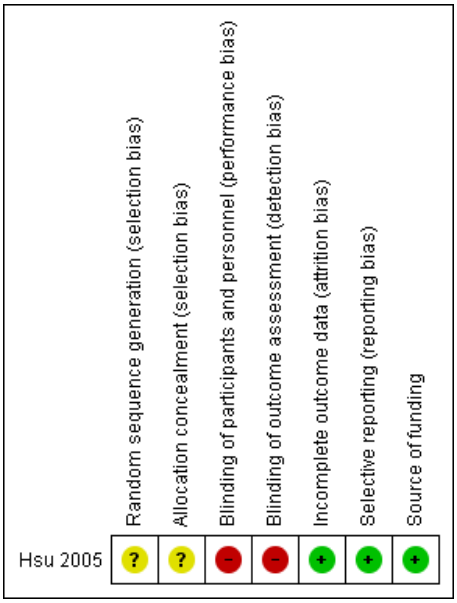
Figure 0-10 Risk of Bias Summary (PUD: E vs O)



3.7.1.8 PUD comparison 8: Esomeprazole vs Pantoprazole

Included in this comparison was 1 RCTs examining Esomeprazole with Pantoprazole in 200 patients with PUD. This comparison has overall high risk of selection bias (randomization and allocation concealment was unclear). Due to lack of blinding of participant, physician and outcome assessor, performance and detection bias was judged as high risk. The other 3 factors incomplete outcome data, selective reporting and source of funding were judged as low risk of bias.

Figure 0-11 Risk of Bias Summary (PUD: E vs P)



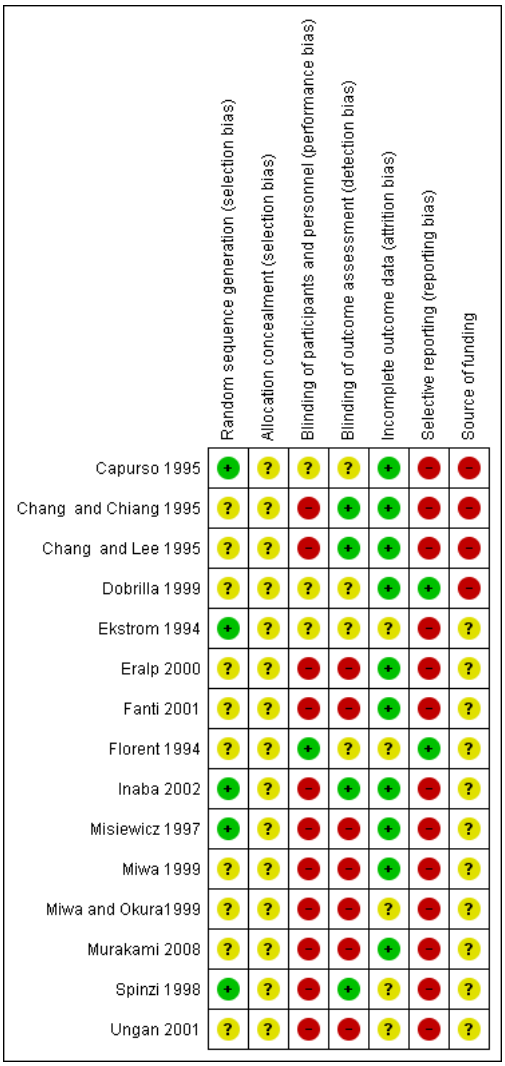
3.7.1.9 PUD comparison 9: Esomeprazole vs Rabeprazole (0 RCT)

No RCT met the inclusion criteria.

3.7.1.10 PUD comparison 10: Lansoprazole vs Omeprazole

Included in this comparison were 15 RCTs examining Lansoprazole with Omeprazole in 2265 patients with PUD. This comparison has overall high risk of selection bias (randomization unclear in 10 studies and allocation concealment was unclear in all 15 studies). Due to lack of blinding of participant, physician in 11 studies and outcome assessor in 7 studies, both performance and detection bias was judged as high. There was unclear risk of attrition bias in 5 studies. Selective reporting bias was judged as high in 13 RCTs. Four studies were sponsored by the manufacturer and 11 studies the source of funding was not reported.

Figure 0-12 Risk of Bias Summary (PUD: L vs O)



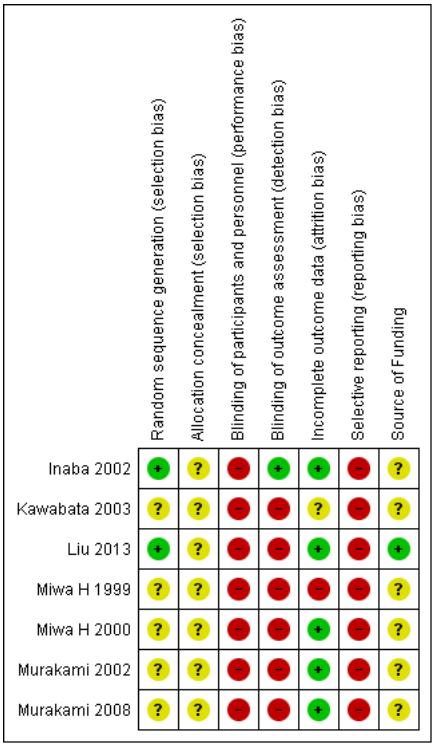
3.7.1.11 PUD comparison 11: Lansoprazole vs Pantoprazole (0 RCT)

No RCT met the inclusion criteria.

3.7.1.12 PUD comparison 12: Lansoprazole vs Rabeprazole

Included in this comparison were 7 RCTs examining Lansoprazole with Rabeprazole in 1,574 patients with PUD. This comparison has overall high risk of selection bias (randomization unclear in 5 studies and allocation concealment was unclear in all 7 studies). Due to lack of blinding of participant, physician in 11 studies and outcome assessor in 7 studies, both performance and detection bias was judged as high. There was unclear risk of attrition bias in 5 studies. Selective reporting bias was judged as high in all 7 RCTs. In 6 of the 7 studies, the source of funding was not reported.

Figure 0-13 Risk of Bias Summary (PUD: L vs R)



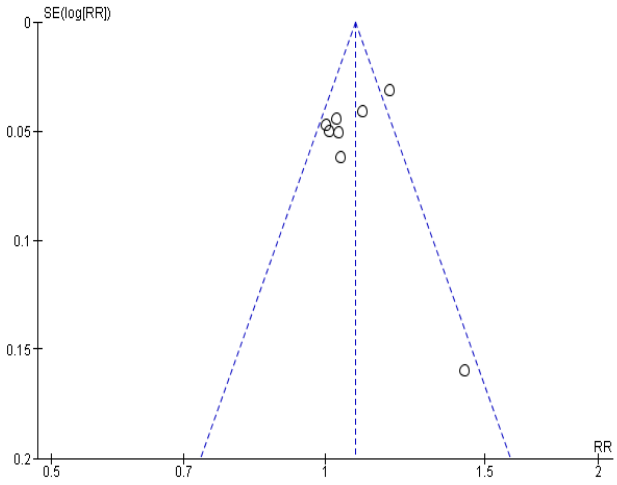
3.7.2 Other Sources of Bias

3.7.2.1 Publication bias

Funnel plots were graphed to determine publication bias when at least 10 or more RCTs met the inclusion criteria. This analysis could not be performed for many comparisons since fewer than 10 RCTs met the inclusion criteria. In patients with GERD, two comparisons Esomeprazole compared to Omeprazole or Pantoprazole included 10 or more trials. In patients with PUD Lansoprazole compared to Omeprazole included 15 RCTs. Funnel plot for the primary outcome measure of these comparisons are plotted below.

Figure 0-14 Funnel Plots for Esomeprazole vs Omeprazole (10 GERD RCTs met inclusion criteria)

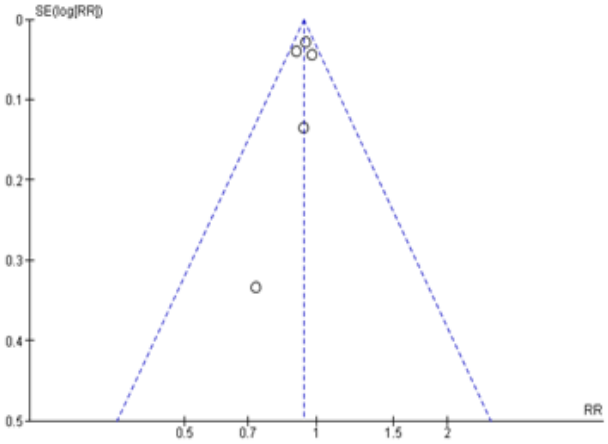
Outcome: Heartburn relief (Funnel plot)



Trials are missing in lower half of the funnel plot above signifying presence of publication bias.

Figure 0-15 Funnel Plots for Esomeprazole vs Pantoprazole (12 GERD RCTs met inclusion criteria)

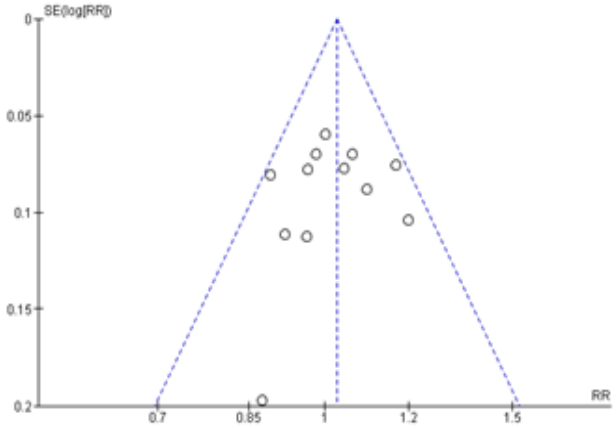
Outcome: Total symptomatic relief (Funnel plot)



Trials are missing in lower half of the funnel plot above signifying presence of publication bias.

Figure 0-16 Funnel Plots for Lansoprazole vs Omeprazole (15 PUD RCTs met inclusion criteria)

Outcome: *H. pylori* eradication (Funnel plot)



Trials are missing at the top and lower right side of the inverted funnel plot above signifying presence of publication bias.

3.7.2.2 Handling of missing information

There is very limited data on adverse events in the trials meeting the inclusion criteria for both GERD and PUD patients. Due to limited time to do this review, we have not contacted authors of trials meeting the inclusion criteria to obtain missing information of outcomes of interest for this review. Since many trials did not report on how many patients discontinued the study and how they were accounted in data analysis, we performed an intention to treat analysis using conservative analysis (patients lost were deemed as not to have experienced a positive response).

3.7.2.3 Methodological limitations

Not all outcomes of interest were reported in trials meeting the inclusion criteria. Data has been reported in a subset of trials meeting the inclusion criteria for each comparison and a high risk of selective reporting bias between and within trials was observed.

Three large studies Labenz 2005b (N=2813, E vs P), Kahrilas 200 (N=1971, E vs O), Lightdale 2006 (N=1176, E vs O) provided life-table estimates instead of raw data for healing of esophagitis outcome. Data could not be directly compared with other studies that provided the raw rates because life-table method tends to overestimate the treatment effect as patients who are lost to follow-up or have withdrawn from the study are excluded.

The harm data in RCTs were poorly reported. Mortality, serious adverse events and details of these events, withdrawal due to adverse events and reasons for withdrawals were not reported in over half the trials meeting the inclusion criteria.

Very limited data was provided in sub group of patients included in RCTs meeting the inclusion criteria. Subgroup analyses for all comparisons based on age, gender, race, BMI, smoking, alcohol consumption,

genotype of CYP2C19 and CYP3A4 liver enzyme, associated co-morbidity (liver disease); and concomitant medications could not be performed.

For trials meeting inclusion criteria in GERD, most subgroup analysis was limited to small number of trials based on several factors - various grades of severity of ulcer at baseline, *H. pylori* status at baseline, or at end of treatment. Four out of 10 trials comparing Esomeprazole to Omeprazole provided data on endoscopic healing of esophagitis in a subgroup of patients based on severity of ulcer at baseline; two out of 12 RCTs comparing Esomeprazole to Pantoprazole provided data on this outcome; and two out of 5 RCTs comparing Esomeprazole to Rabeprazole provided data on this outcome. For Lansoprazole versus other PPI comparison of a total of 19 RCTS, only one RCT provided data for each of the comparisons (with Omeprazole, Pantoprazole and Lansoprazole respectively) for healing of esophagitis. Subgroup analysis for remission rate was provided in 1 RCT based on status of *H. pylori* at baseline.

Of the 25 trials meeting the inclusion criteria for PUD for various comparisons, subgroup analyses based on type of metabolizer and sensitivity or resistance to specific antibiotics was selectively reported based on 3 RCTS. Therefore, no conclusions can be drawn from subgroup analysis.

3.7.3 External validity

As most studies were performed as multinational, multicentre trials in Europe, USA, Japan and Taiwan including some studies that were performed in multi centres in Canada generalizability to the Canadian health care system may be feasible but limited. In addition, the generalizability issues associated with randomized controlled trials, where patients are carefully monitored need to be considered. In particular, the inclusion and exclusion criteria identifying the patients' eligibility for the study may be different than in clinical practice.

Applicability

Applicability of trial results to community/clinical practice was difficult to determine. The studies generally excluded patients with bleeding disorder or signs of GI bleeding within 3 days prior to randomization; history of gastric or esophageal surgery; evidence of Zollinger-Ellison syndrome; primary motility disorder; esophageal stricture; Barrett's esophagus; upper GI malignancy; severe concomitant disease (liver cirrhosis, COPD, diabetes, renal failure, congestive heart failure, anemia); pregnant or lactating; patients taking PPI or H2RA on a daily basis 2 weeks prior endoscopy; patients taking diazepam, quinidine, dilantin, warfarin, anticholinergic, prostaglandin, sucralfate, corticosteroids or anti-coagulants, hypersensitive to Omeprazole or aluminium/magnesium hydroxide; patients with history of drug abuse, chronic alcoholism or other conditions with poor compliance; patients on NSAID, COX-2 inhibitors, aspirin, PPI or H2RA use in last 10 days prior to study entry. This pre-selection of patients may have resulted in a group of patients whose disease is less severe in comparison to patients who were not enrolled. Another concern was that most trials were either funded by the manufacturer or source of funding was not reported which is known to lead to high risk of bias by either overestimating or underestimating the effect size of a particular PPI.

In the maintenance trials, patients were enrolled on the basis of successful treatment with acute PPI treatment. This pre-selection may have resulted in a patient population that was adherent to treatment and could tolerate adverse effects of the PPI previously used in the acute phase.

3.8 Results of Individual studies

Meta-analysis of Key efficacy outcomes are shown in the following forest plots according to each comparison. In the forest plot, results of each study are presented as **RR with 95% CI** (the square is the mean RR and the line is the 95% CI of each study). The diamond is the overall estimate of RR with 95% CI.

3.8.1 Efficacy results from RCTs

Tables I [E] to VI [E] in Appendix 6 describe efficacy outcomes of included GERD studies. Tables VII [E], VIII [E], X [E], and XII [E] in Appendix 6 describe efficacy outcomes of included PUD studies

3.8.1.1 GERD Comparison 1: Esomeprazole vs. Omeprazole

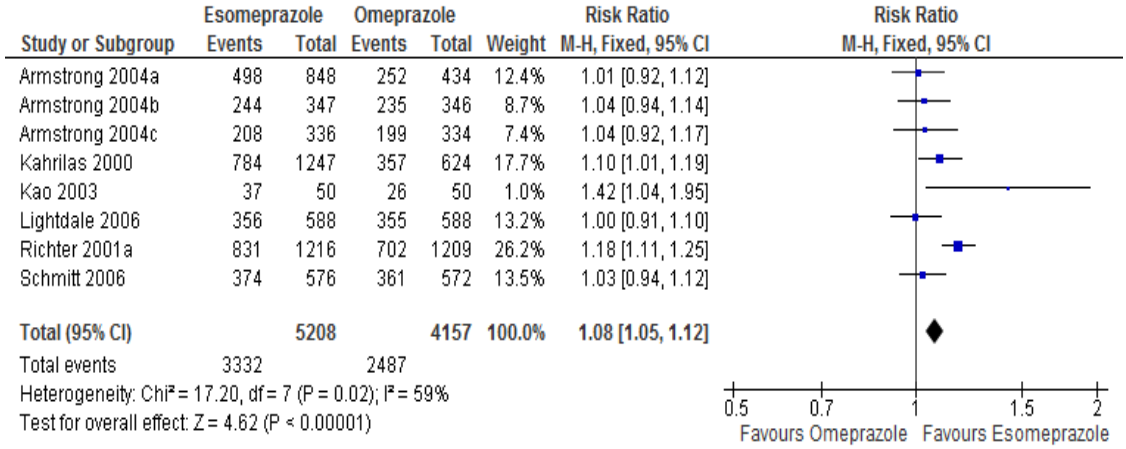
3.8.1.1.1 Key efficacy outcome 1: Patients with symptom resolution at 4 weeks (fixed effects model)

Eight RCTs in 9365 patients reported the rate of heartburn relief at 4 weeks. Significantly higher proportion of patients in Esomeprazole reported heartburn relief at 4 weeks compared to Omeprazole group (RR 1.08 [1.05, 1.12]. Heterogeneity was significant (I^2 = 59%).

Random effect model showed smaller effect size (1.07 [1.01, 1.13]). Richter 2001a was the large trial that caused the heterogeneity. Sensitivity analysis showed that if Richter 2001a was removed from the analysis, the effect size and 95% CI would become (1.04 [1.00, 1.09] and I^2 = 9% (Forest plot not shown). The reason for heterogeneity could not be determined.

Only one RCT, Kao 2003, reported heartburn and acid reflux relief. It was a small RCT with 100 patients that showed significant benefit in Esomeprazole group compared to Omeprazole group (RR 1.42 [1.04, 1.95].

Figure 0-17 Forest Plot: (GERD) E vs O - Heartburn relief at 4 weeks



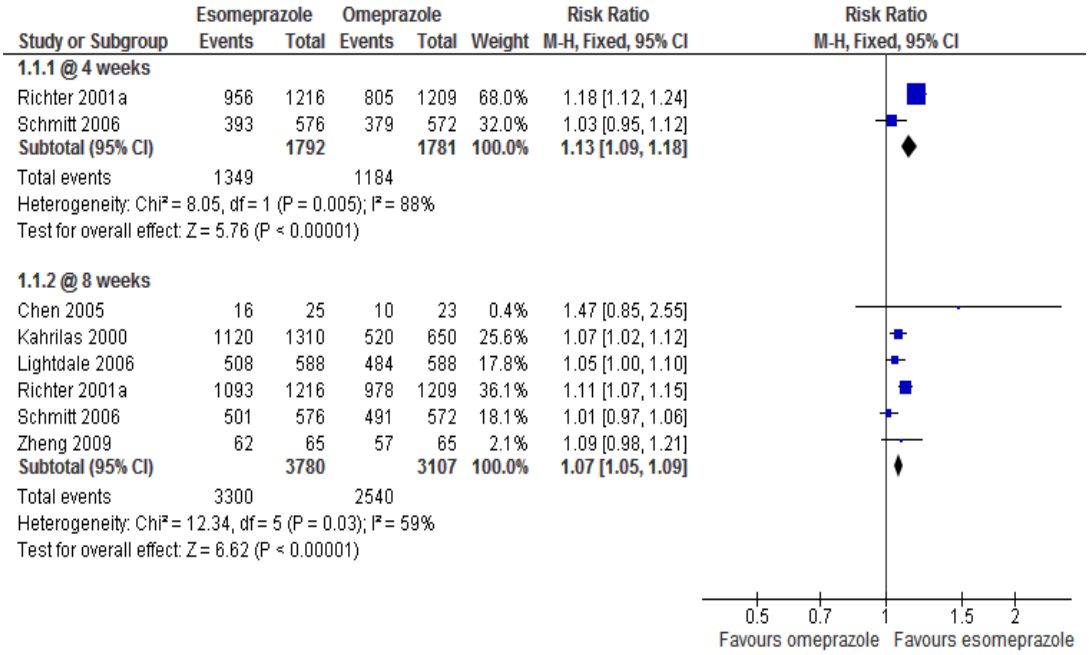
3.8.1.1.2 Key efficacy outcome 2: Endoscopic confirmed healing at 4 weeks and 8 weeks

Two RCTs (n=3,573) reported endoscopic confirmed esophagitis healing at 4 weeks and 6 RCTs (n=6,887) reported this outcome at 8 weeks. Significantly more patients in Esomeprazole group were healed compared to Omeprazole group [at 4 weeks RR 1.13 (1.09, 1.18); at 8 weeks RR 1.07 (1.05, 1.09)]. Significant heterogeneity was present (I^2 = 88% and 59%). When random effect model was used, the 4-week estimate was no longer was significant [1.11 (0.97, 1.27)] while 8-week estimate remained unchanged [1.07 (1.03, 1.11)]. (Forest plot not shown)

At week 4, the heterogeneity between the 2 studies could not be explained as the baseline characteristics between the two studies were not significantly different. Because only 2 studies were included, a sensitivity analysis was not performed.

At week 8, the heterogeneity was mostly caused by Richter 2001a. A sensitivity analysis showed if Richter 2001a was removed the estimate would change to 1.05 (1.02, 1.08); heterogeneity was no longer significant P = 0.31 and I^2 = 17%. However, reason for heterogeneity could not be determined.

Figure 0-18 Forest Plot: (GERD) E vs O - Healing of esophagitis at 4 and 8 weeks



3.8.1.1.3 Key efficacy outcome 3: Time to first resolution of symptoms

Four RCTs reported the median time to first resoultion of symptom. The median ranged from 1 to 4 days. All four studies reported no difference between Esomeprazole and Omeprazole group in term of this outcome.

3.8.1.1.4 Key efficacy outcome 4: Time to sustained resolution of symptoms

Five RCTs reported the median time to sustained resolution of symptom. The median days range from 5 to 12 days. The Armstrong 2004 studies A, B and C reported that the median days needed to sustained resolution of symptom was similar in Omeprazole and Esomeprazole group (9 to 12 days). Kahrilas 2000

and Richter 2001a reported that Esomeprazole 40 mg daily showed a shorter time (5 days) to sustained resolution of symptom compared to Omeprazole 20 mg daily (8 to 9 days).

3.8.1.1.5 Key efficacy outcome 5: Percentage of symptom free days and nights

Seven RCTs reported the percentage of symptom free days and nights. In 9,265 patients, the weighted mean average percentage of symptom free days for Esomeprazole group was 70.3% and for Omeprazole group was 68.0%. The weighted mean average percentage of symptom free nights for Esomeprazole group was 82.7%% and for Omeprazole group was 81.2%.

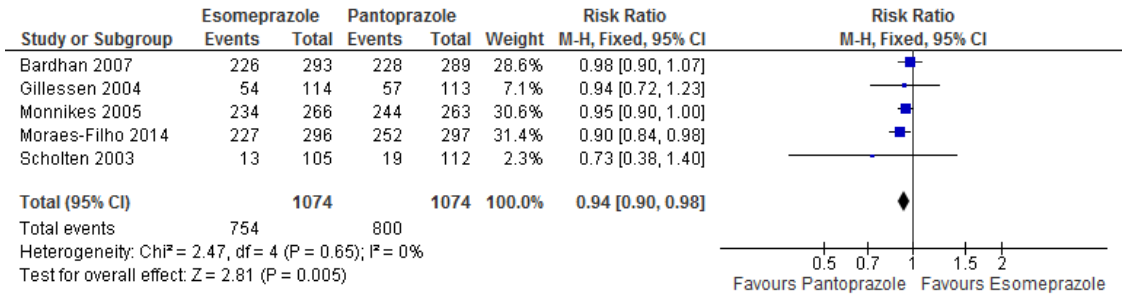
3.8.1.2 GERD Comparison 2: Esomeprazole vs. Pantoprazole

3.8.1.2.1 Key efficacy outcome 1: Total symptom resolution

Five RCTs examined the effect of total symptom resolution in 2,145 GERD patients for 4 to 12 weeks. Total symptom resolution was not significantly different between Esomeprazole group and Pantoprazole group for at 4 weeks [0.97 (0.91, 1.03)] or at 10-12 weeks [0.97 (0.89, 1.06)]. Pantoprazole showed significant advantage in total symptom resolution in 8 weeks [RR 0.94 (0.88, 0.99)]. (Forest plot not shown)

The number of patients achieving total symptom resolution at week 4-12 combined is significantly greater in the Pantoprazole group (RR 0.94 [0.90, 0.98]).

Figure 0-19 Forest Plot: (GERD) E vs P - Total symptom resolution at 4 to 12 weeks



3.8.1.2.2 Key efficacy outcome 2: Heartburn relief

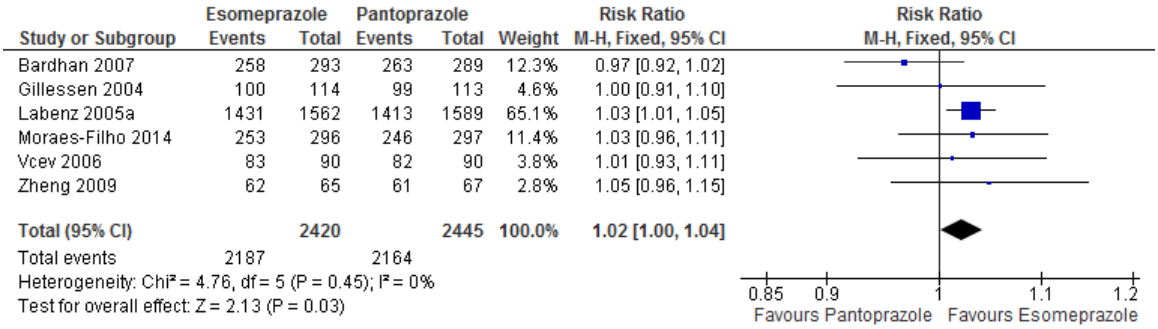
Only Scholten 2003 reported the number of patients with heartburn resolution. In Esomeprazole group, 74/105 patients reported heartburn resolution and 80/112 patients reported heartburn resolution in Pantoprazole group at 4 weeks. The estimate of risk ratio is 0.99 (0.83, 1.17).

3.8.1.2.3 Key efficacy outcome 3: Endoscopic confirmed healing of esophagitis

Six RCTs examining endoscopic confirmed healing of esophagitis in 4,659 GERD patients were included in this analysis. Esomeprazole showed significant advantage in term of endoscopic confirmed healing of esophagitis at week 4 (RR 1.06 [1.03, 1.10]) and at week 8 [1.02 (1.00, 1.04)]. Differences between treatment groups were not seen at week 10-12 [0.98 (0.93, 1.03)] (Forest plot not shown).

Pooling the data from week 4 to 12 gives a RR of 1.02 (1.00, 1.04) favouring Pantoprazole.

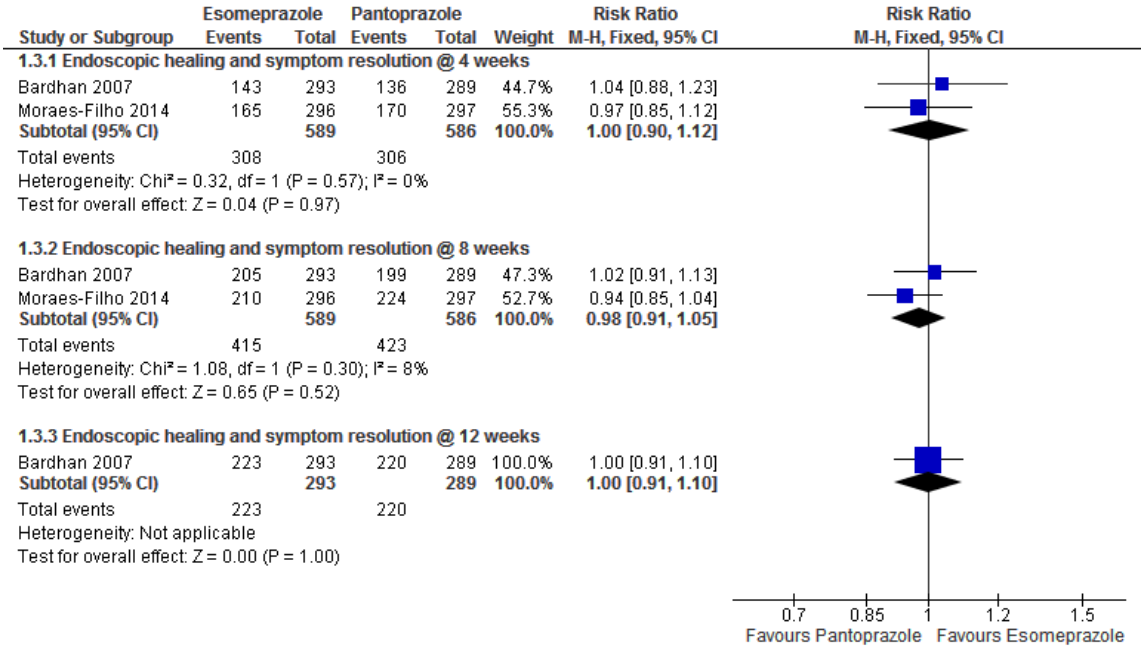
Figure 0-20 Forest Plot: (GERD) E vs P - Healing of esophagitis at week 4 to 12



3.8.1.2.4 Key efficacy outcome 4: Endoscopic healing of esophagitis and symptom resolution

Two RCTs examining patients with both endoscopic healing of esophagitis and symptom resolution for 4 to 8 weeks were included. Esomeprazole was not significantly different from Pantoprazole in terms of this outcome in both week 4 and week 8.

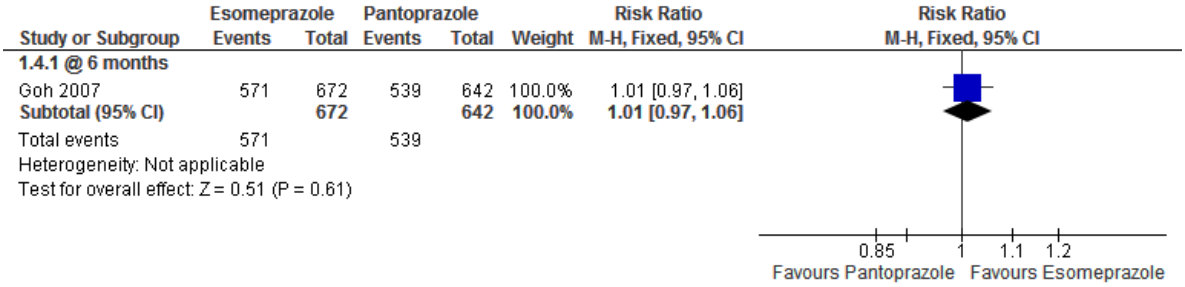
Figure 0-21 Forest Plot: (GERD) E vs P - Healing of esophagitis and symptom resolution



3.8.1.2.5 Key efficacy outcome 5: Patients on remission at 6 months (endoscopic healing of esophagitis and symptom resolution)

One RCT examining remission of endoscopic confirmed healing of esophagitis and symptom resolution in 1,314 GERD patients was included in this analysis. There was no significant different in remission rate at 6 months between Esomeprazole and Pantoprazole group.

Figure 0-22 Forest Plot: (GERD) E vs P - remission at 6 months



3.8.1.2.6 Key efficacy outcome 6: Time to first resolution of symptoms

Monnikes 2005 and Glatzel 2006 reported the median time to first resolution of symptom. Both RCTs reported a median of 2 days in both Esomeprazole group and Pantoprazole group for time to first resolution of symptoms.

3.8.1.2.7 Key efficacy outcome 7: Time to sustained resolution of symptoms

Four RCTs reported the time to sustained resolution of symptoms. The median day needed to sustained resolution of symptoms range between 6 to 17 days. In Labenz 2005a, Esomeprazole group (median: 6 days) reached sustained symptom resolution earlier than Pantoprazole group (median: 8 days). But in Monnikes 2005, patients in Pantoprazole group (median: 10 days) reached sustained symptom resolution faster compared to Esomeprazole group (median 13 days). Other studies showed that both groups have the same median.

3.8.1.2.8 Key efficacy outcome 8: Patients with symptom free days and nights

Labenz 2005a and Vcev 2006 reported the percentage of symptom free days. The only symptom they reported was heartburn. The weighted mean percentage of symptom free days 70%. Both Pantoprazole and Esomeprazole groups showed similar results.

GERD Comparison 3: Esomeprazole vs. Rabeprazole

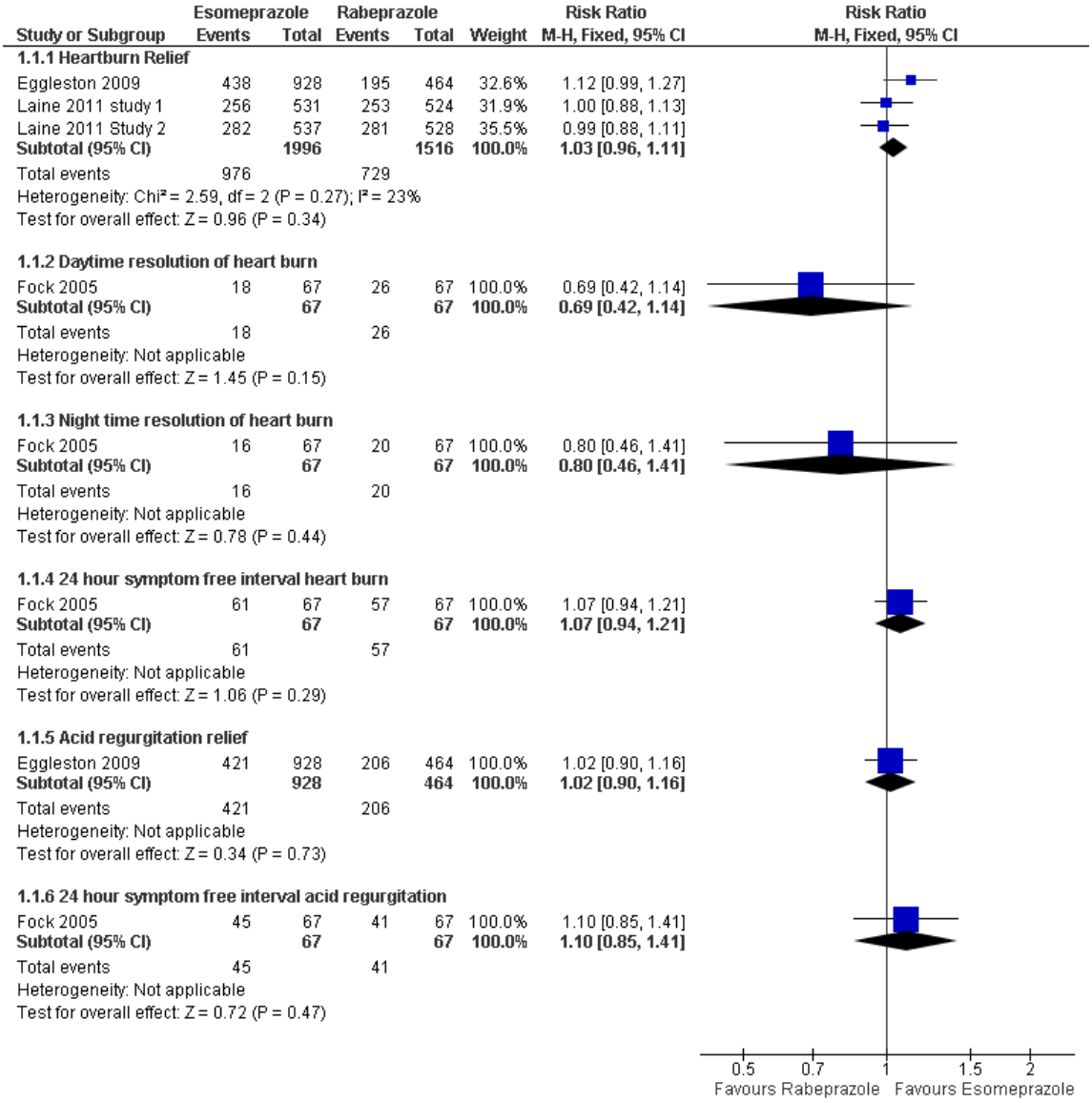
3.8.1.2.9 Key efficacy outcome 1: Total Symptomatic Relief

Total symptomatic relief outcome was not reported in any trial meeting the inclusion criteria.

3.8.1.2.10 Key efficacy outcome 2: Individual Symptomatic relief at week 4

3 RCTs (N=3512 patients) reported heartburn relief at 4 weeks of treatment. No statistically significant difference was found between Esomeprazole and Rabeprazole groups. Other symptomatic relief such as acid regurgitation, day and night time heartburn relief and 24 hour heartburn or acid regurgitation free intervals were provided by only 1 RCT each. No differences in these outcomes were noted between treatment groups.

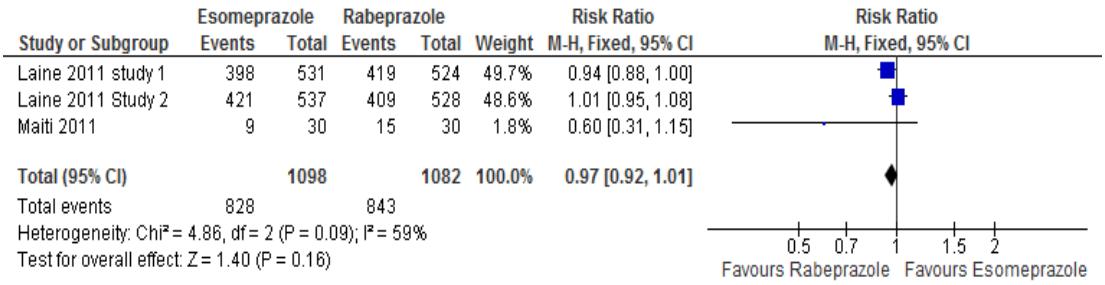
Figure 0-23 Forest Plot: (GERD) E vs R - Individual Symptomatic relief at week 4



3.8.1.2.11 Key efficacy outcome 3: Healing of esophagitis at week 4 and week 8

No significantly differences was observed between Rabeprazole and Esomeprazole groups in esophageal healing rate at 4 weeks (3 RCTs, N=2180 patients) or at 8 weeks (2RCTs, N=2150) of treatment. The overall RR for week 4 to 8 combined is 0.97 [0.92, 1.01]. Since heterogeneity was significant I^2 =59%, using a random effect model resulted in an overall effect size of 0.97 (0.88, 1.06). The reason for heterogeneity could not be determined.

Figure 0-24 Forest Plot: (GERD) E vs R - Healing of esophagitis at week 4 and week 8



3.8.1.2.12 Key efficacy outcome 4: Time to first resolution of symptoms

The time to first 24 hour symptom free interval was reported by Fock 2005. For heartburn relief, the median time was 9.0 days for Lansoprazole and 8.5 days for Rabeprazole. For regurgitation relief, the median time was 7.6 and 6 days respectively.

3.8.1.2.13 Key efficacy outcome 5: Time to sustained resolution of symptoms

The time to sustained (first of 7 consecutive days) of heartburn resolution was reported in one trial Eggleston 2009. The median time was 9 to 12 days for Esomeprazole and 11 days for Rabeprazole. For acid regurgitation relief, the median time was 11-13 days for Esomeprazole and 9 days for Rabeprazole

GERD Comparison 4: Lansoprazole vs. Omeprazole

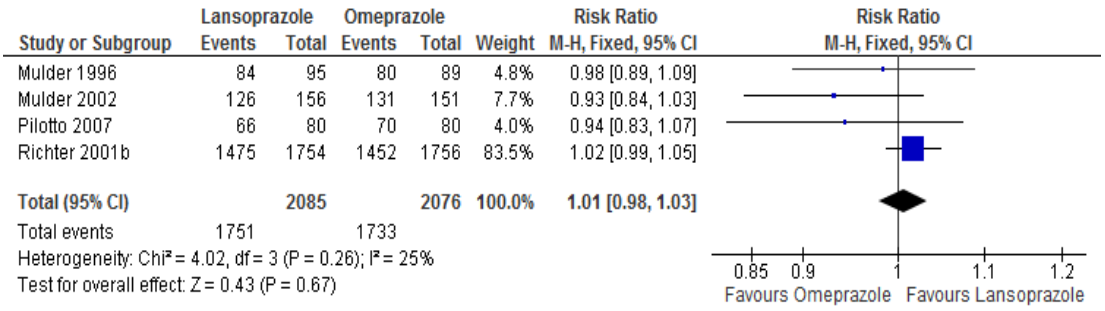
3.8.1.2.14 Key efficacy outcome 1: Total Symptomatic Relief

This outcome was not reported by any of the 12 included RCTs.

3.8.1.2.15 Key efficacy outcome 2: Heartburn relief at week 4, 6, and 8

No significantly differences was observed between Rabeprazole and Esomeprazole groups in the number of patients with heartburn relief at 4 weeks (3 RCTs, N=4001 patients) or at 8 weeks (2RCTs, N=3977) of treatment. One smaller RCT in 96 patients reported no statistically differences in the proportion of patients reporting daytime and nighttime heartburn relief at week 6 of treatment.

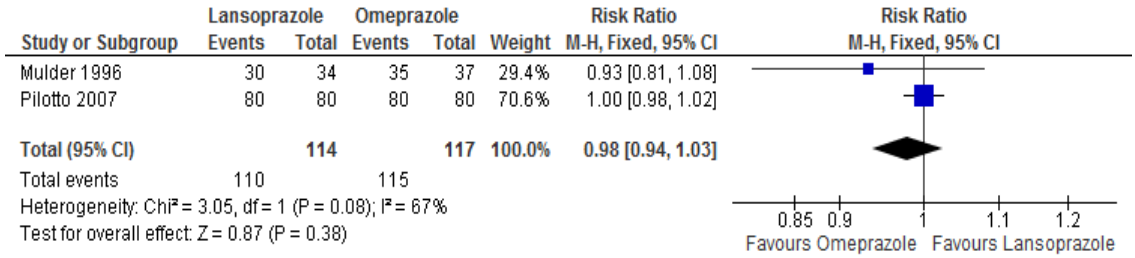
Figure 0-25 Forest Plot: (GERD) L vs O - Heartburn relief at 4 to 8 weeks



3.8.1.2.16 Key efficacy outcome 3: Dysphagia relief at week 4 and 8

The proportion of patients with dysphagia relief was reported 1 RCT (N=71) at week 4 and by 1 RCT (N=160) at week 8. No statistically significant difference in this outcome was observed (RR: 0.98[0.94, 1.03] P = 0.38). Since heterogeneity was significant I^2 =67%, using a random effect model resulted in an overall effect size of 0.98 (0.86, 1.10). The reason for heterogeneity could not be determined.

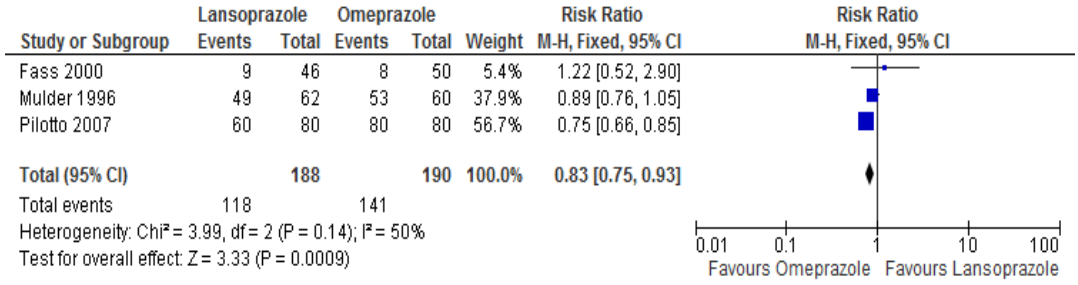
Figure 0-26 Forest Plot: (GERD) L vs O - Dysphagia relief at week 4 and 8



3.8.1.2.17 Key efficacy outcome 4: Acid regurgitation relief at week 4, 6, and 8

The proportion of patients achieving acid regurgitation relief was reported by 1 RCT each at week 4, 6, and 8. The results are present in Figure 4-24 below. No statistically significant differences were observed at week 4 and 6. Based on 1 open label RCT, Pilotto 2007 (N=160, a smaller proportion of patients in the Lansoprazole group compared to the Pantoprazole group achieved acid regurgitation relief (75% vs 100%; RR: 0.75 [0.66, 0.85]). Overall from 4 to 8 weeks Omeprazole significantly improved relief from acid regurgitation as compared to Esomeprazole RR: 0.83 [0.75, 0.93].

Figure 0-27 Forest Plot: (GERD) L vs O - Acid regurgitation relief at 4 to 8 weeks

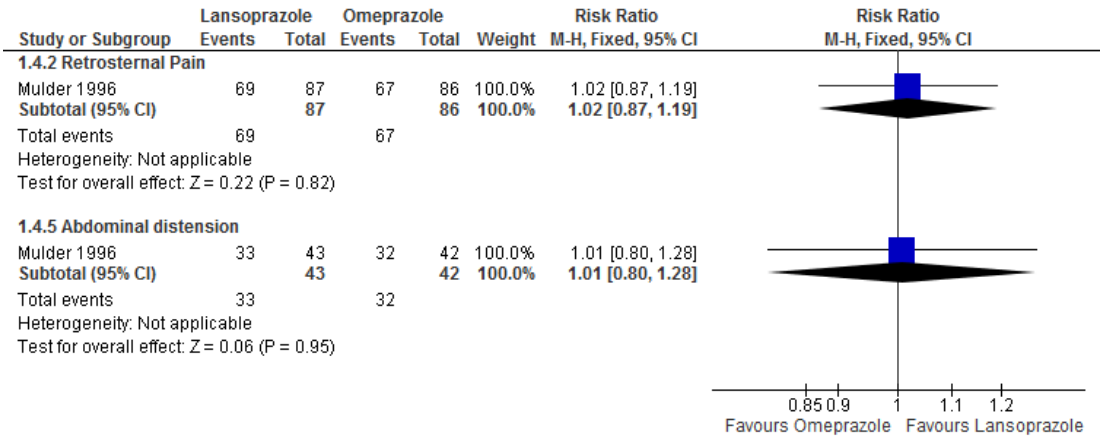


3.8.1.2.18 Key efficacy outcome 5: Other symptomatic relief at week 4 and at week 8

Mulder 1996 reported on retrosternal pain relief and on abdominal distension relief at week 4. No difference in this outcome was observed between Lansoprazole and Omeprazole groups.

One RCT (Pilotto 2007) reported relief of epigastric pain, vomiting and anemia at week 8 of treatment. However, this was not a double-blind RCT and therefore has a high risk of detection and performance bias. Based on results from this study, a greater proportion of patients achieved epigastric pain relief in the Omeprazole group compared Lansoprazole group (RR 0.87 [0.78, 0.97]) [Forest plot not shown. No patient in either group had vomiting or anemia at 8 weeks.

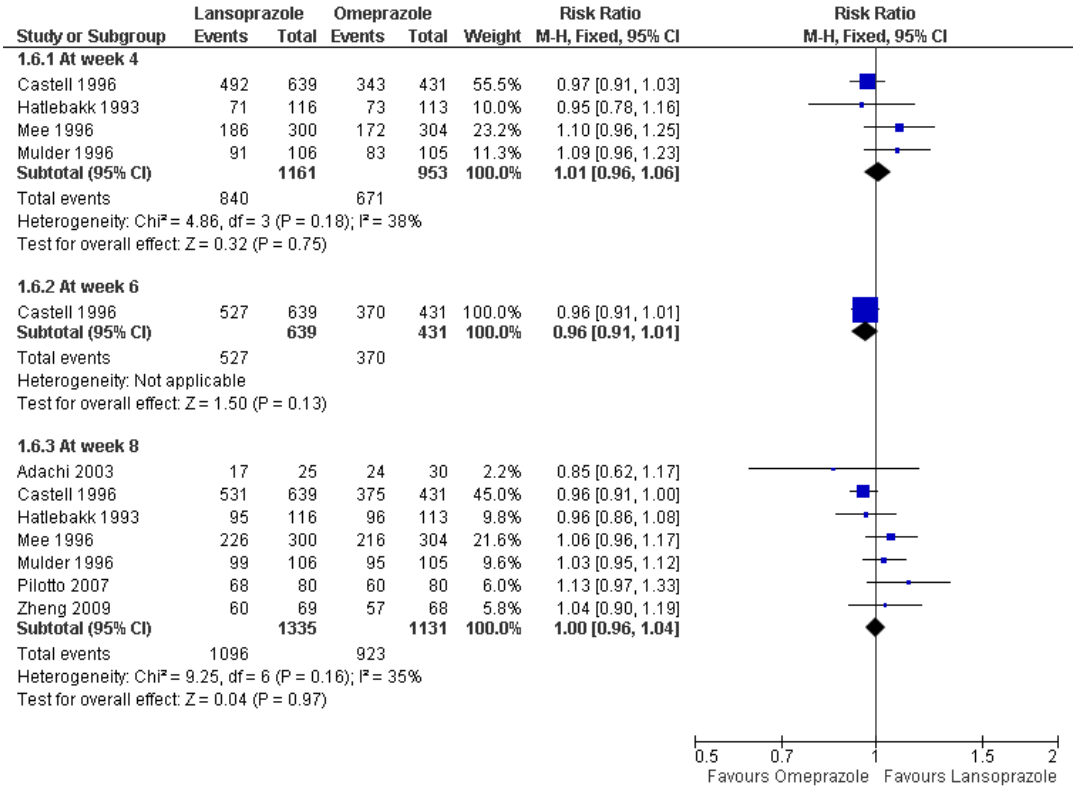
Figure 0-28 Forest Plot: (GERD) L vs O - Other symptomatic relief at week 4



3.8.1.2.19 Key efficacy outcome 6: Healing of esophagitis at week 4, 6, and 8

No statistically significant differences was found between and Omeprazole treatments in esophageal healing rates at week 4 (4 RCTs, N=2114), at week 6 (2 RCTs, N=1070), or at week 8 (7 RCTs, N=2466).

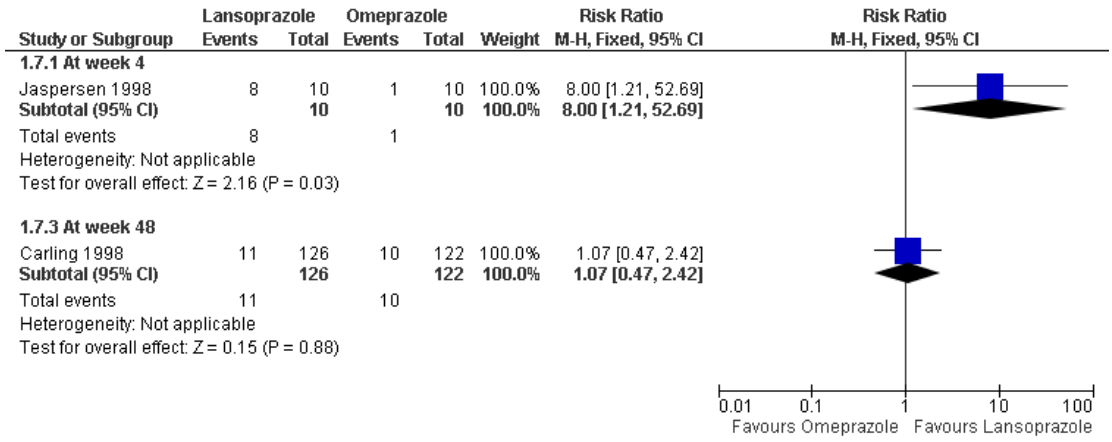
Figure 0-29 Forest Plot: (GERD) L vs O - Healing of esophagitis at week 4, 6, and 8



3.8.1.2.20 Key efficacy outcome 7: Endoscopic relapse or recurrences at week 4 and 48

Endoscopic relapse/recurrences were reported by 1 RCT each at week 4 and at week 48. Jasperson 1998 reported a higher number of patients in Lansoprazole group (8/10 patients) with endoscopic relapse at week 4 compared to Lansoprazole group (1/10 patients). No differences in this outcome at week 48 was reported by Carling 1998 (11/126 patients vs 10/122 patients respectively).

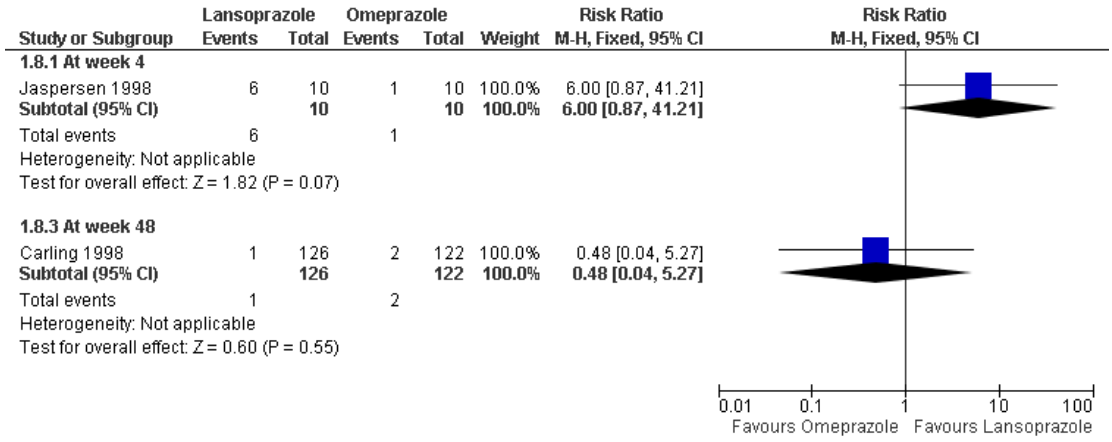
Figure 0-30 Forest Plot: (GERD) L vs O - Endoscopic relapse or recurrences at week 4 and 48



3.8.1.2.21 Key efficacy outcome 8: Symptomatic relapse or recurrences at week 4 and 48

Jasperson 1998 and Carling 1998 also reported symptomatic relapse at week 4 and week 48 respectively. No differences in this outcome between treatment groups were observed at both weeks.

Figure 0-31 Forest Plot: (GERD) L vs O - Symptomatic relapse or recurrences at week 4 and 48



3.8.1.3 GERD Comparison 5: Lansoprazole vs. Pantoprazole

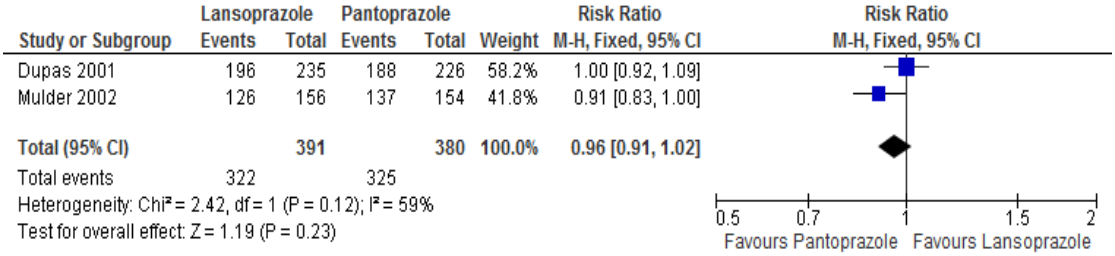
3.8.1.3.1 Key efficacy outcome 1: Total symptomatic relief

A total of 2 RCTs (Dupas 2001 and Mulder 2002) in 771 patients reported on total symptomatic relief at week 4. No difference in this outcome was observed between treatment groups. Mulder 2002 also measured this outcome in 310 patients at week 8. A greater number of patients in the Pantoprazole

group reported symptomatic relief at week 8 compared to Lansoprazole group, but this did not reach statistical significant differences. (Forest plot not shown)

Pooled analysis of both studies showed no differences at week 4 to 8 with overall effect size of 0.96[0.91, 1.02]. Since heterogeneity was significant I^2 =59%, using a random effect model resulted in an overall effect size of 0.96(0.87, 1.05). The reason for heterogeneity could not be determined.

Figure 0-32 Forest Plot: (GERD) L vs P - Total symptomatic relief at week 4 to 8

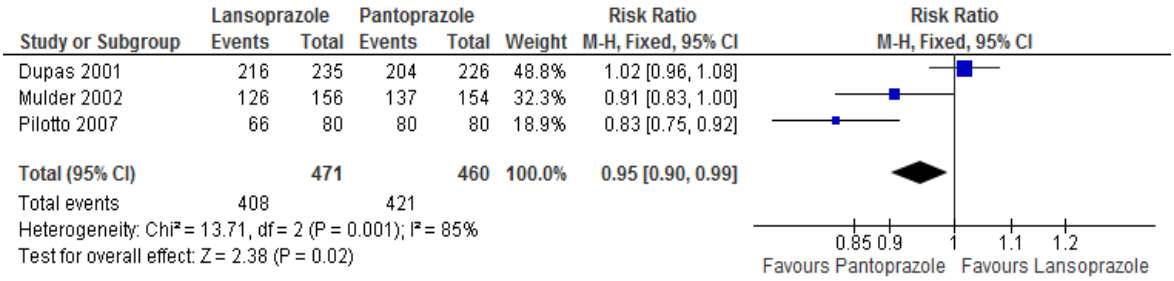


3.8.1.3.2 Key efficacy outcome 2: Relief of heart burn

2 RCTs (N=768) reported the proportion of patients achieving heartburn relief at week 4. No difference in outcome was found between treatment groups. Mulder 2002 and an open label study (Pilotto 2007) reported this outcome at week 8 in 470 patients. A meta-analysis of the 3 RCTs showed that a lower number of patients in the Lansoprazole group as compared to Pantoprazole group achieved heartburn relief at week 4 to 8 (RR 0.95 [0.90, 0.99]). Heterogeneity was significant I^2 =85%. Using a random effect model resulted in a non-significant overall effect size of 0.92 (0.81, 1.04).

Sensitivity analysis was conducted by deselecting Dupas 2001 which reduced heterogeneity I^2 from 85% to 45% with RR with 95% CI: 0.88(0.82, 0.94) and P = 0.18 (p value for heterogeneity was not significant). The reason for heterogeneity could not be determined.

Figure 0-33 Forest Plot: (GERD) L vs P - Relief of heart burn at 4 to 8 weeks



3.8.1.3.3 Key efficacy outcome 3: Other symptomatic relief at week 4 and week 8

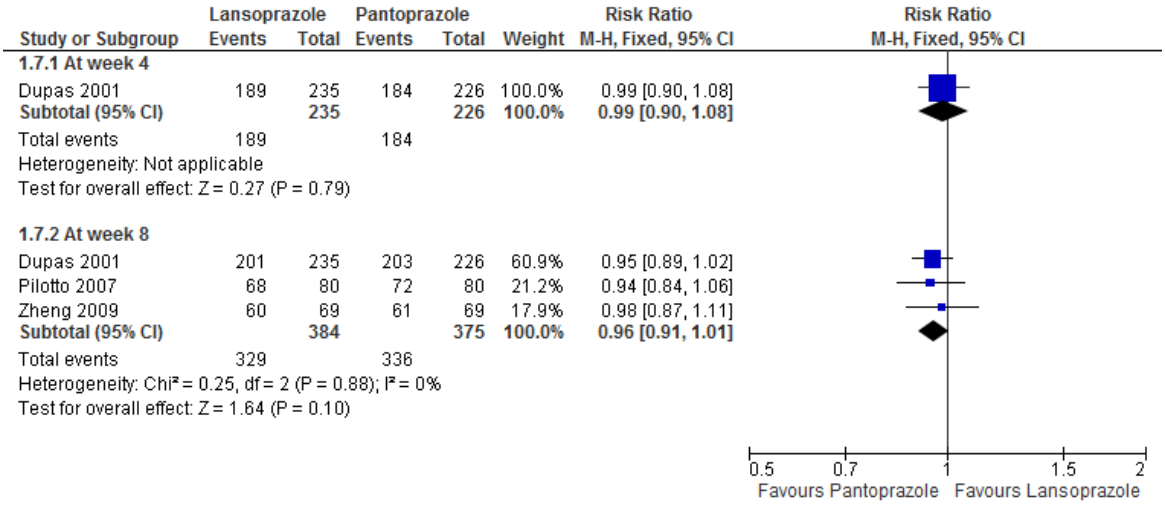
Other individual symptom relief was also reported at week 4. One RCT, Dupas 2001 (N=471), reported relief of acid regurgitation and relief of pain on swallowing at week 4. No difference was observed between treatment groups in relief of acid regurgitation (L: 211/235 vs P: 205/226; RR: 0.99 [0.93, 1.05]) and in relief of pain on swallowing (L: 225/235 vs P: 217/226; RR: 1.00 [0.96, 1.04]).

Other individual symptomatic relief at week 8 was reported by 1 open label RCT, Pilotto 2007 (N=160). Relief in dysphagia, in vomiting and in anemia was achieved in all treated patients. A smaller proportion of patients in the Lansoprazole group compared to the Pantoprazole group achieved acid regurgitation relief (92.2% vs 75%; P<0.01) and epigastric pain relief (95.2% vs 82.6%; P=0.01).

3.8.1.3.4 Key efficacy outcome 4: Healing of esophagitis at week 4 and 8

Only one RCT, Dupas 2001, reported esophageal healing rate at week 4. No difference was observed in this outcome between the Lansoprazole- and Pantoprazole-treated groups. In addition, no difference was observed in this outcome at week 8 as well based on results in 759 patients from this RCT and an open-label RCT, Pilotto 2007.

Figure 0-34 Forest Plot: (GERD) L vs P - healing of esophagitis at week 4 and 8



3.8.1.3.5 Key efficacy outcome 5: Recurrences or relapse at 4 weeks

Endoscopic relapse at week 4 was reported in 1 trial Jaspersen 1998 as in L = 8/10 vs P = 7/10; RR with 95% CI 1.14 (0.69, 1.90) P = 0.61. Symptomatic relapse was also reported in the same trial L = 6/10 vs P = 6/10; RR with 95% CI 1.00 (0.49, 2.05) P = 1.00

3.8.1.4 GERD Comparison 6: Lansoprazole vs. Rabeprazole

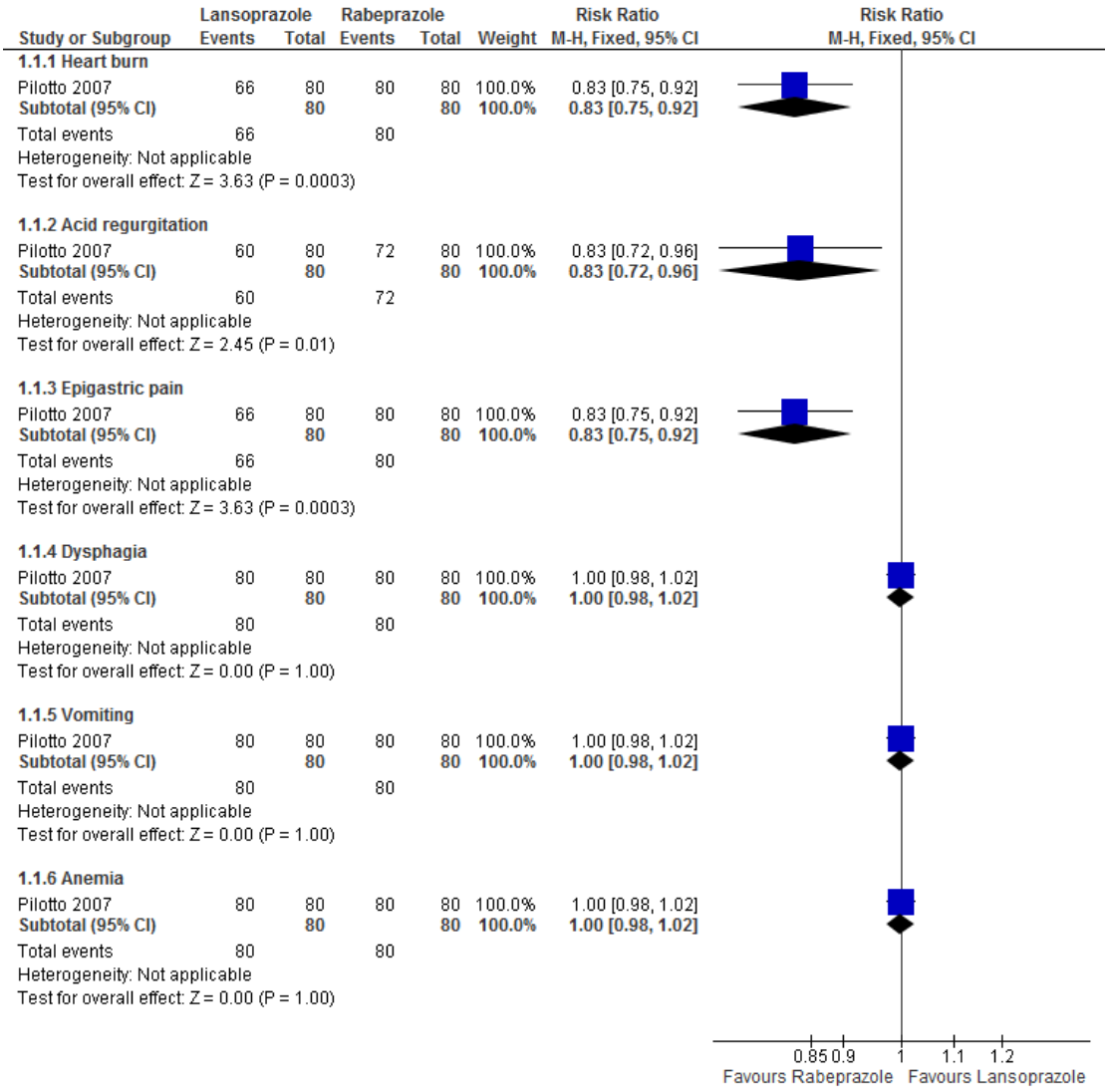
3.8.1.4.1 Key efficacy outcome 1: Total symptomatic relief

None of the included RCT reported this outcome.

3.8.1.4.2 Key efficacy outcome 2: Individual symptom resolution at 8 weeks

Pilotto 2007 was the only included RCT that reported on other individual symptom resolution at week 8. In this open label study (N=160), all patients in both treatment groups achieved relief of dysphagia, vomiting and anemia at week 8. The rates of symptom disappearance was higher in the Pantoprazole group (100% for heartburn, 90.1% for acid regurgitation and 100% for epigastric pain) than in Lansoprazole group (92.4%, 75% and 82.6% respectively)

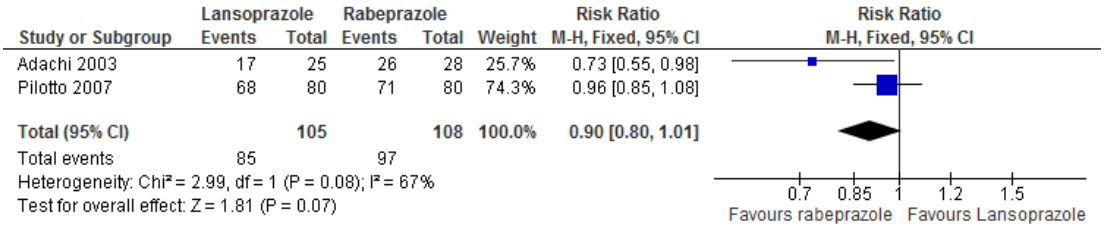
Figure 0-35 Forest Plot: (GERD) L vs R - Individual symptom resolution at 8 weeks



3.8.1.4.3 Key efficacy outcome 3: Healing of esophagitis at 8 weeks

No RCT reported esophageal healing rate at week 4. A total of 2 open-label RCTs (N=213) reported this outcome at week 8 for this comparison. No statistically significant difference in week 8 esophageal healing was noted between the two groups 0.90[0.80, 1.01]. Since heterogeneity was significant I^2 = 67%, using a random effect model resulted in an overall effect size of 0.86 (066, 1.12). The reason for heterogeneity could not be determined.

Figure 0-36 Forest Plot: (GERD) L vs R - Healing of esophagitis at 8 weeks

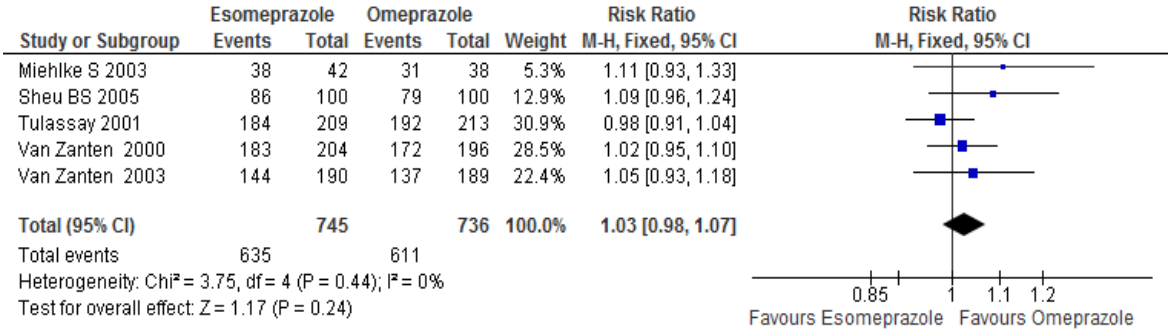


3.8.1.5 PUD Comparison 7: Esomeprazole vs. Omeprazole

3.8.1.5.1 Key efficacy outcome 1: *H. pylori* eradication at 6 and 8 weeks

Two RCTS in 541 patients reported eradication of *H. pylori* at 6 weeks [1.01 (0.95, 1.07)] and 3 RCTs in 705 patients reported eradication of *H. pylori* at 8 weeks [1.04 (0.98, 1.11)], and no significant difference was observed between treatment groups. Combined analysis at 6 to 8 weeks also showed no significant difference in eradication rates between treatment groups.

Figure 0-37 Forest Plot: (PUD) E vs O - *H. pylori* eradication at 6 and 8 weeks



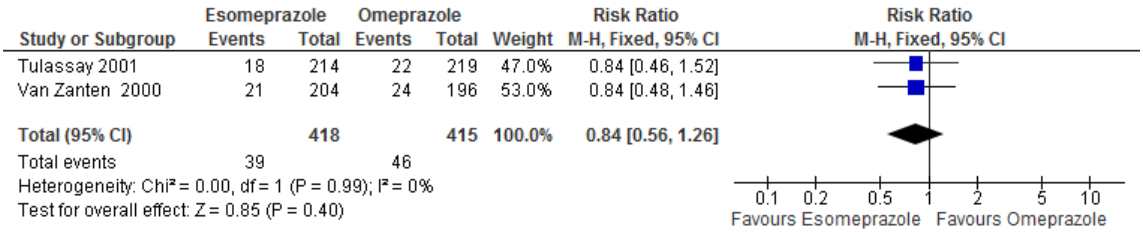
3.8.1.5.2 Key efficacy outcome 2: Ulcer healing @ 4 weeks

This outcome was reported in one study Tulassay 2001 E = 195/214 vs O = 202/219; RR 95% CI of 0.99(0.93, 1.05); P = 0.67 and there was no significant difference in ulcer healing at 4 weeks.

3.8.1.5.3 Key efficacy outcome 3: Epigastric pain @ 4 weeks

2 RCTs in 833 patients reported on epigastric pain at 4 weeks and no significant difference was observed between treatment groups.

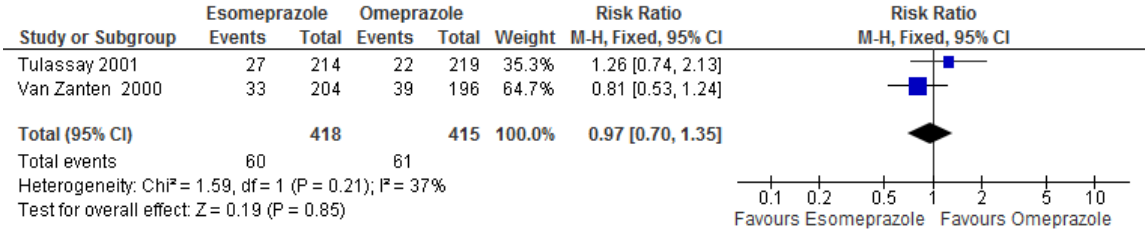
Figure 0-38 Forest Plot: (PUD) E vs O - Epigastric pain at 4 weeks



3.8.1.5.4 Key efficacy outcome 4: Heartburn at 4 weeks

2 RCTs in 833 patients reported on heartburn at 4 weeks and no significant difference was observed between treatment groups.

Figure 0-39 Forest Plot: (PUD) E vs O - Heartburn at 4 weeks

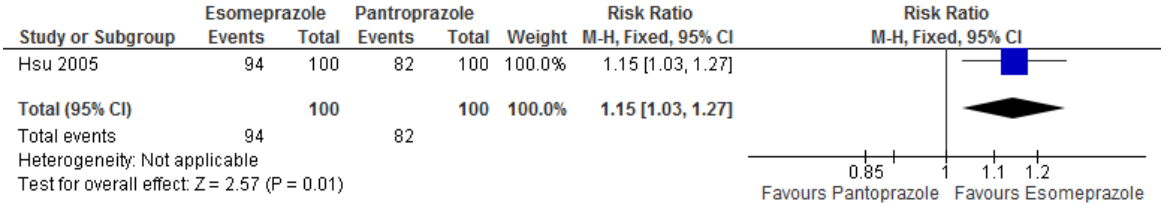


3.8.1.6 PUD Comparison 8: Esomeprazole vs. Pantoprazole

3.8.1.6.1 Key efficacy outcome 1: *H. pylori* eradication at 8 weeks

1 RCT in 200 patients reported on *H. pylori* eradication at 8 weeks and Esomeprazole was significant better in *H. pylori* eradication at 8 weeks compared to Pantoprazole 1.15[1.03, 1.27].

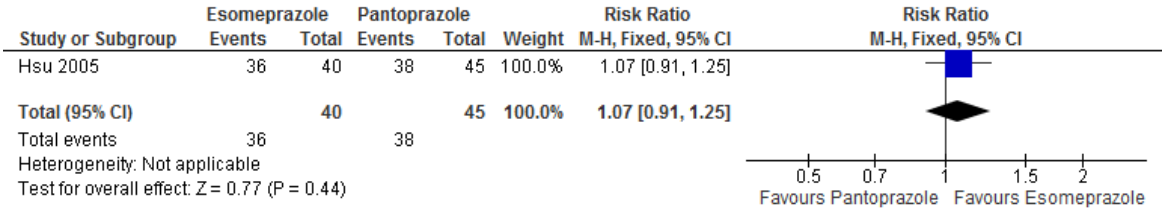
Figure 0-40 Forest Plot: (PUD) E vs P - *H. pylori* eradication at 8 weeks



3.8.1.6.2 Key efficacy outcome 2: Ulcer healing at 8 weeks

One RCT in 85 patients reported on ulcer healing at 8 weeks and no significant difference was observed between treatment groups.

Figure 0-41 Forest Plot: (PUD) E vs P - Ulcer healing at 8 weeks



3.8.1.7 PUD Comparison 9: Esomeprazole vs. Rabeprazole

No RCT met the inclusion criteria.

3.8.1.8 PUD comparison 10: Lansoprazole vs. Omeprazole

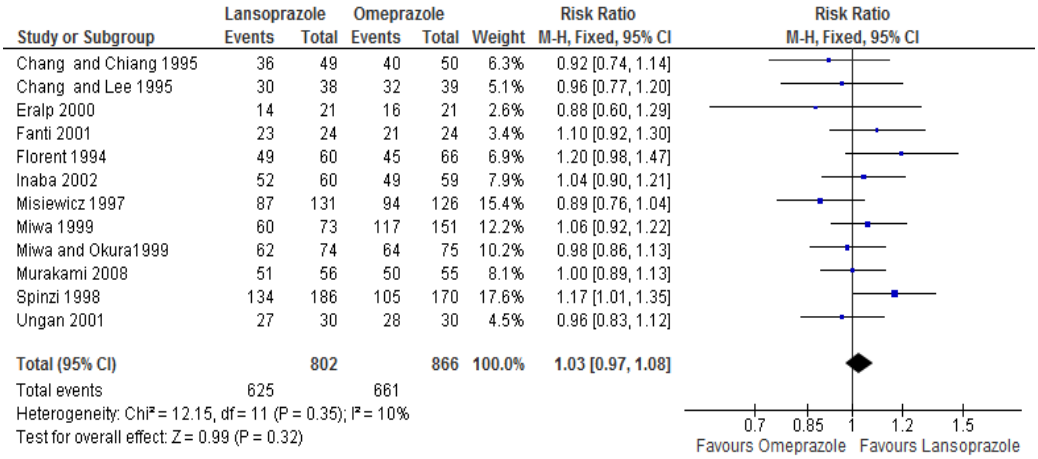
3.8.1.8.1 Key efficacy outcome 1: *H. pylori* eradication at week 1, 4, 6, 8 and at month 6

One RCT in 101 patients showed no difference in *H. pylori* eradication at 1 week between treatment groups [1.04 (0.90, 1.21)]. Eight RCTs in 1056 patients showed no difference in *H. pylori* eradication at 4 weeks between treatment groups [1.03 (0.97, 1.09)]. Two RCTs in 102 patients showed no difference in *H. pylori* eradication at 6 weeks between treatment groups [0.93 (0.79, 1.10)]. One RCT in 48 patients showed no difference in *H. pylori* eradication at 8 weeks between treatment groups [1.10 (0.92, 1.30)] (Forest plots not shown).

Based on 12 RCTs, H. Pylori eradication at 1 to 8 weeks showed no difference between Lansoprazole and Omeprazole groups [1.03 (0.97, 1.08)].

One RCT in 60 patients showed no difference in *H. pylori* eradication at 6 months between treatment groups [1.04 (0.84, 1.29)].

Figure 0-42 Forest Plot: (PUD) L vs O - *H. pylori* eradication at week 1 to 8 weeks



3.8.1.8.2 Key efficacy outcome 2: Day time and Night Time Ulcer pain relief at week 4

One RCT in 126 patients showed no difference in day time or night time ulcer pain relief between treatment groups at week 4.

Figure 0-43 Forest Plot: (PUD) L vs O - Ulcer pain relief day time at week 4

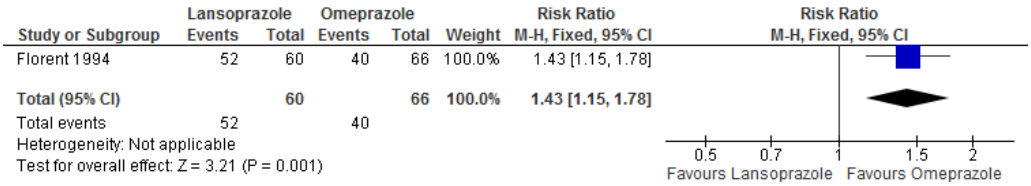
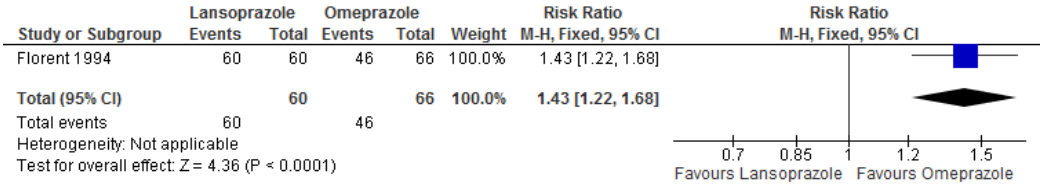


Figure 0-44 Forest Plot: (PUD) L vs O - Ulcer pain relief night time at week 4

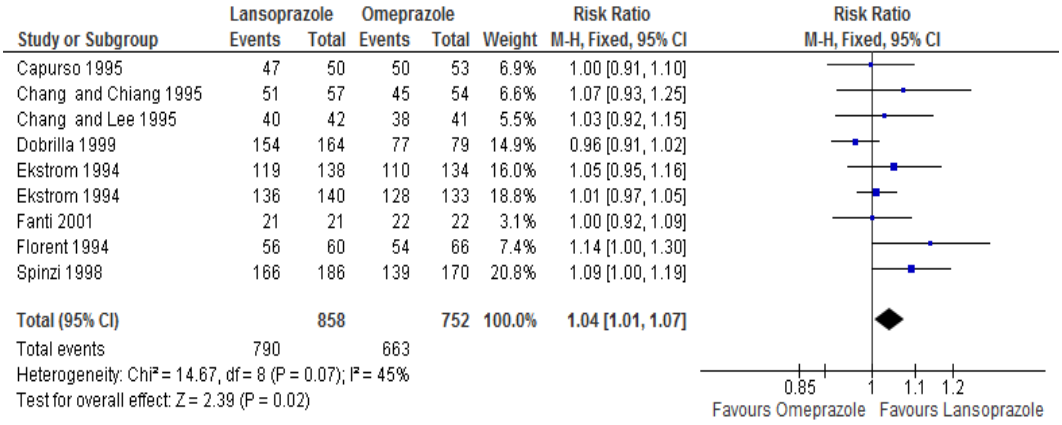


3.8.1.8.3 Key efficacy outcome 4: Ulcer healing rate at 2, 4, 6 and 8 weeks

Two RCTs in 375 patients showed no difference in ulcer healing rate at 2 weeks between treatment groups [1.05 (0.94, 1.16)]. Seven RCTS in 1295 patients showed a significant increase in healing rate in Lansoprazole group as compared to Omeprazole group at 4 weeks [1.04 (1.01, 1.08)]. One RCT in 103 patients showed no difference in ulcer healing rate at 6 weeks between treatment groups [1.00 (0.91, 1.10)]. Two RCTs in 169 patients showed no difference in ulcer healing rate at 8 weeks between treatment groups [1.10 (1.00, 1.21)] (Forest plot not shown).

Nine RCTs in 1610 patients showed a significant difference in ulcer healing rate at 4 to 8 weeks between treatment groups [1.04 (1.01, 1.07)].

Figure 0-45 Forest Plot: (PUD) L vs O - Ulcer healing rate at 4 to 8 weeks



3.8.1.9 PUD Comparison 11: Lansoprazole vs. Pantoprazole

No RCT met the inclusion criteria

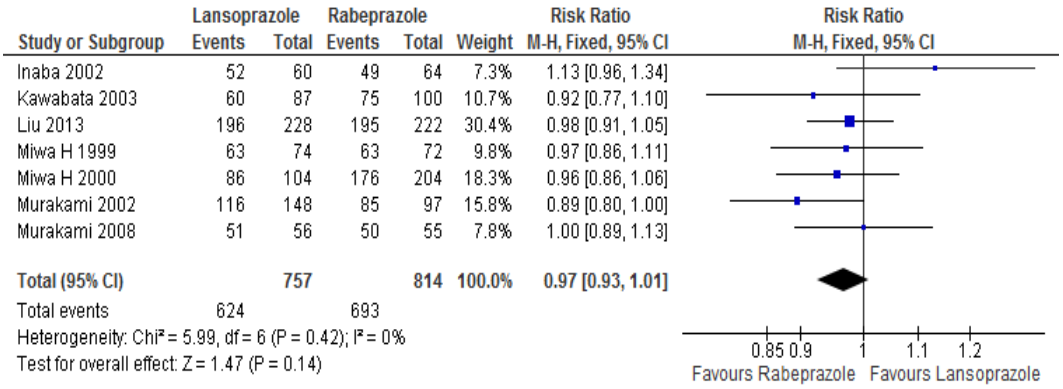
3.8.1.10 PUD Comparison 12: Lansoprazole vs. Rabeprazole

3.8.1.10.1 Key efficacy outcome 1: ***H. Pylori eradication***

One RCT in 124 patients at 1 week [1.13 (0.96, 1.34)]; Five RCTs in 997 patients at 4 week [0.94 (0.89, 1.00)]; and one RCT in 450 patients at 16 weeks [0.98 (0.91, 1.05)] showed no difference in *H. pylori* eradication rate between treatment groups (Forest plot not shown).

Based on 7 RCTs in 1571 patients, no significant difference was observed in *H. Pylori* eradication rate in Lansoprazole compared to Rabeprazole group [0.97 (0.93, 1.01)].

Figure 0-46 Forest Plot: (PUD) L vs R - *H. pylori* eradication 1 to 16 weeks



3.8.2 Subgroup analysis from included RCTs

3.8.2.1.1 GERD Comparison 1: Esomeprazole versus Omeprazole

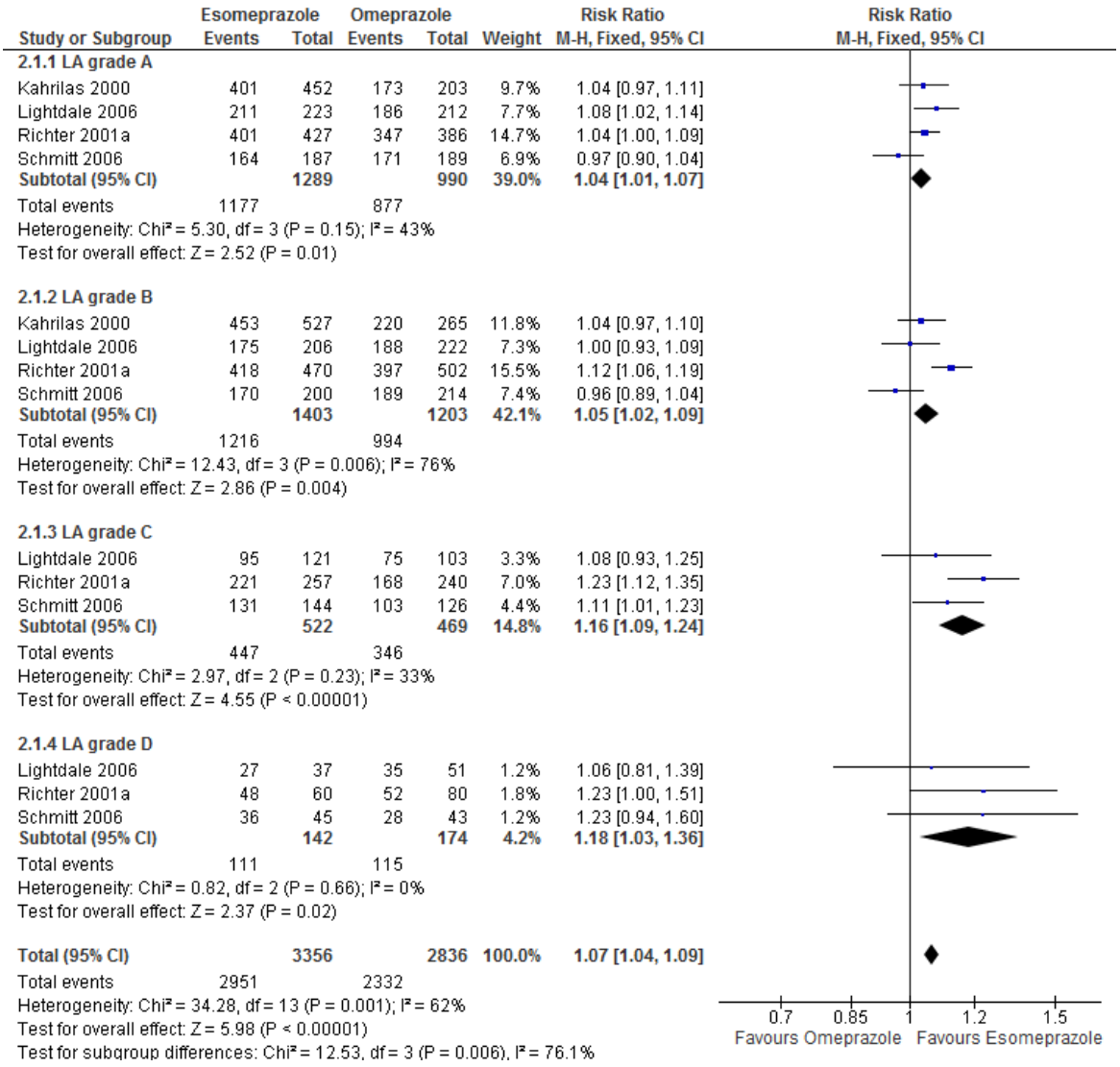
Of the 10 RCTs in 9638 patients, subgroup analysis for Esomeprazole compared to Omeprazole has examined only one factor - LA grade severity at baseline.

A subset of 4 RCTs in (N =6192) 64% of randomized patients provided endoscopic confirmed esophagitis healing data. All 4 LA grades (A, B, C and D) subgroups showed that Esomeprazole provide significant advantage compared to Omeprazole. Patient group with more severe disease showed a greater degree of benefit.

Significant heterogeneity was present in the subgroup with LA grade B severity of GERD at baseline. Random effects model resulted in RR with 95% CI of 1.03[0.96, 1.11] (Forest plot not shown). Deselecting Richter 2001a study in sensitivity analysis reduced heterogeneity from 76% to 4% with RR with 95% CI of 1.01[0.96, 1.05].

Future randomized controlled comparative trials comparing both PPIs in patients with different LA grade severity at baseline are needed to examine if patients with more severe disease are more likely to benefit from Esomeprazole.

Figure 0-47 Forest Plot: (GERD) E vs O - Healing of esophagitis according baseline LA severity grade baseline

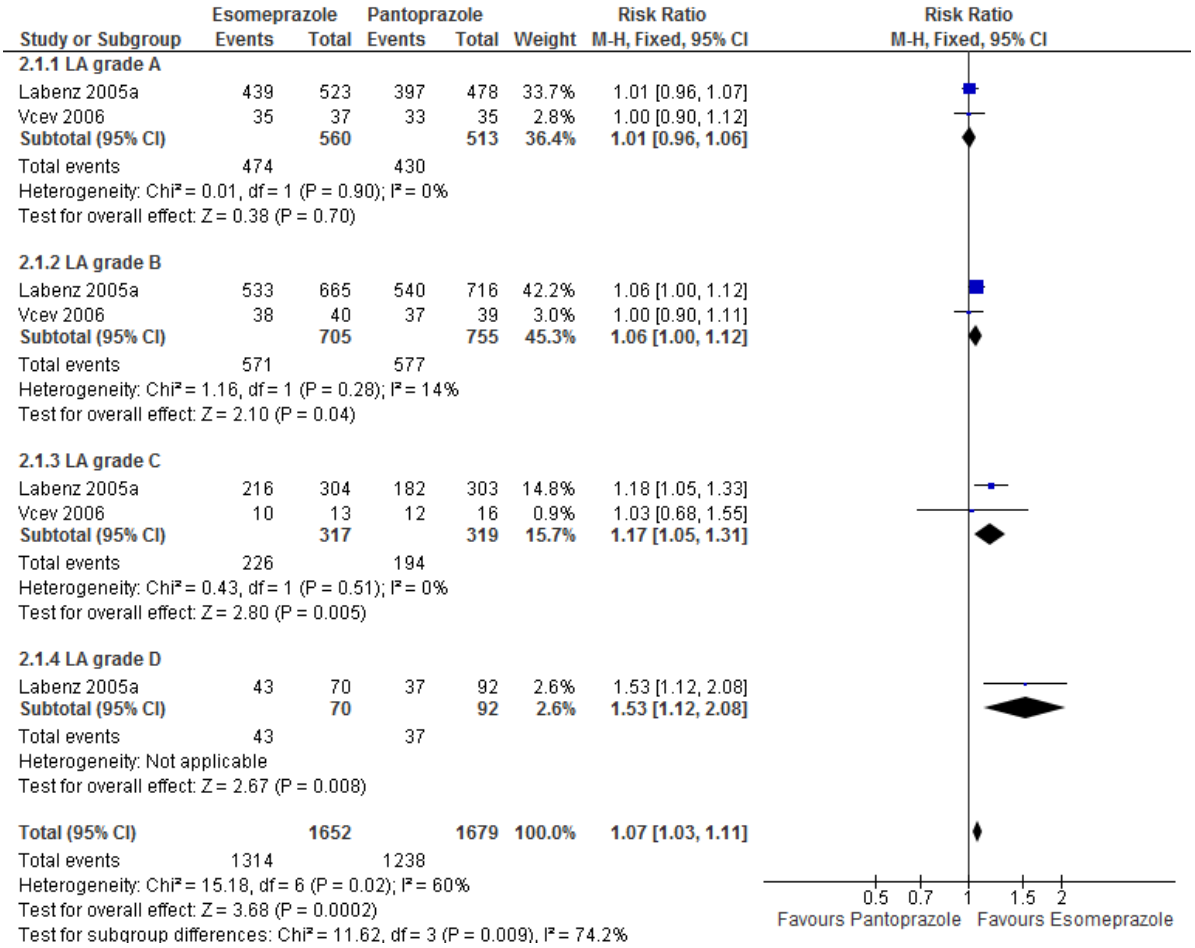


3.8.2.1.2 GERD Comparison 2: Esomeprazole versus Pantoprazole

Of the 12 RCTS in 10, 503 patients, subgroup analysis for Esomeprazole compared to Pantoprazole have examined two factors.

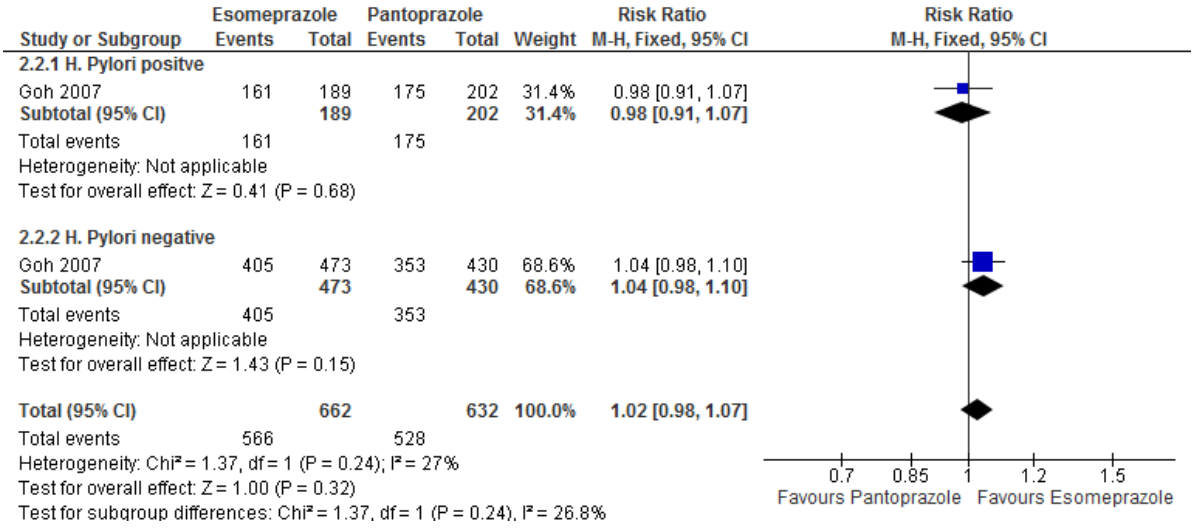
Endoscopic confirmed esophagitis healing based on LA grade severity at baseline is based on only 2 RCTs (N =3,331) in 31.7% of total randomized patients. Grade A GERD patients showed no significant difference in esophageal healing rate between treatment groups. However, at all other grades (B, C and D) Esomeprazole provides a significant advantage compared to Pantoprazole.

Figure 0-48 Forest Plot: (GERD) E vs P - Healing of esophagitis according baseline LA severity grade



Remission rates based on subgroup of patients with presence or absence of *H. pylori* infection at baseline showed no significant difference between Lansoprazole and Pantoprazole treatment groups based only on 1 RCT in 1,294 patients.

Figure 0-49 Forest Plot: (GERD) E vs P - Remission based on presence or absence of *H. pylori*

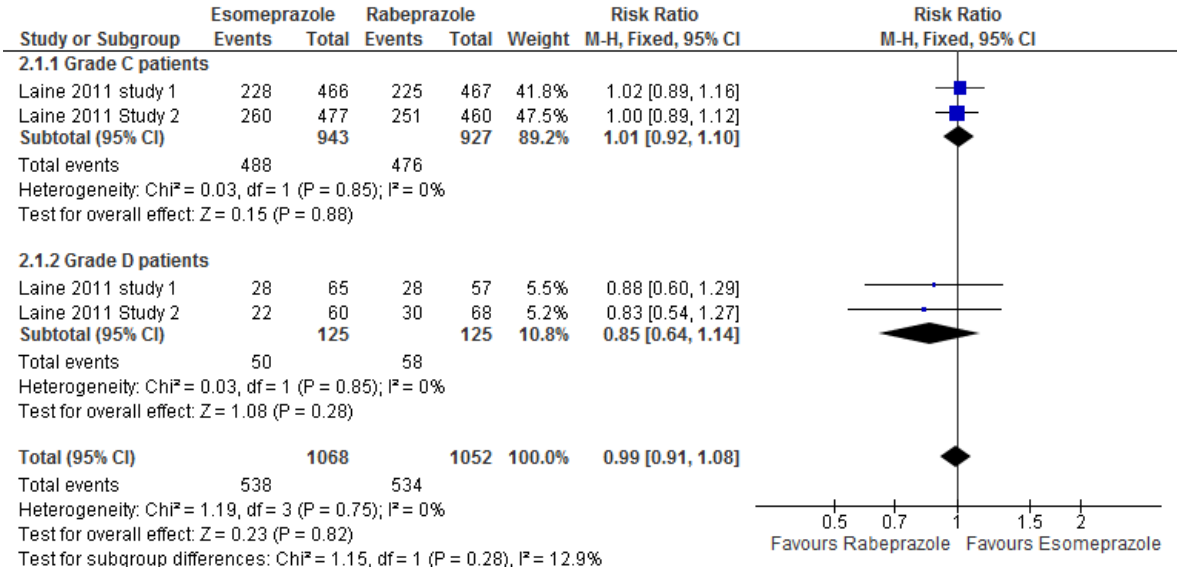


3.8.2.1.3 GERD Comparison 3: Esomeprazole versus Rabeprazole

Of the 5 RCTs in 3,716 patients, subgroup analysis for Esomeprazole compared to Rabeprazole has examined 2 factors.

Sustained resolution at week 4 based on grade C or grade D of GERD severity according to LA classification at baseline showed no significant difference between treatment groups based on 2 RCTs in (N =2120) 57% of total randomized patients.

Figure 0-50 Forest Plot: (GERD) E vs R - Sustained resolution at week 4 based on LA severity grade of GERD at baseline



Healing of esophagitis at week 4, based on subgroup of 1870 patients with grade C GERD at baseline in 2 RCTs, was not significantly different between treatment groups. However, in a sub group of 240

patients with grade D GERD at baseline, healing of esophagitis at week 4 was significantly greater in Rabeprazole group as compared to Esomeprazole group. At week 8, treatment groups were similar for both subgroups in terms of healing of esophagitis.

Figure 0-51 Forest Plot: (GERD) E vs R - Healing of esophagitis at week 4 based on LA severity grade of GERD at baseline

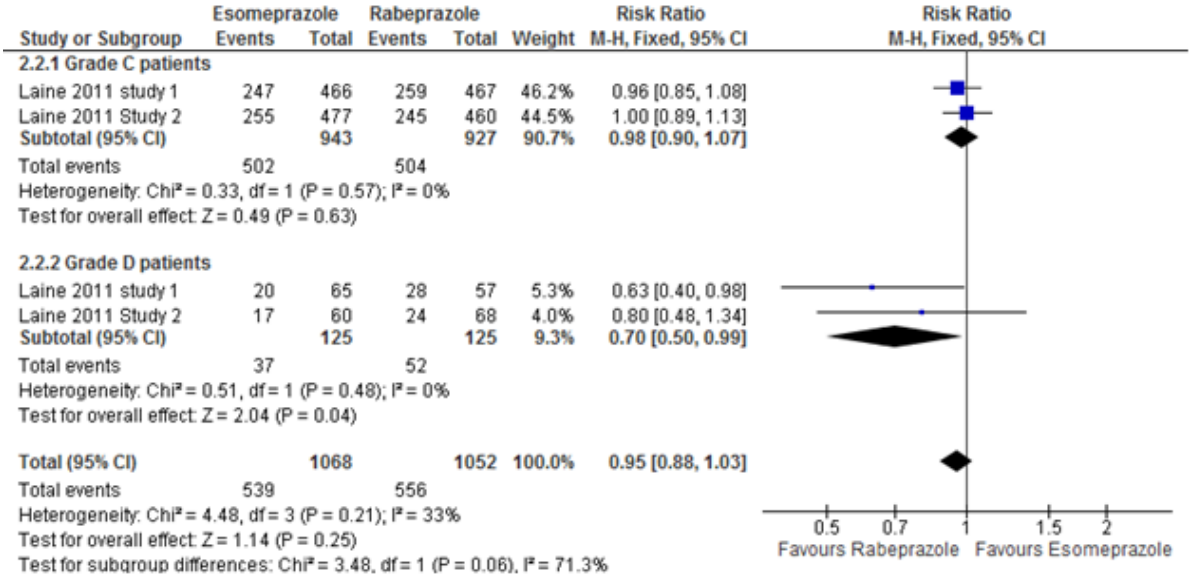
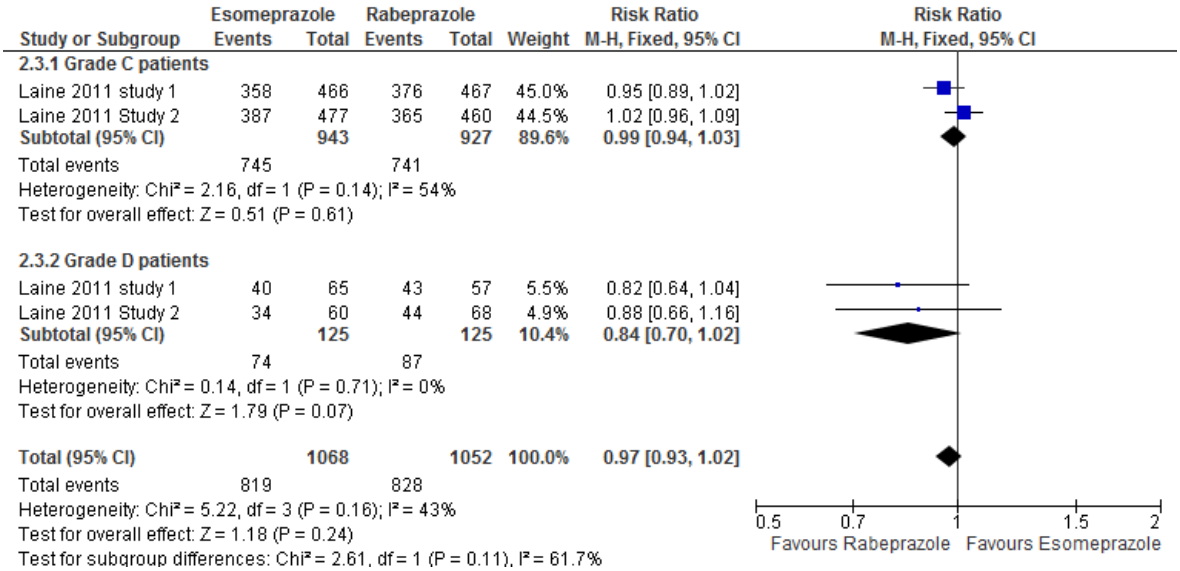


Figure 0-52 Forest Plot: (GERD) E vs R - Healing of esophagitis at week 8 based on grade of GERD at baseline



3.8.2.1.4 GERD Comparison 4: Lansoprazole versus Omeprazole

Of the 12 RCTS in 6,648 patients, subgroup analysis for Lansoprazole compared to Rabeprazole has examined 3 factors.

Data for healing of esophagitis at week 4 and week 8 according to different grades of severity of GERD at baseline (Savary-Miller classifications I, II, III-IV) was provided for 4 RCTs. Because Mulder 2002 (N=211) only provided this result in percentages, this trial was not pooled for this subgroup analysis as the denominator used to calculate the percentages were unclear. Based on the other 3 trials (not ITT analysis), no significant difference between treatments groups at all grades was observed at week 4. The only significant difference was at week 8 in which Omeprazole had a greater esophageal healing rate in Grade III-IV patients than Lansoprazole (RR 0.90 [0.82, 0.98]). This was mainly due to Castell 1996 which received about 78% of the weight. Of the 4 RCTs, this was the only study that included a lower dose group (Lansoprazole 15mg). This study has concluded that Lansoprazole 15mg was less effective in esophageal healing than Lansoprazole 30mg and Omeprazole 20mg.

Figure 0-53 Forest Plot: (GERD) L vs O -Healing of esophagitis at week 4 based on grade of GERD at baseline

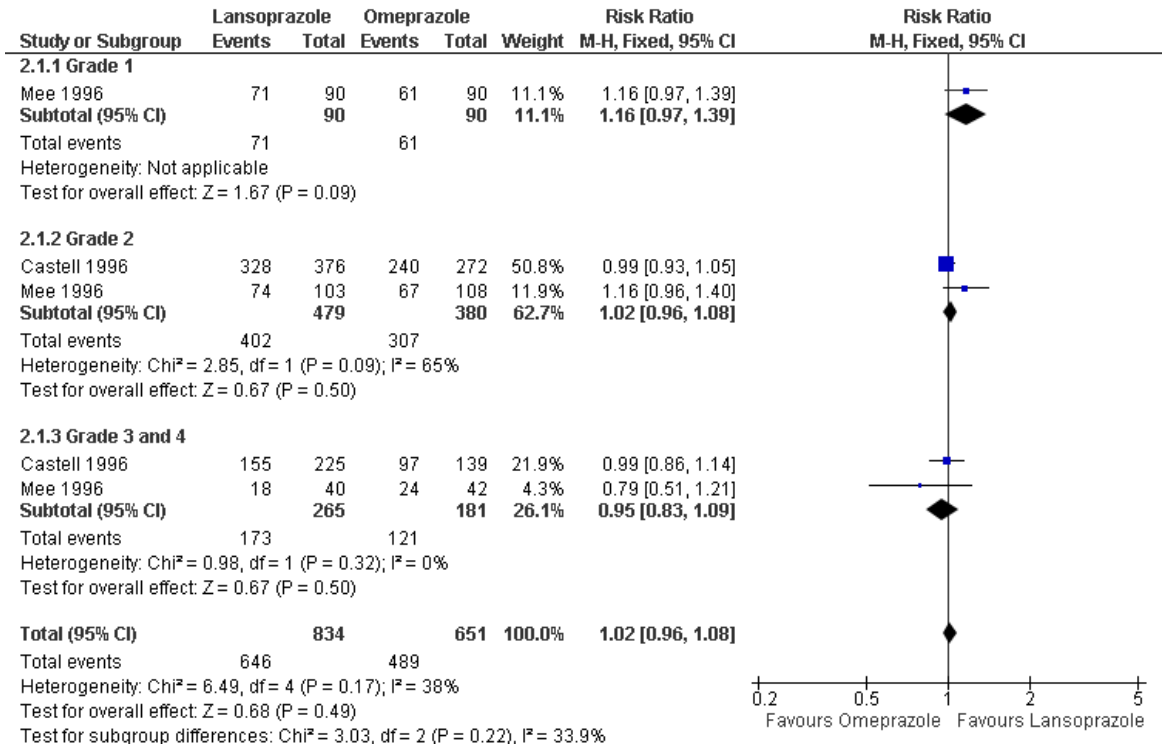
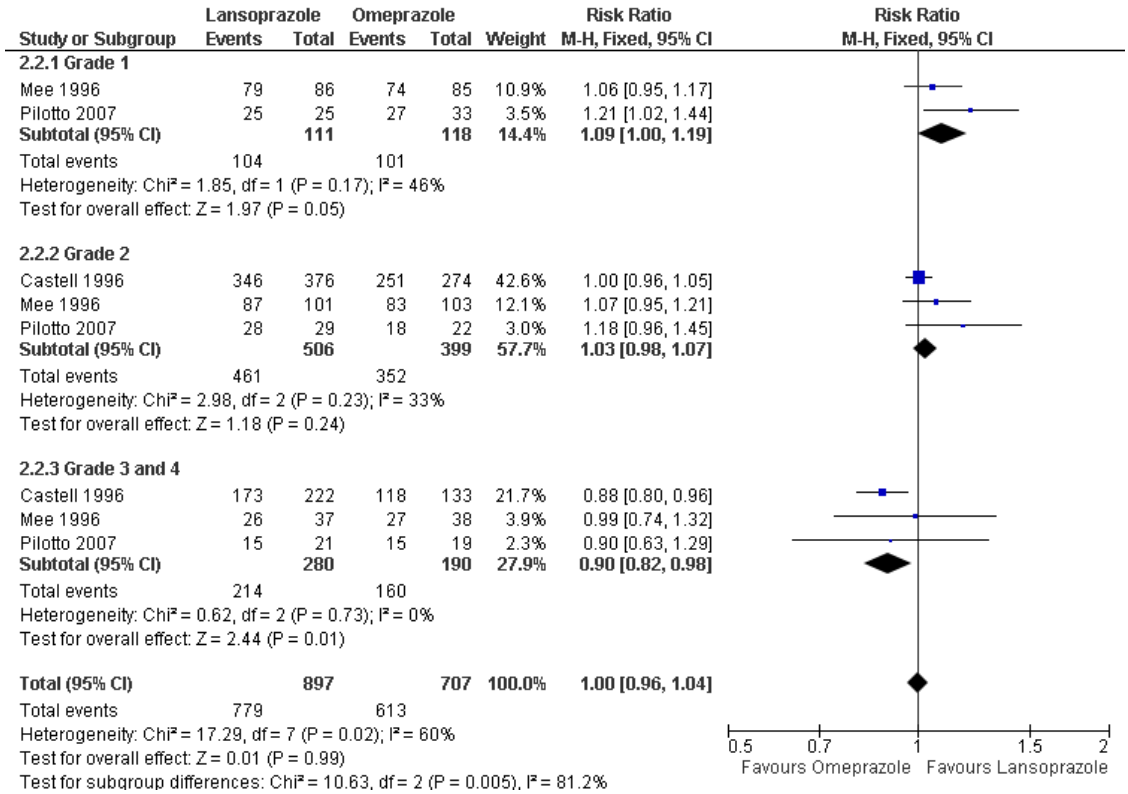
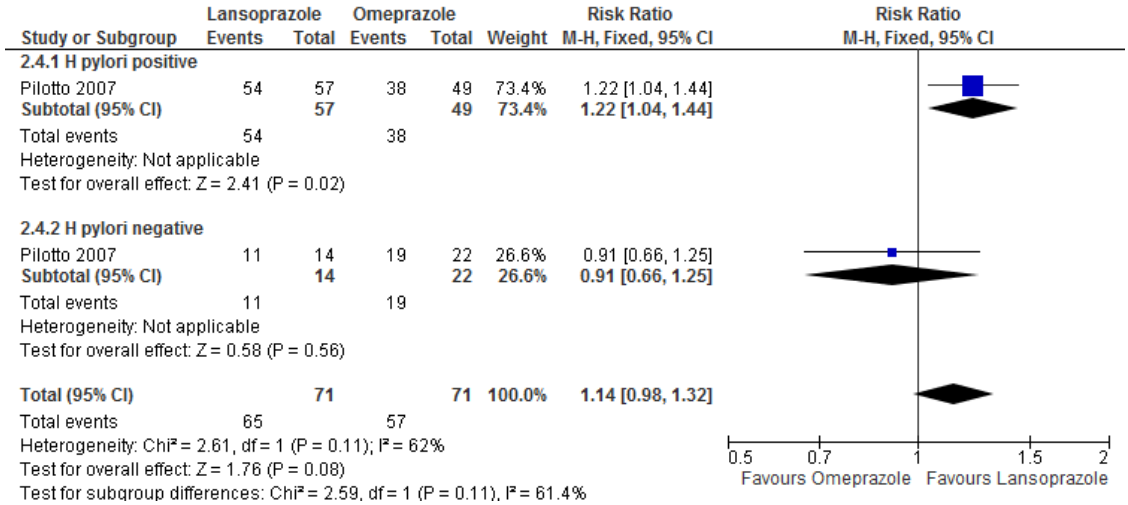


Figure 0-54 Forest Plot: (GERD) L vs O - healing of esophagitis at week 8 based on grade of GERD at baseline



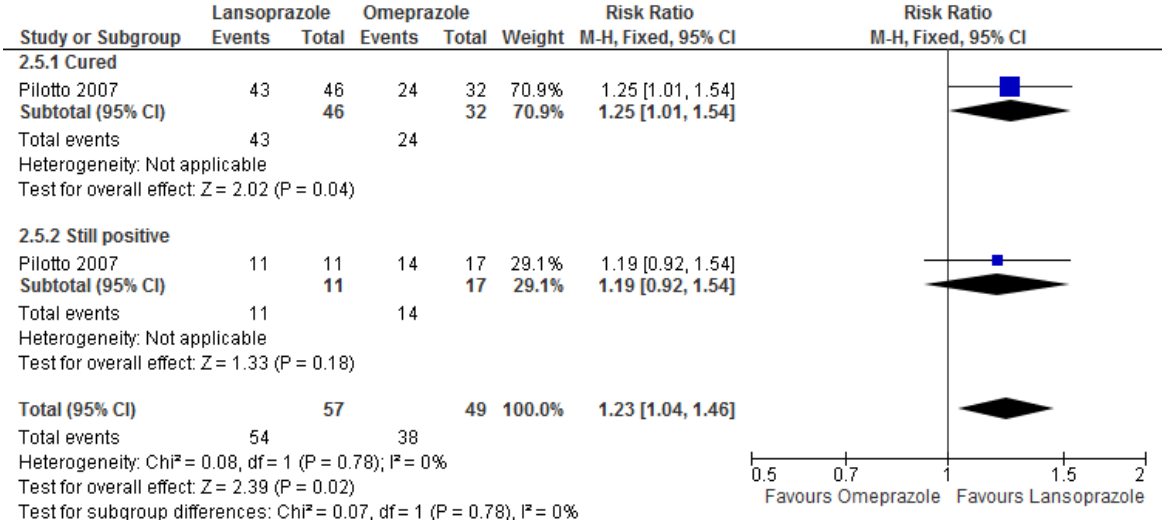
Healing of esophagitis at week 8 in a sub group of 142 patients in one RCT, based on the presence of *H. pylori* infection at baseline, was significantly greater in Lansoprazole group compared to Omeprazole group, but no significant difference was observed between treatment groups for patients who were *H. pylori* negative at baseline.

Figure 0-55 Forest Plot: (GERD) L vs O - Healing of esophagitis at week 8 based on *H. pylori* status at baseline



Healing of esophagitis at week 8 in a subgroup of 78 patients in one RCT, who were cured of *H. pylori* at end of treatment, was significantly greater healing rate with Lansoprazole compared to Omeprazole treatment group. No significant difference was observed in healing of esophagitis in a subgroup of 28 patients who were *H. pylori* positive at end of treatment.

Figure 0-56 Forest Plot: (GERD) L vs O - Healing of esophagitis at week 8 based on *H. pylori* status at end of treatment



3.8.2.1.5 GERD Comparison 5: Lansoprazole versus Pantoprazole

Of the 5 RCTS in 1,089 patients subgroup analysis for Lansoprazole compared to Pantoprazole has examined 3 factors.

Healing of esophagitis, based on a subgroup of 14% (n =152) of total randomized patients with different severity of GERD at baseline (Savary-Miller classification: Grade I to IV) in one RCT was not significantly different at each grade between Lansoprazole and Pantoprazole treatment groups.

Healing of esophagitis at week 8, based on a subgroup of 14% (n =155) of total randomized patients who were *H. pylori* positive or negative at baseline, was not significantly different between Lansoprazole and Pantoprazole treatment groups.

Healing of esophagitis at week 8, based on a subgroup of 10% (n=105) total randomized patients who were cured of *H. pylori* infection after treatment or were still positive, was not significantly different between Lansoprazole and Pantoprazole treatment groups.

Figure 0-57 Forest Plot: (GERD) L vs P - Healing of esophagitis at week 8 based on grade of GERD at baseline

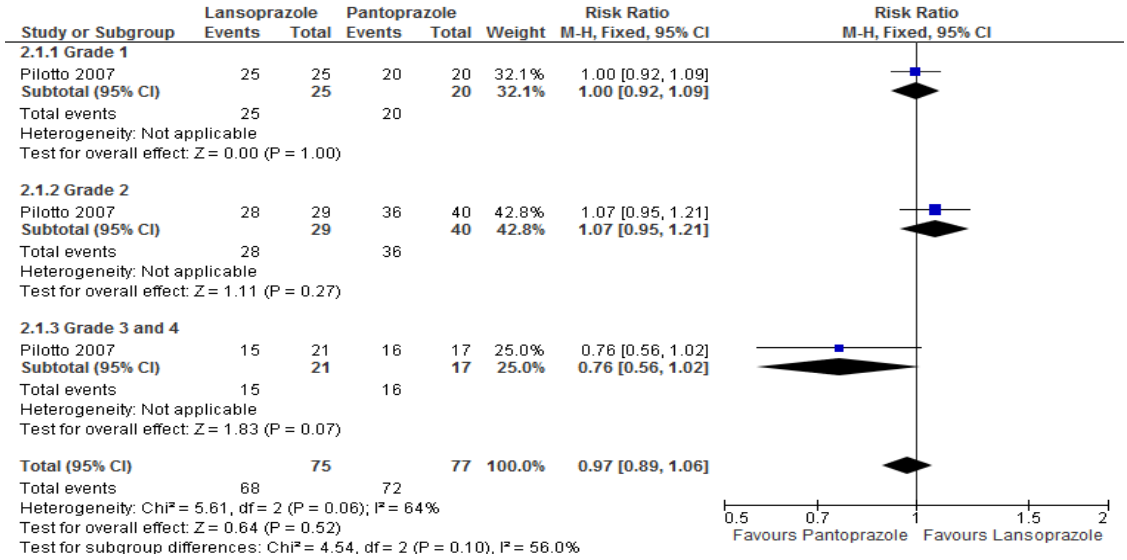


Figure 0-58 Forest Plot: (GERD) L vs P - Healing of esophagitis at week 8 based on *H. pylori* status at baseline

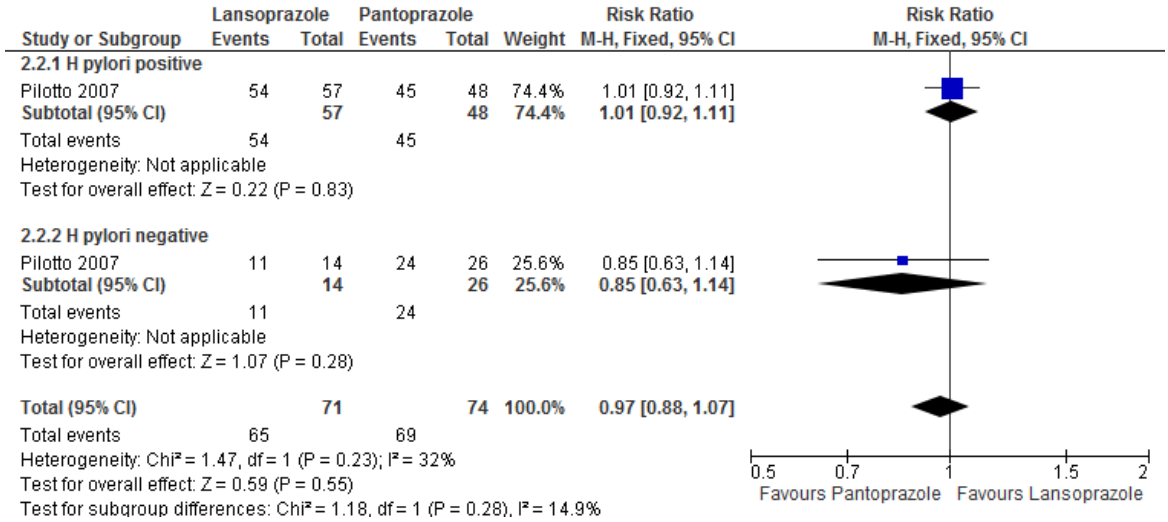
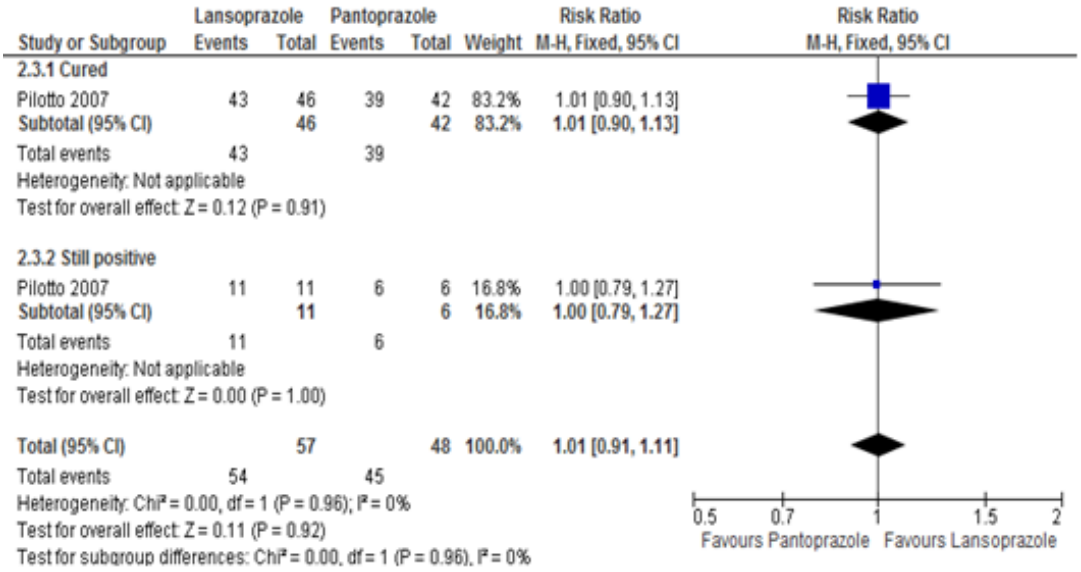


Figure 0-59 Forest Plot: (GERD) L vs P - Healing of esophagitis based on *H. pylori* status after treatment

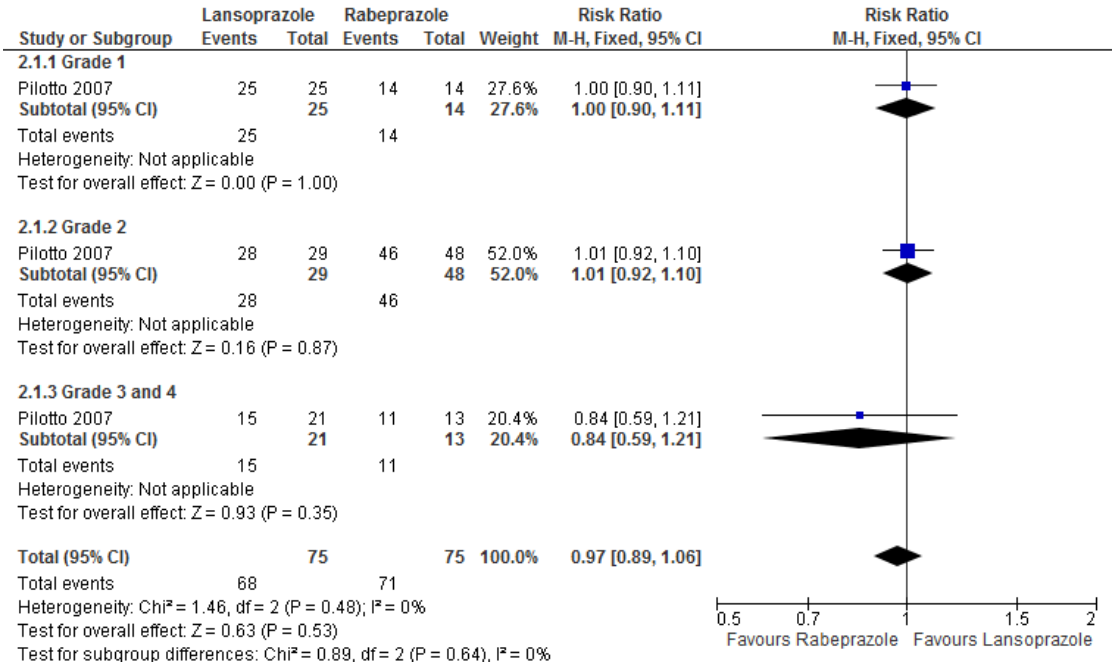


3.8.2.1.6 GERD Comparison 6: Lansoprazole versus Rabeprazole

Of the 2 RCTs in 215 patients, subgroup analysis for Lansoprazole compared to Rabeprazole has examined 3 factors.

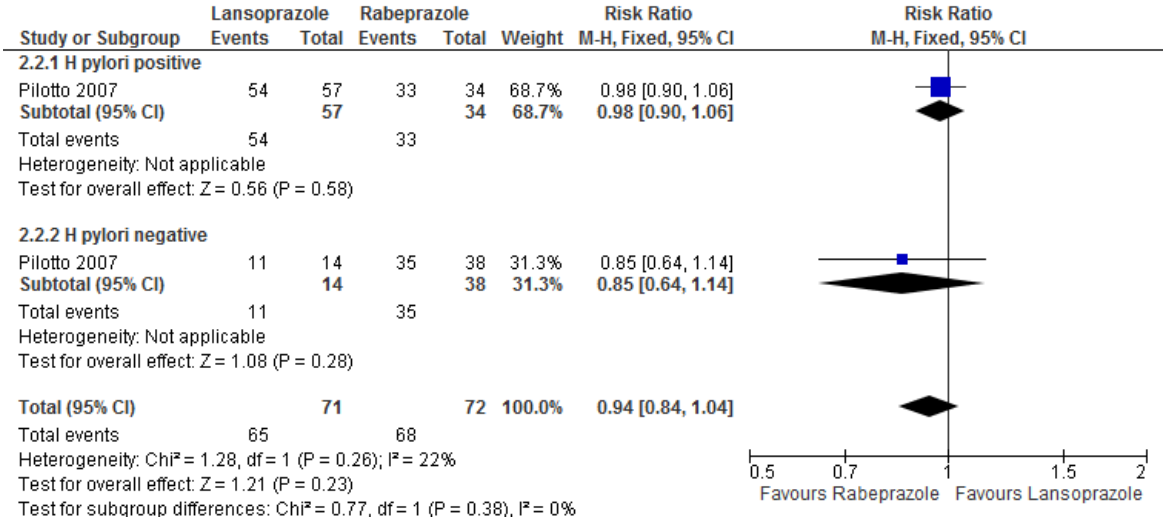
Healing of esophagitis at week 8, based on a subgroup of 70% (n =150) of total randomized patients with different severity of GERD at baseline (Savary-Miller Grade 1, 2,3 and 4) showed no significant difference between Lansoprazole and Rabeprazole treatment groups.

Figure 0-60 Forest Plot: (GERD) L vs R - Healing of esophagitis based on Savary-Miller severity grade of ulcer at baseline



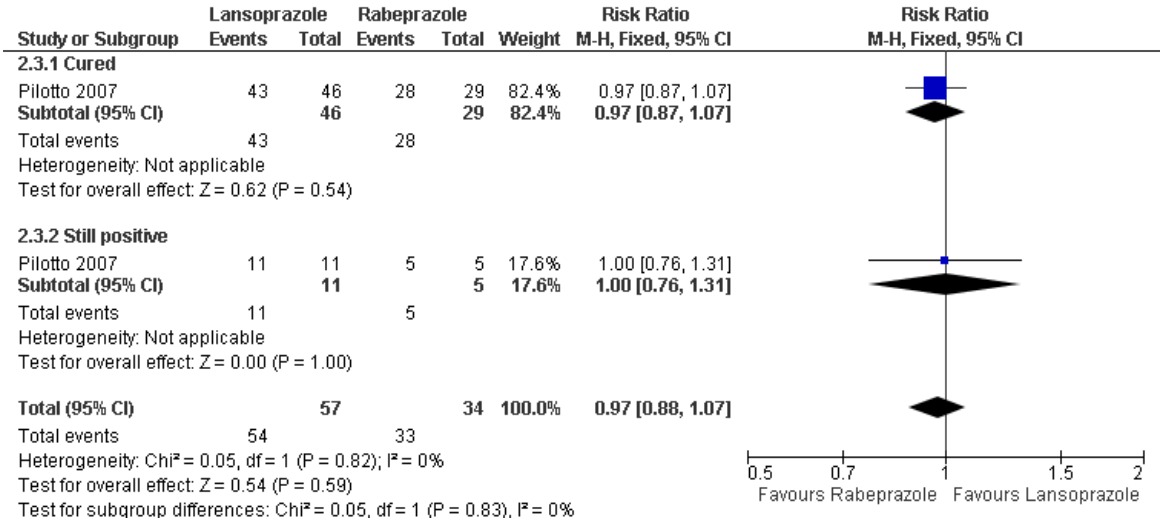
Healing of esophagitis at week 8, based on a subgroup of 67% (n = 143) of total randomized patients who were *H. pylori* positive or negative at baseline, no significant difference was observed between Lansoprazole and Rabeprazole treatment groups.

Figure 0-61 Forest Plot: (GERD) L vs R- Healing of esophagitis based on *H. pylori* status at week 8



Healing of esophagitis at week 8, based on a subgroup of 42% (n=91) of total randomized patients who were cured of *H. pylori* infection after treatment or were still positive, no significant difference was observed between Lansoprazole and Rabeprazole treatment groups.

Figure 0-62 Forest Plot: (GERD) L vs R- Healing of esophagitis at week 8 based on *H. pylori* status after treatment



3.8.2.1.7 PUD Comparison 7: Esomeprazole versus Omeprazole

No analysis of subgroups was provided in the RCTs meeting inclusion criteria.

3.8.2.1.8 PUD Comparison 8: Esomeprazole versus Pantoprazole

No analysis of subgroups was provided in the RCTs meeting inclusion criteria.

3.8.2.1.9 PUD Comparison 9: Esomeprazole versus Rabeprazole

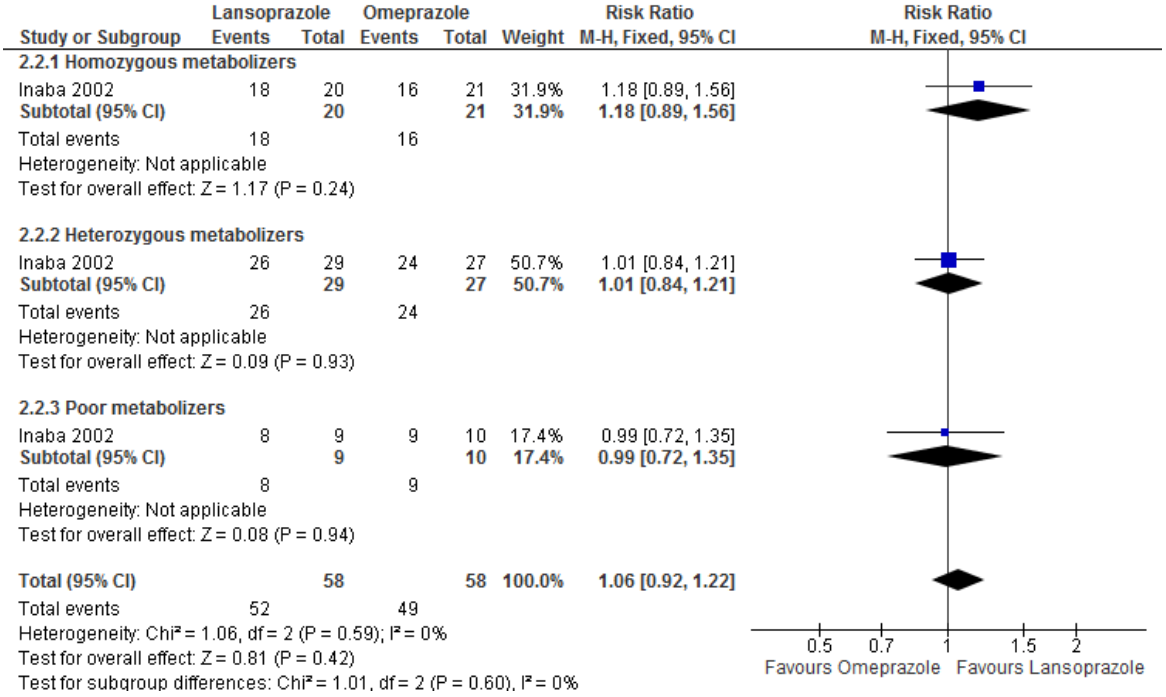
No RCT met the inclusion criteria.

3.8.2.1.10 PUD Comparison 10: Lansoprazole versus Omeprazole

Of the 15 RCTs in 2,265 patients, subgroup analysis for Lansoprazole compared to Omeprazole has examined 2 factors.

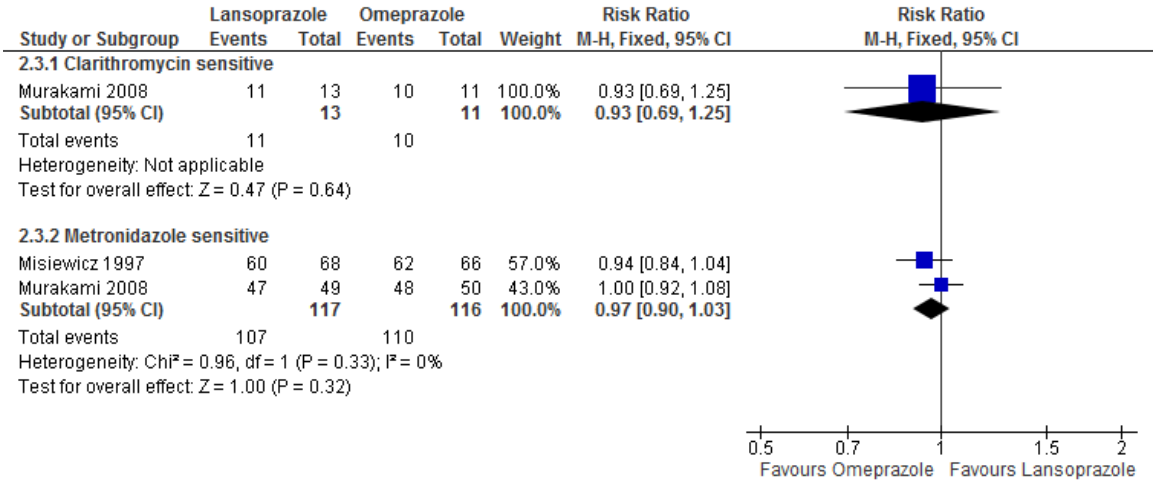
H. pylori eradication rates at week 1, based on a subgroup of 5% (n = 116) of total randomized patients who were homozygous, heterozygous or poor metabolizers of CYP2C19 enzyme , no significant difference was observed between Lansoprazole and Omeprazole treatment groups.

Figure 0-63 Forest Plot: (PUD) L vs O- *H. pylori* eradication at week 1 in different metabolizers



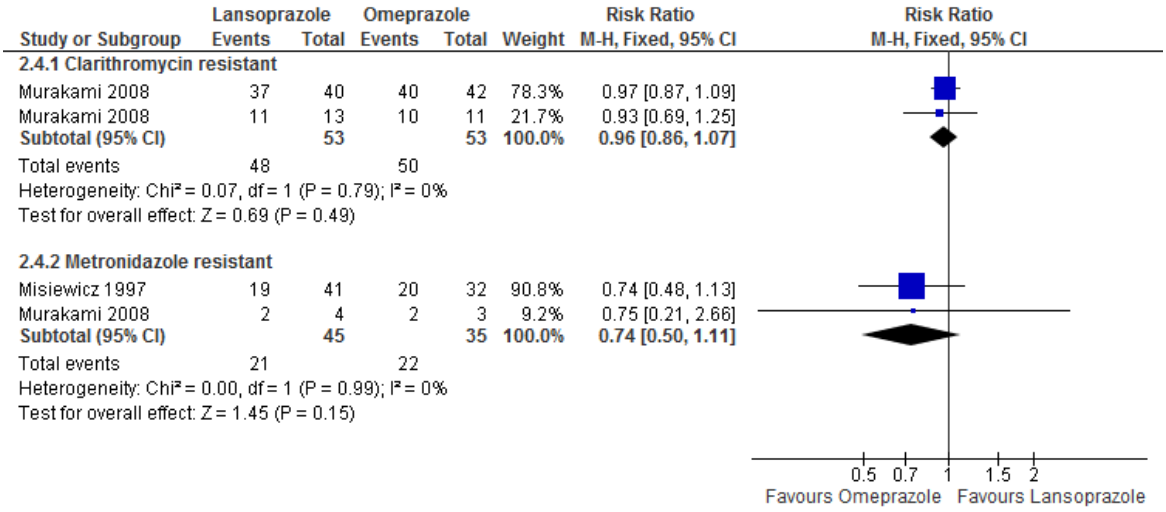
H. pylori eradication rates at week 4, based on a subgroup of patients sensitive to antibiotics, (24 who were Clarithromycin sensitive and 233 who were Metronidazole sensitive) no significant difference was observed between Lansoprazole and Omeprazole treatment groups.

Figure 0-64 Forest Plot: (PUD) L vs O- *H. pylori* eradication at week 4 in antibiotic sensitive patients



H. pylori eradication rates at week 4 based on a subgroup of patients resistant to antibiotics, (106 who were Clarithromycin resistant and 80 patients who were metronidazole resistant) no significant difference was observed in between Lansoprazole and Omeprazole treatment groups.

Figure 0-65 Forest Plot: (PUD) L vs O- *H. pylori* eradication at week 4 in antibiotic resistant patients



3.8.2.1.11 PUD Comparison 11: Lansoprazole versus Pantoprazole

No RCT met the inclusion criteria.

3.8.2.1.12 PUD Comparison 12: Lansoprazole versus Rabeprazole

Of the 7 RCTs in 1574 patients, subgroup analysis for Lansoprazole compared to Rabeprazole has examined 2 factors.

H. pylori eradication rates at week 1, based on a subgroup of 8% (n = 121) of total randomized patients who were homozygous, heterozygous or poor metabolizers of CYP2C19 enzyme, no significant difference was observed between Lansoprazole and Omeprazole treatment groups. Similarly, no

differences between treatment groups were found at week 6 based on a subgroup of 11% (n = 173) of total randomized patients.

Figure 0-66 Forest Plot: (PUD) L vs R - *H. pylori* eradication at week 1 in different metabolizers

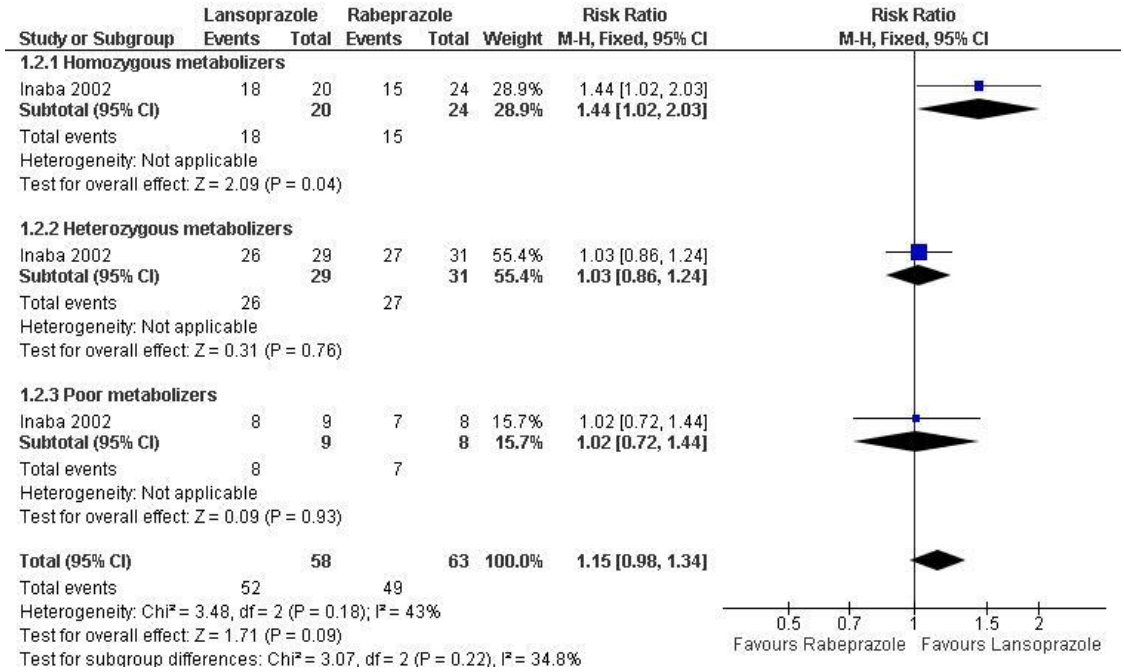
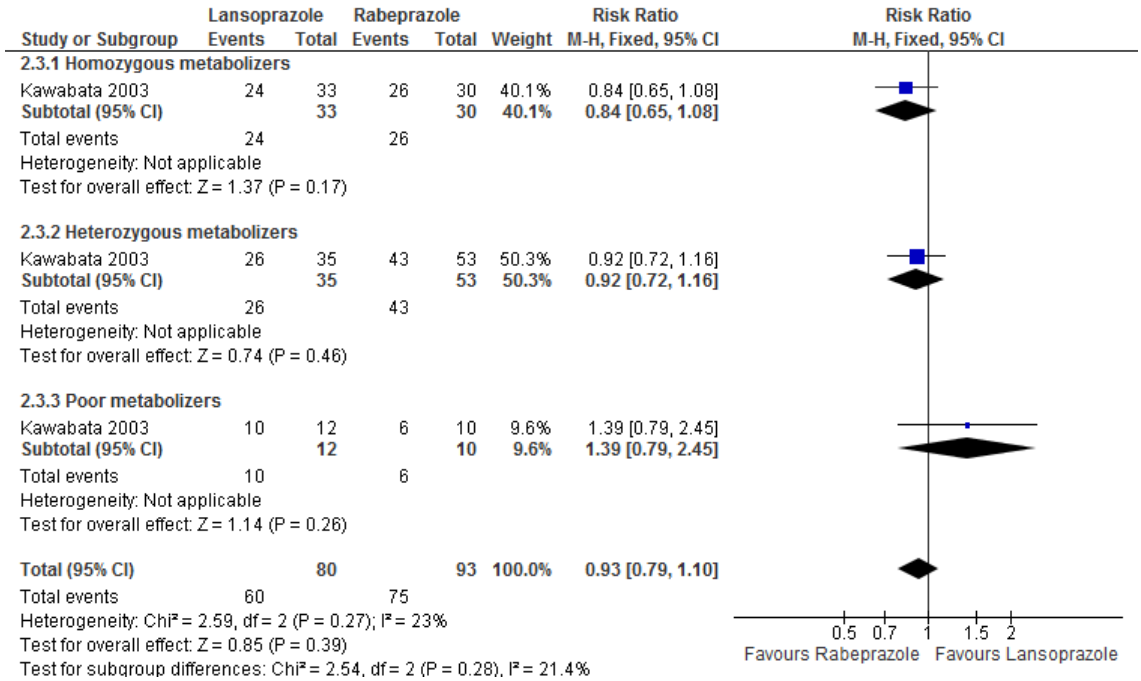


Figure 0-67 Forest Plot: (PUD) L vs R - *H. pylori* eradication at week 6 in different metabolizers



H. pylori cure rates at week 4, based on subgroup of 25% (n =393) of total randomized patients who were antibiotic sensitive from 3 RCTS, no significant difference was observed between Lansoprazole and Rabeprazole treatment groups. Similarly, no differences in *H. pylori* cure rates at week 4 was found between treatment groups based on subgroup of 8% (n =124) of total randomized patients who were antibiotic resistant.

Figure 0-68 Forest Plot: (PUD) L vs R - *H. pylori* eradication at week 4 in antibiotic sensitive patients

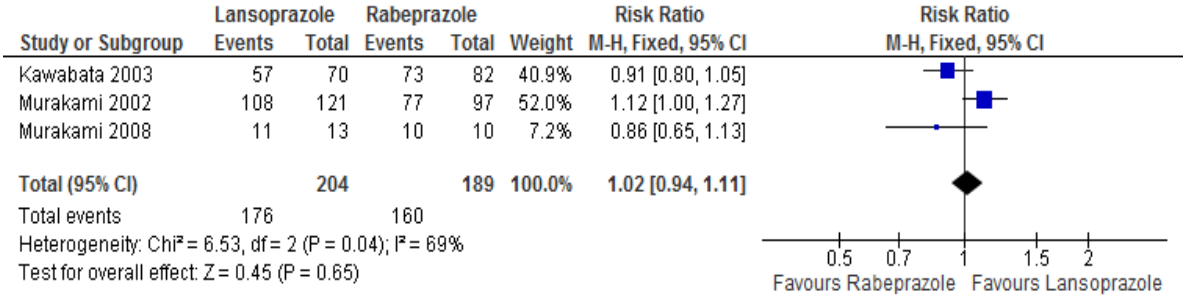
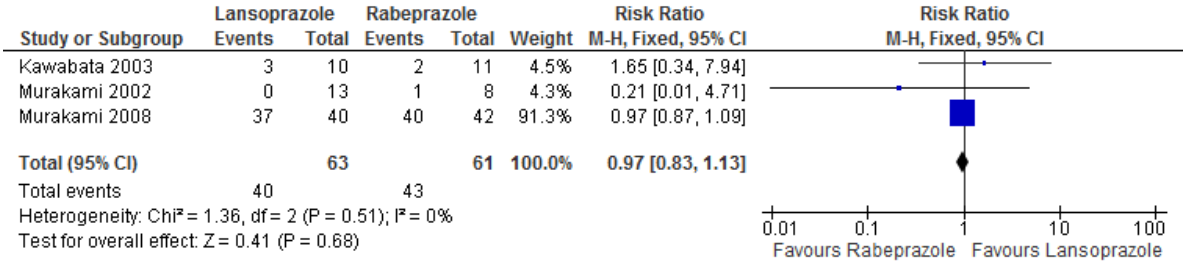


Figure 0-69 Forest Plot: (PUD) L vs R - *H. pylori* eradication at week 4 in antibiotic resistant patients



3.8.3 Harms from RCTs

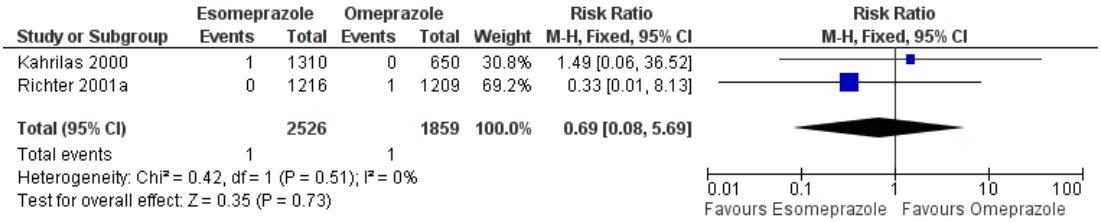
Tables I[F] to VI[F] in Appendix 6 describe harm outcomes of included GERD studies.

3.8.3.1 GERD Comparison 1: Esomeprazole vs. Omeprazole

3.8.3.1.1 Key harm outcome 1: Mortality

Two RCTs (n=4385) reported data on all-cause mortality. Esomeprazole was not significantly different compared to Omeprazole group in terms of all-cause mortality (RR 0.69 [0.08, 5.69]).

Figure 0-70 Forest Plot: (GERD) E vs O - Mortality



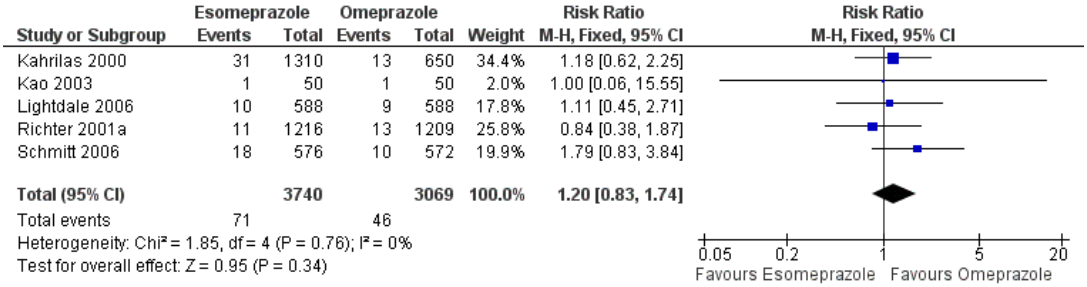
3.8.3.1.2 Key harm outcome 2: Serious adverse events

No RCT reported data on serious adverse events in this comparison.

3.8.3.1.3 Key harm outcome 3: Withdrawal due to adverse events

Five RCTs (n= 6809) reported data on withdrawal due to adverse effects. There was no significant difference between Esomeprazole and Omeprazole group in terms of withdrawal due to adverse effects (RR 1.20 [0.83, 1.74])

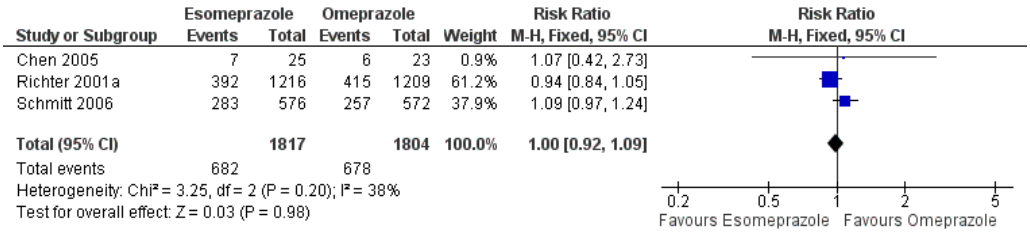
Figure 0-71 Forest Plot: (GERD) E vs O - Withdrawal due to adverse events



3.8.3.1.4 Key harm outcome 4: Patients with at least one adverse event

Three RCTs (n=3621) reported data on number of patients who report at least one adverse effect. There was no significant different between Esomeprazole and Omeprazole in terms of number of patients with at least one adverse effect (RR 1.00 [0.92, 1.09]).

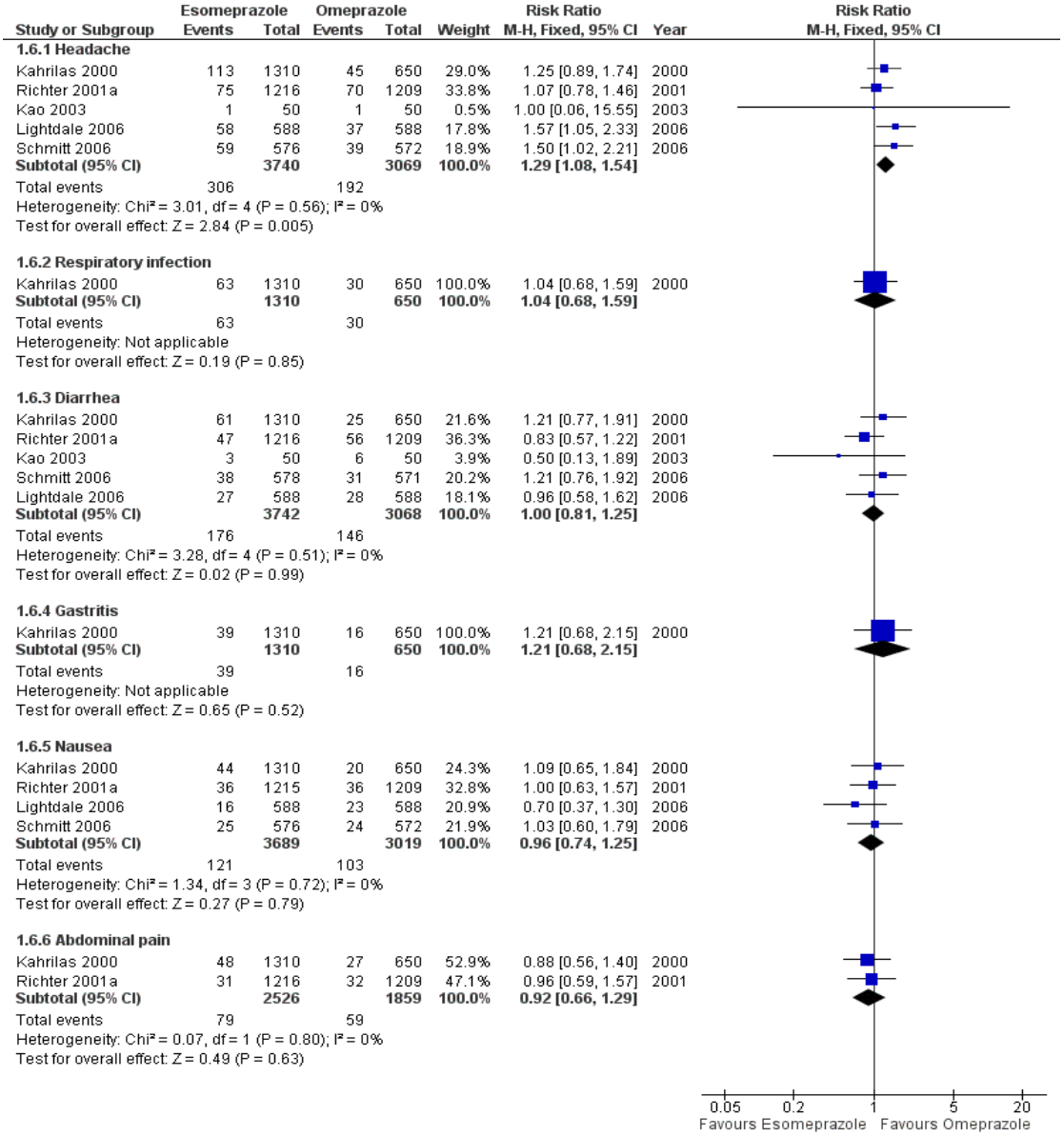
Figure 0-72 Forest Plot: (GERD) E vs O - Patients with at least one adverse event



3.8.3.1.5 Key harm outcome 5: Specific adverse events

Five RCTs (n=6809) reported data on number of patients who have headache. Patients in Esomeprazole group were more likely to have headache compared to patients in Omeprazole group (RR 1.29 [1.08, 1.54]). There was no significant different between Esomeprazole and Omeprazole group in terms of other common adverse effects.

Figure 0-73 Forest Plot: (GERD) E vs O - Specific adverse events

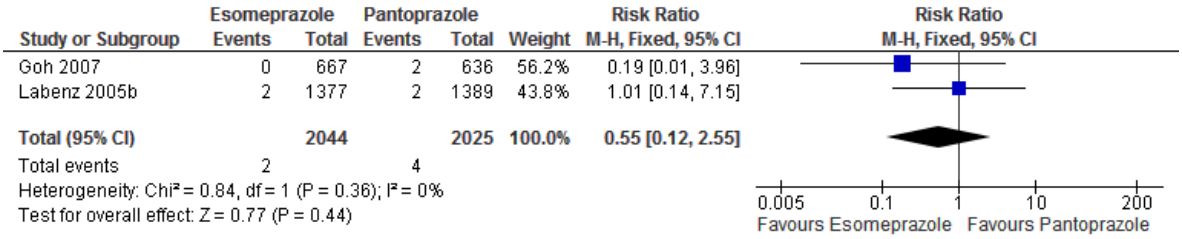


3.8.3.2 GERD Comparison 2: Esomeprazole vs. Pantoprazole

3.8.3.2.1 Key harm outcome 1: Mortality

Based on 2 RCTs in 4069 patients, no significant difference in mortality was observed between Esomeprazole and Pantoprazole treatment groups.

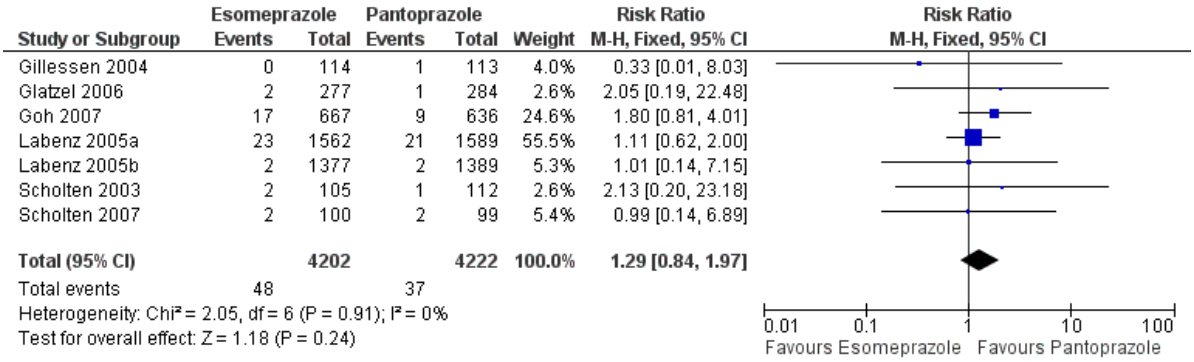
Figure 0-74 Forest Plot: (GERD) E vs P - Mortality



3.8.3.2.2 Key harm outcome 2: Serious adverse events

Based on 8 RCTs in 8424 patients, no significant difference serious adverse events was observed between Esomeprazole and Pantoprazole treatment groups.

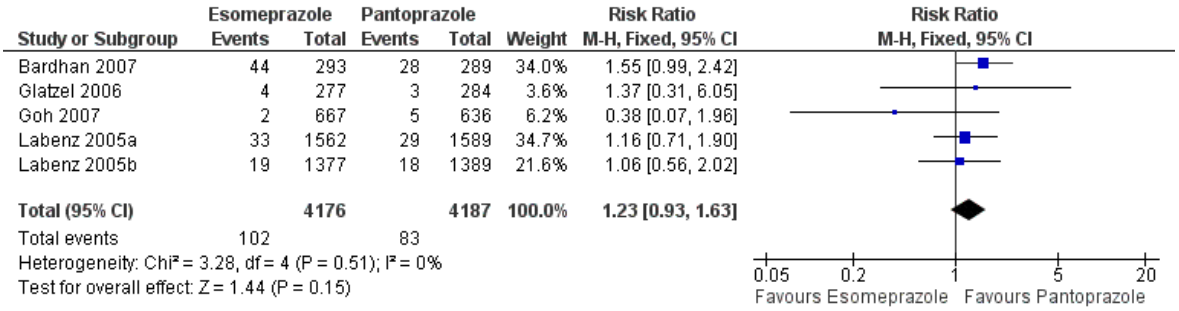
Figure 0-75 Forest Plot: (GERD) E vs P - Serious adverse events



3.8.3.2.3 Key harm outcome 3: Withdrawal due to adverse events

Based on 5 RCTs in 8363 patients, no significant difference in withdrawal due to adverse events was observed between Esomeprazole and Pantoprazole treatment groups.

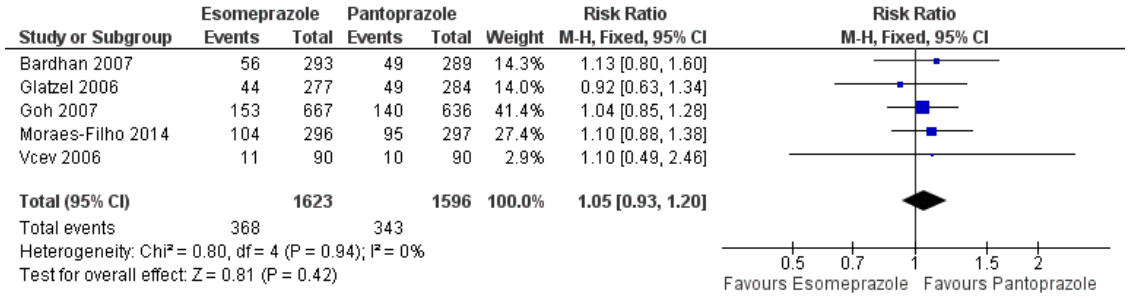
Figure 0-76 Forest Plot: (GERD) E vs P - Withdrawal due to adverse events



3.8.3.2.4 Key harm outcome 4: Total adverse events

Based on 5 RCTs in 3219 patients, no significant difference in total adverse events was observed between Esomeprazole and Pantoprazole treatment groups.

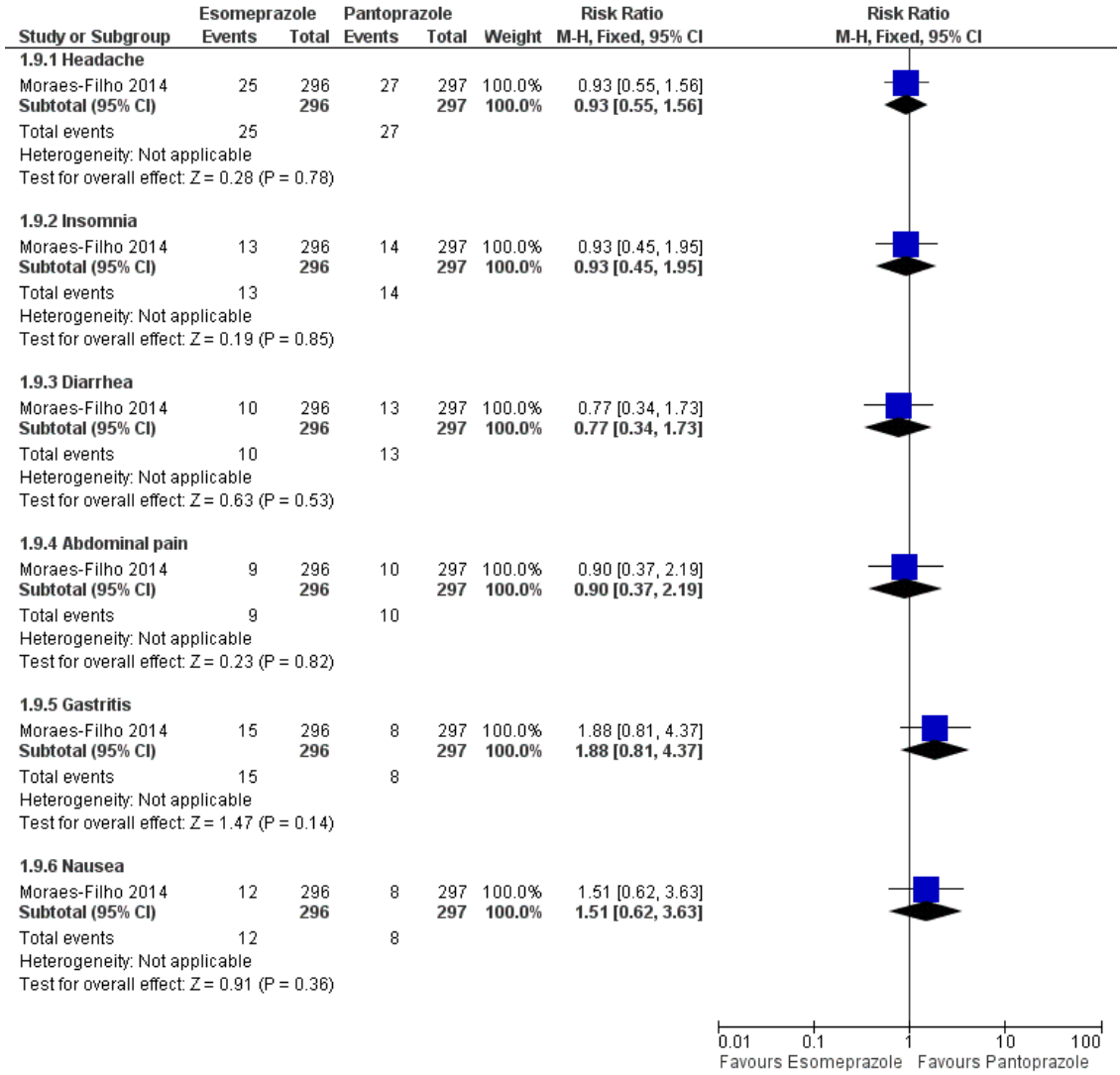
Figure 0-77 Forest Plot: (GERD) E vs P - Total adverse events



3.8.3.2.5 Key harm outcome 5: Specific adverse events

Based on 1 RCT in 593 patients, no significant difference in any specific adverse event was observed between Esomeprazole and Pantoprazole treatment groups.

Figure 0-78 Forest Plot: (GERD) E vs P - Specific adverse events



3.8.3.3 GERD Comparison 3: Esomeprazole vs. Rabeprazole

3.8.3.3.1 Key harm outcome 1: Mortality

No mortality was observed in Laine Study 1 and Study 2. Total Mortality was not reported in the other 3 RCTs

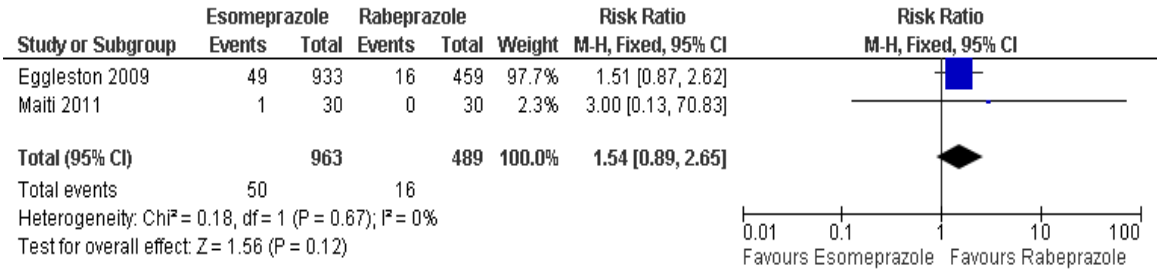
3.8.3.3.2 Key harm outcome 2: Serious adverse events

Of the 5RCTs, Maiti 2011 reported no serious adverse events in the study in both treatment groups. Laine 2011provided combined data for study 1 and 2 with 7 patients in Esomeprazole group and 7 in Pantoprazole group reporting serious adverse events. The remaining 2 trials did not report data.

3.8.3.3.3 Key harm outcome 3: Withdrawal due to adverse events

Based on 2 RCTs in 1452 patients, no significant difference in withdrawal due to adverse events was observed between Esomeprazole and Rabeprazole treatment groups.

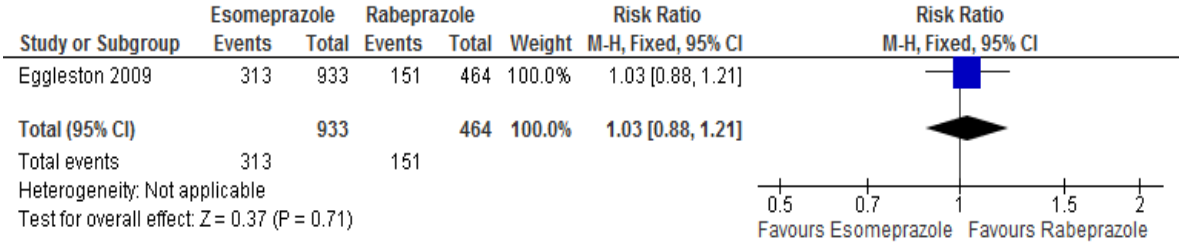
Figure 0-79 Forest Plot: (GERD) E vs R - Withdrawal due to adverse events



3.8.3.3.4 Key harm outcome 4: Total adverse events

Based on 1 RCT in 1397 patients, no significant difference in total adverse events was observed between Esomeprazole and Rabeprazole treatment groups.

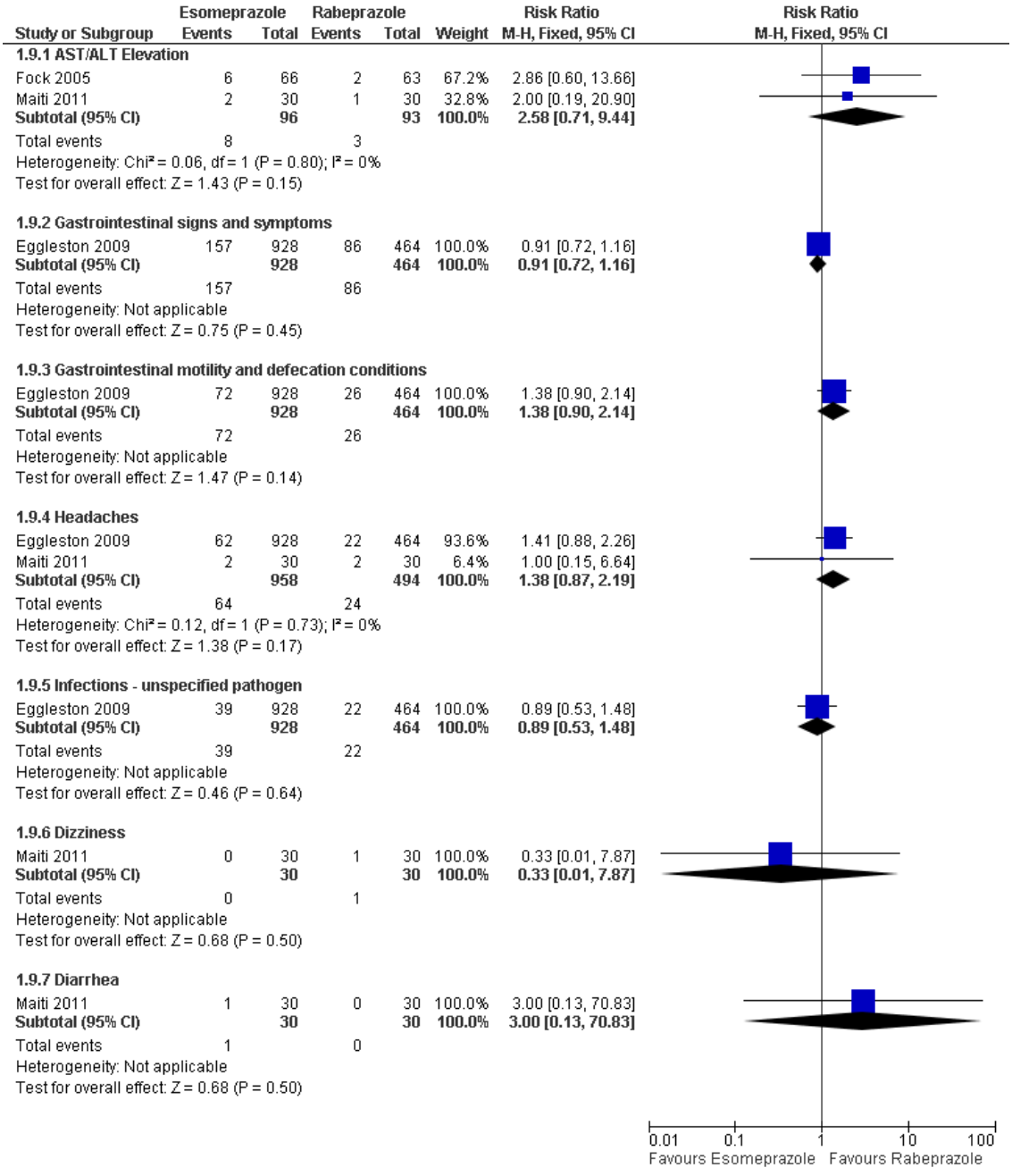
Figure 0-80 Forest Plot: (GERD) E vs R – Total adverse events



3.8.3.3.5 Key harm outcome 5: Specific adverse events

Based on 3 RCTs, no significant difference in any specific adverse events was observed between Esomeprazole and Rabeprazole treatment groups.

Figure 0-81 Forest Plot: (GERD) E vs R - Specific adverse events



3.8.3.4 GERD Comparison 4: Lansoprazole vs. Omeprazole

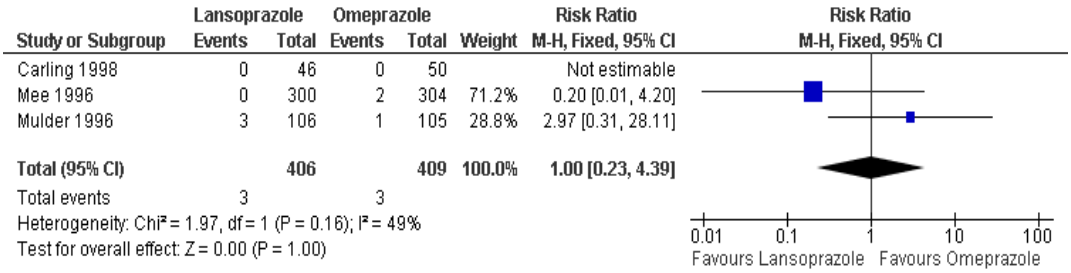
3.8.3.4.1 Key harm outcome 1: Mortality

Mortality data was not reported in 9 studies. No mortality in 3 RCTS (Mee 1996, Zheng 2009 and Jaspersen 1998).

3.8.3.4.2 Key harm outcome 2: Serious adverse events

Based on 3 RCTs in 815 patients, no significant difference in serious adverse events was observed between Lansoprazole and Omeprazole treatment groups.

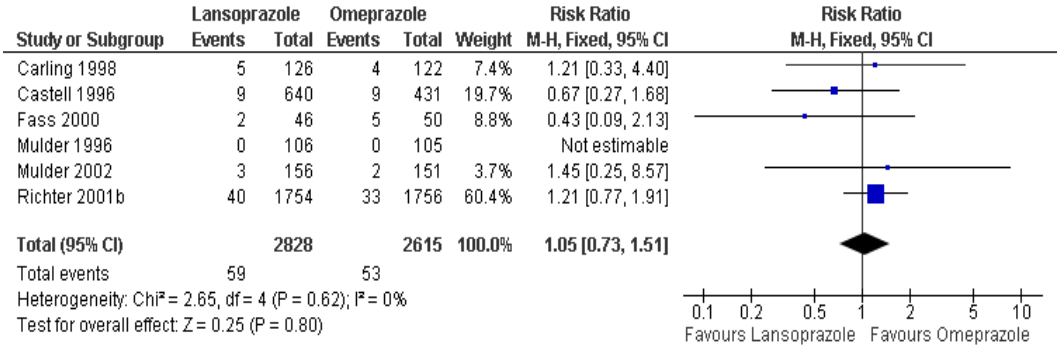
Figure 0-82 Forest Plot: (GERD) L vs O - Serious adverse events



3.8.3.4.3 Key harm outcome 3: Withdrawal due to adverse events

Based on 6 RCTs in 5443 patients, no significant difference in withdrawal due to adverse events was observed between Lansoprazole and Omeprazole treatment groups.

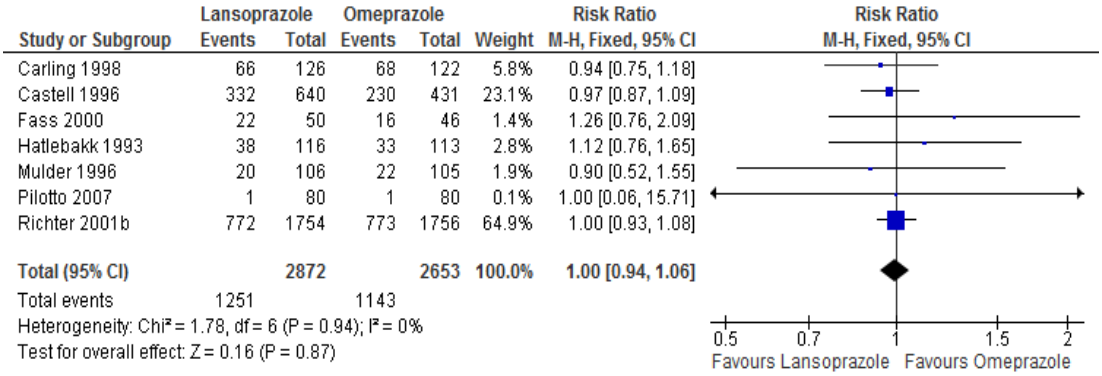
Figure 0-83 Forest Plot: (GERD) L vs O - Withdrawal due to adverse events



3.8.3.4.4 Key harm outcome 4: Total adverse events

Based on 7 RCTs in 5525 patients, no significant difference in total adverse events was observed between Lansoprazole and Omeprazole treatment groups.

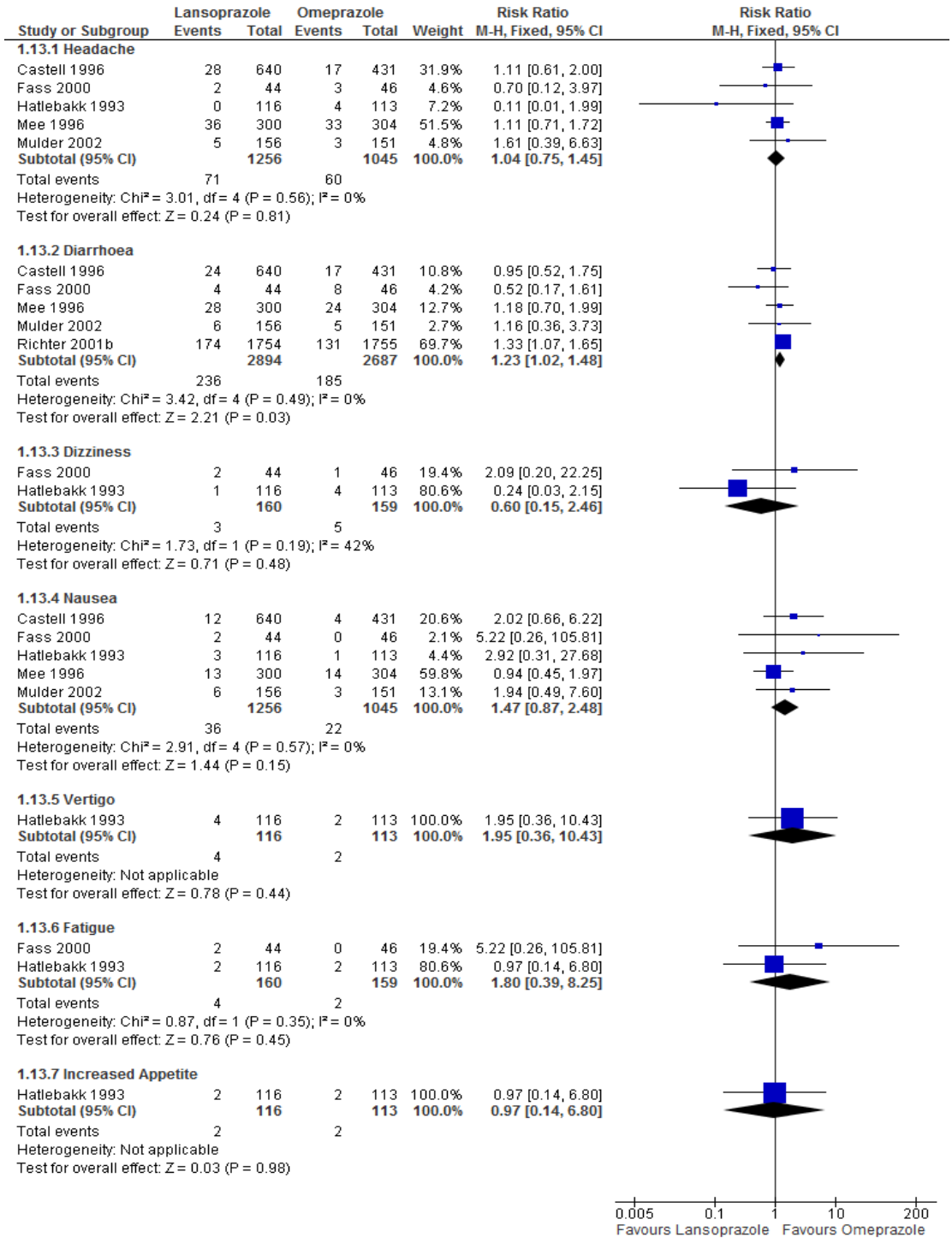
Figure 0-84 Forest Plot: (GERD) L vs O - Total adverse events



3.8.3.4.5 Key harm outcome 5: Specific adverse events

Based on 5 RCTs, no significant difference in specific adverse events was observed between Lansoprazole and Omeprazole treatment groups except for diarrhea (RR: 1.23[1.02, 1.48]) which was significantly greater in Lansoprazole group compared to Omeprazole group.

Figure 0-85 Forest Plot: (GERD) L vs O - Specific adverse events



3.8.3.5 GERD Comparison 5: Lansoprazole vs. Pantoprazole

3.8.3.5.1 Key harm outcome 1: Mortality

2 RCTs Jaspersen 1998 and Zheng 2009 reported no mortality in both treatment groups. No data was reported in 2 RCTs Pilotto 2007 and Mulder 2002.

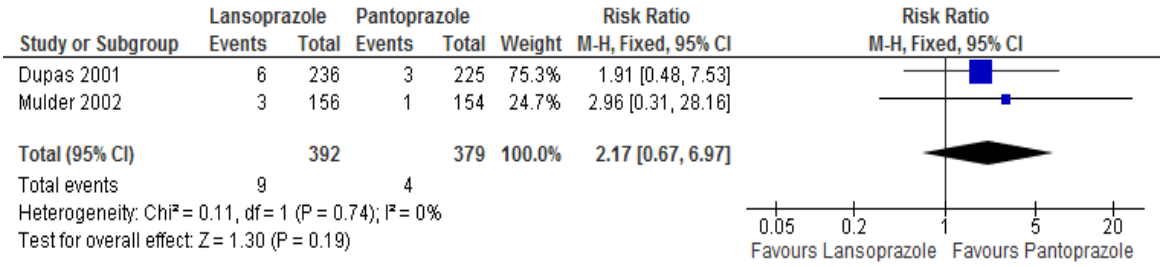
3.8.3.5.2 Key harm outcome 2: Serious adverse events

One trial Dupas 2001 reported serious adverse events (L = 6/236 vs P = 5.225 RR with 95% CI 1.14(0.35, 3.70) P = 0.82. Two RCTs Jaspersen 1998 and Pilotto 2007 did not report data on serious adverse events. Mulder 2002 reported 4 patients with serious adverse events but did not report data separately in each treatment group.

3.8.3.5.3 Key harm outcome 3: Withdrawal due to adverse events

Based on 2 RCTs in 7895 patients, no significant difference in withdrawal due to adverse events was observed between Lansoprazole and Pantoprazole treatment groups.

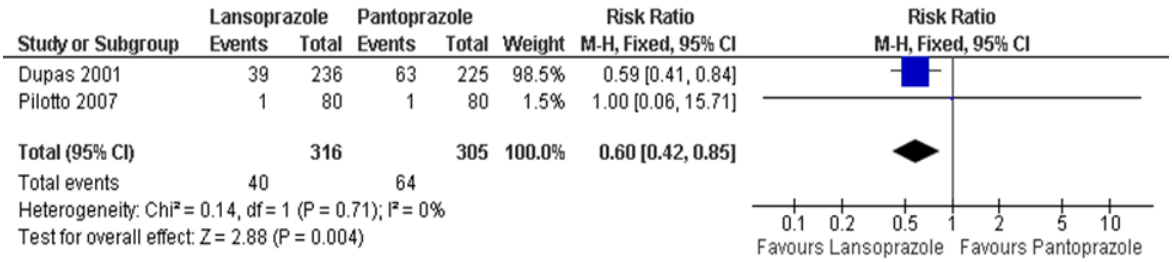
Figure 0-86 Forest Plot: (GERD) L vs P- Withdrawal due to adverse events



3.8.3.5.4 Key harm outcome 4: Total adverse events

Based on 2 RCTs in 621 patients, total adverse events were significantly lower in Lansoprazole group as compared to Pantoprazole group.

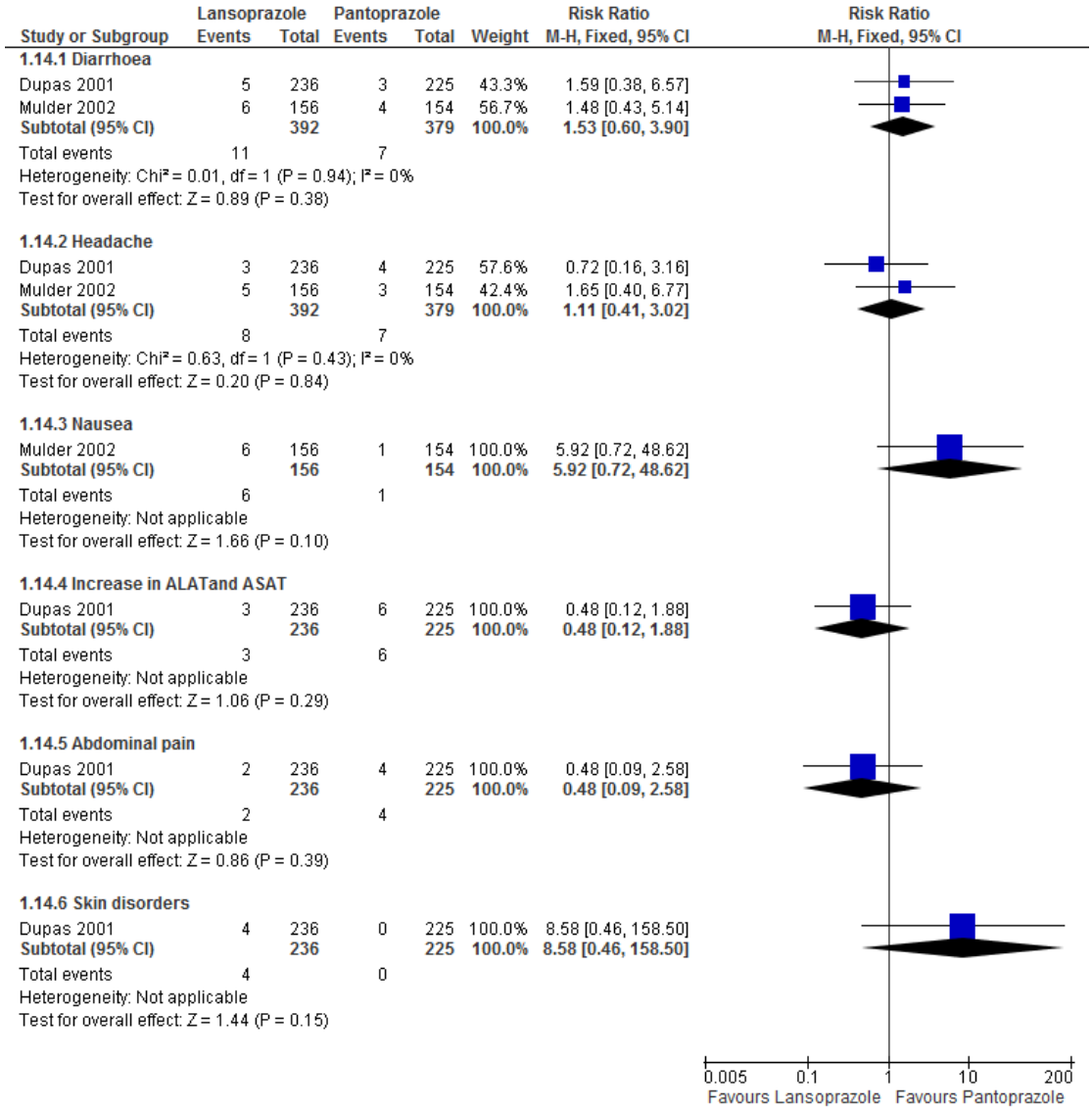
Figure 0-87 Forest Plot: (GERD) L vs P - Total adverse events



3.8.3.5.5 Key harm outcome 5: Specific adverse events

Based on 2 RCTs, no significant difference in specific adverse events was observed between Lansoprazole and Pantoprazole treatment groups.

Figure 0-88 Forest Plot: (GERD) L vs P - Specific adverse events



3.8.3.6 GERD Comparison 6: Lansoprazole vs. Rabeprazole

3.8.3.6.1 Key harm outcome 1: Mortality

Mortality was not reported in both trials meeting the inclusion criteria.

3.8.3.6.2 Key harm outcome 2: Serious adverse events

Serious adverse event was not reported in both trials meeting the inclusion criteria.

3.8.3.6.3 Key harm outcome 3: Withdrawal due to adverse events

Withdrawal due to adverse events was not reported in Pilotto 2007 study. Adachi 2003 reported 2 events in 4 treatment groups and did not report data separately for Lansoprazole and Pantoprazole groups.

3.8.3.6.4 Key harm outcome 4: Total adverse events

Total adverse events were reported in 1 RCT Pilotto 2007 and 1 patient in each treatment group had adverse events. L = 1/80 vs. P = 1/80 RR with 95% Ci 1.00(0.06, 15.71)

3.8.3.6.5 Key harm outcome 5: Specific adverse events

Specific adverse events were not reported in Adachi 2003 study and in Pilotto 2007 study data was not reported separately in Lansoprazole and Pantoprazole treatment groups.

Peptic Ulcer disease

Tables VII[D], VIII[D], X[D], and XII[D] in Appendix 6 describe harm outcomes of included PUD studies.

3.8.3.7 PUD Comparison 7: Esomeprazole vs. Omeprazole

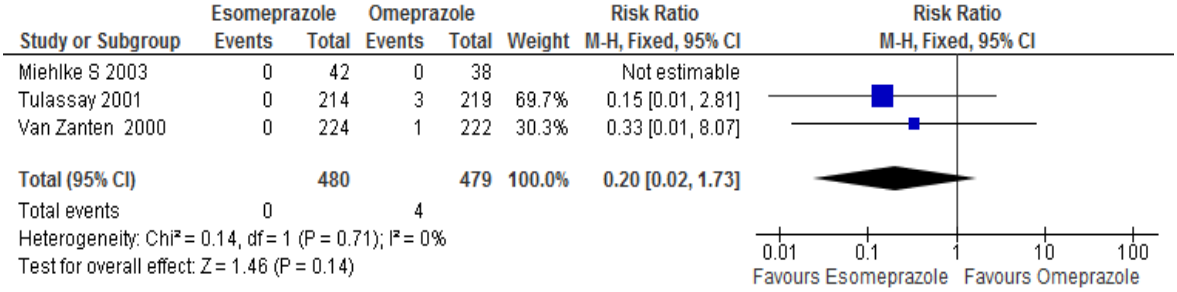
3.8.3.7.1 Key harm outcome 1: Mortality (No forest plot)

Mortality was not reported in four out of five trials. One trial Mielhkle S 2003 reported no deaths in both treatment groups.

3.8.3.7.2 Key harm outcome 2: Serious adverse events

Total serious adverse events were reported in 3 out of 5 RCTs. No SAE was reported in Esomeprazole arm and 4 in Omeprazole group. Based on 3 RCTs in 959 patients, no significant difference in serious adverse events was observed between Esomeprazole and Omeprazole treatment groups.

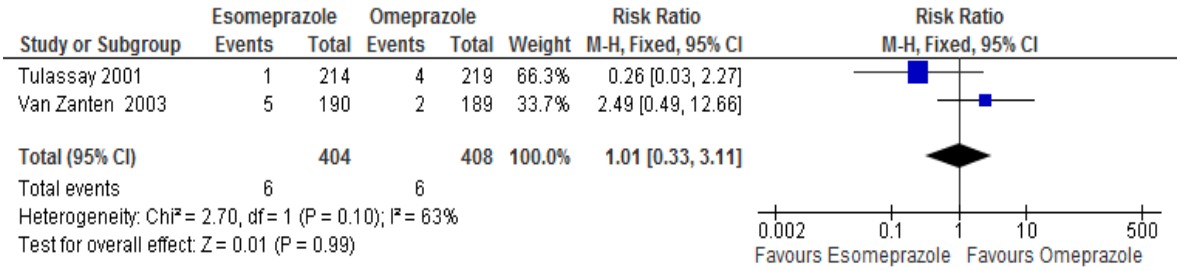
Figure 0-89 Forest Plot: (PUD) E vs O - Serious adverse events



3.8.3.7.3 Key harm outcome 3: Withdrawal due to adverse events

Based on 2 RCTs in 812 patients, no significant difference in withdrawal due to adverse events was observed between Esomeprazole and Omeprazole treatment groups.

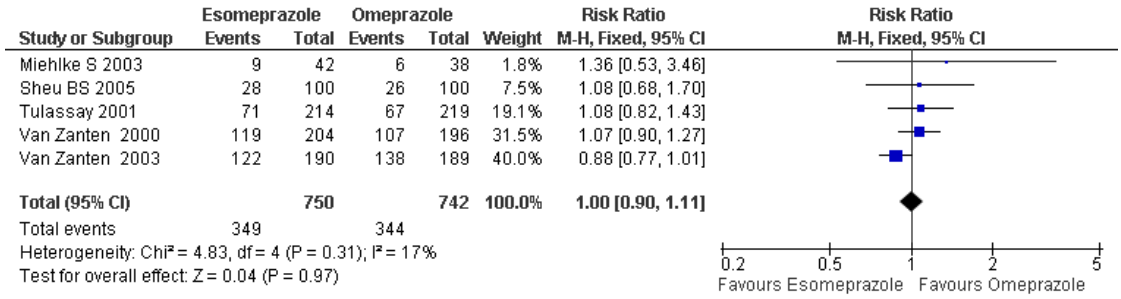
Figure 0-90 Forest Plot: (PUD) E vs O - Withdrawal due to adverse events



3.8.3.7.4 Key harm outcome 4: Total adverse events

Based on 5 RCTs in 1492 patients, no significant difference in total adverse events was observed between Esomeprazole and Omeprazole treatment groups.

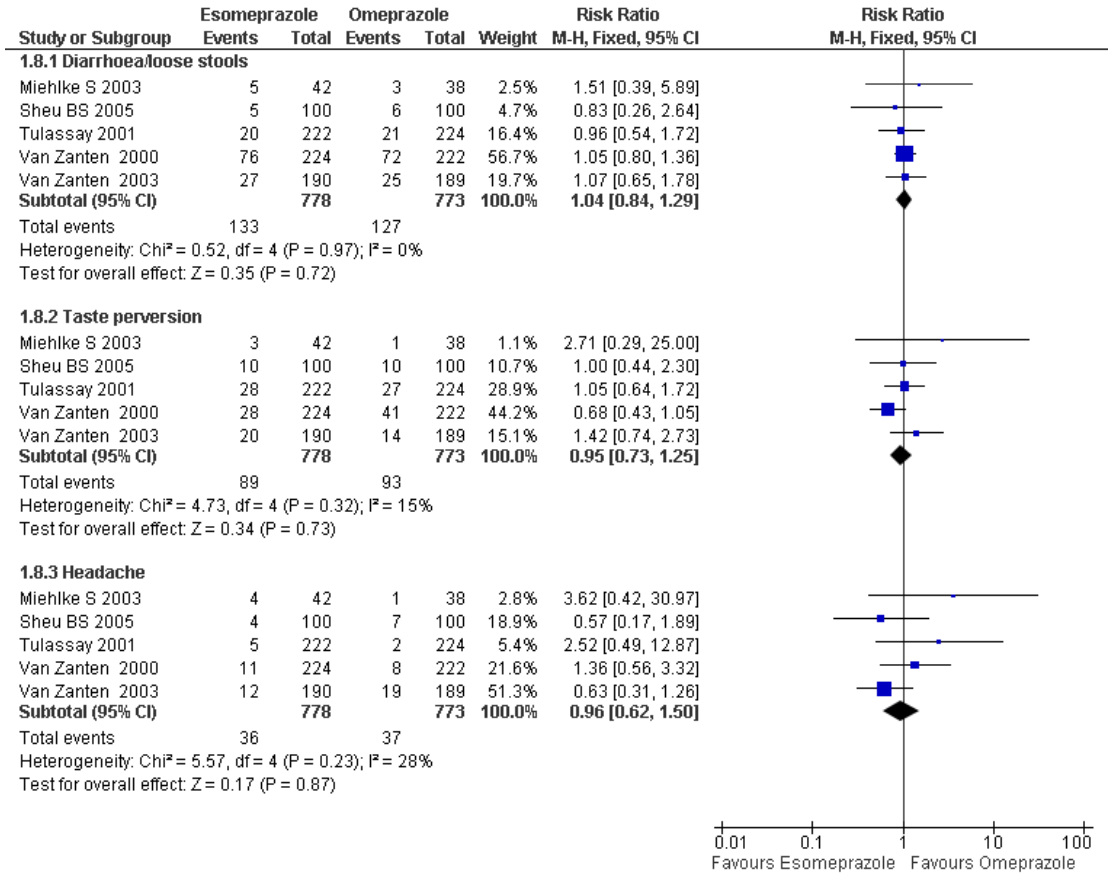
Figure 0-91 Forest Plot: (PUD) E vs O - Total adverse events



3.8.3.7.5 Key harm outcome 5: Specific adverse events

Based on 5 RCTS, no significant difference in any specific adverse events was observed between Esomeprazole and Omeprazole

Figure 0-92 Forest Plot: (PUD) E vs O - Specific adverse events



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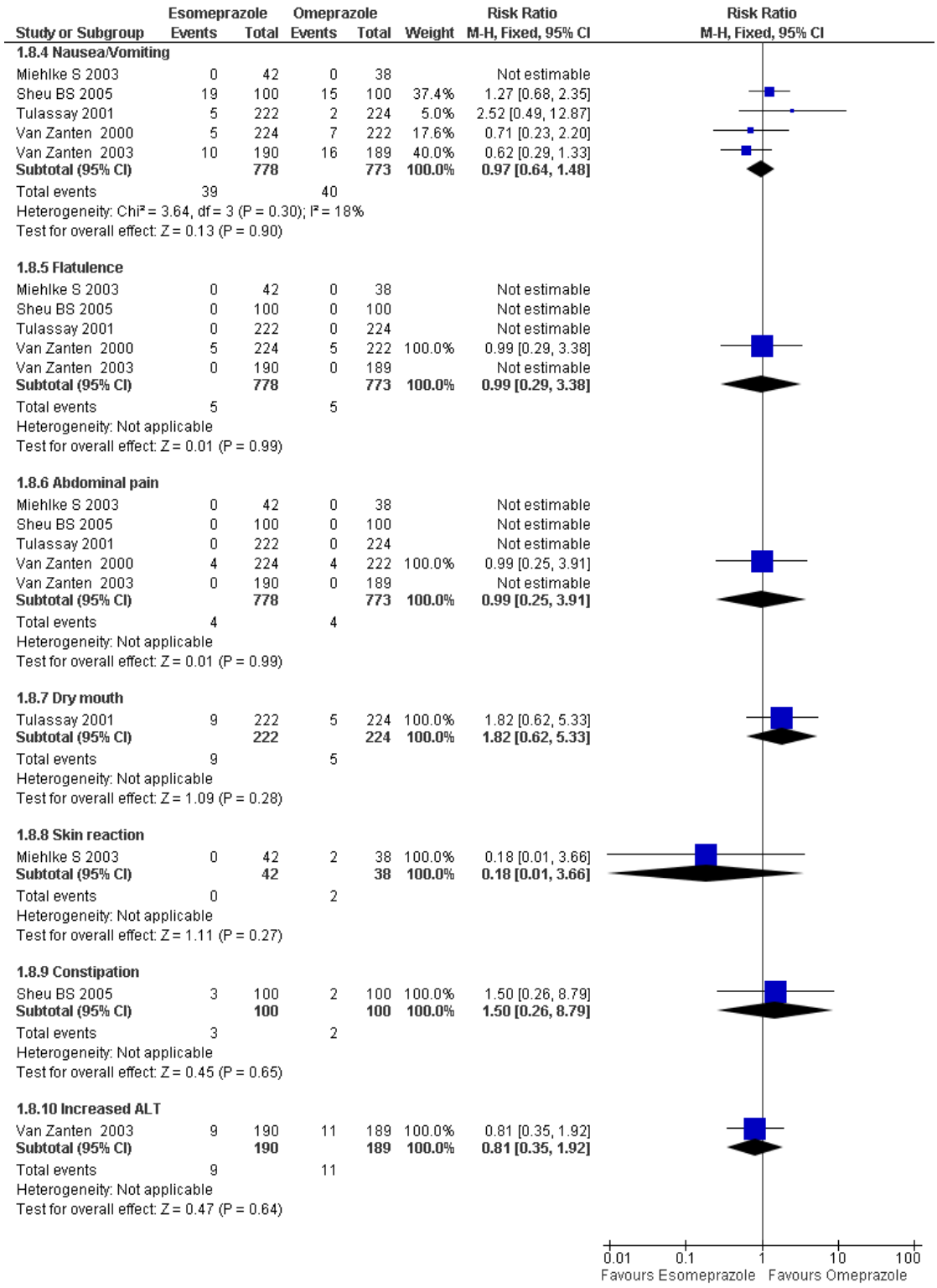


3.8.3.8 PUD Comparison 8: Esomeprazole vs. Pantoprazole

3.8.3.8.1 Key harm outcome 1: Mortality

Mortality was not reported in the single study Hsu 2005.

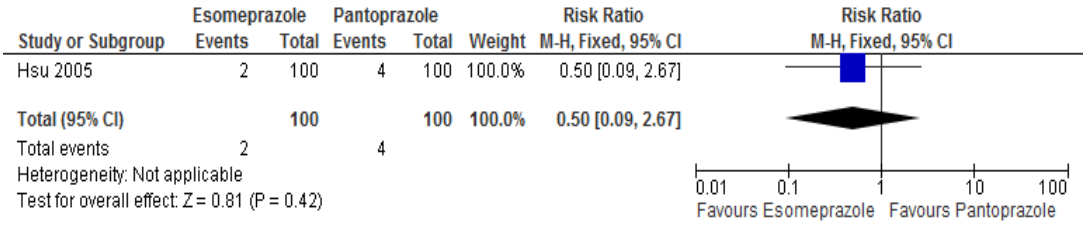
3.8.3.8.2 Key harm outcome 2: Serious adverse events

Serious adverse event was not reported in the single study Hsu 2005.

3.8.3.8.3 Key harm outcome 3: Withdrawal due to adverse events

Based on 1 RCT in 200 patients, no significant difference in withdrawal due to adverse events was observed between Esomeprazole and Pantoprazole treatment groups.

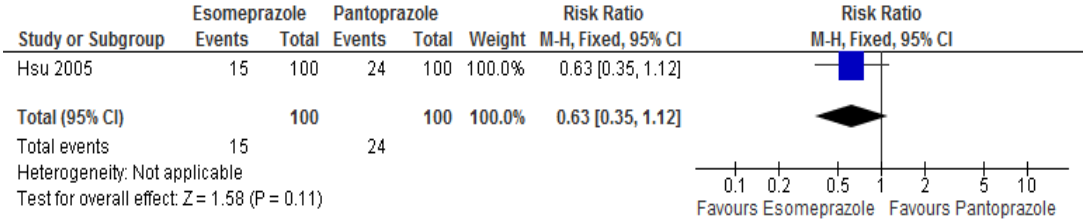
Figure 0-93 Forest Plot: (PUD) E vs P - Withdrawal due to adverse events



3.8.3.8.4 Key harm outcome 4: Total adverse events

Based on 1 RCT in 200 patients, no significant difference in total adverse events was observed between Esomeprazole and Pantoprazole treatment groups.

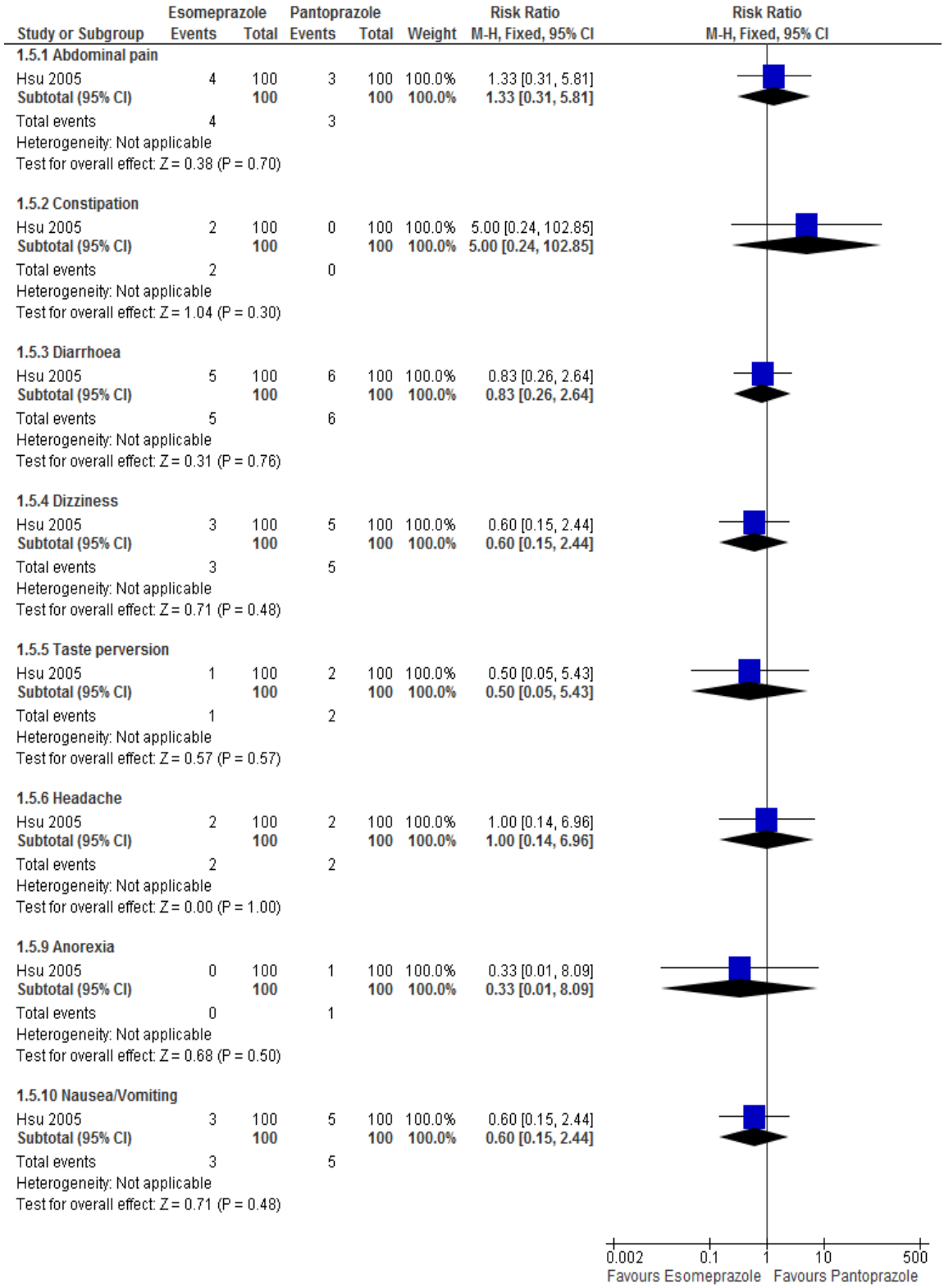
Figure 0-94 Forest Plot: (PUD) E vs P - Total adverse events



3.8.3.8.5 Key harm outcome 5: Specific adverse events

Based on 1 RCT in 200 patients, no significant difference in any specific adverse event was observed between Esomeprazole and Pantoprazole treatment groups.

Figure 0-95 Forest Plot: (PUD) E vs P - Specific adverse events



3.8.3.9 PUD Comparison 9: Esomeprazole vs. Rabeprazole

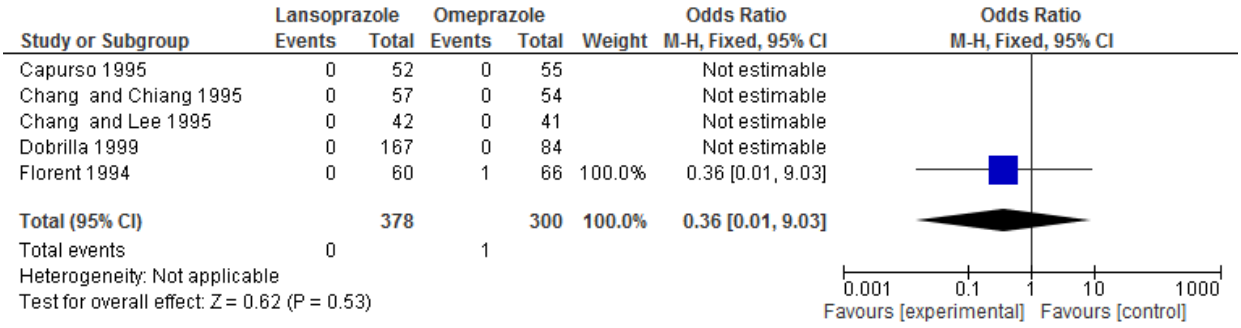
No RCT met the inclusion criteria

3.8.3.10 PUD Comparison 10: Lansoprazole vs. Omeprazole

3.8.3.10.1 Key harm outcome 1: Mortality

Based on 5 RCT in 678 patients, no significant difference in mortality was observed between Lansoprazole and Omeprazole treatment groups.

Figure 0-96 Forest Plot: (PUD) E vs R - Mortality



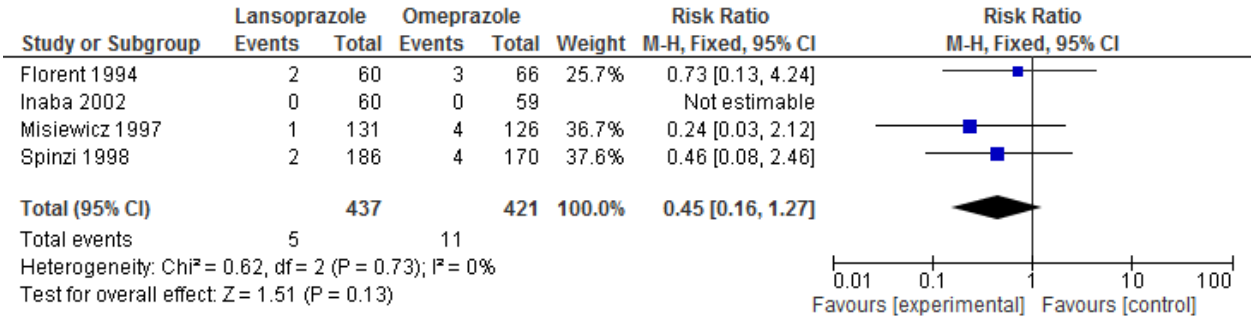
3.8.3.10.2 Key harm outcome 2: Serious adverse events

Serious adverse events were reported in 5 RCTs Florent 1994; Capurso 1995; Chang and Chiang 1995; Chang and Lee 1995; and Dobrilla 1999 [0/318 vs 0/234 = RR is not estimable.

3.8.3.10.3 Key harm outcome 3: Withdrawal due to adverse events

Based on 4 RCT in 858 patients, no significant difference in withdrawal due to adverse events was observed between Lansoprazole and Omeprazole treatment groups.

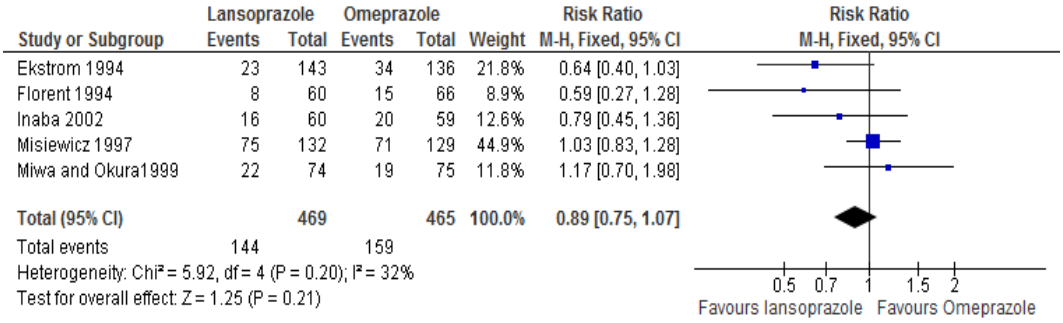
Figure 0-97 Forest Plot: (PUD) E vs R - Withdrawal due to adverse events



3.8.3.10.4 Key harm outcome 4: Total adverse events

Based on 5 RCT in 934 patients, no significant difference in total adverse events was observed between Lansoprazole and Omeprazole treatment groups.

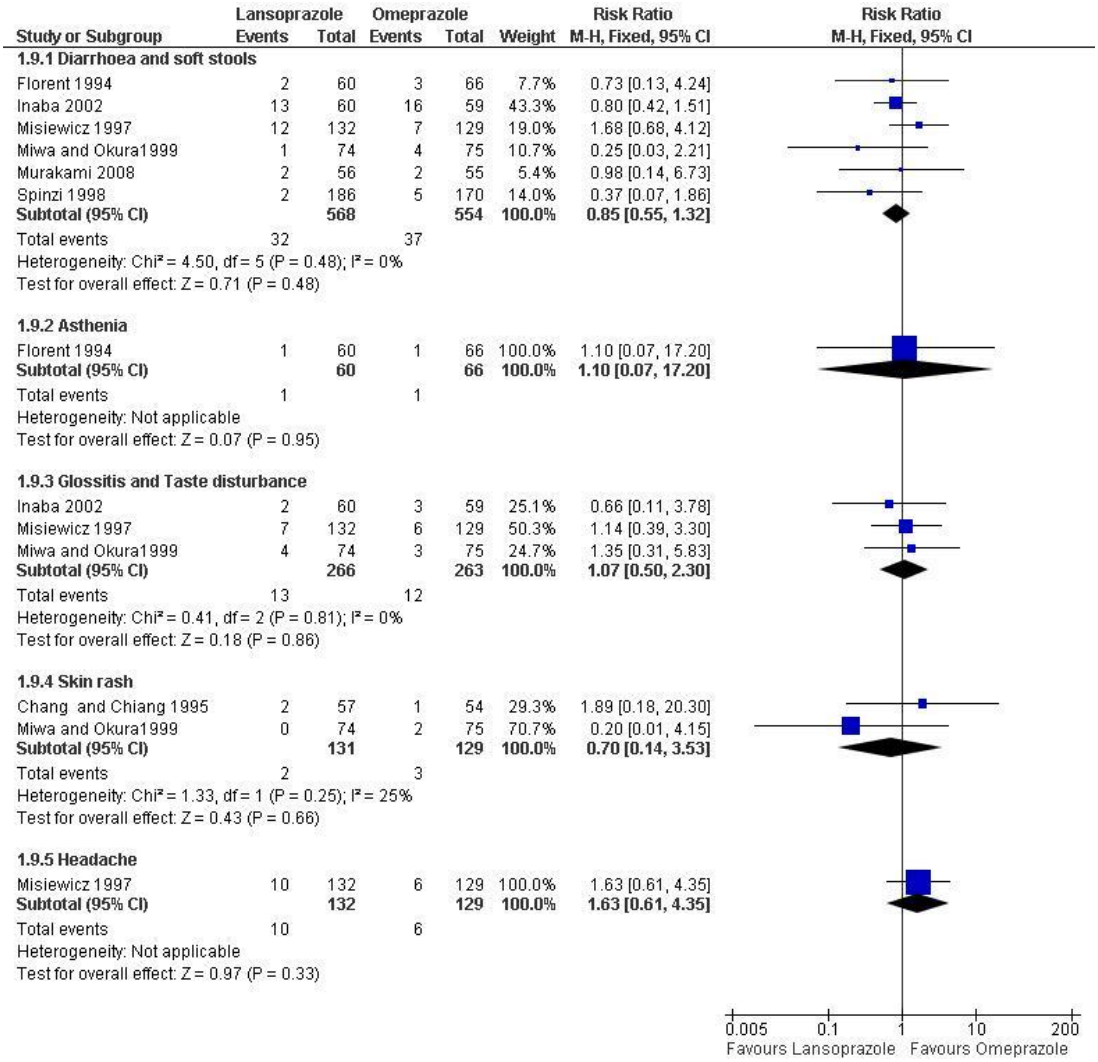
Figure 0-98 Forest Plot: (PUD) E vs R - Total adverse events



3.8.3.10.5 Key harm outcome 5: Specific adverse events

Based on 6 RCTs, no significant difference in any specific adverse event was observed between Lansoprazole and Omeprazole treatment groups.

Figure 0-99 Forest Plot: (PUD) E vs R - Specific adverse events



3.8.3.11 PUD Comparison 11: Lansoprazole vs. Pantoprazole

No RCT met the inclusion criteria

PUD Comparison 12: Lansoprazole vs. Rabeprazole

3.8.3.11.1 Key harm outcome 1: Mortality

Mortality was not reported in all seven trials.

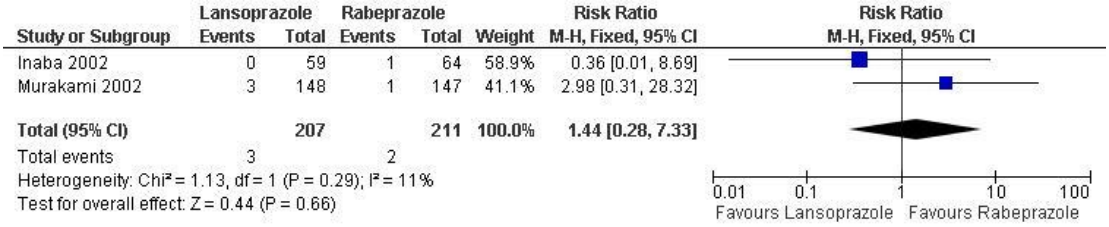
3.8.3.11.2 Key harm outcome 2: Serious adverse events

Total serious adverse events were not reported in all 7 trials.

3.8.3.11.3 Key harm outcome 3: Withdrawal due to adverse events

Based on 2 RCTs in 418 patients, no significant difference in withdrawal due to adverse events was observed between Lansoprazole and Pantoprazole treatment groups.

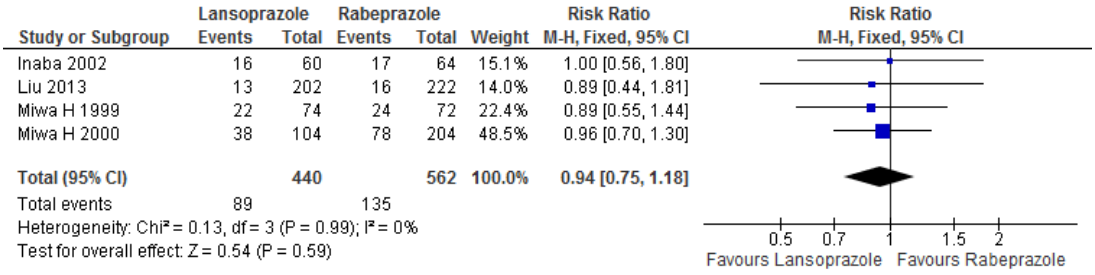
Figure 0-100 Forest Plot: (PUD) L vs R - Withdrawal due to adverse events



3.8.3.11.4 Key harm outcome 4: Total adverse events

Based on 4 RCT in 1002 patients, no significant difference in total adverse events was observed between Lansoprazole and Rabeprazole treatment groups.

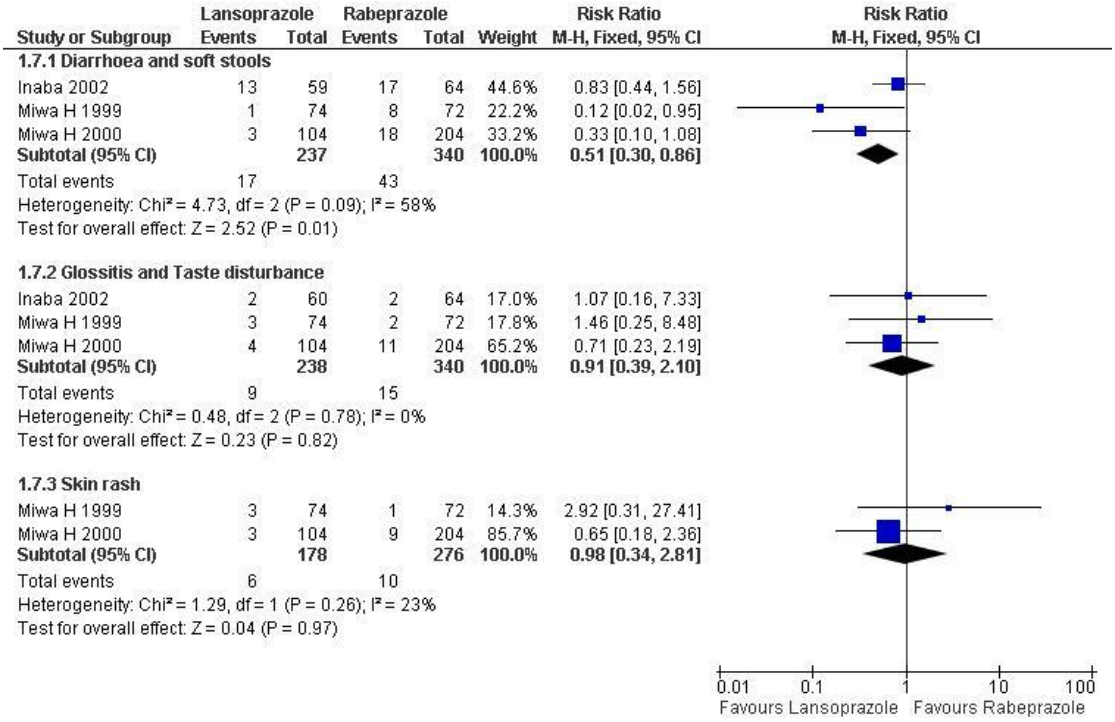
Figure 0-101 Forest Plot: (PUD) L vs R - Total adverse events



3.8.3.11.5 Key harm outcome 5: Specific adverse events

Based on 3 RCTs in 577 patients, more patients in the Lansoprazole group reported diarrhea and soft stools than in the Pantoprazole group with a risk benefit ratio of 0.51 (95% CI 0.30, 0.86).No significant difference in other specific adverse events (glossitis and taste disturbance and in skin rash)

Figure 0-102 Forest Plot: (PUD) L vs R - Specific adverse events



3.9 Comparative and overall safety of PPI drug class

DERP 2009 report concluded there was very limited comparative evidence on long term adverse effects of PPIs. There was no long-term, head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects. An updated search from 2009 until May 2014 did not result in any additional studies on comparative effectiveness.

This report updates overall safety profile of PPIs. Riemer C 2013 has summarized several long term adverse events associated with use of PPIs. Since this class of drugs are used inappropriately over long period of time it is important to summarize these adverse effects.

PPI and risk of fracture

There are several proposed theories behind a possible association between PPI and risk of fracture and includes decreased absorption of calcium and impaired activity of osteoclasts. Acid suppression caused by PPI therapy has been shown to decrease in vivo absorption of calcium in elderly fasting women. (O'Connell 2005) PPIs are suggested to impair osteoclast activity which is dependent of H-K ATPase resembling the proton pump in parietal cells. (Mizunashi 1993) Both mechanisms could theoretically lead to impaired bone strength, osteoporosis and bone fractures. No randomized controlled studies on a causal relationship have been conducted. The association from 2 retrospective studies is weak with ORs ranging from 1.18 (95%CI, 1.12–1.45) to 1.6 (95%CI, 1.4–1.8). (Vestergaard 2006; Yang 2006) These results are challenged by case-control studies unable to find an association between use of PPI and hip fractures when controlling for other independent risk factors**.** **(**Kaye 2008; Corley 2010)

A meta-analysis by Ngamruengphong 2011 from 4 cohort and 6 case-control studies, based on 223,210 fracture cases in concluded a modest association between PPI use and risk of both hip and vertebral fractures. In PPI users the odds ratio for hip fracture based on 9 studies was 1.25 (95%CI; 1.14–1.37) compared to nonusers. In subgroup analysis of hip fracture, this association was observed in both high-dose and low-dose PPI exposure. Short duration of PPI therapy was associated with an increased risk of hip fracture with an OR of 1.24 (95%CI; 1.19–1.24) whereas long-term use of PPI was not shown to lead to an increased risk (OR 1.30, 95%CI; 0.95–1.24). The odds ratio for vertebral fractures based on 4 studies was 1.50 (95%CI; 1.32–1.72) and for wrist/forearm fractures based on 3 studies was 1.09 (95%CI; 0.95–1.24). The pooled studies showed significant both clinical and statistical heterogeneity, were of low quality and had serious limitations and a high risk of bias due to potential confounding. The authors concluded it is unclear whether the observed association reflects a causal relationship or residual confounding. They recommended RCTs are required to confirm or refute these results.

In a study of post-menopausal women the adjusted difference in three-year hip BMD according to baseline PPI use was 0.74 (95% CI; 0.01–1.51), favouring non-use of PPI. No significant difference in the three-year change in spine or total body BMD between users and non-users of PPI was found. (Gray 2010). In a large population-based Canadian cohort the association of use of PPI and BMD at baseline and after five and ten years was investigated. PPI users had lower BMD at baseline than non-users but showed no significantly accelerated loss of BMD after five and ten years of follow-up. (Targownik 2010)

Hypomagnesaemia

The underlying biological mechanism for severe hypomagnesaemia, refractory to supplemental therapy, has been reported with long-term PPI treatment. (Cundy 2008) Hypomagnesaemia is a rare condition and the association between PPIs and hypomagnesaemia is based on case reports and a total of 36 cases are published since 2006. (Cundy 2011; Hess 2012) The symptoms reported were severe and included paresthesia, tetany, seizures, ataxia and GI symptoms and required hospitalization but resolved within 1–2 weeks once the PPI therapy was withdrawn.

A retrospective nested case control study was conducted by Koulouridis 2013 in a tertiary acute-care facility with an aim to examine whether hypomagnesemia at the time of hospital admission is associated with out-of-hospital use of PPIs. Eligible cases consisted of 402 adults with hypomagnesemia (serum magnesium < 1.4 mEq/L) at the time of hospital admission to medical services, age- and sex-matched with 402 control individuals with normal serum magnesium levels (1.4-2.0 mEq/L). Out-of-hospital PPI use was identified in the hospital record. An Omeprazole equivalent dose was calculated when possible. Covariates included the Charlson-Deyo comorbidity index, diabetes, diuretic use, estimated glomerular filtration rate, and gastroesophageal reflux. PPI use was not associated with hypomagnesemia (adjusted OR, 0.82; 95% CI, 0.61-1.11). Neither PPI type nor Omeprazole equivalent daily dose was associated with hypomagnesemia. The limitations of this study are exposure misclassification and hospitalized patients on medical services may not be representative of a broader ambulatory-based population. Authors recommend prospective cohort studies are needed to address this rare potential medication-related adverse effect.

Vitamin B12 deficiency

Theoretically, PPI induced achlorhydria could consequently lead to malabsorption and B12 deficiency, especially in long-term treated patients. In short-term studies on 10 healthy volunteers B12 absorption was measured before and after two weeks of therapy with Omeprazole 20 mg or 40 mg OD. Absorption decreased in a dose-dependent manner from 3.2 to 0.9% and from 3.4 to 0.4% in the two groups respectively. (Marcuard 1994) In a study on the effect of short- and long-term PPI therapy on the absorption and serum levels of cobalamin, no change in serum cobalamin levels was observed in patients with GERD after treatment with Omeprazole for up to seven years. (Schenk 1996)

In a study by Rozgony 2010, 17 elderly patients on long-term PPI therapy were compared with 19 non-PPI users in a chronic care facility. At baseline the chronic PPI users had lower serum B12 levels and greater percentages were vitamin B12 deficient (75 vs. 11%, $p < 0.006$). In a cross-sectional study comparing B12 levels in nursing home and community care patients treated long-term (>six years) with PPIs and non-users, it was observed that use of PPI up to 72 months was associated with declining B12 levels with increasing duration of PPI use. (Dharmarajan 2007) In contrast, a study of 125 subjects over 65 years with a history of three or more years of continuous PPI therapy found no significant association after when compared with their partners not taking PPI. (den Elzen 2008)

Iron deficiency

Iron deficiency caused by PPI therapy is theoretically possible since gastric acid facilitates the absorption of non-heme iron by oxidation to a more soluble ferrous form. In a case report of two patients with iron deficiency anaemia the patients failed to respond to iron replacement therapy until their PPI therapy were withdrawn. (Sharma 2004) Patients with hereditary hemochromatosis receiving long-term PPI therapy had a significant reduction in the volume of blood that had to be removed to maintain acceptable ferritin levels. (Hutchinson 2007)

Enteric infections

Gastric pH <4 has a potent bactericidal effect and rapidly kills acid sensitive bacteria introduced in the stomach. An increase in gastric pH >4 by PPIs increases the susceptibility to these pathogens and allows at least 50% of the ingested bacteria to escape the gastric acid barrier. (Tennant 2008) Additionally, PPIs seem to disrupt the natural gut bacteria ecology probably because of lack of destruction of ingested microorganism and/or by allowing an increased ascending bacterial colonization from the intestine. (Fried 1994) The altered micro flora in the stomach, the small- and the lower-intestine, caused by PPIs represents a plausible biological explanation for any increased susceptibility to GI infections.

The association between the use of PPI and infections within particular Salmonella, Campylobacter jejuni and Clostridium difficile has been studied in a number of retrospective cohort and case-control studies.

In 2007, a meta-analysis by Leonard 2007 of 12 observational studies in 2948 patients showed an increased risk of taking anti secretory therapy in patients with C. Difficile OR 1.94 (95% CI 1.37, 2.75).

There was significant heterogeneity between the studies (*P =0.0006*) that was not explained by subgroup analysis. The association was greater for PPI use (OR 1.96, 95% CI 1.28–3.00) compared with H_2RA use (OR 1.40, 95% CI 0.85–2.29). A total of six studies evaluated *Salmonella*, *Campylobacter*, and other enteric infections in 11,280 patients. There was an increased risk of taking acid suppression in those with enteric infections (OR 2.55, 95% CI 1.53–4.26). There was significant heterogeneity between the studies ($P < 0.0001$) that was not explained by subgroup analysis. The association was greater for PPI use (OR 3.33, 95% CI 1.84–6.02) compared with H_2RA use (OR 2.03, 95% CI 1.05–3.92). The authors concluded that there is an association between acid suppression and an increased risk of enteric infection. Further prospective studies on patients taking long-term acid suppression are needed to establish whether this association is causal.

In a systematic review by Doorduyn 2010 an association was found between Salmonella infections and treatment with PPI based on two case-control studies. The adjusted RRs were ranging from 4.2 to 8.3. (Doorduyn 2006) Four studies with a total of more than 3000 cases and 7000 controls on risk for C. jejuni diarrhoea and use of PPI have been published and the reported RRs which varied between 4.3 and 11.7. (Doorduyn 2006; Doorduyn 2008; and Doorduyn 2010)

A systematic review by Bavishi 2011 reported enhanced susceptibility to enteric infection caused by Salmonella, Campylobacter and C. difficile by PPI use, with adjusted relative risk ranges of 4.2 to 8.3 (two studies); 3.5 to 11.7 (four studies); and 1.2 to 5.0 (17 of 27 studies) for the three respective organisms. The authors concluded that severe hypochlorhydria generated by PPI use leads to bacterial colonisation and increased susceptibility to enteric bacterial infection. The clinical implication of chronic PPI use among hospitalized patients placed on antibiotics and travellers departing for areas with high incidence of diarrhoea should be considered by their physicians.

A retrospective case control study was conducted by Kim 2012 of patients with Clostridium Difficle Associated Disease (CDAD) diagnosed by the presence of C. difficile toxin in the stool. Those with recurrent disease were matched with non-recurrent controls using multivariate matched sampling methods that incorporated the propensity score. Recurrent CDAD developed in 28 (14.1%) of the 198 patients with diarrhea and positive C. difficile stool toxin assays. 21 recurrent CDAD subjects were matched with 21 controls without recurrent CDAD. Among the matched patients only PPI use was associated with recurrent CDAD (i.e., 47.6% vs. 4.8%, P=0.004 for recurrent vs. non-recurrent CDAD, respectively). The primary limitations of the study were its retrospective nature and the relatively small sample size. The authors concluded that prospective randomized placebo controlled studies are needed to address the risk of PPI use in promoting of recurrent C. difficile-associated diarrhea.

In the meta-analysis by Janarthanan 2012, 17 case-control and six cohort studies with a total of 288,620 study subjects reported a relative risk of Clostridium Difficle infection (CDI) in PPI treated patients of 1.69 (95% CI 1.40–1.97) equalling a 65% increase in the incidence of CDI among patients on PPI. The increase in incidence of CDI was significant regardless of study design and ranged from 1.48 (95%CI 1.25–1.75) in the case-control studies to 2.31 (95%CI 1.72–3.10) in the cohort studies.

In the second meta-analysis by Kwok 2012 based on 30 case-control and 12 cohort studies with a total of 313,000 study subjects, a pooled odds ratio of 1.74 (95%CI 1.47–2.85; I^2 = 85%) for developing CDI among PPI users compared with non-users was reported. Concomitant use of PPI and antibiotics conferred a greater-risk OR 1.96 (95 % CI 1.03 – 3.70) above that of PPIs alone. Adjusted indirect comparison demonstrated that use of H_2RAs as an alternative carried a lower-risk OR 0.71 (95 % CI 0.53 – 0.97) compared with PPIs. Despite the substantial statistical and clinical heterogeneity, findings of this review indicate a probable association between PPI use and incident and recurrent CDI. This risk is further increased by concomitant use of antibiotics and PPI, whereas H_2RAs may be less harmful. There are several limitations of this review - the quality of the included studies is variable with regards to ascertainment of dose and duration of actual PPI use (including intermittent symptomatic use, or over-the-counter availability); all the studies were observational in nature, and are thus subject to residual confounding despite statistical adjustment; there may be unmeasured risk factors in the PPI-exposed patients; and confounding by indication as well as severity of comorbid condition may differ between groups. Differences in the exposure duration, patient characteristics, and types of antibiotic use could have potentially contributed to the significant heterogeneity. The authors concluded there is sufficient low grade evidence to suggest that PPIs increase the incidence of CDAD. Further prospective studies are needed to fully explore the association between PPIs and CDAD.

Pneumonia

Theoretically, the increase in gastric pH caused by acid suppressive treatment could increase the susceptibility to respiratory infections by permitting survival of pathogens and possible colonization of the upper gastrointestinal tract, leading to potential micro aspiration or translocation into the lungs. A Danish population-based case-control study showed a 50% increase in risk of pneumonia among PPI users with an OR of 1.5 (95%CI 1.30–1.70). (Gulmez 2007) A nested case-control study from the UK showed no overall association between current use of PPI and community-acquired pneumonia or pneumonia requiring hospitalization. (Sarkar 2008) The crude analysis revealed a strong association that vanished when adjusting for different co-morbidity variables suggesting a substantial influence of confounding effect on the association initially observed.

A meta-analysis of six nested case-control studies by Johnstone 2010 examining the association between PPI use and risk of community-acquired pneumonia (CAP) showed an increased risk associated with PPI use (OR 1.36, 95%CI 1.12–1.65) with an even increased risk with short duration of use that attenuated and became non-significant with chronic use. The results were confounded by significant heterogeneity and precluded interpretation of results.

In a prospective, cohort study of consecutive patients attending a hospital emergency department, PPI use increased the risk of CAP due to Streptococcus pneumonia more than two-fold (OR 2.23; 95%CI; 1.28–3.75). However, the authors emphasize the risk of confounding in their study. (de Jager 2012)

A systematic review by Eom 2011 identified 31 studies - five case-control studies and three cohort studies on use of both PPI and H_2RA therapy and risk of pneumonia and 23 randomized controlled

studies on use of H_2RA therapy only primarily in intensive care units. Meta-analysis of data from the eight observational studies conducted between 1987 and 2006 on PPI use showed that the overall risk of pneumonia was higher among patients using PPIs (adjusted OR 1.27, 95%CI 1.11–1.46; I^2 = 90.5%) and H_2RA (adjusted OR 1.22, 95%CI 1.09–1.36; I^2 = 0%). In the randomized controlled trials, use of H_2RA was associated with an elevated risk of hospital-acquired pneumonia (RR 1.22, 95% CI 1.01–1.48, I^2 = 30.6%).

1. Subgroup analyses by dose indicated a dose-response relationship. A higher dose of proton pump inhibitors was more strongly associated with pneumonia (adjusted OR 1.52, 95% CI 1.31–1.76, I^2 =27.5%) than the usual dose (adjusted OR 1.37, 95% CI 1.08–1.74, I^2 = 86.5).
2. Subgroup analyses by duration of exposure, the increase in risk of pneumonia in association with PPIs was observed in the first week of therapy (OR 3.95, 95%CI 2.86–5.45; I^2 = 0%). The risk attenuated with increasing duration of exposure but was significant between 30 and 180 days of therapy (adjusted OR 1.36, 95% CI 1.05–1.78, I^2 = 84.3%).
3. Subgroup meta-analyses of the observational studies by methodologic quality showed a significant positive association for both high-quality studies (adjusted OR 1.29, 95% CI 1.17–1.42, I^2= 0.0%) and low-quality studies (adjusted OR 1.15, 95% CI 1.00–1.32, I^2= 82.1%)

The authors concluded that use of a proton pump inhibitor or H_2RA may be associated with an increased risk of both community and hospital-acquired pneumonia.

Acid rebound

Long-term, elevated gastric pH stimulates compensatory gastrin release which induces hypertrophy of the enterochromaffin-like cells which results in an increased capacity to stimulate gastric acid secretion that sets off once PPI therapy is withdrawn [Sanduleanu 1999; Laine 2000]. Two randomized controlled trials showed an increased frequency of acid-related symptoms in healthy subjects after withdrawal of PPI therapy. (Riemer 2009; Niklasson 2010)

In the study by Waldum 1996, 119 asymptomatic healthy volunteers were randomized to treatment with a PPI for eight weeks followed by a blinded shift to placebo for four weeks or to placebo in all 12 weeks. Significantly more subjects in the PPI treated group reported acid-related symptoms after withdrawal (26/59 vs 9/59: $p < 0.001$). In a Swedish study by Gillen 1999, 48 healthy subjects were randomized to PPI or placebo for four weeks. Acid-related symptoms were registered daily two weeks before, during and six weeks after the treatment was discontinued. A total of 11 out of 25 (44%) subjects in the PPI group developed acid-related symptoms in the week after withdrawal of PPI therapy compared to two out of 23 (9%) in the placebo group ($p < 0.01$). In a cross-over study by Farup 2001, with 62 patients with GERD, five days of therapy with a PPI did not induce acid related symptoms after withdrawal. In an open, non-randomized study by Juul-Hansen 2009, with 28 patients treated with PPI on demand there was no difference in symptom score after therapy compared to pre-treatment levels.

Neoplasia

The constantly elevated pH in the stomach caused by long-term PPI treatment leads to a compensatory increased gastrin secretion resulting in an increased plasma gastrin concentration. (Pounder 1990) Because of the trophic effect of gastrin, there have been concerns that long-term treatment with PPI leads to development of gastric polyps, gastric cancer, carcinoids and colorectal cancer.

Gastric polyps

The incidence of fundic gland polyps (FGPs) ranges from 1 to 36% with an increasing occurrence with therapy longer than 12 months based on case reports and smaller series. (Choudhry 1998; Graham 1992) In a larger case-control study on patients referred for endoscopy, long-term PPI use was associated with an increased risk of FGPs with an OR of 2.2 (95%CI; 1.3–3.8) after 1 to 4.9 years of PPI treatment and an OR of 3.8 (95%CI 2.2–6.7) after more than five years of therapy. Low-grade dysplasia was found in only one fundic gland polyp. Short-term therapy (less than one year) was not associated with an increased risk for FGPs. (Jalving 2006)

Gastric cancer

Kuipers and Lundell 1996 found that patients with reflux oesophagitis and *H. pylori* infection on PPI therapy had an increased risk of atrophic gastritis compared to *H. pylori* negative patients. After an average of five years of PPI therapy one out of three patients had developed atrophic gastritis. A seven-year follow-up study of GERD patients on long-term PPI therapy by Lundell 2006 found a successive increase in the severity of mucosal inflammation in the *H. pylori*-infected patients. Observational study by Kuipers 2006 from a Dutch database containing medical records of more than 25,000 PPI treated patients showed that during eight years of follow-up, 45 patients (0.16%) were diagnosed with gastric cancer compared with 22 (0.01%) among more than 3,50,000 patients not using PPIs. However, confounding by indication may explain this observation. Poulsen 2009 in a Danish study showed an increased overall incidence risk ratio of gastric cancer in PPI users disappeared when a one-year lag time was incorporated in the analysis.

Gastric carcinoids

ECL cell hyperplasia is observed in approximately 10 to 30% of patients treated long-term with a PPI, most frequently in patients with concomitant *H. pylori* infection. (Klinkenberg-Knol 2000; Solcia 1992) The hypothesis that hypergastrinemia and ECL cell hyperplasia caused by PPI treatment is associated with carcinoid development is based on observations from animal studies. (Lee 1992; Mattsson 1991) No human studies have been conducted and are most likely not feasible, because of the low incidence of carcinoids.

Colon cancer

Theoretically hypergastrinaemia could lead to development of colonic adenoma and colorectal cancer (CRC). (Watson 1989) In a UK general practice research database in a case control study by Yang 2007, based on more than 4400 CRC cases, long-term PPI therapy for five or more years was not associated with an increased risk of CRC (OR 1.1, 95%CI, 0.7–1.9). This is consistent with data from the two other equally large case control studies from Denmark and the Netherlands where PPI use for up to seven years did not increase the risk of CRC. (Robertson 2007; van Soest 2008) No association was found between PPI therapy and colonic polyps in case-control study comparing the frequency, growth, and histology of colon polyps between patients on chronic PPI therapy and controls.

Based on 4 case control studies Chen S 2011 found PPI use was statistically significantly associated with an increase in the risk of CRC assuming a fixed-effects model (OR=1.37; 95%CI=1.28-1.47), but not

statistically significant assuming a random-effects model (OR=1.19; 95% CI=0.90-1.57). Most of the studies had an intervention and follow-up time less than 5 years compared with the latency time for at least 10 years between the initiation and the clinical detection of cancer. The shorter the follow-up time is, the bigger effect of potential leading time bias is. The authors concluded that it is important to continue more high quality studies with longer follow up times.

PPI and renal disease

Case reports have suggested that PPI may be linked to acute kidney injury, which may in turn lead to chronic injury or failure. A nested case control study by Klepser 2013 was conducted in a privately insured population of 184,480 patients aged 18 years or older who were continuously enrolled with the insurer for at least 24 months between September 2002 and November 2005. The objective of this study was to determine if an association between PPIs and kidney failure exists and to estimate an effect size for the relationship between PPI use and renal disease. 854 cases were identified as having at least two claims for an acute renal disease diagnosis. Cases were randomly matched with up to four controls (n = 3,289) based on age, gender, county of residence, and date of entry into the cohort. Renal disease was positively associated with PPI use (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.27, 2.32, $p < 0.001$) even after controlling for potential confounding conditions. After removing patients with potential confounding disease states from the study population, the number of cases (195 of the 854) and controls (607) was lower, but the relationship between renal disease and PPI use remained consistent (OR 2.25, CI 1.09-4.62, $p < 0.001$). Limitations of this study are misclassification bias which could overestimate or underestimate the true relationship between PPI use and renal disease, depending on their distribution between exposure categories. Lack of the over the counter PPI use can also lead to misclassification bias but leads to an underestimation of effect. Surveillance bias was accounted for by removing patients with chronic disease from the analysis but association still remained in population without chronic disease (OR = 2.25). The authors concluded that patients with a renal disease diagnosis were twice as likely to have used a previous prescription for a PPI. It is important that future research seek to establish a definitive causal relationship between PPI and acute kidney injury.

Safety during pregnancy

In a meta-analysis based on seven observational studies with more than 1500 women exposed to PPI primarily in their first trimester of pregnancy and more than 1,30,000 controls the overall OR for major malformations was 1.12 (95%CI: 0.86–1.4). No increased risk for spontaneous abortions (OR ¼ 1.29, 95%CI: 0.84–1.97); or for preterm delivery (OR = 1.13, 95%CI: 0.96–1.33) was found. (Gill 2009)

In a more recent nation-wide, registry-based cohort study from Denmark, major birth defects, diagnosed within the first year of life, were registered as well as the use of PPIs from four weeks before conception through 12 weeks of gestation. Based on 5082 cases out of more than 8,40,000 births, exposure to PPIs during the first trimester of pregnancy were not associated with a significantly increased risk of major birth defects. (Pasternak 2010)

In the Hungarian Case-Control Surveillance of Congenital Abnormalities, Banhidy 2011 studied the prevalence of PUD in pregnant women who later delivered babies with different congenital anomalies

(cases) and compared it to pregnant women who delivered newborns without congenital anomalies (controls). Of 22, 843 cases with congenital abnormalities, 182 (0.80%) had mothers with reported/recorded PUD, while of 38 151 controls, 261 (0.68%) were born to mothers with reported/recorded PUD. 20 case mothers and 58 control mothers with PUD and related drugs were evaluated in detail. Specific congenital abnormalities groups in cases were assessed versus controls, but specified congenital abnormalities had no higher risk in the offspring of pregnant women with PUD and related drug treatments. The authors concluded that a higher rate of congenital anomalies was not found in the offspring of mothers with PUD.

PPI and Mortality

In a study by Bateman 2003, information on the causes of death over four years in nearly 18,000 patients in UK prescribed Omeprazole showed a significantly greater mortality than population expectation (OR 1.44, 95%CI 1.34–1.55) in the first year after registration but normalized to the level of population expectation by the fourth year. The authors concluded that increases in mortality associated with treatment are due to pre-existing illness, including pre-existing severe oesophageal disease. There was no evidence of an increased risk of oesophageal adenocarcinoma in those without oesophageal mucosal damage recorded at registration.

Bell 2010 conducted a post-hoc analysis on use of PPI and mortality from 2 prospective cohort studies. In a cohort of 1004 Finnish residents, 70 years or older in acute geriatric wards (N = 230) and in nursing homes (N = 195), 12-month mortality was increased (after adjusting for age, sex, co-morbidity and malnutrition) in both cohorts with ORs of 1.37 (95%CI, 1.05–1.78) and 1.82 (95%CI, 1.20–2.78) respectively. In a second publication Bell 2010 analyses of the same data were extended and a third cohort comprised by 1389 residents in assisted living facilities with an equal burden of co-morbidity was included. There was no association between use of PPI and one-year mortality in the third cohort. The authors concluded that there is need for urgent research into the risks versus benefits of routinely prescribing PPIs to older people in long-term care.

Maggio 2013 studied the association between use of PPIs and the risk of death or a combined endpoint of death or re-hospitalization in 491 older patients discharged from acute care hospitals. The study showed co-morbidity was significantly more prevalent in the group of PPI users compared to non-users. However, an increased risk of one-year mortality (hazard ratio, 1.51; 95%CI, 1.03 -2.77) was observed in the group of PPI users in a time-dependent multivariable analysis. Contrarily there was no association between use of PPI and the combined endpoint of death or re-hospitalization which should lead to rather cautious interpretation of the significant results.

PPI and concomitant use of clopidogrel

Rassen 2009 evaluated the clopidogrel - PPI interaction in low-income patients enrolled in three health insurance programs in British Columbia, New Jersey, and Pennsylvania. They studied patients aged $\geq$ 65 years who were hospitalized for ACS or PCI between 2001 and 2005. They found that concomitant use of clopidogrel and PPIs was associated with an increased but not statistically significant risk of myocardial infarction or death (OR: 1.22; 95% CI: 0.99–1.51). The associations between concurrent clopidogrel and

PPI use and occurrence of individual outcomes of death (OR: 1.20; 95% CI: 0.84–1.70) and revascularization (OR: 0.97; 95% CI: 0.79–1.21) were also found to be non-significant in this study.

In a Canadian study, Juurlink 2009 studied elderly AMI patients who were prescribed clopidogrel within 3 days of discharge from a local hospital. They found a significant association between readmission for AMI and current use of a PPI (most recent prescription fill for a PPI within 30 days before readmission for AMI or death) (OR: 1.27; 95% CI: 1.03–1.57).

Mahabaleshwarkar 2013 conducted a nested case control study from a 5% national sample of Medicare claims data of elderly Medicare beneficiaries who initiated clopidogrel and did not have any gap of ≥30 days between clopidogrel fills between July 1, 2006 and December 31,2008. Within this cohort, cases (beneficiaries who experienced any major cardiovascular event [MCE] [acute myocardial infarction, stroke, coronary artery bypass graft, or percutaneous coronary intervention] or all-cause mortality) and controls (beneficiaries who did not experience any MCE or all-cause mortality) were identified from inpatient and outpatient claims. Cases and controls were matched on age and the time to first clopidogrel fill, for the presence of major cardiovascular comorbidities such as hypertension, diabetes, and congestive heart failure, which usually lead to adverse cardiovascular events. A total of 43,159 clopidogrel users were identified. Among them, 15,415 (35.7%) received clopidogrel and a PPI concomitantly at any time during the study period, 3502 (8.1%) experienced a major cardiovascular event (MCE), 7306 (17.1%) died, and a total of 9908 (22.8%) experienced the primary composite outcome (any MCE or all-cause mortality) during follow-up. The odds ratio (OR) for the primary composite outcome was 1.26 (95% confidence interval [CI]: 1.18–1.35). Secondary analyses indicated that elderly patients using clopidogrel and a PPI concomitantly were more likely to experience all-cause mortality (OR: 1.40; 95% CI: 1.29–1.53) as compared to those receiving clopidogrel only, but not MCEs (OR: 1.06; 95% CI: 0.95–1.18). Limitations of this study include inability to identify poor metabolizers in the database, over the counter use of PPIs, aspirin, accounting of patients for factors such as smoking, blood pressure level, serum cholesterol level, family history of cardiovascular disease.

Conclusions regarding safety:

DERP 2009 report concluded there was very limited comparative evidence on long term adverse effects of PPIs. There was no long-term, head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects. An updated search from 2009 until May 2014 did not result in any additional observational studies meeting the inclusion criteria on comparative effectiveness of PPIs.

Regarding overall long term safety, PPIs are known to be associated with risk of fracture, hypomagnesemia, iron deficiency, vitamin B12 deficiency, enteric infection, pneumonia, acid rebound, acute renal injury and neoplasia (gastric polyps, gastric cancer, carcinoids, and colon cancer). For the majority of the potential adverse effects of PPI therapy, a reasonable biological hypothesis exists. Most of the information is based on retrospective observational studies and some of the associations observed are most likely not causal but due to bias, confounding or chance. Summary of studies regarding adverse effects showed significant heterogeneity and inconsistent results between

observational studies, inadequate control for potential confounding and a lack of data on a dose–response or temporal relationship. The best evidence supports a relevant risk of enteric infections, in particular C. difficile infections in hospitalized patients with significant co-morbidity. Also significant association between PPI use and increase risk of community and hospital acquired pneumonia was observed. These adverse effects might have clinical consequences and should lead to an even more careful evaluation of the appropriateness of PPI treatment since those patients treated without proper indication are only exposed to potential risks.

The above mentioned specific adverse effects with long term PPI use needs to be studied in high quality, prospective well designed long term observational studies incorporating data on dosage and duration of treatment with extended follow up.

3.10 Synthesis of Results

E vs other PPI (26 RCTs) in patients with GERD

26 RCTs (23 double blind and 3 open label) compared Esomeprazole to other PPIs (5 RCTs had multiple treatment arms) in 23,789 adult patients with symptomatic GERD. These studies were conducted in centres across USA, Canada, Australia, Singapore, India, Brazil, Taiwan, China and various countries in Europe including Germany. Patients were randomized to receive Esomeprazole 20 mg or 40 mg OD compared to Omeprazole 20 mg OD for 4 to 8 weeks; or Pantoprazole 20 to 40 mg OD for 4 week to 6 months of duration; or Rabeprazole 10 to 50mg for duration of 4 weeks except for Maiti 2011 which included an additional 4 weeks treatment for patients with unhealed esophagitis at week 4. The primary efficacy outcome is endoscopic confirmed healing of reflux esophagitis in 15 studies; sustained symptomatic relief in 2 studies (Kao 2003 and Fock 2005); both symptomatic relief and endoscopic healing in Maiti 2011; complete relief of heart burn in 3 studies (Armstrong 2004a; 2004b and 2004 c study); and for the 3 remission studies were healing or symptom remission at 6 months.

Esomeprazole to Omeprazole

Ten RCTs (8 were double blind and 2 were open label) compared Esomeprazole to Omeprazole in 9638 patients (56% were men and 44% were women; mean age ranged from 45 to 59 years; Over 90% of the participants in the 3 RCTs that reported race are Caucasians; Kao 2003 reported that 30% of participants were smokers and 24% consumed alcohol; 3 studies included about 10% patients with *H. pylori* positive status whereas in Armstrong 2004 (a, b and c) (>60%), Chen 2005 (>40%), Zheng 2009 (>80%) included larger portion of patient who are *H. pylori* positive; 9 RCTs reported the LA grade of esophagitis at baseline, 34.3% of patients were grade A, 38.9% of patients were grade B, 20.1% of patients were grade C, and 6.6% (of patients were grade D. Of the 10 RCTs comparing Esomeprazole vs. Omeprazole 5 RCTs in 6,857 patients reported that 6,437 (94%) patients completed and 420 (6%) patients discontinued early.

Esomeprazole to Pantoprazole

Twelve RCTs compared Esomeprazole to Pantoprazole in 10,503 patients (61.0% were men and 39% were women; mean age ranged from 42 to 58 years; mean BMI ranged from 26 to 27 Kg/m^2; 7 RCTs reported race and more than 80% were Caucasian; 4 RCTs reported that on average about 20% of

patients were smokers; Only 2 RCTs reported that less than 10% of participants consumed alcohol; 11 RCTs reported that on average 22 to 50% of patients were *H. pylori* positive; 10 RCTs reported the disease severity by LA grade at baseline, which 36.6% of patients were grade A, 43.5% were grade B, 16.1% were grade C and 3.8% were grade D. Of the 12 RCTs comparing Esomeprazole vs. Pantoprazole 6 RCTs in 6090 randomized patients reported that 5413 (88.9%) patients completed and 677 (11.1%) discontinued early.

Esomeprazole to Rabeprazole

Five RCTs compared Esomeprazole and Rabeprazole in 3716 patients (60% patients were men and 40% women; mean age ranged from 35 to 51 years; One study, Fock 2005, randomised 134 non-erosive GERD (NERD) patients which included 80% Chinese, 9% smokers, 16% alcohol users; Eggleston 2009 included patients with GERD with associated heartburn (97% Caucasian; 66% smokers; 28% alcohol users); Maiti 2011 was conducted in India included Grade A and B patients while Laine 2011 included only Grade C and D patients according to the LA classification (88% white; smoker and alcohol user not provided); BMI data was provided only in 2 studies Laine 2011 (57% with BMI<30kg/m2) and Eggleston (mean BMI of 29 kg/m2); *H. Pylori* status was provided in 3 studies: Maiti 2011 (43% positive); Fock 2005 (45% positive); and Laine 2011 (<1% positive). Of the 5 RCTs comparing Esomeprazole vs. Rabeprazole 4 RCTs in 3582 patients reported that 3202 (89.6%) patients completed and 380 (10.6%) discontinued early.

Table 0-4 Overall Summary of Efficacy and Safety Outcomes (GERD - Esomeprazole vs other PPIs)

Outcome as reported in RCTs	E vs O 10 RCTS; N = 9,638	E vs P 12 RCTs; N = 10,503	E vs R 5 RCTs; N = 3,716
EFFICACY OUTCOMES according to hierarchy presented as # RCTs; RR (with 95% CI)			
Total Symptom relief	Not reported	5 RCTs; 0.94 (0.90, 0.98)	Not reported
Relief of heart burn at 4 weeks	8 RCTs; 1.08 (1.05, 1.12)	1 RCT; 0.99 (0.83, 1.17)	3 RCTs, 1.03 (0.96, 1.11)
Daytime resolution of heartburn	Not reported	Not reported	At 4 weeks 1 RCT; 0.69 [0.42, 1.14]
Nighttime resolution of heartburn	Not reported	Not reported	At 4 weeks 1 RCT; 0.80 [0.46, 1.41]
Relief of acid Regurgitation	Not reported	Not reported	1 RCT; 1.02 [0.90, 1.16]
Median time to first resolution of symptoms	4 RCTs; 1 to 4 days. No difference between E and O groups	2 RCTs, 2 days No difference between E and P groups	1 RCT; E vs R Median time to first 24 hour symptom free interval Heartburn =9.0 vs 8.5 days Regurgitation =7.5 vs 6 days
Median time to sustained resolution of symptom	5 RCTs; 5 to 12 days.	4 RCTs ; 6 to 17 days	1 RCT; Heartburn E : 9 to 12 days and R: 11 days Acid regurgitation E : 11 to 13 days and R: 9 days
Endoscopic confirmed esophagitis healing	At 4-8 weeks 6 RCTs; 1.07(1.05, 1.09)	At 8 to 12 weeks: 6 RCTs; 1.02 (1.00, 1.04)	At 4 to 8 weeks: 3 RCTs; 0.97 [0.92, 1.01]
Quality of Life scores	Not reported	Not reported	Not reported
Patients in remission (endoscopic healing of esophagitis and symptom resolution)	Not reported	Life table estimate provided no usable data	Not reported

Table 0-4 Overall Summary of Efficacy and Safety Outcomes (GERD - Esomeprazole vs other PPIs)			
Outcome as reported in RCTs	**E vs O 10 RCTS; N = 9,638**	**E vs P 12 RCTs; N = 10,503**	**E vs R 5 RCTs; N = 3,716**
% symptom free days and nights	7 RCTs; Symptom free days: E =70.3% and O = 68.0% Symptom free nights: E = 82.7% and O = 81.2%	2 RCTs; % of heartburn free days reported in E and P groups ranged from 67.3% to 70.7%.	1 RCT; 24-h periods free of heartburn E = 56 to 63% and R = 56% Acid regurgitation E = 58 to 62% and R = 60%
HARM OUTCOMES according to hierarchy presented as # RCTs; RR (with 95% CI)			
Mortality	2 RCTs; 0.69 (0.08, 5.69)	2 RCTs; 0.55 (0.12, 2.55)	Not reported in 3 RCTs; No deaths in 2 studies
Serious adverse events	Not reported	7 RCTs; 1.29 (0.84, 1.97)	Not reported in 4 RCTs, No SAE in Maiti 2011;
Withdrawal due to adverse effects	5 RCTs; 1.20 (0.83, 1.74)	5 RCTs; 1.23 (0.93, 1.63)	2 RCTs; 1.54 (0.89, 2.65)
Patients with at least 1 adverse event	3 RCTs; 1.00 (0.92, 1.09)	5 RCTs; 1.05 (0.93, 1.20)	1 RCT; 1.03 (0.88, 1.21)
Most common adverse effects (significant difference)	Headache: 5 RCTs, 1.29 (1.08, 1.54)	No significant difference between E vs P	No significant difference between E vs R

L vs other PPI (13 RCTs) in patients with GERD

13 RCTs (8 double blind and 5 open-label) compared Lansoprazole to other PPIs (5 RCTs had multiple treatment arms) in 7532 adult patients with symptomatic GERD. These studies were conducted in centres across USA, Canada, China, Japan, Scandinavia, Germany, Italy France and 31 Netherlands. Of the 7813 randomized patients. Patients in these RCTs were randomized to treatment with Lansoprazole 30mg OD or BD or to Omeprazole O20mg to O40mg OD or Pantoprazole P40 OD or BD or Rabeprazole 20mg OD. The mean duration of study ranged from 4 to 8 weeks except for Carling 1998 which is 48 weeks in durations. The primary outcome analysis included symptomatic relief or endoscopic healing; or symptomatic and/or endoscopic relapse or remission. Jasperson 1998 is a 4 weeks maintenance study in 30 patients who had achieved esophagitis healing and symptom relief following therapy with Omeprazole. In this study, the primary outcome is the maintenance of remission at week 4, defined as the absence of esophagitis and symptoms.

Twelve RCTs compared Lansoprazole to Omeprazole in 6648 patient (61% were men and 39% were women; mean age of patients ranged from 46 to 60 years except in 2 Pilotto 2007 (mean age: 78 years) and Adachi 2003 (mean age: 66 years); the number *H. pylori* positive patients ranged from 28% to 43% in 4 RCTs and was 68% to 80% in Pilotto 2007. Approximately one-quarter of the patients were smokers (reported only in 6 studies) and about half were alcohol users (reported in 4 studies). Ethnicity was reported in only 3 RCTS and ranged from 73 to 88%). Seven RCTs reported on 4246/4744 (89.5%) of the total randomized patients completing the study in these trials.

Five RCTs compared Lansoprazole to Pantoprazole in 1089 patients (63% were men and 37% women; mean age ranged from 50 to 62 years except for PIlotto 2007 (mean age 77 years); baseline data on ethnicity, smokers and alcohol users were not reported in any of the studies except for Dupas 2001 which included 22% smokers and 20% with daily alcohol consumption; BMI data was only reported in

one study Mulder 2002 with mean BMI of 27). Four RCTs reported on 534/628 (85%) of the total randomized patients completing the study in these trials.

Two RCTs compared Lansoprazole to Rabeprazole in 215 patients (48% were male and 52% females; mean age ranging from 65 to 78 years; Adachi 2003 included patients with baseline esophagitis Grade A to D (A: 20%; B: 53%; C: 25%; D: 2%) and 40% *H. pylori* positive patients. Pilotto 2007 included patients with baseline esophagitis severity Grade I to IV (I: 79%; II: 47%; III-IV: 24%) and 73% Pylori positive patients. The baseline data on BMI, ethnicity, smoking habits and alcohol consumption were not reported in any of the studies. One RCT reported on 150/160 (94%) patients completing the study.

Table 0-5 Overall Summary of Efficacy and Safety Outcomes (GERD - Lansoprazole vs other PPIs)

Outcome	L vs O 12 RCTs; N = 6648	L vs P 5 RCTs; N = 1089	L vs R 2 RCTs ; N = 215
EFFICACY OUTCOMES according to hierarchy presented as # RCTs; RR (with 95% CI)			
Total symptomatic relief	Not reported	At 4 to 8 weeks 2 RCTs, 0.96 (0.91, 1.02)	Not reported
Relief of heartburn	At 4 to 8 weeks 4 RCTs, 1.01 (0.98, 1.03)	At 4 to 8 weeks 3 RCTs; 0.95 (0.90, 0.99)	At 8 weeks 1 RCT; 0.83 (0.75, 0.92)
Relief of acid regurgitation	At 4 to 8 weeks 3 RCTs, 0.83 (0.75, 0.93)	At 4 to 8 weeks 2 RCTs; 0.94 (0.89, 1.00)	At 8 weeks 1 RCT; 0.83(0.72, 0.96)
Relief of dysphagia	At 4 to 8 weeks 2 RCTs; 0.98 (0.94, 1.03)	At 4 to 8 weeks 2 RCTs; 1.00 (0.97, 1.03)	At 8 weeks 1 RCT; 1.00 (0.98, 1.02)
Relief of epigastric pain	At 8 weeks 1RCT; 0.87 (0.78, 0.97)	At 8 weeks 1 RCT; 0.87 (0.78, 0.97)	At 8 weeks 1 RCT; 0.83(0.75, 0.92)
Median time to sustained resolution of symptom	Median time to first episode of 3 consecutive days of heartburn-free interval: 3 days; P=0.285 retrosternal pain free interval: 4 days; P=0.875	Not applicable	Not applicable
Endoscopic confirmed esophagitis healing	At 4 to 8 weeks 7 RCTs, 1.00 (0.96, 1.04)	At 4 to 8 weeks 3 RCTs, 0.96 (0.91, 1.01)	At 8 weeks 2 RCTs; 0.90 (0.80, 1.01)
Quality of Life scores	Not reported	Not reported	Not reported
Endoscopic relapse or recurrence	At 4 weeks 1 RCT; 8.00 (1.21, 52.69) At 48 weeks 1 RCT; 1.07 (0.47, 2.42)	At 4 weeks 1 RCT; 1.14 (0.69, 1.90)	Not applicable
Symptomatic relapse or recurrences	At 48 weeks 1 RCT, 0.48 (0.04, 5.27)	At 4 weeks 1 RCT; 1.00 (0.49, 2.05)	Not applicable
HARM OUTCOMES according to hierarchy presented as # RCTs; RR (with 95% CI)			
Mortality	Not reported in 9 studies. No deaths in 3 RCTs	Not reported in 3 studies, No deaths in 2 RCTs	Not reported
Serious adverse events	Not reported in 9 RCTs 3 RCTs, 1.00 [0.23, 4.39]	1 RCT; 1.14 (0.35, 3.70)	Not reported
Withdrawal due to adverse events	6 RCTs; 1.05 (0.73, 1.51)	2RCTs, 2.17 (0.67, 6.97)	Not reported
Patients with at least 1 adverse event	7 RCTs; 1.00 (0.94, 1.06)	2 RCTs, 0.60 (0.42, 0.85)	1 RCT; 1.00 (0.06, 15.71)
Most common adverse event (significant)	Diarrhea 5 RCTs; 1.23 (1.02, 1.48)	No significant difference between L and P	Not reported

Peptic ulcer disease

Esomeprazole to other PPIs (6 RCTs) in patients with PUD

A total of 6 RCTS in 1753 patients (3 double blind; 1 RCT outcome assessor was blinded; and 2 open label RCTs) compared Esomeprazole to other PPIs. No RCT met the inclusion criteria comparing Esomeprazole to Rabeprazole. Five RCTs compared Esomeprazole to Omeprazole in 1553 patients and one RCT compared Esomeprazole to Pantoprazole in 200 adult patients with peptic ulcer or gastritis who were *H. pylori* positive. These RCTs were conducted in Europe, Canada, Czech Republic, Hungary, Poland, Germany and Taiwan. 1691(96%) randomized patients completed the study. Patients were randomized to treatment with Esomeprazole 20mg BD or 40mg BD or Omeprazole 20 mg BD or Pantoprazole 40 mg BD in addition to antibiotics (Clarithromycin 500mg BD plus Amoxicillin 1g BD; Metronidazole, 400mg BD or 500 mg BD, and Clarithromycin 250 mg BD) for duration of 1 week. The duration of follow up in studies ranged from 4 to 8 weeks. Only 1 study Van Zanten 2003 after 1 week of treatment with PPI and antibiotics continued patients randomized to Omeprazole 20mg BD for additional 3 weeks of treatment and administered placebo BD to patients randomized to Esomeprazole treatment group. In one RCT Hsu 2005 comparing Esomeprazole to Rabeprazole, patients with peptic ulcers during initial endoscopy received an additional 3 weeks of monotherapy with Pantoprazole 40 mg orally once daily, while patients with gastritis only took 3 weeks of antacid following eradication therapy. Of the 1753 patients 969 (55%) were men and 784 (45% women with mean age ranging from 42 to 59 years. BMI data was not provided in any trial. One study comparing Esomeprazole to Omeprazole, Van Zanten 2003 with 379 patients included 354 (93%) Caucasian patients; 124 patients (33%) were smokers; and 228 (60%) consumed alcohol. One study (Hsu 2005) comparing Esomeprazole to Pantoprazole in 200 patients provided baseline characteristics of patients - 27% were smokers; 14% ingested coffee; 25% ingested tea; 24% had underlying diseases; 12% consumed alcohol; and 41% had history of peptic ulcer.

The primary efficacy variable was *H. pylori* eradication determined by follow-up endoscopy with histology and culture and/or rapid urease test. Eradication was defined differently in trials. Trials comparing Esomeprazole to Omeprazole defined it as only patients with a negative UBT result at both follow-up visits were considered to be *H. pylori*-negative. Trials comparing Esomeprazole to Pantoprazole defined it as (1) negative results of both rapid urease test and histology, or (2) a negative result of urea breath test.

Table 0-6 Overall Summary of Efficacy and Safety Outcomes (PUD - Esomeprazole vs other PPIs)

Outcomes	E vs O 5 RCTS; N = 1553	E vs P 1 RCT; N = 200	E vs R No RCT identified
EFFICACY OUTCOMES according to hierarchy presented as # RCTs; RR (with 95% CI)			
Total symptomatic relief	Not reported	Not reported	
Individual symptom relief Heart burn @ 4 weeks	2 RCTs; 0.97 (0.70, 1.35)	Not reported	
Individual symptom relief Epigastric pain @ 4 weeks	2RCTs; 0.84 (0.56, 1.26)	Not reported	
Time to first resolution of symptoms	Not reported	Not reported	
Healing of ulcer	At 4 weeks 1RCT; 0.99 (0.93, 1.05)	At 8 weeks 1RCT; 1.07 (0.91, 1.25)	

Table 0-6 Overall Summary of Efficacy and Safety Outcomes (PUD - Esomeprazole vs other PPIs)			
Outcomes	**E vs O 5 RCTS; N = 1553**	**E vs P 1 RCT; N = 200**	**E vs R No RCT identified**
***H. pylori* eradication**	At 6 to 8 weeks 5 RCTs; 1.03 (0.98, 1.07);	At 8 weeks 1RCT; 1.15 (1.03, 1.27)	
Quality of life	Not reported	Not reported	
Recurrence or relapse of symptoms	Not reported	Not reported	
HARM OUTCOMES according to hierarchy presented as # RCTs; RR (with 95% CI)			
All-cause mortality	1 RCT reported no deaths	Not reported	
Total serious adverse events	3 RCTS; 0.20 (0.02, 1.73)	Not reported	
Withdrawal due to adverse event	2 RCTs; 1.01 (0.33, 3.11);	1 RCT; 0.50 (0.09, 2.57)	
Patients with at least 1 adverse event	5 RCTs; 1.00 (0.90, 1.11)	1 RCT; 0.63 (0.35, 1.12)	
Specific adverse event (Significant)	None	None	

Lansoprazole to other PPIs (19 RCTs) in patients with PUD

A total of 19 RCTs (4 double blind; 4 single blind with blinding of outcome assessor and 11 open label RCTs) compared Lansoprazole to other PPIs. No RCT was identified that compared Lansoprazole to Pantoprazole. Fifteen RCTs compared Lansoprazole to Omeprazole in 2265 patients and seven RCTs compared Lansoprazole to Rabeprazole in 1574 adult patients with endoscopically confirmed peptic ulcer and *H. pylori* positive. Three RCTs had multiple treatment arms. These RCTs were conducted in Sweden, Italy, Japan and Taiwan. Patients were randomized to treatment with PPI- Lansoprazole (30mg OD or 30mg BD) or to Omeprazole (20mg OD or 40mg OD, or 20mg BD) or to Rabeprazole 10mg BD or 20 mg BD in addition to antibiotics (Clarithromycin 500mg BD or 200mg BD or TDS or 400mg BD) or (Metronidazole 250 mg BD or 400mg BD) plus (Amoxicillin 200mg BD OR 250 mg TDS or 750 mg BD or 1000mg BD or 500mg TDS) or Tinidazole (500mg BD) for duration of 1 week. The duration of follow up in studies ranged from 4 to 16 weeks in most trials and up to a year in Fanti 2001 study. Three studies (Florent 1994; Murakami and Sato 2003; and Murakami 2008) allowed half dose of H_2RA was continued until eradication was assessed. In one study Eralp 2000 both treatment groups received maintenance therapy of famotidine 40 mg OD for six weeks, followed by endoscopic examination.

Of the 2265 patients included in 15 RCTs comparing Lansoprazole to Omeprazole, 1698(75%) were men and 567 (25%) were women with mean age ranging from 46 to 56 years. BMI data was not provided in 13/15 trials. Two trials provided data on mean BMI $\pm$ SD was 23 $\pm$ 3.0 and race (Taiwanese patients) in 2 RCTs Chang and Chiang 1995 and Chang and Lee 1995). Two trials included Japanese patients (Inaba 2002 and Murakami 2008). Race was not reported in 11/15 trials. Smoking was reported in 8 of 15 RCTs (Ekstrom 1994; Florent 1994; Chang and Chiang 1995; Chang and Lee 1995; Dobrilla 1995; Fanti 2001; Ungan 2001 and Inaba 2002) and 442(19.5%) of total randomized patients in these RCTs were reported as smokers. Alcohol consumption was reported in 6 RCTs (Ekstrom 1994; Florent 1994; Chang and Chiang 1995; Dobrilla 1999; Fanti 2001; and Ungan 2001) and 309(13.6%) of randomized patients in these RCTs consumed alcohol. Five RCTs in 754 patients did not report on how many patients completed the study. Of the remaining 1511 patients from 10 RCTS, 1238 (82%) completed the study and 273 (18%) discontinued.

Of the 1574 patients in 7 RCTS comparing Lansoprazole to Rabeprazole (3 RCTS also had Omeprazole treatment arm), 66% participants were men and 44% women with mean age ranging from 48 to 52 years. BMI data was not provided in any trial. Three studies included Japanese patients (Inaba 2002; Kwabata 2003; and Murakami 2008). Smoking was reported in 4 out of 7 RCTs (Miwa 2000; Inaba 2002; Kwabata 2003; and Liu 2013) and 318(20.2%) of randomized patients in these RCTs were smokers. Alcohol consumption was reported in 2 RCTs (Miwa 2000 and Liu 2013) and 205 (13%) of randomized patients in these RCTs consumed alcohol. Of the 1574 patients in 7 RCTS, 2 RCTs in 333 patients did not report on how many patients completed the study. Based on 5 RCTS in 1231 patients 1196 (97%) completed the study and 35 (3%) discontinued.

In RCTs comparing Lansoprazole to Omeprazole or Rabeprazole, the primary efficacy variable included were *H. pylori* eradication determined by follow-up endoscopy with histology and culture and/or rapid urease test and healing of ulcer. Treatment was considered successful if the results of both endoscopy and/or rapid urease test were negative. In one study (Murakami 2008) treatment success was considered when rapid urease test, culture, histologic examination, and the urea breath test (UBT) were all negative.

Table 0-7 Overall Summary of Efficacy and Safety Outcomes (PUD - Lansoprazole vs other PPIs)

Outcomes	L vs O 15 RCTs ; N = 2265	L vs R 7 RCTS; N = 1574	L vs P No RCT identified
EFFICACY OUTCOMES according to hierarchy presented as # RCTs; RR (with 95% CI)			
Total symptomatic relief	Not reported	Not reported	
Individual symptom relief **Daytime relief of ulcer pain @ 4 weeks**	1 RCT; 1.43(1.15, 1.78)	Not reported	
Individual symptom relief **Night time relief of ulcer pain @ 4 weeks**	1 RCT; 1.43(1.22, 1.68);	Not reported	
Healing of ulcer @ 2 weeks	2 RCTs; 1.05(0.94, 1.16)	Not reported	
Healing of ulcer @ 4 to 8 weeks	8 RCTs; 1.04(1.01, 1.07)		
Quality of life	Not reported	Not reported	
Recurrence or relapse of symptoms	Not reported	Not reported	
***H. pylori* eradication**	At 1 to 8 weeks 12 RCTs; 1.03(0.97, 1.08)	At 1 to 16 weeks 7 RCTs; 0.97(0.93, 1.01)	
***H. pylori* eradication at 6 months**	1 RCT; 1.04(0.84, 1.29)	Not applicable	
HARM OUTCOMES according to hierarchy presented as # RCTs; RR (with 95% CI)			
Mortality	5 RCTs; 0.37(0.02, 8.82)	Not reported	
Serious adverse events	4 RCTs; 0/318 vs 0/234; RR is not estimable	Not reported	
Withdrawal due to adverse events	4 RCTs; 0.45(0.16, 1.27)	2 RCTs; 1.02(0.23, 4.47)	
Patients with at least 1 adverse event	5 RCTs; 0.89(0.75, 1.07)	4 RCTs; 0.94(0.75, 1.18)	
Specific adverse event **(significant)**	No significant difference between L vs O treatment groups	Diarrhea 3 RCTs; 0.51(0.30, 0.85)	

SUMMARY OF SUBGROUP ANALYSIS

Data on analyses of subgroups was provided in a small subset of RCTs meeting the inclusion criteria for patients with GERD as well as PUD. It is important to note that subgroup analyses are hypothesis generating and the findings need to be tested in future adequately powered randomized controlled trials.

Esomeprazole compared to Omeprazole in patients with GERD

Of the 10 RCTs (N = 9638) meeting the inclusion criteria, subgroup analysis was presented for one outcome measure - endoscopic confirmed healing of esophagitis based on LA grade severity of GERD at baseline in 4 RCTS.

1) Based on 4 RCTs (N =6,192) in 64% of total randomized patients all 4 LA severity grades (A, B, C and D) subgroups showed that Esomeprazole provide significant advantage compared to Omeprazole. Patient group with more severe disease (Grade C and D) showed a greater degree of benefit.

Esomeprazole vs. Pantoprazole in patients with GERD

Of the 12 RCTS (N =10 503), subgroup analysis was presented for two outcome measures in 3 RCTs.

1) Endoscopic confirmed healing of esophagitis based on LA grade severity of GERD at baseline was reported in 2 RCTs (N =3,331) in 31.7% of total randomized patients. Grade A ulcer patients showed no significant difference in esophageal healing rate between treatment groups. In Grade B, C and D patients, Esomeprazole provided a significant advantage compared to Pantoprazole.
2) Remission rates based on subgroup of patients with presence or absence of *H. pylori* infection at baseline showed no significant difference between Lansoprazole and Pantoprazole treatment groups based only on 1 RCT in 1,294 patients.

Esomeprazole vs. Rabeprazole in patients with GERD

Of the 5 RCTs in 3,716 patients, subgroup analysis was presented for two outcome measures in 4 RCTs.

1) Based on 2 RCTs in (N =2120) in 57% of total randomized patients, sustained resolution at week 4 in patients with Grade C or Grade D severity of GERD at baseline showed no significant difference between treatment groups
2) Based on 2 RCTs (N =1870)
    - Healing of esophagitis at week 4 in patients with grade C severity of GERD at baseline, showed no significant difference between treatment groups. However, in 240 patients with grade D severity at baseline, healing of esophagitis was significantly greater in Rabeprazole group as compared to Esomeprazole group.
    - Healing of esophagitis at week 8 in patients with grade C or Grade D severity at baseline showed no significant difference between treatment groups.

Lansoprazole vs. Omeprazole in patients with GERD

Of the 12 RCTS (N =6,648), subgroup analysis was presented for three outcome measures in 2 RCTs.

- Based on 2 RCTs in 1485 patients, healing of esophagitis at week 4 in patients with different grade severity (Savary-Miller classification: I to IV) at baseline, showed no significant difference between treatments groups at all grades. As well, based on 3 RCTs in 1604 patients, no difference was observed at week 8 except in Grade III-IV patients in which Omeprazole showed a significantly greater healing rate of esophagitis compared to Lansoprazole.
- Based on 1 RCT in 142 patients, healing of esophagitis at week 8 in patients with *H. pylori* infection at baseline showed a significantly greater response in Lansoprazole group compared to Omeprazole group but no significant difference between treatment groups for patients who were *H. pylori* negative patients at baseline.
- Based on 1 RCT, healing of esophagitis at week 8 in a subgroup of 78 patients who were cured of *H. pylori* at end of treatment, showed a significantly greater healing rate with Lansoprazole compared to Omeprazole treatment group. No significant difference was observed in healing of esophagitis in a subgroup of 28 patients who were *H. pylori* positive at end of treatment.

Lansoprazole vs. Pantoprazole in patients with GERD

Of the 5 RCTS (N =1,089) subgroup analysis was presented for two outcome measures in 3 RCTs.

- Based on one RCT (N =152) in 14% of total randomized patients, with different severity of GERD at baseline (Savary-Miller classification: Grade I to IV), healing of esophagitis was not significantly different between Lansoprazole and Pantoprazole treatment groups.
- Based on one RCT (N=155) in 14% of total randomized patients, healing rate of esophagitis at week 8 in patients who were *H. pylori* positive or negative at baseline was not significantly different between Lansoprazole and Pantoprazole treatment groups.
- Based on one RCT (N =105) in 10% of total randomized patients, healing rate of esophagitis at week 8 in patients who were cured of *H. pylori* at end of treatment was significantly greater with Lansoprazole compared to Omeprazole. No significant difference was observed in patients who were *H. pylori* positive at end of treatment.

Lansoprazole vs. Rabeprazole in patients with GERD

Of the 2 RCTs (N =215) subgroup analysis was presented for three outcome measures in 3 RCTs.

- Based on 1 RCT (N = 150) in 70% of total randomized patients, healing of esophagitis at week 8, in patients with different severity of GERD at baseline (Grade 1, 2,3 and 4) showed no significant difference between Lansoprazole and Rabeprazole treatment groups.
- Based on 1 RCT (N = 91) in 42% of total randomized patients, healing of esophagitis at week 8, in patients who were *H. pylori* positive or negative at baseline, no significant difference was observed between Lansoprazole and Rabeprazole treatment groups.
- Based on 1 RCT (N = 143) in 67% of total randomized patients, healing of esophagitis at week 8, in patients who were cured of *H. pylori* infection after treatment or were still positive, no significant difference was observed between Lansoprazole and Rabeprazole treatment groups.

Peptic ulcer disease

Esomeprazole vs. Omeprazole in patients with PUD

No RCT provided data on any subgroup analysis.

Esomeprazole vs Pantoprazole in patients with PUD

No RCT provided data on any subgroup analysis.

Esomeprazole vs. Rabeprazole in patients with PUD

No RCT met the inclusion criteria.

Lansoprazole vs Omeprazole in patients with PUD

Of the 15 RCTs in 2,265 patients, subgroup analysis was presented for two outcome measures in 2 RCTs.

- Based on 1 RCT (N = 116) in 5% of total randomized patients, *H. pylori* eradication rates at week 1 showed no significant difference between Lansoprazole and Omeprazole treatment groups in patients who were homozygous, heterozygous or poor metabolizers of CYP2C19 enzyme.
- Based on 1 RCT in 24 patients who were Clarithromycin sensitive and 233 who were Metronidazole sensitive, *H. pylori* eradication rates at week 4 showed no significant difference between Lansoprazole and Omeprazole treatment groups.
- Based on 1 RCT in 106 patients who were Clarithromycin resistant and 80 who were Metronidazole resistant, *H. pylori* eradication rates at week 4 showed no significant difference between Lansoprazole and Omeprazole treatment groups.

Lansoprazole vs. Pantoprazole in patients with PUD

No RCT met the inclusion criteria.

Lansoprazole vs. Rabeprazole in patients with PUD

Of the 7 RCTs (N =1574), subgroup analysis was presented for two outcome measures in 3 RCTs.

- Based on 1 RCT (N = 121) in 7% of total randomized patients, *H. pylori* eradication rates at week 1 showed no significant difference between Lansoprazole and Rabeprazole treatment groups in patients who were homozygous, heterozygous or poor metabolizers of CYP2C19 enzyme.
- Based on 1 RCT (N = 173) in 11% of total randomized patients, *H. pylori* eradication rates at week 6 showed no significant difference between Lansoprazole and Rabeprazole treatment groups in patients who were homozygous, heterozygous or poor metabolizers of CYP2C19 enzyme.
- Based on 1 RCT (N = 393) in 25% of total randomized patients who were antibiotic sensitive, *H. pylori* eradication rates at week 4 showed no significant difference between Lansoprazole and Rabeprazole treatment groups

4 DISCUSSION

4.1 Summary of Available Evidence

In this systematic review, 38 unique RCTs met the inclusion criteria for patients with GERD and 25 RCTs for patients with PUD. Critical appraisal of all included trials was graded based on Cochrane Risk of bias tool evaluating the following factors – randomization; allocation concealment; blinding of participant, physician and outcome assessor; patient attrition; selective outcome reporting; and source of funding. Each factor was judged as low, unclear or high risk of bias. Results are presented for GERD and PUD separately based on comparing Esomeprazole versus other PPIs (Omeprazole, Pantoprazole and Rabeprazole) and Lansoprazole versus other PPIs (Omeprazole, Pantoprazole and Rabeprazole).

Outcomes are presented according to hierarchy of outcome measures as stated in the protocol with outcome specific grading of evidence presented in Summary of Findings Table 1 to 10 (Refer to Appendix 8). Also section 4.8 provides data of outcomes for specific comparisons in Tables 4-4, 4-5 for patients with GERD and in Tables 4-6 and 4-7 for patients with peptic ulcer disease.

4.2 Interpretation of Results

Due to the paucity of high-quality data, the results presented in this review provide weak or poor quality evidence of the comparative efficacy and harm of different PPIs. For outcomes graded as low quality - future research is very likely to have an important impact on our confidence in the estimate and may change the estimate. We are very uncertain about the effect estimate for outcomes that are graded as very low quality.

The limited data provided in specific subgroups are hypothesis generating and future randomized controlled comparative trials are needed to confirm whether specific PPIs are more efficacious in certain subgroup of patients with GERD or PUD.

No high quality observational study comparing different PPIs to specifically study long term adverse events was identified.

4.3 Strengths and Limitations

4.3.1 Strengths

This review provides the most comprehensive evidence for comparative efficacy and harm outcomes of specific PPI comparisons (Esomeprazole or Lansoprazole compared to Omeprazole or Pantoprazole or Rabeprazole) in patients with GERD or PUD. We followed the rigorous gold standard systematic review methodology of the Cochrane Collaboration and included all published randomized controlled trials comparing PPIs of interest in this review. We evaluated the risk of bias of each included study using the Risk of Bias tool of the Cochrane collaboration. We used the Cochrane review Manager 5.2 software to meta-analyze data when appropriate. Also evidence for each specific efficacy or harm outcome is

reported according to the hierarchy of outcomes stated in the protocol and it was graded as high, moderate, low or very low quality of evidence using the GRADE pro software and presented as Summary of Findings table (SoF Table 1 to 10 in Appendix 8).

4.3.2 Limitations

Although the review included randomized controlled trials of comparative effectiveness, the highest level study design as the inclusion criteria, critical appraisal of included studies showed varying quality. The factors evaluating selection bias, performance and detection bias, attrition bias, selective reporting bias and source of funding bias resulted in judgement of most studies as unclear or high risk of bias in several categories. Studies used varying definition of outcomes (total symptomatic relief or individual symptomatic relief).

Not all outcomes of interest were reported in trials meeting the inclusion criteria. Data has been reported in a subset of trials meeting the inclusion criteria for each comparison and a high risk of selective reporting bias between and within trials was observed. We did not contact authors of these studies to obtain missing information due to time constraints. Mortality, serious adverse events and details of these events, withdrawal due to adverse events and reasons for withdrawals were not reported in over half the trials meeting the inclusion criteria and limited our ability to draw definitive conclusions. No new randomized trials or observational studies for comparative safety of PPI were identified in this updated review. Since many trials did not report on how many patients discontinued the study and how they were accounted in data analysis, we performed an intention to treat analysis using conservative analysis (patients lost were deemed as not to have experienced a positive response).

Publication bias was assessed in comparisons for which at least 10 trials met the inclusion criteria. The funnel plot for the outcomes heartburn relief (Esomeprazole vs Omeprazole) and total symptomatic relief (Esomeprazole vs Pantoprazole comparison) in patients with symptomatic GERD showed evidence of publication bias. In patients with PUD, funnel plot for the outcome *H. pylori* eradication (Lansoprazole compared to Omeprazole) showed the presence of publication bias.

Very limited data was provided in sub group of patients included in RCTs meeting the inclusion criteria. Subgroup analyses for all comparisons based on age, gender, race, BMI, smoking, alcohol consumption, genotype and CYP3A4 liver enzyme, associated co-morbidity (liver disease); and concomitant medications could not be performed.

For trials meeting inclusion criteria in GERD, most *subgroup analysis* was limited to small number of trials based on several factors - various grades of severity of GERD at baseline, *H. pylori* status at baseline, or at end of treatment. Four out of 10 trials comparing Esomeprazole to Omeprazole provided data on endoscopic healing of esophagitis in a subgroup of patients based on severity of GERD at baseline; two out of 12 RCTs comparing Esomeprazole to Pantoprazole provided data on this outcome; and two out of 5 RCTs comparing Esomeprazole to Rabeprazole provided data on this outcome. For Lansoprazole versus other PPI comparison of a total of 19 RCTS, only one RCT provided data for each of the comparisons (with Omeprazole, Pantoprazole and Lansoprazole respectively) for healing of

esophagitis. Subgroup analysis for remission rate was provided in 1 RCT based on status of *H. pylori* at baseline. Therefore, no conclusions can be drawn from subgroup analysis in patients with GERD.

Of the 25 trials meeting the inclusion criteria for PUD for various comparisons, subgroup analyses based on type of CYP2C19 metabolizer and sensitivity or resistance to specific antibiotics was selectively reported based on 5 RCTs. Therefore, no conclusions can be drawn from subgroup analysis in patients with PUD.

As most studies were performed as multinational, multicentre trials in Europe, USA, Japan and Taiwan including some studies that were performed in multi centres in Canada generalizability to the Canadian health care system may be feasible but limited. In addition, the generalizability issues associated with randomized controlled trials, where patients are carefully monitored need to be considered.

Applicability of trial results to community/clinical practice was difficult to determine. The studies generally excluded patients with bleeding disorder or signs of GI bleeding within 3 days prior to randomization; history of gastric or esophageal surgery; evidence of Zollinger-Ellison syndrome; primary motility disorder; esophageal stricture; Barrett's esophagus; upper GI malignancy; severe concomitant disease (liver cirrhosis, COPD, diabetes, renal failure, congestive heart failure, anemia); pregnant or lactating; patients taking PPI or H2RA on a daily basis 2 weeks prior endoscopy; patients taking diazepam, quinidine, dilantin, warfarin, anticholinergic, prostaglandin, sucralfate, corticosteroids or anti-coagulants, hypersensitive to Omeprazole or aluminium/magnesium hydroxide; patients with history of drug abuse, chronic alcoholism or other conditions with poor compliance; patients on NSAID, COX-2 inhibitors, aspirin, PPI or H_2RA use in last 10 days prior to study entry. This pre selection of patients may have resulted in a group of patients whose disease was less severe in comparison to patients who were not enrolled.

Another concern was that most trials were either funded by the manufacturer or source of funding was not reported which is known to lead to high risk of bias by either overestimating or underestimating the effect size of a particular PPI.

In the maintenance trials, patients were enrolled on the basis of successful treatment with acute PPI treatment. This pre selection may have resulted in a patient population that was adherent to treatment and could tolerate adverse effects of the PPI previously used in the acute phase.

4.4 Other Issues for Consideration

4.4.1 Key gaps in evidence

GERD is a chronic disease where patients usually require prolonged therapy. Only five of the 38 included RCTs looked at maintenance or long-term PPI therapy. The two largest *maintenance studies* looked at Esomeprazole versus Pantoprazole therapy, but only Goh 2007 (N=1314) provided the number of patients on remission at 6 months. A smaller trial Scholten 2007 (N=199) provided only symptom score and was an on-demand therapy and therefore could not be pooled together with Goh 2007. The largest

study Labenz 2005b (N=2813) provided life-table estimates instead of raw data for this outcome. Because life-table estimates provide an overestimate of the observed effect, data from this study could not be used to generate an overall estimate in meta-analysis.

In patients with PUD, no head-to-head studies have been included that compared Esomeprazole vs Rabeprazole as well as Lansoprazole vs Pantoprazole. Only one small trial (N=200) compared Esomeprazole to Pantoprazole in patients with PUD. For GERD comparisons, two open-label RCTs are included and no double-blind RCT was conducted comparing Esomeprazole with Rabeprazole.

There are a total of 38 head-to-head RCTs included in the GERD review, and for each drug-drug comparison, the number of RCTs range from 2 RCTS (L vs R comparison) to 12 RCTs (L vs O; E vs P). Not all outcomes of interest are reported by all of the included studies. In many efficacy outcomes, data usable for meta-analysis was provided by 2-3 trials and this small number limited our ability to adjust for heterogeneity using sensitivity analysis or perform separate analysis for open-label trials.

5 CONCLUSIONS

Implications for Practice

Due to the paucity of high-quality data, the results presented in this review provide weak/poor evidence of the comparative efficacy and harm of different PPIs. For outcomes graded as low quality - future research is very likely to have an important impact on our confidence in the estimate and may change the estimate. For outcomes graded as very low quality - we are very uncertain about the estimate.

Implications for Research

Adequately powered randomized controlled trials comparing different PPIs are needed to evaluate long term benefits and harm of PPI therapy and should report on all outcome measures specified in the hierarchy of health outcomes in this review.

Trials in specific subgroups based on baseline characteristics (age, gender, race, BMI, smoking, alcohol consumption, genotype of CYP2C19 and CYP3A4 liver enzyme, associated co-morbidity; concomitant medications, severity of grade of GERD; and presence of *H. pylori* infection) are required to determine if differences in efficacy exist between different PPIs.

Specific adverse effects associated with long-term therapy using different PPIs need to be studied in high quality, prospective well designed long term observational studies incorporating data on dosage and duration of treatment with extended follow up.

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TRIALS MEETING INCLUSION CRITERIA

(Sorted by ascending publication year)

GERD comparison 1: Esomeprazole vs. Omeprazole (10 RCTS)

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GERD comparison 2: Esomeprazole vs. Pantoprazole (12 RCTs)

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GERD comparison 3: Esomeprazole vs. Rabeprazole (5 RCTs)

1) Fock KM, Teo EK, Ang TL, Chua TS, Ng TM, Tan YL. Rabeprazole vs Esomeprazole in non-erosive gastro-esophageal reflux disease: a randomized, double-blind study in urban Asia. World journal of gastroenterology: WJG. 2005;11(20):3091-3098
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GERD comparison 4: Lansoprazole vs. Omeprazole (12 RCTs)

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GERD comparison 5: Lansoprazole vs. Pantoprazole (5 RCTS)

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GERD comparison 6: Lansoprazole vs. Rabeprazole (2 RCT)

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<u>Peptic ulcer disease</u> (total = 25 RCTs)

PUD comparison 7: Esomeprazole vs. Omeprazole (5 RCTs)

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clarithromycin and metronidazole is effective in eradicating *Helicobacter pylori* in the absence of antimicrobial resistance. Aliment Pharmacol Ther 2003; 18:799–804.
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PUD comparison 8: Esomeprazole vs. Pantoprazole (1 RCT)

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PUD comparison 9: Esomeprazole vs. Rabeprazole (No RCT)

PUD comparison 10: Lansoprazole vs. Omeprazole (15 RCTs)

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PUD comparison 11: Lansoprazole vs. Pantoprazole (No RCT)

PUD comparison 12: Lansoprazole vs. Rabeprazole (7 RCTs) of which 3 are duplicate RCTs)

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3) Inaba T, Mizuno M, Kawai K, et al. Randomized open trial for comparison of proton pump inhibitors in triple therapy for *Helicobacter pylori* infection in relation to CYP2C19 genotype. Journal of Gastroenterology & Hepatology. 2002; 17(7):748-753.
4) Murakami K, Sato R, Okimoto T, et al. Eradication rates of clarithromycin-resistant *Helicobacter pylori* using either Rabeprazole or Lansoprazole plus amoxicillin and clarithromycin. Alimentary Pharmacology & Therapeutics. 2002; 16(11):1933-1938.
    - Murakami K, Nasu M, Fujioka T, et al. Evaluation of the eradication effect for *Helicobacter pylori* against clarithromycin sensitive strains and clarithromycin resistant strains in triple therapy with Rabeprazole, amoxycillin and clarithromycin: randomized comparison with triple therapy using Lansoprazole. Gut 2002; 51 A99 (Abstract).
5) Kawabata H, Habu Y, Tomioka H, et al. Effect of different proton pump inhibitors, differences in CYP2C19 genotype and antibiotic resistance on the eradication rate of *Helicobacter pylori* infection

by a 1-week regimen of proton pump inhibitor, amoxicillin and clarithromycin. Alimentary Pharmacology & Therapeutics. 2003; 17(2):259-264.

6) Murakami K, Okimoto T, Kodama M, Sato R, Watanabe K, Fujioka T. Evaluation of three different proton pump inhibitors with amoxicillin and metronidazole in retreatment for *Helicobacter pylori* infection. Journal of Clinical Gastroenterology. Feb 2008; 42(2):139-142.

7) Liu MK. Wu IC. Lu CY. Kuo CH. Yu FJ. Liu CJ. Hsu PI. Hsu WH. Su YC. Chen A. Wu DC. Kuo FC. Chen JJ. Randomized trial comparing Rabeprazole- versus Lansoprazole-based *Helicobacter pylori* eradication regimens. Kaohsiung Journal of Medical Sciences. 2013 Jul.; 29(7):379-84.

7 APPENDICES

Appendix 1: Literature Search Strategy

GERD RCTs Medline (282); Embase (1182); CENTRAL (225)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 exp Gastroesophageal Reflux/ (21398)
2 gerd.mp. (5432)
3 or/1-2 (22529)
4 exp Proton Pump Inhibitors/ (13725)
5 proton pump inhibitor$.mp. (11319)
6 (Pantoprazole or Lansoprazole or Esomeprazole or Omeprazole or Rabeprazole).mp. (11966)
7 or/4-6 (18945)
8 3 and 7 (4026)
9 animals/ not (humans/ and animals/) (3812075)
10 8 not 9 (4001)
11 limit 10 to english language (3468)
12 systematic review.tw. (45098)
13 meta-analysis.pt. (45856)
14 randomized controlled trial.pt. (367653)
15 pragmatic clinical trial.pt. (20)
16 controlled clinical trial.pt. (87895)
17 randomized.ab. (287481)
18 clinical trials as topic/ (168694)
19 randomly.ab. (208599)
20 trial.ti. (123413)
21 or/12-20 (916112)
22 11 and 21 (858)
23 22 and (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).ed. (282)

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Database: Embase <1974 to 2014 March 05>
Search Strategy:

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1 exp gastroesophageal reflux/ (44867)
2 gerd.mp. (9679)
3 1 or 2 (46529)
4 exp proton pump inhibitors/ (51117)
5 proton pump inhibitor$.mp. (27036)
6 (Pantoprazole or Lansoprazole or Esomeprazole or Omeprazole or Rabeprazole).mp. (36980)
7 or/4-6 (53408)
8 3 and 7 (11657)
9 meta-analysis.tw. (66803)
10 systematic review.tw. (57459)
11 MEDLINE.tw. (70109)
12 randomized controlled trial/ (371797)
13 random$.tw. (905054)
14 double-blind$.tw. (151883)

15 or/9-14 (1126382)
16 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5584194)
17 15 not 16 (1000789)
18 8 and 17 (1728)
19 18 and (2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).em. (1261)
20 limit 19 to english language (1182)
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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>
Search Strategy:

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1 (gastroesophageal reflux or gerd).mp. (1893)
2 (gastrooesophageal reflux or gord).mp. (130)
3 1 or 2 (1920)
4 (Pantoprazole or Lansoprazole or Esomeprazole or Omeprazole or Rabeprazole).mp. (4037)
5 (proton pump$ adj3 (antagon$ or inhibit$)).mp. (1614)
6 4 or 5 (4398)
7 3 and 6 (735)
8 limit 7 to yr="2009 -Current" (225)

Peptic ulcer disease RCTs Medline (213); Embase (1015); Cochrane (151)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 peptic ulcer.mp. or exp Peptic Ulcer/ (79112)
2 gastric ulcer.mp. or exp Stomach Ulcer/ (27085)
3 Duodenal ulcer.mp. or exp Duodenal Ulcer/ (27714)
4 1 or 2 or 3 (82561)
5 exp Proton Pump Inhibitors/ (13702)
6 proton pump inhibitor$.mp. (11268)
7 (Pantoprazole or Lansoprazole or Esomeprazole or Omeprazole or Rabeprazole).mp. (11949)
8 5 or 6 or 7 (18885)
9 4 and 8 (5487)
10 animals/ not (humans/ and animals/) (3807926)
11 9 not 10 (5081)
12 limit 11 to english language (3998)
13 systematic review.tw. (44775)
14 meta-analysis.pt. (45620)
15 randomized controlled trial.pt. (366899)
16 pragmatic clinical trial.pt. (18)
17 controlled clinical trial.pt. (87837)
18 randomized.ab. (286541)
19 clinical trials as topic/ (168554)
20 randomly.ab. (207894)
21 trial.ti. (122973)
22 or/13-21 (913631)
23 12 and 22 (1328)
24 23 and (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).ed. (213)
25 or/13-15 (445401)
26 24 or 19 or 20 or 21 (464081)

27 12 and 26 (682)
28 27 and (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).ed. (213)
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Database: Embase <1974 to 2014 March 11>
Search Strategy:

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1 exp proton pump inhibitors/ (50242)
2 proton pump inhibitor$.mp. (26364)
3 (Pantoprazole or Lansoprazole or Esomeprazole or Omeprazole or Rabeprazole).mp. (36067)
4 or/1-3 (52048)
5 meta-analysis.tw. (63195)
6 systematic review.tw. (54288)
7 MEDLINE.tw. (65409)
8 randomized controlled trial/ (339584)
9 random$.tw. (862190)
10 double-blind$.tw. (143899)
11 or/5-10 (1067924)
12 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5350296)
13 11 not 12 (946250)
14 exp peptic ulcer/ (104072)
15 peptic ulcer.mp. or exp peptic ulcer/ (110687)
16 gastric ulcer.mp. or exp stomach ulcer/ (37784)
17 Duodenal ulcer.mp. or duodenum ulcer/ (34427)
18 15 or 16 or 17 (114025)
19 4 and 18 (14076)
20 13 and 19 (2060)
21 20 and (2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).em. (1121)
22 limit 21 to english language (1015)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>
Search Strategy:

1 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. (3608)
2 (Pantoprazole or Lansoprazole or Esomeprazole or Omeprazole or Rabeprazole).mp. (4037)
3 (proton pump$ adj3 (antagon$ or inhibit$)).mp. (1614)
4 2 or 3 (4398)
5 1 and 4 (890)
6 limit 5 to yr="2009 -Current" (151)

GERD or Peptic ulcer observational study Medline (602); Embase (1724)

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Date: 20 March 2014

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1 exp Gastroesophageal Reflux/ (21418)
2 ((gastric acid or gastro esophageal or gastroesophageal) adj reflux).tw. (13503)
3 gerd.tw. (4921)
4 or/1-3 (24873)
5 exp peptic ulcer/ (72411)
6 ((duodenal or duodenum or gastroduodenal$ or gastro duodenal$ or marginal or peptic) adj (ulcer$ or ulcus)).tw. (39543)

7 acid peptic disease?.tw. (231)
8 or/5-7 (80939)
9 exp Proton Pump Inhibitors/ (13731)
10 proton pump inhibit$.tw. (7934)
11 (Pantoprazole or Lansoprazole or Esomeprazole or Omeprazole or Rabeprazole).tw. (9259)
12 or/9-11 (17863)
13 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ (1325186)
14 (cohort or longitudinal or prospective or retrospective).tw. (797224)
15 Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ (181435)
16 ((case* adj5 control*) or (case adj3 comparison*) or control group*).tw. (357049)
17 or/13-16 (1938660)
18 animals/ not (humans/ and animals/) (3813515)
19 17 not 18 (1818707)
20 (4 or 8) and 12 and 19 (2239)
21 limit 20 to abstracts (2142)
22 limit 20 to english language (1969)
23 21 and 22 (1907)
24 remove duplicates from 23 (1878)
25 24 and (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).ed. (602)
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Database: Embase <1974 to 2014 Week 11>
Search Date: 20 March 2014

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1 exp gastroesophageal reflux/ (42920)
2 ((gastric acid or gastro esophageal or gastroesophageal) adj reflux).tw. (19335)
3 gerd.tw. (9025)
4 or/1-3 (46307)
5 exp peptic ulcer/ (104086)
6 ((duodenal or duodenum or gastroduodenal$ or gastro duodenal$ or marginal or peptic) adj (ulcer$ or ulcus)).tw. (48458)
7 acid peptic disease?.tw. (304)
8 or/5-7 (113267)
9 exp proton pump inhibitors/ (50264)
10 proton pump inhibit$.tw. (13039)
11 (Pantoprazole or Lansoprazole or Esomeprazole or Omeprazole or Rabeprazole).tw. (13856)
12 or/9-11 (52000)
13 exp cohort analysis/ (161155)
14 double-blind$.tw. (143962)
15 exp longitudinal study/ (64534)
16 exp prospective study/ (242932)
17 exp follow up/ (771881)
18 exp case-control study/ (82530)
19 (case$ and control$).tw. (419178)
20 or/13-19 (1631743)
21 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5351725)
22 20 not 21 (1581081)
23 (4 or 8) and 12 and 22 (3942)
24 23 and (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).em. (1787)
25 limit 24 to english language (1724)
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Appendix 2: Excluded Studies and Reasons for Exclusion

Gastroesophageal reflux disease RCTS

Table 7-1 GERD Excluded Studies and Reasons for Exclusion

Author, Year	Full Citation
Reason for exclusion: Study Duration < 4 weeks (n=11)	
Rohss, 2002	Rohss KH: Effect of Esomeprazole 40 mg vs Omeprazole 40 mg on 24-hour intragastric ph in patients with symptoms of gastroesophageal reflux disease. Dig Dis Sci 2002; 47:954-958.
Miner, 2003	Miner J: Gastric Acid Control with Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole: A Five-Way Crossover Study. American Journal of Gastroenterology 2003; 98:2616-2620.
Wilder-Smith, 2008	Wilder-Smith CB: Effect of increasing Esomeprazole and Pantoprazole doses on acid control in patients with symptoms of gastro-oesophageal reflux disease: A randomized, dose-response study. Clin Drug Invest 2008; 28:333-343.
Miyamoto et al, 2009	Miyamoto MT: A randomized, comparative trial of the speed of onset of symptom relief of gastroesophageal reflux disease by the proton pump inhibitors: Rabeprazole vs Lansoprazole vs Omeprazole. Gastroenterology 2009; Conference:A445.
Miner et al, 2010	Miner PBJ, McKean LA, Gibb RD, Erasala GN, Ramsey DL, McRorie JW: Omeprazole-Mg 20.6 mg is superior to Lansoprazole 15 mg for control of gastric acid: a comparison of over-the-counter doses of proton pump inhibitors. Aliment Pharmacol Ther 2010; 31:846-851.
Morgan et al, 2010.	Morgan D, Pandolfino J, Katz PO, Goldstein JL, Barker PN, Illueca M: Clinical trial: gastric acid suppression in Hispanic adults with symptomatic gastro-oesophageal reflux disease - comparator study of Esomeprazole, Lansoprazole and Pantoprazole. Aliment Pharmacol Ther 2010; 32:200-208.
Miehlke et al, 2011	Miehlke S L: Intragastric acidity during administration of generic Omeprazole or Esomeprazole - a randomised, two-way crossover study including CYP2C19 genotyping. Aliment Pharmacol Ther 2011; 33:471-476.
Loots, 2011	Loots CMS: Esophageal impedance baselines in infants before and after placebo, antacid and proton pump inhibitor therapy. J Pediatr Gastroenterol Nutr 2011; Conference: December.
Tonomura et al, 2012	Tonomura HN: Effect of oral administration of a new proton pump inhibitor E3710 on 24-h intra-gastric pH in Japanese subjects. Gastroenterology 2012; Conference: S586.
Shimatani, 2012	Shimatani T, I: Comparison of night-time acid-suppressive efficacies of different proton pump inhibitors in helicobacter pylori-negative CYP2C19 homozygous extensive metabolizers: Effect of Rabeprazole at high and twice daily doses. Gastroenterology 2012; Conference: S588-S589.
Sahara et al, 2013	Sahara S.Sugimoto: Twice-daily dosing of Esomeprazole effectively inhibits acid secretion in CYP2C19 rapid metabolisers compared with twice-daily Omeprazole, Rabeprazole or Lansoprazole. Alimentary Pharmacology and Therapeutics 2013; 38:1129-1137.
Reason for exclusion: No reference drug or comparator (n=23)	
Corinaldesi et al,	Corinaldesi R, Valentini M, Belaiche J, Colin R, Geldof H, Maier C. Pantoprazole and

Table 7-1 GERD Excluded Studies and Reasons for Exclusion	
Author, Year	**Full Citation**
1995	Omeprazole in the treatment of oesophagitis: a European multicenter study. *Alimentary Pharmacology & Therapeutics.* 1995; 9:667-671.
Dekkers et al, 1999	Dekkers CPM, Beker JA, Thjodleifsson B, et al. Double-blind, placebo-controlled comparison of Rabeprazole 20 mg vs. Omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics.* 1999; 13(1):49-57.
Delchier et al, 2000	Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to Omeprazole, 20 mg once daily, in the healing of erosive gastro oesophageal reflux disease. *Scandinavian Journal of Gastroenterology.*2000;35:1245-1250
Thjodleifsson et al, 2000	Thjodleifsson B, Beker JA, Dekkers C, Bjaaland T, Finnegan V, Humphries TJ. Rabeprazole versus Omeprazole in preventing relapse of erosive or ulcerative gastroesophageal reflux disease: a double-blind, multicenter, European trial. The European Rabeprazole Study Group. *Digestive Diseases & Sciences.* 2000; 45(5):845-853.
Bardhan et al, 2001	Bardhan KD, Van Rensburg C. Comparable clinical efficacy and tolerability of 20 mg Pantoprazole and 20 mg Omeprazole in patients with grade I reflux oesophagitis. *Alimentary Pharmacology & Therapeutics.* 2001;15(10):1585-1591
Howden et al, 2002	Howden CW, Ballard EDI, Robieson W. Evidence for therapeutic equivalence of Lansoprazole 30mg and Esomeprazole 40mg in the treatment of erosive oesophagitis. *Clinical Drug Investigation.* 2002;22(2):99-109
Holtmann et al, 2002	Holtmann G, Bytzer P, Metz M, Loeffler V, Blum AL. A randomized, double-blind, comparative study of standard-dose Rabeprazole and high-dose Omeprazole in gastro oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics.* 2002;16(3):479-485
Castell et al, 2002	Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with Lansoprazole (30 mg) in the treatment of erosive esophagitis. *American Journal of Gastroenterology.* CR 2002;97(3):575-583
Lauritsen et al, 2003	Lauritsen K, Deviere J, Bigard MA, et al. Esomeprazole 20 mg and Lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. *Alimentary Pharmacology & Therapeutics.* 2003; 17(3):333-341.
Korner et al, 2003	Korner T, Schutze K, van Leendert RJ, et al. Comparable efficacy of Pantoprazole and Omeprazole in patients with moderate to severe reflux esophagitis. *Digestion.* 2003;67(1-2):6-13
Thjodleifsson et al 2003	Thjodleifsson B, Rindi G, Fiocca R, et al. A randomized, double-blind trial of the efficacy and safety of 10 or 20 mg Rabeprazole compared with 20 mg Omeprazole in the maintenance of gastro-oesophageal reflux disease over 5 years [comment]. *Alimentary Pharmacology & Therapeutics.* 2003; 17(3):343-351.
Tsai, 2004	Tsai HHC: Esomeprazole 20 mg on-demand is more acceptable to patients than continuous Lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastro-oesophageal reflux patients: The COMMAND Study. Alimentary Pharmacology and Therapeutics 2004; 20:657-665.
Fennerty, 2005	Fennerty MBJ: Efficacy of Esomeprazole 40 mg vs. Lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Alimentary Pharmacology and Therapeutics 2005; 21:455-463.

Table 7-1 GERD Excluded Studies and Reasons for Exclusion	
Author, Year	**Full Citation**
Pace et al, 2005	Pace F, Annese V, Prada A, et al. Rabeprazole is equivalent to Omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of Rabeprazole and Omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with Rabeprazole. *Digestive & Liver Disease.* 2005;37(10):741-750
Bytzer et al, 2006	Bytzer P, Morocutti A, Kennerly P, Ravic M, Miller N, Investigators RT. Effect of Rabeprazole and Omeprazole on the onset of gastro-oesophageal reflux disease symptom relief during the first seven days of treatment. *Scandinavian Journal of Gastroenterology.* Oct 2006; 41(10):1132-1140.
Frazzoni, 2006	Frazzoni MM: Intra-oesophageal acid suppression in complicated gastro-oesophageal reflux disease: Esomeprazole versus Lansoprazole. Digestive and Liver Disease 2006; 38:85-90.
DeVault, 2006	DeVault KRJ: Maintenance of Healed Erosive Esophagitis: A Randomized Six-Month Comparison of Esomeprazole Twenty Milligrams With Lansoprazole Fifteen Milligrams. Clinical Gastroenterology and Hepatology 2006; 4:852-859.
Katz, 2007	Katz POK: Comparison of the effects of immediate-release Omeprazole oral suspension, delayed-release Lansoprazole capsules and delayed-release Esomeprazole capsules on nocturnal gastric acidity after bedtime dosing in patients with night-time GERD symptoms. Alimentary Pharmacology and Therapeutics 2007; 25:197-205.
Tseng et al, 2009	Tseng PH, Lee YC, Chiu HM, Wang HP, Lin JT, Wu MS: A comparative study of proton-pump inhibitor tests for Chinese reflux patients in relation to the CYP2C19 genotypes. J Clin Gastroenterol 2009; 43:920-925.
Spechler, 2009	Spechler SJB: Clinical trial: Intragastric acid control in patients who have Barrett's oesophagus - Comparison of once- and twice-daily regimens of Esomeprazole and Lansoprazole. Alimentary Pharmacology and Therapeutics 2009; 30:138-145.
Miner et al, 2010	Miner P, Delemos B, Xiang J, Lococo J, Ieni J: Effects of a single dose of Rabeprazole 20 mg and Pantoprazole 40 mg on 24-h intragastric acidity and oesophageal acid exposure: a randomized study in gastro-oesophageal reflux disease patients with a history of nocturnal heartburn. Aliment Pharmacol Ther 2010; 31:991-1000.
Nagahara, 2012	Nagahara AS: A multicenter randomized trial to compare the efficacy of Omeprazole versus Rabeprazole on early symptom relief in reflux esophagitis. Gastroenterology 2012; Conference: S588.
Park, 2013	Park JHP: A randomized, double blinded, clinical trial to assess the efficacy and cost effectiveness of Omeprazole compared to Rabeprazole in the maintenance therapy of patients with gastroesophageal reflux disease. J Neurogastroenterol Motil 2013; 19:219-226
Reason for exclusion: Abstract only. No full report (n=3)	
Unakami, 2009	Unakami HK: On-demand proton-pump inhibitor therapy for erosive gastroesophageal reflex disease in Japanese patients. Gastroenterology 2009; Conference: A445-A446.
Johnson, 2011	Johnson DAK: Rabeprazole extended-release 50 mg vs. Esomeprazole 40 mg in healing of mild erosive esophagitis: A double-blind randomized trial. Gastroenterology 2011; Conference: S584.

Table 7-1 GERD Excluded Studies and Reasons for Exclusion	
Author, Year	**Full Citation**
Inaba, 2012	Inaba T, I: On-demand therapy using common dosage of proton pump inhibitor is effective in the maintenance therapy for Japanese mild GERD patients. J Gastroenterol Hepatol 2012
Reason for exclusion: No useable data for meta-analysis (n=2)	
Vivian et al, 1999	Vivian E, Morreale A, Boyce E, Lowry K, Ereso O, Hlavin P. Efficacy and cost effectiveness of Lansoprazole versus Omeprazole in maintenance treatment of symptomatic gastroesophageal reflux disease. *American Journal of Managed Care.*1999; 5(7):881-886.
De Bortoli 2011	De Bortoli NM, I: Randomised clinical trial: Twice daily Esomeprazole 40 mg vs. Pantoprazole 40 mg in Barrett's oesophagus for 1 year. Alimentary Pharmacology and Therapeutics 2011; 33:1019-1027.

*Some studies have been excluded for several reasons. Studies are group under the first reason they were excluded.

Peptic Ulcer Disease RCTs

Table 7-2 PUD Excluded Studies and Reasons for Exclusion	
Author, Year	**Full Citation**
Reason for exclusion: Wrong comparator (n= 20)	
Beker JA 1995	Beker JA, Bianchi Porro G, Bigard MA, et al. Double-blind comparison of Pantoprazole and Omeprazole for the treatment of acute duodenal ulcer. European Journal of Gastroenterology & Hepatology. 1995; 7(5):407-410.
Adamek RJ 1997	Adamek RJ, Szymanski C, Pfaffenbach B. Pantoprazole versus Omeprazole in one-week low-dose triple therapy for curve of *H. pylori* infection. American Journal of Gastroenterology. 1997; 92(10):1949-1950.
Dekkers CP 1998	Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Comparison of Rabeprazole 20 mg vs. Omeprazole 20 mg in the treatment of active gastric ulcer -a European multicentre study. The European Rabeprazole Study Group. Alimentary Pharmacology & Therapeutics. 1998; 12(8):789-795.
Miwa H 1999	Miwa H, Ohkura R, Murai T, et al. Impact of Rabeprazole, a new proton pump inhibitor, in triple therapy for *Helicobacter pylori* infection comparison with Omeprazole and Lansoprazole. Alimentary Pharmacology & Therapeutics. 1999; 13:741-746.
Furuta T 2000	Furuta T, Shirai N, Takashima M. Effects of genetic differences in CYP2C19 status on cure rates of *Helicobacter pylori* infection by dual Rabeprazole/amoxicillin therapy in comparison with dual Omeprazole/amoxicillin therapy. Gastroenterology. 2000;118(4,1,2):2663
Miyoshi M 2001	Miyoshi M, Mizuno M, Ishiki K, et al. A randomized open trial for comparison of proton-pump inhibitors, Omeprazole versus Rabeprazole, in dual therapy for *Helicobacter pylori* infection in relation to CYP2C19 genetic polymorphism. Journal of Gastroenterology & Hepatology. 2001;16(7):723-728
Yang KC 2003	Yang KC, Wang GM, Chen JH, Chen TJ, Lee SC. Comparison of Rabeprazole-based four- and seven-day triple therapy and Omeprazole-based seven-day triple therapy for *Helicobacter pylori* infection in patients with peptic ulcer. Journal of the Formosan

Table 7-2 PUD Excluded Studies and Reasons for Exclusion	
Author, Year	**Full Citation**
	Medical Association. 2003;102(12):857-862
Ando T 2005	Ando T, Kato H, Sugimoto N, et al. A comparative study on endoscopic ulcer healing of Omeprazole versus Rabeprazole with respect to CYP2C19 genotypic differences. Digestive Diseases & Sciences. Sep 2005; 50(9):1625-1631.
Ji S 2006	Ji S, Kim HS, Kim JW, et al. Comparison of the efficacy of Rabeprazole 10 mg and Omeprazole 20 mg for the healing rapidity of peptic ulcer diseases. Journal of Gastroenterology & Hepatology. Sep 2006; 21(9):1381-1387.
Liang X-Y 2008	Liang X-Y, Gao Q, Gong N-P, Tang L-P, Wang P-L, Tao X-H. Comparison of Esomeprazole enteric-coated capsules vs Esomeprazole magnesium in the treatment of active duodenal ulcer: a randomized, double-blind, controlled study. World Journal of Gastroenterology. Mar 28 2008; 14(12):1941-1945.
Tsai J 2009	Tsai, J.-J. Hsu. Oral or intravenous proton pump inhibitor in patients with peptic ulcer bleeding after successful endoscopic epinephrine injection. British Journal of Clinical Pharmacology. 2009; 67(3): 326-332 (O vs R)
Ho KY 2009	Ho, K.Y.K. Randomized, parallel, double-blind comparison of the ulcer-healing effects of Ilaprazole and Omeprazole in the treatment of gastric and duodenal ulcers. Journal of Gastroenterology. 2009; 44(7): 697-707 (I vs O)
Zhang L 2010	Zhang L. Mei Q. Li QS. Hu YM. Xu JM. The effect of cytochrome P2C19 and interleukin-1 polymorphisms on *H. pylori* eradication rate of 1-week triple therapy with Omeprazole or Rabeprazole, amoxycillin and clarithromycin in Chinese people. Journal of Clinical Pharmacy & Therapeutics. 35(6):713-22, 2010 Dec (O vs R)
Zhou WL 2011	Wang, L. Zhou. A new PPI, Ilaprazole compared with Omeprazole in the treatment of duodenal ulcer: A randomized double-blind multicenter trial. Journal of Clinical Gastroenterology. 2011; 45(4) : 322-329 (I vs O)
Wang L 2011	Wang, L. Zhou. A new PPI, Ilaprazole compared with Omeprazole in the treatment of duodenal ulcer: A randomized double-blind multicenter trial. Journal of Clinical Gastroenterology. 2011; 45 (4): 322-329
Mostaghni AA 2011	Mostaghni AA. Hashemi SA. Heydari ST. Comparison of oral and intravenous proton pump inhibitor on patients with high risk bleeding peptic ulcers: a prospective, randomized, controlled clinical trial. Iranian Red Crescent Medical Journal. 2011 Juy;13(7):458-63 (O vs P)
Kim H-K 2012	Hyung-Keun Kim, Jin-Soo Kim, Tae-Ho Kim, Chang-Whan Kim, et al. Effect of High-Dose Oral Rabeprazole on Recurrent Bleeding after Endoscopic Treatment of Bleeding Peptic Ulcers. Gastroenterology Research and Practice. 2012; 317125 doi:10.1155/2012/317125.
Wang L 2012	Wang L. Zhou L. Hu H. Lin S. Xia J. Ilaprazole for the treatment of duodenal ulcer: a randomized, double-blind and controlled phase III trial. Current Medical Research & Opinion. 2012 Jan 28; (1):101-9. (I vs O)
Basu 2012	Basu, P.P, Rayapudi K. Pacana T. Shah NJ. Krishnaswamy N. Flynn M. A randomized study comparing levofloxacin, Omeprazole, nitazoxanide, and doxycycline versus triple therapy for the eradication of *Helicobacter pylori*. American Journal of Gastroenterology. 106(11):1970-5, 2011 Nov. (L vs O with different antibiotics)

Table 7-2 PUD Excluded Studies and Reasons for Exclusion	
Author, Year	**Full Citation**
Bohidar NP 2013	Bohidar NP. Krishna K. Panda BK. Patel C. Ilaprazole: Is this a superior proton pump inhibitor for duodenal ulcer? Tropical Gastroenterology. 2013 Apr-June; 34(2):95-8 (I vs O)
Same PPI with different antibiotics	
Gopal R 2013	Gopal R. Elamurugan TP. Kate V. Jagdish S. Basu D. Standard triple versus levofloxacin based regimen for eradication of *Helicobacter pylori*. World Journal of Gastrointestinal Pharmacology and Therapeutics. 2013 May 6; 4(2):23-7
Chen L 2010	Chen LW. Chien RN. Chang JJ. Fang KM. Chang LC. Comparison of the once-daily levofloxacin-containing triple therapy with the twice-daily standard triple therapy for first-line *Helicobacter pylori* eradication: a prospective randomised study. International Journal of Clinical Practice. 64(11):1530-4, 2010 Oct.
Reason for exclusion: Abstract only (n= 11)	
Catalano F 1997	Catalano F, Privitera U, Branciforte G, et al. Omeprazole versus two different doses of Lansoprazole in triple therapy on *Helicobacter pylori* positive duodenal ulcer. Gut 1997; 39: A32 (Abstract).
Aydin A 1998	Aydin A, Gunsar F, Yilmaz M, et al. Omeprazole, Lansoprazole or ranitidine bismuth citrate in combination with amoxicillin plus clarithromycin in *Helicobacter pylori* eradication. Gut 1998; 43: A307 (Abstract).
Maev IV 2003	Maev IV, Kurilo AE, V'iuchnova ES, Shchekina MI: Esomeprazole in treating duodenal ulcer in various modes of anti-Helicobacter therapy. Ter Arkh 2003; 75:23–26. (Non-English article with English abstract)
Zhang YT 2004	Zhang YT, Jiang Y, Li P: The comparison of Esomeprazole- and Omeprazole-based triple therapy regimens for the eradication of *Helicobacter pylori* infection. Acad J Guangdong Pharmacy 2004; 20:561–563. (Chinese article, no English abstract)
Xie SB 2005	Xie SB: Esomeprazole-based triple therapy for *Helicobacter pylori* correlated peptic ulcer for 32 cases. Clin Drug 2005; 14:76. (abstract)
Chen YH 2005	Chen YH, Wang WM, Wang H, Li HY: Comparison of Esomeprazole- and Omeprazole-based triple therapy regimens for duodenal ulcer with *Helicobacter pylori* infection. Di Yi Jun Yi Da Xue Xue Bao 2005; 25:1045–1047. Chinese article English abstract only
Basu P 2009	Basu, P.P.R. A randomized open-label clinical trial with Levofloxacin, Omeprazole, Alinia (nitazoxanide), and Doxycycline (LOAD) versus Lansoprazole, Amoxicillin and Clarithromycin (LAC) in the treatment naive *Helicobacter pylori* population. Gastroenterology Conference 2009 A24 (wrong comparator)
Troche 2010	Troche, J.M.R. Sequential therapy vs. Standard triple therapy as treatment of helicobacter pylori infection. A prospective, randomized, parallel-group, open-label study in Mexico. Gastroenterology Conference. 2010. S336. L vs. P but different antibiotics used in comparator groups.
Yen H 2011	Yen, H.-H.Yang. Oral vs intravenous proton pump inhibitors for peptic ulcer bleeding, a preliminary report. Gastrointestinal Endoscopy Conference. 2011 AB228. Compared oral Lansoprazole 30mg to IV Esomeprazole 40mg.
Yang YHH 2011	Yen, H.-H. Yang. Oral vs intravenous proton pump inhibitors for peptic ulcer bleeding, a

Table 7-2 PUD Excluded Studies and Reasons for Exclusion	
Author, Year	**Full Citation**
	preliminary report. Gastrointestinal Endoscopy Conference. 2011. AB228 (wrong comparator) (L vs E)
Lanas A et al	Angel Lanas, Mónica Polo-Tomás, Luis A. Garcia Rodriguez, Joseph J. Sung. Effect of Intravenous Proton Pump Inhibitors on Outcomes of Peptic Ulcer Bleeding: Comparison Between Event Rates in Routine Clinical Practice and Clinical Trials.

Appendix 3 Data Extraction tables (template)

Table 1: Inclusion Criteria of each study	
Population	Patients with GERD or peptic ulcer disease
Intervention	Lansoprazole or Esomeprazole
Comparator	Omeprazole, Pantoprazole or Rabeprazole
Outcomes	As specified in Section Table 4 of the report
Study design	Randomized comparative clinical trials for effectiveness and nested case control or cohort studies for safety evaluation

Table 2: Trial characteristics of included studies	
Study design	
Location	
Total Randomized patients	
Patient Type	
Intervention/ Comparator	
Duration of treatment	
Outcomes	

Table 3: Patient Inclusion and Exclusion Criteria from Included Studies		
Author, year	**Inclusion criteria**	**Exclusion criteria**

Table 4: Baseline characteristics of patients		
	Intervention	**Comparator**
Sex (male)		
Age		
BMI		
Smoking		
Alcohol consumption		
***H. pylori* status**		
Severity of ulcer (grade)		
Other triail specific criteria		

Table 5: Summary of Patient Disposition		
Author, Year,	**Intervention**	**Comparator**
Randomized and Treated		
Completed		

Discontinued		
Reasons for withdrawal		
Additional details		

Table 6: Duration of exposure		
Author, Year,	**Intervention**	**Comparator**
Mean or median duration of follow up		

Table 7: Efficacy and safety endpoints		
Type of analysis: Intention to treat or per protocol analysis		
	Intervention	**Comparator**
Symptomatic relief		
Time to first resolution of symptoms		
Endoscopic healing of esophagitis or ulcer		
Eradication of *H. pylori* in peptic ulcer disease		
Quality of life (using validated scores)		
Recurrences or relapse of GERD or peptic ulcer symptoms		
Other outcomes specific to the RCT		
Safety endpoints		
Mortality and reasons		
Serious adverse events and reasons		
WDAE and reasons		
Subjects with > 0AE		
Most common AEs		

Table 8: Risk of Bias evaluation for RCT			
	Low risk	**Unclear risk**	**High risk**
Random sequence generation			
Allocation concealment			
Blinding of patient and physician			
Blinding of outcome assessor			
Patient withdrawal			
Selective reporting of outcomes			
Other concerns about bias Funding of the study			

Appendix 4: Criteria used to asses Risk of bias using Cochrane Risk of bias tool

Factors	Judgment		
	Low risk of bias	**Unclear risk of bias**	**High risk of bias**
Random sequence generation (selection bias)	Computer-generated random numbers; Random-numbers table; coin tossing; shuffling cards or envelopes; throwing dice If adequate then randomized groups baseline characteristics will be similar	Not described Insufficient information to permit judgment of yes or no	Use of alternation, case record number, birth date, or day of week
Allocation concealment (selection bias)	Centralized or pharmacy-controlled randomization; Serially numbered identical containers; On-site computer-based system with a randomization sequence that is not readable until allocation	Not described. Insufficient information to permit judgment of yes or no	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)
Blinding of participant and physician (performance bias)	Knowledge of the allocated intervention was adequately prevented and it is unlikely that blinding of the participant and physician could have been broken	Not described Insufficient information to permit judgment of yes or no	Knowledge of the allocated intervention was NOT adequately prevented and it is likely that outcome is likely to be influenced by lack of blinding
Blinding of outcome assessor (detection bias)	Knowledge of the allocated intervention was adequately prevented and it is unlikely that blinding of the outcome assessor could have been broken	Not described Insufficient information to permit judgment of yes or no	Knowledge of the allocated intervention was NOT adequately prevented and it is likely that outcome is likely to be influenced by lack of blinding of the outcome assessor
Incomplete outcome data	Incomplete outcome data was adequately addressed.	Not described	Incomplete outcome data was inadequately addressed.

(attrition bias)	No missing outcome data; reasons for missing data not related to the outcome; Missing outcome balanced between 2 groups with similar reasons; missing outcome data not enough to have a clinically relevant impact on the intervention effect estimate; missing data imputed using appropriate methods	Insufficient information to permit judgment of yes or no	Reason for missing data related to outcome, with either imbalance in numbers or reasons; For dichotomous outcome data, the proportion of missing outcome compared with observed event risk is enough to induce clinically relevant bias in intervention effect estimate ; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization ; Inappropriate use of imputation
Selective reporting (reporting bias)	Study protocol is available and all pre-specified primary and secondary outcomes are reported	Not described Insufficient information to permit judgment of yes or no	Not all pre-specified study outcomes are reported; reports on subgroups that are not pre-specified; incomplete reporting of outcome so cannot be used in analysis; key outcomes not reported in the study
Other bias	No conflict of interest relating to funding the study (CIHR, NIH)	Insufficient information to permit judgment of yes or no Evaluate effects of cross over to other treatment arm; adherence of medication; and contamination;	Industry funded; conduct of study affected by interim analyses; stopped early due to some data driven process; deviation from study protocol that does not reflect clinical practice; pre-randomization administration of an intervention that could enhance or diminish the effect of subsequent randomized intervention; extreme baseline imbalance between groups; claimed to be fraudulent

Appendix 5: Esophagitis grading scales used in RCTs

LA Classification:

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

Grade A: One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds

Grade B: One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds

Grade C: One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference

Grade D: Mucosal breaks which involve at least 75% of the esophageal circumference.

Savary-Miller Classification:

Grade I: One or more non-confluent erythematous spots or superficial erosions

Grade II: Confluent erosive or exudative mucosal lesions which do not extend around the entire esophageal circumference

Grade III: Erosive or exudative mucosal lesions which cover the whole esophageal circumference and lead to inflammation of the wall without stricture.

Grade IV: Chronic mucosal lesions, interpreted as esophageal ulcer, mural fibrosis, stricture, shortening, and scarring with columnar (Barrett's) epithelium

Criteria used in Richter 200b and Castell 2006

Grade 0: Mucosa normal in appearance

Grade 1: Mucosal edema, hyperemia, and /or friability of mucosa

Grade 2: One or more erosions/ulcerations involving <10% of distal 5 cm of the esophagus

Grade 3: Erosions/ulcerations involving 10-50% of distal 5 cm of esophagus, or an ulcer measuring 3-5 mm in diameter

Grade 4: Multiple erosions/ulcerations involving >50% of distal 5 cm of esophagus, or a single large ulcer >5 mm in diameter

Criteria used in Hatlebakk 2003

Grade 1: red streaks or spots along the ridge of the folds in the distal oesophagus, covered or not by fibrinous exudate

Grade 2: broader lesions, each involving the entire width of a fold or coalescing into fields of erythema, covered or not with fibrinous exudate

Grade 3: Stricture or endoscopically visible ulcer in distal oesophagus

Appendix 6: Details of GERD randomized trials meeting the inclusion criteria (TABLES)

I. Comparison 1: Esomeprazole vs. Omeprazole (10 RCTs)

Table I[A]: (GERD) E vs O - Description of trials meeting the inclusion criteria

Author, Year, Trial Name	Study Design	Location	Randomised sample size (n)	Patient Type	Intervention/ Comparator and dosage	Study Duration	Outcome(s)
Kahrilas 2000	DBRCT	USA	E20: 656 E40: 654 O20: 650	1960 patients with confirmed reflux esophagitis by EGD & *H. pylori* negative	E20 or 40 mg OD O20 mg OD	8 weeks	Primary outcome: Endoscopic reflux esophagitis healing at 8 weeks Investigator confirmed resolution of heartburn @ 4 or 8 weeks, % heartburn free days and night, time to 1st resolution of symptom and sustained relief, safety
Richter 2001a	DBRCT	USA	E40:1216 O20:1209	2425 adults (age 18-75) with erosive esophagitis (EE), *H. pylori* negative	E 40 mg OD O 20 mg OD	8 weeks	Primary outcome: Endoscopic EE Healing @ 8 weeks Resolution of heartburn, time to 1st resolution, sustained resolution of heartburn, % of heartburn free days and nights, safety
Kao 2003	RCT	Taiwan	E40: 50 O20: 50	100 patients with reflux esophagitis who had clinical symptoms of either acid regurgitation or heartburn sensation.	E40 mg OD O20 mg OD	4 weeks	Primary outcome: sustained symptomatic relief at 4 weeks Time to 1st symptom relief, safety.

Table I[A]: (GERD) E vs O - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention/ Comparator and dosage**	**Study Duration**	**Outcome(s)**
Armstrong 2004a	DBRCT	Canada, England, Ireland	E20: 423 E40: 425 O20: 434	1282 ENRD patients who had experienced heartburn as their main symptom for $\geq$ 6 months and for > 4 days during the week before randomization	E 20 mg OD E 40 mg OD O 20 mg OD	4 weeks	Primary outcome: complete resolution of heartburn @ 4 weeks Median days for 1st sustained symptom relief, resolution of heartburn @ 2 weeks, % symptom free days & nights, relief of regurgitation and dysphagia symptoms
Armstrong 2004b	DBRCT	France, Germany, Switzerland	E40: 347 O20: 346	Same as Armstrong 2004a. 693 patients were randomized.	E 40 mg OD O20 mg OD	4 weeks	Same as Armstrong 2004a
Armstrong 2004c	DBRCT	Denmark, Finland, Norway, Sweden	E20: 336 O20: 334	Same as Armstrong 2004a. 670 patients were randomized.	E 20 mg OD O 20 mg OD	4 weeks	Same as Armstrong 2004a
Chen 2005	DBRCT	Taiwan	E40: 25 O20: 23	48 patients who sought medical care due to GERD for at least 1 month were enrolled.	E 40 mg OD (Tablets) O 20 mg OD	8 weeks	Primary outcome: Endoscopic EE healing rate @ 8 weeks Symptom score, time to 1st heartburn relief, safety
Lightdale 2006	DBRCT	USA	E20:588 O20:588	1176 adults (age 18-75) with erosive esophagitis confirmed by EGD & *H. pylori* negative	E 20 mg OD O 20 mg OD	8 weeks	Primary outcome: Endoscopic EE Healing @ 8 weeks. Endoscopic EE healing @ 4 weeks, resolution rate of heartburn, time to 1st resolution, % of heartburn free days and nights, safety

Table I[A]: (GERD) E vs O - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention/ Comparator and dosage**	**Study Duration**	**Outcome(s)**
Schmitt 2006	DBRCT	USA	E40:576 O20:572	1148 adults (age 18-75) with erosive esophagitis confirmed by EGD & *H. pylori* negative	Esomeprazole 40 mg OD vs Omeprazole 20 mg OD	8 weeks	Primary outcome: Endoscopic EE Healing @ 4 or 8 weeks Rate of Heartburn resolution, % of heart burn free days & nights, safety
Zheng 2009	RCT	China	E40: 68 O20: 68 L30: 69 P40: 69	274 adults with endoscopically proven reflux esophagitis	E 40 mg OD O 20 mg OD L 30 mg OD P 40 mg OD	8 weeks	Primary outcome : Symptom score in the first week of drug administration Endoscopic healing at week 8.
Abbreviations: GERD, Gastroesophageal Reflux Disease, DBRCT, double blind; RCT, randomized control trial; E, Esomeprazole; O, Omeprazole; L, Lansoprazole; P, Pantoprazole; EE, erosive esophagitis; OD, once daily; EGD, esophagogastric duodenoscopy; ENRD, Endoscopy-negative reflux disease							

Table I[B]: (GERD) E vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Kahrilas 2000	Patients with symptomatic GERD and reflux esophagitis confirmed by EGD and graded at baseline screening.	Patients with *H. pylori* positive at baseline; Bleeding disorder or signs of GI bleeding within 3 days prior to randomization; History of gastric or esophageal surgery; Evidence of Zollinger-Ellison syndrome; Primary motility disorder; Esophageal stricture; Barrett's esophagus; Upper GI malignancy; Severe concomitant disease; Pregnant or lactating; Patients taking PPI or H2RA on a daily basis 2 weeks prior endoscopy were excluded. Patients taking diazepam, quinidine, dilantin, warfarin, anticholinergic, prostaglandin or sucralfate or hypersensitive to Omeprazole or aluminium/magnesium hydroxide were also excluded.	Antacid (Aluminium/Magnesium hydroxide) was allowed.

Table I[B]: (GERD) E vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Richter 2001a	Adults age 18-75, male or female, with erosive esophagitis confirmed by esophagogastroduodenoscopy (EGD) and grade according to LA classification 1 week before randomization.	Patients with *H. pylori* positive before randomization; Patients with bleeding disorder or history of gastrointestinal bleeding; Patients with history of gastro-surgery; Zollinger-Ellison syndrome; Primary esophageal motility disorder; Esophageal stricture; Endoscopic Barrett's esophagus (> 3 cm); Significant dysplastic change in esophagus; Duodenal or gastric ulcer; Inflammatory bowel disease; Upper gastrointestinal malignancy; Unstable diabetes; or other severe concomitant disease was excluded.	Concomitant antacid was allowed for acute symptom relief (Max. 6 tablet a day).
Kao 2003	Patients who had clinical symptoms of either acid regurgitation or heartburn sensation. Reflux esophagitis was diagnosed and graded by pan endoscopy	Patients with major medical problem (liver cirrhosis, COPD, diabetes, renal failure, congestive heart failure; Previous gastric surgery; Drug allergy to PPI; Pregnancy were excluded.	NR
Armstrong 2004 (Study A, B & C)	Symptomatic patients with ENRD (defined as GERD in individuals who do not have either Barrett's oesophagus or definite endoscopic oesophageal 'mucosal breaks') who had experience heartburn as their main symptom for 6 months or longer and for more than 4 days during the week before randomization were enrolled.	Exclusion criteria were not reported.	NR
Chen 2005	Patients who sought medical care for symptom of GERD for at least 1 month were enrolled.	Patients with history of healed or active peptic ulcer; GI malignancy; Esophageal gastric surgery; Esophagitis result from diseases other than GERD; Pregnancy, lactation or child-bearing potential without adequate contraception; Chronic alcoholism; Drug abuse; Continuous concomitant therapy with anticholinergic, cisapride, prostaglandin, NSAID, aspirin were excluded.	NR

Table I[B]: (GERD) E vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Lightdale 2006	Adults age 18-75, male or female, with erosive esophagitis confirmed by esophagogastroduodenoscopy (EGD) and grade according to LA classification 1 week before randomization.	Patients *H. pylori* positive at baseline ; Bleeding disorder or signs of gastrointestinal bleeding; History of gastric or esophageal surgery, except for simple closure of perforated ulcer; History of Zollinger-Ellison syndrome; Primary esophageal motility disorder, esophageal stricture or other serious condition, including cancer and Barrett's esophagus were excluded.	Concomitant antacid was allowed for acute symptom relief (Max. 6 tablet a day).
Schmitt 2006	Adults age 18-75, male or female, with erosive esophagitis confirmed by esophagogastroduodenoscopy (EGD) and grade according to LA classification 1 week before randomization.	Patients *H. pylori* positive at baseline; Bleeding disorder or signs of gastrointestinal bleeding; History of gastric or esophageal surgery, except for simple closure of perforated ulcer; History of Zollinger-Ellison syndrome; Primary esophageal motility disorder, esophageal stricture or other serious condition, including cancer and Barrett's esophagus were excluded.	Concomitant antacid was allowed for acute symptom relief (Max. 6 tablet a day).
Zheng 2009	Patients with endoscopically proven reflux esophagitis in the Affiliated Hospital of Yanbian University from January, 2006 to September, 2007 and the Affiliated Hospital of Hainan Medical College from October, 2007 to November, 2008	Patients with active peptic ulcer; upper gastrointestinal cancers, malignant diseases of other organs; severe cardiac, hepatic, or renal diseases; anemia (hemoglobin concentration < 10 g/dL); pregnant and/or lactating women were excluded.	Subjects were not permitted to take H2-RAs or prokinetic drugs during the study period.
Abbreviations: GERD, Gastroesophageal Reflux Disease; E, Esomeprazole; O, Omeprazole; EGD, esophagogastric duodenoscopy; H2-RA, Histamine-2 receptor blocker; NR, not reported; ENRD, endoscopy-negative reflux disease			

Table I[C]: (GERD) E vs O - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs ± SD)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol Consumption (n, %)**	***H. pylori* positive (n, %)**	**Severity (LA Grades) (n, %)**	**Other**
Kahrilas 2000	E20 (n=656)	391 (59.6%)	45.3 ± 13.3	NR	NR	NR	NR	NR	A: 217 (33.1%) B: 274 (41.8%) C: 119 (18.1%) D: 46 (7.0%)	-
	E40 (n=654)	384 (58.7%)	44.8 ± 13	NR	NR	NR	NR	NR	A: 235 (35.9%) B: 253 (38.7%) C: 119 (18.2%) D: 47 (7.2%)	-
	O20 (n=650)	399 (61.4%)	46.5 ± 13.5	NR	NR	NR	NR	NR	A: 203 (31.2%) B: 265 (40.8%) C: 137 (21.1%) D: 45 (6.9%)	-
Richter 2001a	E40 (n=1216)	722 (59.4 %)	46.5	NR	Caucasian: 1134 (93.3%)	NR	NR	90 (7.4%)	A: 427 (35.1%) B: 470 (38.7%) C: 257 (21.1%) D: 60 (4.9%)	-
	O20 (n=1209)	760 (62.9%)	46.8	NR	Caucasian: 1133 (93.7%)	NR	NR	96 (7.9%)	A: 386 (31.9%) B: 502 (41.5%) C: 240 (19.9%) D: 80 (6.6%)	-
Kao 2003	E40 (n=50)	35 (70.0%)	49.8	BMI: 23.2	NR	16 (32.0%)	12 (24.0%)	NA	A: 25 (50%) B: 25 (50%)	-
	O20 (n=50)	34 (68.0%)	49.2	BMI: 23.1	NR	14 (28.0%)	12 (24.0%)	NA	A: 26 (52%) B: 24 (48%)	-
Armstrong 2004a	E20 (n=423)	183 (43.3%)	48.0	NR	NR	NR	NR	262 (61.9%)	Endoscopy negative	-
	E40 (n=425)	183 (43.1%)	48.4	NR	NR	NR	NR	290 (68.2%)	Endoscopy negative	-
	O20 (n=434)	187 (43.1%)	48.3	NR	NR	NR	NR	292 (67.3%)	Endoscopy negative	-

Table I[C]: (GERD) E vs O - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs ± SD)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol Consumption (n, %)**	***H. pylori* positive (n, %)**	**Severity (LA Grades) (n, %)**	**Other**
Armstrong 2004b	E40 (n=347)	154 (44.4%)	50.6	NR	NR	NR	NR	208 (59.9%)	Endoscopy negative	-
	O20 (n=346)	156 (45.1%)	50.0	NR	NR	NR	NR	216 (62.4%)	Endoscopy negative	-
Armstrong 2004c	E20 (n=336)	175 (52.1%)	48.5	NR	NR	NR	NR	226 (67.3%)	Endoscopy negative	-
	O20 (n=334)	168 (50.3%)	48.5	NR	NR	NR	NR	237 (71.0%)	Endoscopy negative	-
Chen 2005	E40 (n=25)	20 (80%)	49.2 ± 3.7	68.4 kg ± 2.4 166.7 cm ± 1.3	NR	NR	NR	10 (40%)	A: 15 (60%) B: 7 (28%) C: 2 (8%) D: 1 (4%)	-
	O20 (n=23)	18 (78.3%)	59 ± 3.4	70.9 kg ± 2.5 169 cm ± 1.4	NR	NR	NR	11 (47.8%)	A: 11 (47.8%) B: 7 (30.4%) C: 2 (8.7%) D: 3 (13%)	-
Lightdale 2006	E20 (n=588)	372 (63.3%)	44.7	NR	Caucasian: 537 (91.3%)	NR	NR	55 (9.4%)	A: 223 (37.9%) B: 206 (35.0%) C: 121 (20.6%) D: 37 (6.3%)	-
	O20 (n=588)	376 (63.9%)	45.3	NR	Caucasian: 543 (92.3%)	NR	NR	56 (9.5%)	A: 212 (36.1%) B: 222 (37.8%) C: 103 (17.5%) D: 51 (8.7%)	-
Schmitt 2006	E40 (n=576)	346 (60.1%)	47.1	NR	Caucasian: 539 (93.6%)	NR	NR	52 (9.0%)	A: 187 (32.5%) B: 200 (34.7%) C: 144 (25.0%) D: 45 (7.8%)	-

Table I[C]: (GERD) E vs O - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs ± SD)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol Consumption (n, %)**	***H. pylori* positive (n, %)**	**Severity (LA Grades) (n, %)**	**Other**
	O20 (n=572)	335 (58.6%)	46.2	NR	Caucasian: 542 (94.8%)	NR	NR	60 (10.5%)	A: 189 (33.0%) B: 214 (37.4%) C: 126 (22.0%) D: 43 (7.5%)	-
Zheng 2009 (L and R group not shown)	E40 (n=68)	33 (48.5%)	57.4	NR	NR	NR	NR	29 (87.9%)	Grade A: 20 (%) Grade B: 26 (%) Grade C: 20 (%) Grade D: 2 (%)	-
	O20 (n=68)	33 (48.5%)	57.9	NR	NR	NR	NR	29 (87.9%)	Grade A: 20 (%) Grade B: 26 (%) Grade C: 20 (%) Grade D: 2 (%)	-
Abbreviations: GERD, Gastroesophageal Reflux Disease; E, Esomeprazole; O, Omeprazole; BMI, body mass index; SD, standard deviation; NR, not reported										

Table I[D]: (GERD) E vs O - Summary of Patient Disposition						
Trial	**Treatment groups**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for withdrawal**	**Additional Details Provided**
Kahrilas 2000	E20	656	596	60	AE: 18 Lost to follow-up: 21; Other: 21	-
	E40	654	606	48	AE: 13 Lost to follow-up: 20; Other: 15	-
	O20	650	599	51	AE: 13 Lost to follow-up: 13; Other: 25	-
Richter 2001a	E40	1216	1161	55	AE:11 Investigator decision: 13; Lost to follow-up: 13; Consent withdrawn: 17; Lack of therapeutics response: 1	-
	O20	1209	1155	54	AE: 13 Investigator decision: 12; Lost to follow-up: 12; Consent withdrawn: 14; Lack of therapeutics response: 3	-

Table I[D]: (GERD) E vs O - Summary of Patient Disposition						
Trial	**Treatment groups**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for withdrawal**	**Additional Details Provided**
Kao 2005	E40	50	46	4	AE: 1 Lost to follow-up: 3	-
	O20	50	45	5	AE: 1 Lost to follow-up: 4	-
Armstrong 2004 Study A	E20	423 randomized	NR	NR	NR	-
	E40	425 randomized	NR	NR	NR	-
	O20	434 randomized	NR	NR	NR	-
Armstrong 2004 Study B	E40	347 randomized	NR	NR	NR	-
	O20	346 randomized	NR	NR	NR	-
Armstrong 2004 Study C	E20	336 randomized	NR	NR	NR	-
	O20	334 randomized	NR	NR	NR	-
Chen 2005	E40	25	24	1	Lost to follow-up: 2; Discontinued medication: 2	-
	O20	23	20	3		-
Lightdale 2006	O20	1176	1106	70	AE: 18 Loss to follow-up: 23; Withdrawn consent: 17; Sponsor/investigator decision: 12	-
	E20					
Schmitt 2006	O20	1148	1079	69	AE: 26 Sponsor/investigator decision: 20; Withdrawn consent: 12; Loss to follow-up: 11	-
	E40					
Zheng 2009 (P & L groups not shown)	E40	68	Not clearly reported	Not clearly reported	NR	-
	O20	68	Not clearly reported	Not clearly reported	NR	-
Abbreviations: GERD, Gastroesophageal Reflux Disease; E, Esomeprazole; O, Omeprazole; AE, adverse effects; NR, Not reported						

Table I[E]: (GERD) E vs O - Efficacy Outcomes									
Author, Year, Trial Name	**Treatment group (Drug and mg/day)**	**Symptomatic relief (n/N, %)**	**Healing of esophagitis (n/N, %)**		**QoL**	**Recurrences or relapse**	**Time to 1st resolution of symptom**	**Time to sustained resolution of symptom**	**% symptom free days & nights**
Kahrilas 2000		@ 4 weeks (Heartburn)	@ 4 weeks (life table estimates, not in forest plot)	@ 8 weeks					
	E20 (n=626)	382/626 (61.0%)	462/656 (70.5%)	551/656 (84%)	NA	NA	median: 2 days	median: 8 days	Heartburn free days: 69.3% nights: 83.6%
	E40 (n=621)	402/621 (64.7%)	496/654 (75.9%)	569/654 (87%)	NA	NA	median: 2 days	median: 5 days	Heartburn free days: 72.7% nights: 84.7%
	O20 (n=624)	357/624 (57.2%)	421/650 (64.7%)	520/650 (80%)	NA	NA	median: 2 days	median: 9 days	Heartburn free days: 67.1% nights: 80.1%
Richter 2001a		@ 4 weeks (Heartburn)	@ 4 weeks	@ 8 weeks					
	E40 (n=1216)	831/1216 (68.3%)	956/1216 (78.6%)	1093/1216 (89.9%)	NA	NA	median: 2 days	median: 5 days	Heartburn free days: 74.9% nights: 90.8%
	O20 (n=1209)	702/1209 (58.1%)	805/1209 (66.6%)	978/1209 (80.9%)	NA	NA	median: 2 days	median: 8 days	Heartburn free days : 69.7% nights: 87.9%
Kao 2003		@ 4 week (Acid reflux & heartburn)							
	E40 (n=50)	37/50 (73.9%)	NA	NA	NA	NA	median: 4 days	NA	NA
	O20 (n=50)	26/50 (51.1%)	NA	NA	NA	NA	median: 4 days	NA	NA

Table I[E]: (GERD) E vs O - Efficacy Outcomes									
Author, Year, Trial Name	**Treatment group (Drug and mg/day)**	**Symptomatic relief (n/N, %)**	**Healing of esophagitis (n/N, %)**		**QoL**	**Recurrences or relapse**	**Time to 1st resolution of symptom**	**Time to sustained resolution of symptom**	**% symptom free days & nights**
Armstrong 2004a		@ 4 weeks (Heartburn)							
	E20 (n=423)	257/423 (60.5%)	NA	NA	NA	NA	NA	median: 9 days	Heartburn free days: 66.5% nights: 74.7%
	E40 (n=425)	241/425 (56.7%)	NA	NA	NA	NA	NA	median: 11 days	Heartburn free days: 62.2% nights: 70.2%
	O20 (n=434)	252/434 (58.1%)	NA	NA	NA	NA	NA	median: 12 days	Heartburn free days: 63.4% nights: 72.6%
Armstrong 2004b	E40 (n=347)	244/347 (70.3%)	NA	NA	NA	NA	NA	median: 11 days	Heartburn free days: 63.5% nights: 72.5%
	O20 (n=346)	235/346 (67.9%)	NA	NA	NA	NA	NA	median: 11 days	Heartburn free days: 63.5% nights: 71.5%
Armstrong 2004c	E20 (n=336)	208/336 (61.9%)	NA	NA	NA	NA	NA	median: 11 days	Heartburn free days: 60.7% nights: 71.4%
	O20 (n=334)	199/334 (59.6%)	NA	NA	NA	NA	NA	median: 11 days	Heartburn free days: 61.3% nights: 73.5%
Chen 2005			@ 4 weeks	@ 8 weeks					
	E40 (n=25)	NA	NA	16/25 (64.0%)	NA	NA	median: 1 days	NA	NA
	O20 (n=23)	NA	NA	10/23 (43.5%)	NA	NA	median: 1 days	NA	NA

Table I[E]: (GERD) E vs O - Efficacy Outcomes									
Author, Year, Trial Name	**Treatment group (Drug and mg/day)**	**Symptomatic relief (n/N, %)**	**Healing of esophagitis (n/N, %)**		**QoL**	**Recurrences or relapse**	**Time to 1st resolution of symptom**	**Time to sustained resolution of symptom**	**% symptom free days & nights**
Lightdale 2006		@ 4 weeks (Heartburn)	@ 4 weeks (life table estimate, not included in forest plot)	@ 8 weeks					
	E40 (n=588)	356/588 (60.6%)	404/588 (68.7%)	508/588 (86.5%)	NA	NA	NA	NA	Heartburn free days: 72.6% nights: 85.7%
	O20 (n=588)	355/588 (60.5%)	409/588 (69.5%)	484/588 (82.3%)	NA	NA	NA	NA	Heartburn free days: 70.9% nights: 83.2%
Schmitt 2006		@ 4 weeks (Heartburn)	@ 4 weeks	@ 8 weeks					
	E40 (n=576)	374/576 (65.0%)	393/576 (68.2%)	501/576 (87.0%)	NA	NA	NA	NA	Heartburn free days: 74.5% nights: 86.2%
	O20 (n=572)	361/572 (63.1%)	379/572 (66.3%)	491/572 (85.8%)	NA	NA	NA	NA	Heartburn free days: 73.0% nights: 84.5%
Zheng 2009			@ 4 weeks	@ 8 weeks					
	E 40 (n=65)	NA	NA	62/65 (95.4%)	NA	NA	NA	NA	NA
	O 20 (n=65)	NA	NA	57/65 (87.7%)	NA	NA	NA	NA	NA
Zheng 2009 note: When the patients were divided into *H. pylori* positive and negative groups, the healing rate for reflux esophagitis at week 8 in *H. pylori* positive patients tended to be higher than that in negative subjects (92.4% vs 85.8%,P > 0.05, $\chi 2$ =2.95, by $\chi 2$ test).									
Abbreviations: GERD, Gastroesophageal Reflux Disease; E, Esomeprazole; O, Omeprazole; NA, not applicable; QoL, Quality of life.									

Table I[F]: (GERD) E vs O - Harm Outcomes						
Trial	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons**	**WDAE and reasons**	**Subjects with ≥1 AE n/N (%)**	**Most common AEs (n/N)**
Kahrilas 2000	E20 (n=656)	1/656 (MI)	NR	18/656	NR	Headache 57/655 (8.7%) Respiratory infection 35/655 (5.3%) Abdominal pain 24/655 (3.7%) Diarrhea 31/655 (4.7%) Flatulence 23/655 (3.5%) Gastritis 23/655 (3.5%) Nausea 19/655 (2.9%)
	E40 (n=654)	0/654	NR	13/654	NR	Headache 56/653 (8.6%) Respiratory infection 28/653 (4.3%) Abdominal pain 24/653 (3.7%) Diarrhea 30/653 (4.6%) Flatulence 12/653 (1.8%) Gastritis 16/653 (2.5%) Nausea 25/653 (3.8%)
	O20 (n=650)	0/650	NR	13/650	NR	Headache 45/649 (6.9%) Respiratory infection 30/649 (4.6%) Abdominal pain 27/649 (4.2%) Diarrhea 25/649 (3.9%) Flatulence 26/649 (4.0%) Gastritis 16/649 (2.5%) Nausea 20/649 (3.1%)
Richter 2001a	E40 (n=1216)	0/1216	NR	11/1216 (0.9%)	392/1216 (32.2%)	Headache 75/1205 (6.2%) Diarrhea 47/1205 (3.9%) Nausea 36/1205 (3.0%) Abdominal pain 31/1205 (2.6%)
	O20 (n=1209)	1/1209 (stab wound)	NR	13/1209 (1.1%)	415/1209 (34.3%)	Headache 70/1200 (5.8%) Diarrhea 56/1200 (4.7%) Nausea 36/1200 (3.0%) Abdominal pain 32/1200 (2.7%)

Table I[F]: (GERD) E vs O - Harm Outcomes						
Trial	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons**	**WDAE and reasons**	**Subjects with ≥1 AE n/N (%)**	**Most common AEs (n/N)**
Kao 2003	E40 (n=50)	NR	NR	1/50	NR	Headache: 1 (2%) Dizziness: 1 (2%) Diarrhea: 3 (6%) Constipation: 3 (6%)
	O20 (n=50)	NR	NR	1/50	NR	Headache: 1 (2%) Dizziness: 3 (6%) Diarrhea: 6 (12%) Constipation: 1 (2%)
Armstrong 2004 Study A	E20 (n=423)	NR	NR	NR	NR	NR
	E40 (n=425)	NR	NR	NR	NR	NR
	O20 (n=434)	NR	NR	NR	NR	NR
Armstrong 2004 Study B	E40 (n=347)	NR	NR	NR	NR	NR
	O20 (n=346)	NR	NR	NR	NR	NR
Armstrong 2004 Study C	E20 (n=336)	NR	NR	NR	NR	NR
	O20 (n=334)	NR	NR	NR	NR	NR
Chen 2005	E40 (n=25)	NR	NR	NR	7/25 (28.0%)	Constipation 2/25
	O20 (n=23)	NR	NR	NR	6/23 (26.1%)	Dry skin 3/23
Lightdale 2006	E20 (n=588)	NR	NR	10/588	NR	Headache 58/585 (9.9%) Diarrhea 27/585 (4.6%) Nausea 16/585 (2.7%)

Table I[F]: (GERD) E vs O - Harm Outcomes						
Trial	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons**	**WDAE and reasons**	**Subjects with ≥1 AE n/N (%)**	**Most common AEs (n/N)**
	O20 (n=588)	NR	NR	9/588	NR	Headache 37/588 (6.3%) Diarrhea 28/588 (4.8%) Nausea 23/588 (3.9%)
Schmitt 2006	E40 (n=576)	NR	NR	18/576	283/576 (49.1%)	Headache 59/576 (10.2%) Diarrhea 38/578 (6.6%) Nausea 25/576 (4.3%)
	O20 (n=572)	NR	NR	10/572	257/572 (45%)	Headache 39/571 (6.8%) Diarrhea 31/571 (5.4%) Nausea 24/571 (4.2%)
Zheng 2009	E40 (n=68)	NR	NR	NR	NR	NR
	O20 (n=68)	NR	NR	NR	NR	NR
Abbreviations: GERD, Gastroesophageal Reflux Disease; E, Esomeprazole; O, Omeprazole; NR, not reported; SAE, serious adverse event; WDAE, withdrawal due to adverse effects; AE, adverse effects; MI, myocardial infarction.						

II. Comparison 2: Esomeprazole vs. Pantoprazole (13 RCTs)

Table II[A]: (GERD) E vs P - Description of trials meeting the inclusion criteria

Author, Year, Trial Name	Study Design	Location	Randomised sample size (n)	Patient Type	Intervention/ Comparator and dosage	Study Duration	Outcome(s)
Scholten 2003	DBRCT	Germany	E40: 105 P40: 112	217 patient, age 18 and older, with endoscopically proven moderate to severe GERD were randomized	E 40 mg OD P 40 mg OD	4 weeks	**Primary outcome:** Symptom score (patient and investigator evaluated) **Other outcomes:** Safety
Gillessen 2004	DBRCT	Germany	E40: 114 P40:113	227 patients, age 18 and older, exhibited endoscopically proven GERD and typical symptoms of GERD were randomized	E 40 mg OD P 40 mg OD	10 weeks	**Primary outcome:** Endoscopic confirmed EE healing **Other outcomes:** % total symptom relief, safety
Labenz 2005a	DBRCT	14 European countries	E40: 1562 P40: 1589	3170 patients with photographic documentation of EE by endoscopy within 7 days prior to enrollment were randomized	E 40 mg OD P 40 mg OD	8 weeks	**Primary outcome:** Endoscopic healing rate @ 8 weeks **Other outcomes:** time to sustained heartburn resolution, % of heartburn free days, safety
Monnikes 2005	DBRCT	Germany	E20: 266 P20: 263	529 patients, age 18 or older, who have history of GERD and suffered from at least 3 acid episodes within the pre-treatment phase were randomized	E 20 mg OD P 20 mg OD	4 weeks	**Primary outcome:** Time to 1st symptom relief **Other outcomes:** Time to sustained relief, % of patients reaching 1st relief and sustained relief at 4 weeks

Table II[A]: (GERD) E vs P - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention/ Comparator and dosage**	**Study Duration**	**Outcome(s)**
Glatzel 2006	DBRCT	Germany	E40: 277 P40: 284	563 patients, age 18 and older, with endoscopic confirmation of GERD grade A-D were randomized.	E 40 mg OD P 40 mg OD	4 weeks	**Primary outcome:** ReQuest symptom score **Other outcome:** time to 1st symptom relief, time to sustained symptom relief, safety
Vcev 2006	RCT	Croatia	E40: 90 P40: 90	180 patients with history of GERD symptoms for at least 6 months and endoscopic confirmation of esophagitis were randomized	E 40 mg OD P 40 mg OD	8 weeks	**Primary outcome:** Endoscopic confirmed EE healing **Other outcomes:** % of heartburn free days, Time to sustained heartburn resolution, safety
Bardhan 2007	DBRCT	Germany	E40: 293 P40: 289	582 patients, age 18 or older with endoscopically confirmed erosive esophagitis were randomized.	E 40 mg OD P 40 mg OD	12 weeks	**Primary outcome:** Complete remission at 12 weeks defined as endoscopic healing and complete symptom relief **Other outcomes:** Complete remission at 4 and 8 weeks, endoscopic healing rate at 4, 8, and 12 weeks, Symptom relief rates at 4, 8 and 12 weeks, safety.
Zheng 2009 (O and L groups not shown)	RCT	China	E40: 68 P40: 69	274 adults with endoscopically proven reflux esophagitis	E 40 mg OD P 40 mg OD	8 weeks	**Primary outcome:** Symptom score in the first week of drug administration **Other outcome:** Endoscopic healing at week 8.

Table II[A]: (GERD) E vs P - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention/ Comparator and dosage**	**Study Duration**	**Outcome(s)**
Moraes-filho 2014	DBRCT	Brazil	E40: 296 P40: 297	591 adult out-patients age 18-70, with heartburn or regurgitation at least twice a week for 4-8 weeks in the last 3 months and with endoscopic confirmation of erosive esophagitis were randomized	P 40 mg OD E 40 mg OD	8 weeks	**Primary outcome:** % of patient in complete remission at 4 week **Other outcomes:** % of patients in complete remission at 8 weeks, endoscopic healing rate, symptom relief rate, symptom score at 4 and 8 weeks
Maintenance studies							
Labenz 2005b	DBRCT	14 European countries	E20: 1398 P20: 1415	2813 patients, age 18 and older, from the healing phase of EXPO study, with endoscopic confirmation of EE healing were randomized	E 20 mg OD P 20 mg OD	6 months	**Primary outcome:** Endoscopic confirmed remission of EE **Other outcomes:** symptomatic remission, safety
Goh 2007	DBRCT	16 European countries	E20: 672 P20: 642	1316 patients, age 18 or older, who has been healed by taking Pantoprazole 40 mg OD for 4 to 8 weeks, were randomized	E 20 mg OD P 20 mg OD	6 months	**Primary outcome:** Endoscopic and symptomatic remission at 6 months **Other outcomes:** safety
Scholten 2007	DBRCT	Germany	E20: 100 P20: 99	199 patients, age 18 and older, who have taken Pantoprazole 20 mg once daily for 28 days and showed no heartburn symptom were randomized	E 20 mg OD when needed P20 mg OD when needed	6 months	**Primary outcome:** Symptom score **Other outcomes:** safety
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; E, Esomeprazole; P, Pantoprazole; O, Omeprazole; L, Lansoprazole; OD, once daily; RCT, randomized control trial; DB, double-blind							

Table II[B]: (GERD) E vs P - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Scholten 2003	Patients, age 18 and older, with endoscopically proven moderate to severe GERD were enrolled.	Patients with peptic ulcer; Zollinger-Ellison syndrome; Pyloric stenosis; Esophageal and gastrointestinal surgery; Known allergy to PPI; Rare genetic disease; Severe concomitant diseases; History of alcohol or drug abuse; Chronic use of NSAID, COX-2 inhibitors, aspirin, PPI or H2RA use in last 10 days were excluded.	Antacid use within 3 days before randomization was not allowed
Gillessen 2004	Patients, age 18 and older, exhibited endoscopically proven GERD and typical symptoms of GERD were enrolled	Patients with peptic ulcer; Zollinger-Ellison syndrome; Pyloric stenosis; Prior esophageal/GI surgery; Allergic to PPI; Rare genetic diseases; Severe concomitant diseases; Malignant disease within last 5 years; Moderate to severe malfunction of liver or kidney; Alcohol or drug abuse were excluded	The use of concomitant medication for contraception or chronic diseases remained unchanged for the duration of the study and a regular intake of acetyl salicylic acid up to 150 mg/d was considered acceptable.
Labenz 2005a	Patients with photographic documentation of EE by endoscopy within 7 days prior to entailment were randomized	Patients with other significant upper GI disorder; Intake of medication liable to affect the outcome (including NSAID); Pregnancy, childbearing potential or lactation; Alcohol or drug abuse PPI use within 2 weeks prior to the first endoscopy was excluded.	NR
Monnikes 2005	Patients, age 18 or older, who have history of GERD and suffered from at least 3 acid episodes within the pre-treatment phase were randomized	Patients with other GI diseases; Erosive GERD; Barrett's esophagus; Peptic ulcer or ulcer complications; Zollinger-Ellison syndrome; Pyloric stenosis; Esophageal or gastric surgery; Indication of *H. pylori* eradication; Severe diseases of other major body systems; Pregnancy, lactation, or child bearing age without adequate contraception; Taken PPI, H2RA within 5-10 days before randomization were excluded.	NR

Table II[B]: (GERD) E vs P - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Glatzel 2006	Patients, age 18 and older, with endoscopic confirmation of GERD grade A-D were randomized.	Patients with no endoscopic finding of GERD; Other gastric hypersecretory condition; Prior acid lowering surgery; Esophageal or GI surgery; Esophageal stricture; Schatzki's ring; Esophageal diverticula; Esophageal varices, achalasia or Barrett's esophagus; Acute peptic ulcer; Pyloric stenosis; Inflammatory bowel disorder; Severe major body part disorder; Pregnancy, lactation or childbearing potential; PPI or H2RA intake 5 days before study start were excluded.	ASA intake up to 150 mg per day was allowed
Vcev 2006	Patients with history of GERD symptoms for at least 6 months and endoscopic confirmation of esophagitis were enrolled	Patients with other significant upper GI disorders; Intake of medication liable to affect the outcome of the study; Pregnancy, childbearing potential or lactation; Alcohol or drug abuse; PPI use within 4 weeks prior to first endoscopy were excluded.	NR
Bardhan 2007	Patients, age 18 or older with endoscopically confirmed erosive esophagitis were randomized.	Patients with Non erosive esophagitis; Other GI diseases; Severe system diseases; Mark obesity (BMI>35 kg/m^2); Allergy to PPI; Drug and alcohol abuse; Severe psychiatric or neurological disorder Pregnancy, lactation, or child bearing age without adequate contraception	ASA up to 150 mg per day were allowed.
Zheng 2009	Patients with endoscopically proven reflux esophagitis in the Affiliated Hospital of Yanbian University from January, 2006 to September, 2007 and the Affiliated Hospital of Hainan Medical College from October, 2007 to November, 2008	Patients with active peptic ulcer; upper gastrointestinal cancers, malignant diseases of other organs; severe cardiac, hepatic, or renal diseases; anemia (hemoglobin concentration < 10 g/dL); pregnant and/or lactating women were excluded.	Subjects were not permitted to take H2-RAs or prokinetic drugs during the study period.
Moraes-filho 2014	Adult out-patients age 18-70, with heartburn or regurgitation at least twice a week for 4-8 weeks in the last 3 months and with endoscopic confirmation of erosive esophagitis were randomized	Patients with other GI diseases; Barrett's esophagus; Peptic ulcer; Zollinger-Ellison syndrome; Pyloric stenosis; History of GI surgery; Obstructive esophageal stricture; Schatzki ring; Severe neurological and psychiatric diseases; Haematological diseases; Hepatic and renal diseases; Pregnancy, lactation and child bearing age without adequate contraception were excluded.	ASA intake up to 163 mg per day was allowed.

Table II[B]: (GERD) E vs P - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Maintenance studies			
Labenz 2005b	Patients (from the healing phase of EXPO study - Labenz 2005a) with healed erosive oesophagitis and free of moderate/severe heartburn and acid regurgitation, and had no dysplasia in the biopsies taken upon endoscopic suspicion of Barrett's oesophagus.	Patients with other significant upper GI disorder; Intake of medication liable to affect the outcome (including NSAID); Pregnancy, childbearing potential or lactation; Alcohol or drug abuse; PPI use within 2 weeks prior to the first endoscopy was excluded.	NR
Goh 2007	Patients, age 18 or older, who has been healed (defined as the absence of esophagitis, and 'no' or 'mild' heartburn and acid regurgitation) by taking Pantoprazole 40 mg OD for 4 to 8 weeks, were randomized	Patients with Zollinger-Ellison syndrome or other gastric hypersecretory conditions; Pyloric stenosis; Acute peptic ulcer and complications; Obstructive esophageal stricture; Barrett's esophagus; Severe diseases of other body system; Pregnant or nursing women; Childbearing age without adequate contraception were excluded.	ASA up to a daily dose of 163 mg could be taken.
Scholten 2007	Patients, age 18 and older, who have taken Pantoprazole 20 mg once daily for 28 days and showed no heartburn symptom were randomized	Patients with other GI disease; GERD grade C and D; Barrett's esophagus; Florid peptic ulcer; Zollinger-Ellison syndrome; Ulcer complication or pyloric stenosis; Previous GI surgery; Need of *H. pylori* eradication; Severe major body system diseases; Allergy to PPI; Cancer in past 5 years Alcohol or drug abuse; Pregnancy, lactation or inadequate contraception were excluded.	ASA up to 150 mg/day and magaldrate up to 8 tablets a day was allowed.
Abbreviations: GI, Gastrointestinal; GERD, Gastroesophageal reflux disease; E, Esomeprazole; P, PantoprazoleASA, acetylsalicylic acid; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist; NSAID, Non-steroid anti-inflammatory drugs; OD, once daily; EE, erosive esophagitis.			

Table II[C]: (GERD) E vs P - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs ± SD)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol Consumption (n, %)**	***H. pylori* positive (n, %)**	**Severity (LA Grades) (n, %)**	**Other**
Scholten 2003	E40 (n=105)	57 (54.3%)	52.6 ± 13.8	27.6 ± 4.2	Caucasian: 104 (99.1%)	23 (21.9%)	3 (2.9%)	23 (21.9%)	B: 76 (72.4%) C: 29 (27.6%)	-
	P40 (n=112)	69 (61.6%)	54.7 ± 15.1	27.0 ± 4.3	Caucasian: 110 (98.2%)	22 (19.6%)	5 (4.5%)	25 (22.3%)	B: 83 (74.1%) C: 29 (26.9%)	-
Gillessen 2004	E40 (n=114)	57 (50.0%)	54 ± 14	27 ± 4	Caucasian: 112 (98%)	30 (26%)	6 (5%)	35 (31%)	NR	-
	P40 (n=113)	64 (57.0%)	53 ± 15	27 ± 4	Caucasian: 110 (97%)	26 (23%)	9 (8%)	25 (22%)	NR	-
Labenz 2005a	E40 (n=1562)	969 (62.0%)	50.6 ± 14	NR	Caucasian: 1512 (96.8%)	NR	NR	429 (27.5%)	A: 523 (33.5%) B: 665 (42.6%) C: 304 (19.5%) D: 70 (4.5%)	-
	P40 (n=1589)	1012 (63.7%)	50.5 ± 13.8	NR	Caucasian: 1548 (97.5%)	NR	NR	412 (25.9%)	A: 478 (30.1%) B: 716 (45.1%) C: 303 (19.1%) D: 92 (5.8%)	-
Monnikes 2005	E20 (n=266)	266	52.6 ± 15.4	BMI: 27.3 ± 4.4	NR	55 (20.4%)	Daily: 3 (1.1%)	140 (52.6%)	NR	-
	P20 (n=263)	263	51.2 ± 14.2	BMI: 26.6 ± 4.0	NR	55 (20.9%)	Daily: 2 (0.8%)	122 (46.4%)	NR	-
Glatzel 2006	E40 (n=277)	141 (50.9%)	54.0 ± 14.3	27.1 ± 3.4	NR	49 (17.7%)	NR	109 (39.3%)	A: 135 (48.7%) B: 103 (37.2%) C: 31 (11.2%) D: 8 (2.9%)	-
	P40 (n=284)	159 (56.0%)	52.6 ± 14.5	26.7 ± 3.5	NR	53 (18.7%)	NR	110 (38.7%)	A: 146 (51.4%) B: 113 (39.8%) C: 18 (6.3%) D: 7 (2.5%)	-

Table II[C]: (GERD) E vs P - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs ± SD)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol Consumption (n, %)**	***H. pylori* positive (n, %)**	**Severity (LA Grades) (n, %)**	**Other**
Vcev 2006	E40 (n=90)	57 (63.3%)	51.2 ± 14.5	NR	NR	NA	NR	22 (24.4%)	A: 37 (41.1%) B: 40 (44.4%) C: 13 (14.4%)	-
	P40 (n=90)	59 (65.6%)	49.4 ± 13.9	NR	NR	NR	NR	20 (22.2%)	A: 35 (38.9%) B: 39 (43.3%) C: 16 (17.8%)	-
Bardhan 2007	E40 (n=293)	154 (53%)	54 ±14	BMI: 27 ± 4	Caucasian: 287 (98%)	100 (34%)	NR	121 (41%)	A: 139 (47%) B: 106 (36%) C: 35 (12%) D: 13 (4%)	-
	P40 (ITT= 288/289)	141 (51%)	53 ± 14	BMI: 27 ± 4	Caucasian: 282 (98%)	87 (30%)	NR	133 (46%)	A: 145 (50%) B: 106 (37%) C: 25 (9%) D: 12 (4%)	-
Zheng 2009 (O and L groups not shown)	E40 (n=68)	33 (48.5%)	57.4	NR	NR	NR	NR	29 (42.6%)	A: 20 (29.4%) B: 26 (38.2%) C: 20 (29.4%) D: 2 (2.9%)	-
	P40 (n=69)	34 (49.2%)	57.8	NR	NR	NR	NR	30 (43.5%)	A: 20 (29.0%) B: 28 (40.6%) C: 20 (29.0%) D: 1 (1.4%)	-
Moraes-Filho 2014	E40 (n=296)	141 (49.0%)	42.3 ± 12.6	28.4 ± 5.3	Caucasian: 237 (82.3%)	NR	NR	NR	A: 172 (60%) B: 93 (32%) C: 23 (8%) D: 0 (0%)	-
	P40 (n=297)	128 (44.1%)	43.1 ± 11.5	28.7 ± 5.2	Caucasian: 248 (85.5%)	NR	NR	NR	A: 174 (60%) B: 96 (33%) C: 17 (6%) D: 3 (1%)	-

Table II[C]: (GERD) E vs P - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs ± SD)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol Consumption (n, %)**	***H. pylori* positive (n, %)**	**Severity (LA Grades) (n, %)**	**Other**
Maintenance studies										
Labenz 2005b	E20 (ITT= 1377/1398)	888 (64.5%)	50.2 ± 14.1	Weight: 82.6 kg ± 14.8	Caucasian: 97.3%	NR	NR	375 (27.2%)	A: 447 (32.5%) B: 607 (44.1%) C: 263 (19.1%) D: 60 (4.4%)	-
	P20 (ITT= 1389/1415)	849 (61.6%)	50.7 ± 13.8	Weight: 81.9 kg ± 15.5	Caucasian: 97.4%	NR	NR	377 (27.1%)	A: 451 (32.5%) B: 621 (44.7%) C: 251 (18.1%) D: 66 (4.8%)	-
Goh 2007	E20 (n=672)	396 (59.4%)	48.8 ± 14.5	BMI: 26.9 ± 4.3	NR	143 (21.4%)	None: 632 (94.8%)	189 (28.6%)	A: 305 (45.7%) B: 290 (43.5%) C: 59 (8.9%) D: 13 (2.0%)	-
	P20 (n=642)	373 (58.6%)	49.0 ± 14.1	BMI: 26.9 ± 4.1	NR	136 (21.4%)	None: 605 (95.1%)	202 (32.0%)	A: 296 (46.5%) B: 271 (42.6%) C: 58 (9.1%) D: 11 (1.7%)	-
Scholten 2007	E20 (n=100)	44 (44%)	52.7 ± 13.4	BMI: 27.3 ± 4.4	Caucasian: 100 (100%)	NR	NR	17 (17%)	A: 58 (58%) B: 33 (33%) ENRD: 9 (9%)	-
	P20 (n=99)	57 (57%)	54.5 ± 12.6	BMI: 27.6 ± 4.1	Caucasian: 98 (99%)	NR	NR	15 (15.2%)	A: 60 (60.6%) B: 34 (34.3%) ENRD: 5 (5.1%)	-
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; E, Esomeprazole; P, Pantoprazole; NR, not reported; OD, once daily; BMI, body mass index; SD, standard deviation; ENRD, endosopic-negative reflux disease										

Table II[D]: (GERD) E vs P - Summary of Patient Disposition						
Trial	**Treatment groups**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for withdrawal**	**Additional Details Provided**
Scholten 2003	E40	105	NR	NR	Total WDAE: 3	Study did not report total dropout, or WDAE by treatment group.
	P40	112	NR	NR		
Gillessen 2004	E40	114	103	11	Protocol violation: 11	Study did not clearly report WDAE
	P40	113	94	19	Protocol violation: 19	
Labenz 2005a	E40	1562	NR	NR	AE: 33/1562 (2.1%)	Did not report total withdrawal or AE.
	P40	1589	NR	NR	AE: 29/1589 (1.8%)	
Monnikes 2005	E20	266	NR	NR	NR	-
	P20	263	NR	NR	NR	-
Glatzel 2006	E40	277	232	45	WDAE: 4/277 (1.4%)	-
	P40	284	244	40	WDAE: 3/284 (1.1%)	-
Vcev 2006	E40	90	NR	NR	NR	-
	P40	90	NR	NR	NR	-
Bardhan 2007	E40	293	249	44	WDAE: 13	-
	P40	289	261	28	WDAE: 17	-
Zheng 2009 (O and L groups not shown)	E40	68	NR	NR	NR	-
	P40	69	NR	NR	NR	-
Moraes-Filho 2014	E40	296	288	8	Did not receive drug: 1 Withdrew consent: 5 Had no post baseline data: 2	-
	P40	297	290	7	Did not receive drug: 1 Withdrew consent: 4 Had no post baseline data: 2	-
Maintenance studies						
Labenz 2005b	E20	1398	1208	190	WDAE: 21 Lack of efficacy: 78 Discontinuation criteria: 9 Lost to follow-up: 20 Other: 62	-

Table II[D]: (GERD) E vs P - Summary of Patient Disposition

Trial	Treatment groups	Randomized and Treated	Completed	Discontinued	Reasons for withdrawal	Additional Details Provided
	P20	1415	1141	274	WDAE: 19 Lack of efficacy: 181 Discontinuation criteria: 6 Lost to follow-up: 17 Other: 51	-
Goh 2007	E20	672	667	5	Authors did not clearly explain the reason.	-
	P20	642	636	6		-
Scholten 2007	E20	100	NR	NR	5 patients withdrawn due to adverse effects.	-
	P20	99	NR	NR		-

ABBREVIATIONS: GERD, Gastroesophageal reflux disease; E, Esomeprazole; P, Pantoprazole; NR, not reported; WDAE, withdrawal due to adverse effects; AE, adverse effects.

Table II[E]: (GERD) E vs P - Efficacy Outcomes

Author, Year, Trial Name	Treatment group (n)	Symptomatic relief (n/N %)	Healing of esophagitis (n/N %)	QoL	Remission (n/N %)	Time to 1st resolution of symptom	Time to sustained resolution of symptom	% symptom free days & nights
Scholten 2003		@ 4 weeks						
	E40 (n=105)	Heartburn: 74/105 (70.7%) Complete relief: 13/105 (12.4%)	NA	NA	NA	NA	NA	NA
	P40 (n=112)	Heartburn: 80/112 (71.7%) Complete relief: 19/112 (17.1%)	NA	NA	NA	NA	NA	NA

Table II[E]: (GERD) E vs P - Efficacy Outcomes									
Author, Year, Trial Name	**Treatment group (n)**	**Symptomatic relief (n/N %)**	**Healing of esophagitis (n/N %)**		**QoL**	**Remission (n/N %)**	**Time to 1st resolution of symptom**	**Time to sustained resolution of symptom**	**% symptom free days & nights**
Gillessen 2004		@ 10 weeks		@ 10 weeks					
	E40 (n=114)	54/114 (47%)	NA	100/114 (88%)	NA	NA	NA	NA	NA
	P40 (n=113)	57/113 (50%)	NA	99/113 (88%)	NA	NA	NA	NA	NA
Labenz 2005a			@ 4 weeks	@ 8 weeks					
	E40 (n=1562)	NA	1231/1562 (78.8%)	1431/1562 (91.6%)	NA	NA	NA	Median 6 days	Heartburn free days: 67.3%
	P40 (n=1589)	NA	1157/1589 (72.8%)	1413/1589 (88.9%)	NA	NA	NA	Median: 8 days	Heartburn free days: 70.7%
Monnikes 2005		@ 4 weeks							
	E20 (n=266)	234/266 (89.7%)	NA		NA	NA	median: 2 days mean: 6.4 ± 9.0 days	median: 13 days mean: 13.5 ± 11.6 days	NA
	P20 (n=263)	244/263 (92.8%)	NA		NA	NA	median: 2 mean: 5.9 ± 8.1 days	median: 10 days mean: 13.2 ± 11.6 days	NA
Glatzel 2006									
	E40 (n=277)	NA	NA		NA	NA	median= 2 days	median=17 days	NA
	P40 (n=284)	NA	NA		NA	NA	median= 2 days	median=17 days	NA
Vcev 2006			@ 4 weeks	@ 8 weeks					
	E40 (n=90)	NA	70/90 (77.8%	83/90 (92.2%)	NA	NA	NA	median = 6 days	Heartburn free days: 70.2%
	P40 (n=90)	NA	65/90 (72.2%)	82/90 (91.1%)	NA	NA	NA	median= 6 days	Heartburn free days: 69.8%

Table II[E]: (GERD) E vs P - Efficacy Outcomes									
Author, Year, Trial Name	**Treatment group (n)**	**Symptomatic relief (n/N %)**	**Healing of esophagitis (n/N %)**		**QoL**	**Remission (n/N %)**	**Time to 1st resolution of symptom**	**Time to sustained resolution of symptom**	**% symptom free days & nights**
Bardhan 2007						Endoscopic & symptom relief			
	E40 (n=293)	@ 4 weeks 188/293 (64.2%) @8 weeks 220/293 (75.1%) @ 12 weeks 226/293 (77%)	@ 4 weeks 202/293 (68.9%) @ 8 weeks 243/293 (83%)	@ 12 weeks 258/293 (88%)	NA	@ 4 weeks 143/293 (49%) @ 8 weeks 205/293 (70%) @ 12 weeks 223/293 (76%)	NA	NA	NA
	P40 (n=289)	@ 4 weeks 182/289 (63.0%) @ 8 weeks 223/289 (77.2%) @ 12 weeks 228/289 (79%)	@ 4 weeks 199/289 (68.9%) @ 8 weeks 249/289 (86%)	@ 12 weeks 263/289 (91%)	NA	@ 4 weeks 136/289 (47%) @ 8 weeks 199/289 (69%) @ 12 weeks 220/289 (76%)	NA	NA	NA
Zheng 2009 (O and L groups not shown)			@ 4 weeks	@ 8 weeks					
	E 40 (n=65)	NA	NA	62/65	NA	NA	NA	NA	NA
	P 40 (n=67)	NA	NA	61/67 (91.1%)	NA	NA	NA	NA	NA
	Note: When the patients were divided into *H. pylori* positive and negative groups, the healing rate for reflux esophagitis at week 8 in *H. pylori* positive patients tended to be higher than that in negative subjects (92.4% vs 85.8%,P > 0.05, $\chi 2$ =2.95, by $\chi 2$ test).								

Table II[E]: (GERD) E vs P - Efficacy Outcomes									
Author, Year, Trial Name	**Treatment group (n)**	**Symptomatic relief (n/N %)**	**Healing of esophagitis (n/N %)**		**QoL**	**Remission (n/N %)**	**Time to 1st resolution of symptom**	**Time to sustained resolution of symptom**	**% symptom free days & nights**
Moraes-Filho 2014		@ 8 weeks	@ 4 weeks	@ 8 weeks		Endoscopic and symptom relief (complete remission)			
	E40 (n=296)	227/296 (76.7%)	211/296 (55.7%)	253/296 (70.9%)	NA	Complete remission @ 4 weeks 165/296 @ 8 weeks 210/296	NA	NA	NA
	P40 (n=297)	252/297 (84.4%)	208/297 (70.0%)	246/297 (75.4%)	NA	@ 4 weeks 170/297 @ 8 weeks 224/297	NA	NA	NA
Maintenance studies									
Labenz 2005b						% remission @ 6 months (life table estimate, not used in forest plot)			
	E20 (ITT=1377/ 1398)	NA	NA		NA	Endoscopic & symptom remission: 1198/1377 (87.0%) Symptom only: 1270/1377 (92.2%)			
	P20 (ITT=1389/ 1415)	NA	NA		NA	Endoscopic & symptom remission: 1040/1389 (74.9%) symptom only: 1229/1389 (88.5%)			
Goh 2007						% remission @ 6 months			
	E20 (n=672)	NA	NA		NA	Symptomatic and endoscopic remission: 571/672 (85%)			
	P20 (n=642)	NA	NA		NA	Symptomatic and endoscopic remission: 539/642 (84%)			

Table II[E]: (GERD) E vs P - Efficacy Outcomes								
Author, Year, Trial Name	**Treatment group (n)**	**Symptomatic relief (n/N %)**	**Healing of esophagitis (n/N %)**	**QoL**	**Remission (n/N %)**	**Time to 1st resolution of symptom**	**Time to sustained resolution of symptom**	**% symptom free days & nights**
Scholten 2007		Symptom score						
	E20 (n=100)	1.99	NA	NA	NA	NA	NA	NA
	P20 (n=99)	1.72	NA	NA	NA	NA	NA	NA
	Note: The symptom score used in Scholten 2007 was not validated and was not used in other studies.							
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; E, Esomeprazole; P, Pantoprazole; NA, not assessed; QoL, quality of life.								

Table II[F]: (GERD) E vs P - Harm Outcomes						
Trial	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons (n/N)**	**WDAE and reasons**	**Subjects with ≥1 AE n/N (%)**	**Most common AEs (n/N, %)**
Scholten 2003	E40	NR	2/105 (abdominal hernia, arthrosis)	3/217	31/217 (14%)	Study did not report WDAE or AE by treatment group.
	P40	NR	1/112 (Myocardial infarction)			
Gillessen 2004	E40	NR	0/114	Did not reported by treatment group	43/217 (20%)	Author reported the most common adverse effect was dizziness (2% of patients)
	P40	NR	1/113 (Liver cancer)			
Labenz 2005a	E40	NR	23/1562 (1.5%)	33/1562 (2.1%)	NR	Headache 5/1562 Diarrhea 4/1562
	P40	NR	21/1589 (1.3%)	29/1589 (1.8%)	NR	Nausea 6/1589 Dizziness 5/1589

Table II[F]: (GERD) E vs P - Harm Outcomes						
Trial	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons (n/N)**	**WDAE and reasons**	**Subjects with ≥1 AE n/N (%)**	**Most common AEs (n/N, %)**
Monnikes 2005	E20	NR	NR	NR	NR	NR
	P20	NR	NR	NR	NR	NR
Glatzel 2006	E40	NR	2 (drug allergy, hypertensive crisis)	4/277 (1.4%)	44/277 (15.9%)	Aggravated hypertension (1.2%) Bronchitis (1.2%) Diarrhea (1.2%)
	P40	NR	1 (lymphoma)	3/284 (1.1%)	49/284 (17.3%)	
Vcev 2006	E40	NR	NR	NR	11/90 (12%)	Most common adverse effects were nausea, dizziness and headaches.
	P40	NR	NR	NR	10/90 (11%)	Most common adverse effects were nausea, diarrhea and headaches
Bardhan 2007	E40	NR	7 patients had 9 SAE	44/293 (15%)	56/293 (19%)	Headache 7 (1.2%) Gastroenteritis 6 (1%) Bronchitis 5 (0.9%) Nasopharyngitis 4 (0.7%) Diarrhea 3 (0.5%)
	P40	NR		28/289 (10%)	49/289 (17%)	
Zheng 2009 (O and L groups not shown)	E40	NR	NR	NR	NR	NR
	P40	NR	NR	NR	NR	NR
Moraes-Filho 2014	E40	NR	NR	NR	104/296 (36.1%)	Headache 25/296 (8.3%) Insomnia 13/296 (4.5%) Diarrhea 10/296(3.5%) Abdominal pain 9/296 (3.1%) Gastritis 15/296 (5.2%) Nausea 12/296 (4.2%)

Table II[F]: (GERD) E vs P - Harm Outcomes						
Trial	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons (n/N)**	**WDAE and reasons**	**Subjects with ≥1 AE n/N (%)**	**Most common AEs (n/N, %)**
	P40	NR	NR	NR	95/297 (32.8%)	Headache 27/297 (9.0%) Insomnia 14/296 (4.8%) Diarrhea 13/297 (4.5%) Abdominal pain 10/297 (3.4%) Gastritis 9/297 (2.8%) Nausea 8/297 (2.8%)
Maintenance studies						
Labenz 2005b	E20	2 (Cancer, suicide)	45/1377 (3.3%)	19/1377 (1.4%)	NR	NR
	P20	2 (Cancer, lung fibrosis)	38 /1389 (2.7%)	18/1389 (1.3%)	NR	NR
Goh 2007	E20	0/667	17/667 (2.5%)	2/667	153/667 (23%)	NR
	P20	2/636 (ischemic colitis, pulmonary thrombosis	9/636 (1.4%)	5/636	140/636 (22%)	NR
Scholten 2007	E20	NR	2/100	5 patients withdraw due to AE	NR	The most common adverse effects included: Bronchitis, Back pain, Diarrhea, Eczema, Depression, Enterocolitis, Migraine, Osteoarthritis, Sinobronchitis, Tonsillitis, Varicose veins
	P20	NR	2/99		NR	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; E, Esomeprazole; P, Pantoprazole; NR, not reported; WDAE, withdrawal due to adverse effects; AE, adverse effects; SAE, serious adverse events						

III. Comparison 3: Esomeprazole vs. Rabeprazole (5 RCTs)

Table III[A]: (GERD) E vs R - Description of trials meeting the inclusion criteria

Author, Year, Trial Name	Study Design	Location	Randomised sample size (n)	Patient Type	Intervention/ Comparator and dosage	Study Duration	Outcome(s)
Fock 2005	DBRCT	Singapore	E20: 67 R10: 67	134 patients with NERD (Grade 0 according to LA classification) with severe heartburn or regurgitation	E 20 mg OD R 10 mg OD	4 weeks	The primary efficacy endpoint was the time (in days) for patients to achieve their first 24-h interval without any symptoms of heartburn or regurgitation. Number of patients who had complete or satisfactory relief of symptoms during week 1, 2, 3, or 4, symptom severity scores of day-time and night-time. Heart burn or regurgitation, upper GI symptoms, patients' global evaluation at the end of study; Adverse events
Eggleston 2009 The TREAT study	DBRCT	Australia	E20: 459 E40: 469 R20: 464	1392 patients with GERD associated heartburn (with or without regurgitation)	E20 mg OD E40 mg OD R20 mg OD	4 weeks	Primary: Heartburn relief; complete regurgitation relief and satisfactory regurgitation relief (Patient assessment of GERD symptoms daily using PAGI-SYM questionnaire) Secondary: change in primary symptom score; change in PAGI-SYM dimension scores; median times to achieve complete and satisfactory relief of heartburn and regurgitation during first week; proportions of 24hr periods heartburn free and regurgitation free; change in SF-36 on days 0 and 28; investigators rating overall satisfaction of treatment; Adverse events

Table III[A]: (GERD) E vs R - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention/ Comparator and dosage**	**Study Duration**	**Outcome(s)**
Laine 2011 Study 1 2 identical RCTs	DBRCT	Study 1: 276 centres in 18 countries including Canada and USA.	E40: 534 R50: 527	1061 patients with symptomatic GERD and heartburn	E 40 mg OD R 50 mg OD (extended release)	4 or 8 weeks (if esophagitis was unhealed by 4 weeks).	Primary endpoint: Endoscopic healing at week 4 and at week 8 Secondary: Percentage of patients who achieved diary-recorded sustained resolution of heartburn ≥7 consecutive heartburn-free days) at the week 4 visit. Exploratory: time-to-first diary-recorded heartburn-free day, time-to-first diary-recorded sustained resolution of heartburn, percentage of diary-recorded heartburn-free days; percentage of diary-recorded heartburn-free daytimes, percentage of diary-recorded heartburn-free night-times, percentage of patients who achieved investigator-recorded sustained resolution of heartburn and other GERD-associated symptoms at week 4 and percentage of patients who achieved investigator-recorded sustained resolution of heartburn and other GERD associated symptoms at week 8; Adverse events
Laine 2011 Study 2 2 identical RCTs	DBRCT	285 centres in 21 countries including Canada and USA	E40: 540 R50: 529	1069 patients with symptomatic GERD and heartburn	E 40 mg OD R 50 mg OD (extended release)	4 or 8 weeks (if esophagitis was unhealed by 4 weeks)	See Laine 2011 Study 1

Table III[A]: (GERD) E vs R - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention/ Comparator and dosage**	**Study Duration**	**Outcome(s)**
Maiti 2011	Single-blind RCT	India	E40: 30 R40: 30	60 patients with mild-to-moderate erosive GERD (Grade A or B according to LA classification)	E40 mg OD R40 mg OD	4 weeks	Efficacy variables: Severity of GERD symptoms based on GERD symptom scoring, endoscopic findings, QOLRAD scoring at week 4 Adverse events
ABBREVIATIONS: DB, Double-blind; RCT, Randomized controlled trial; GERD, Gastroesophageal reflux disease; OD, once daily; NERD, nonerosive reflux disease; R, Rabeprazole; E, Esomeprazole; QOLRAD, Quality of Life in Reflux and Dyspepsia							

Table III[B]: (GERD) E vs R - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
Fock 2005	Patients aged between 21 and 65 years with GERD symptoms (heartburn or regurgitation or both) were dominant symptoms present for $\geq$ 3 months in the previous year, which need not be continuous. Subjects need to have experienced at least one period of moderate-to-very severe heartburn or regurgitation in the past 7 days prior to treatment. In addition, at endoscopy, no esophageal mucosal break was observed, i.e. grade 0 according to the LA classification. The ability to read and write in either English or Chinese was also a requirement for study entry.	Known history of gastroduodenal ulcer; infectious or inflammatory conditions of the intestine (including inflammatory bowel disease); malabsorption syndromes; obstruction; gastrointestinal malignancy; gastric or intestinal surgery including vagotomy; Barrett's esophagus; esophageal stricture or pyloric stenosis; scleroderma; erosive esophagitis; positive HIV status and pregnancy. Patients were ineligible if they had: abnormal laboratory tests at the initial visit (including liver enzymes greater than twice the upper limit of normal); GERD treatment refractory to a 2-mo course of H2-blocker or PPI therapy; taken a PPI within 14 d of screening or a H2-blocker or prokinetic agent within 7 d of screening; required daily use of NSAIDS, oral steroids, aspirin (>325 mg/d); or were unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates or sucralfate.	Patients were permitted to take an antacid (Mylanta®) as rescue medication for the relief of heartburn symptom, if necessary. No other medication was allowed.

Table III[B]: (GERD) E vs R - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
Eggleston 2009	Patients ≥18 years of age with symptoms of GERD; had episodes of heartburn, with or without regurgitation, for 3 months or longer and for >3 days in the 7 days prior to randomization; could understand and complete questionnaires and have access to a telephone; and could give written consent.	Patients were excluded if they required endoscopy within 4 weeks of randomization or had gastrointestinal symptoms that, in the opinion of the GP investigator, required further investigation prior to or coincident with initiation of PPI therapy; had significant gastrointestinal disease active in the last 12 months; had Barrett's oesophagus (>3 cm); had Zollinger–Ellison Syndrome; scleroderma; malignancy (other than non-melanoma skin cancers) present within the last 5-years which, in the opinion of the investigator, could interfere with the patient's participation in the study; had hypersensitivity to any PPI; were women patients who were pregnant or breastfeeding, or who, in the opinion of the investigator, could become pregnant throughout the study; had used >3 doses of histamine-2 receptor antagonists or PPI within the week before randomization; had used anticholinergics, cholinergics, spasmolytics, opiates, sucralfate, prokinetics, antibiotics or bismuth compounds within 14 days of randomization; had participated in an investigational drug or investigational device study within 30 days prior to the baseline visit.	NR
Laine 2011 Study 1 and Study 2	Patients aged 18–75 years, with a history of GERD symptoms (e.g. heartburn, regurgitation) for at least 3 months before screening, heartburn at least 2 days⁄week for ≥ 1 month before screening endoscopy and moderate-to-severe erosive GERD (LA grade C or D) at screening endoscopy. There was no restriction on baseline body mass index (BMI).	A positive urea breath test for *Helicobacter pylori* performed in the month before screening endoscopy; current or history of oesophageal motility disorders, Barrett's oesophagus, oesophageal strictures, or oesophagitis due to aetiology other than GERD; a history of upper gastrointestinal surgery (except simple suturing of an ulcer); Zollinger–Ellison syndrome or other acid hypersecretory conditions; and current gastric or duodenal ulcer.	Patients were not allowed to use PPIs, histamine H2 receptor antagonists, or prokinetics within 2 weeks before the screening endoscopy or during the treatment phase of the study. Concomitant use of daily NSAIDs, oral corticosteroids (‡20 mg⁄ day prednisone or equivalent), aspirin (>325 mg⁄ day), anticholinergics, or drugs that are

Table III[B]: (GERD) E vs R - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
			significant substrates or modulators of cytochrome P450 2C19 and／or 3A4 (e.g. warfarin, digoxin, fluoxetine, clarithromycin, rifampin) were not allowed. Commercially available antacid tablets (aluminium／magnesium hydroxide) were distributed to the patients as a rescue medication, to be taken in response to acute episodes of intolerable heartburn.
Maiti 2011	Patients aged 18–65 years suffering from GERD symptoms for at least 3 months in the previous year. Subjects experienced at least one period of moderate-to-severe heartburn or regurgitation in the past 7 days prior to treatment and at endoscopy; they had grade A or grade B esophagitis according to the Los Angeles (LA) classification.	Known history of gastroduodenal ulcer; infectious or inflammatory conditions of the intestine (including inflammatory bowel disease); malabsorption syndromes; obstruction; gastrointestinal malignancy; gastric or intestinal surgery including vagotomy; Barrett's esophagus; esophageal stricture or pyloric stenosis; scleroderma; pregnancy; abnormal laboratory tests at the initial visit (including liver enzymes greater than twice the upper limit of normal); GERD treatment refractory to a 2-month course of H2-blocker or PPI therapy; PPIs taken within 14 days of screening or H2-blocker or prokinetic agent taken within 7 days of screening; daily use of NSAIDs, oral steroids, aspirin (>325 mg/day); being unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates, or sucralfate.	NR
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; E, Esomeprazole; R, Rabeprazole; NSAID, Non-steroidal anti-inflammatory drug; NR, not reported			

Table III[C]: (GERD) E vs R - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Severity (LA Grades) (n, %)***	**Other**
Fock 2005	E20 (ITT=64/67	27 (42.2%)	38.4	NR	Chinese: 49 (76.6%) Malay 5 (7.8%) Indian: 9 (14.1%) Other: 1 (1.6%)	7 (10.9%)	11 (17.2%)	26 (44.0%) and not available in 5	All Grade 0 according to LA classification	
	R10 (ITT=63/67)	38 (60.3%)	39.3	NR	Chinese: 52 (82.5%) Malay: 4 (6.3%) Indian: 6 (9.5%) Other: 1 (1.6%)	4 (6.3%)	9 (14.3%)	24 (45.3%) and not available in 10	All Grade 0 according to LA classification	
Eggleston 2009	E20 (n=459)	251 (54.7%)	46.2	29.2	Caucasian: 413 (90.0%)	310 (67.5%)	122 (26.6%)	NR	NR	Heartburn score = 0 at baseline: 63 (13.7%)
	E40 (n=469)	261 (89.3%)	48	29.3	Caucasian: 419 (89.3%)	297 (63.3%)	123 (26.2%)	NR	NR	Heartburn score = 0 at baseline: 77 (16.4%)
	R20 (n=464)	260 (56.0%)	45.8	29.0	Caucasian: 415 (89.4%)	314 (67.3%)	140 (30.2%)	NR	NR	Heartburn score = 0 at baseline: 51 (11.0%)
Laine 2011 Study 1	E40 (ITT= 531/534)	325 (61.2%)	49.0	BMI≤30: 282 (53.1%)	White: 467 (87.9%) Black or African American: 22 (4.1%) Asian: 29 (5.5%) Other: 13 (2.4%)	NR	NR	3 (0.6%); unknown in 1 (0.2%)	Grade C: 466 (87.8%) Grade D: (65 (12.2%)	
	R50 (ITT= 524/527)	322 (61.5%)	48.0	BMI≤30: 301 (57.4%)	White: 466 (88.9%) Black or African American: 20 (3.8%) Asian: 31 (5.9%) Other: 7 (1.3%)	NR	NR	0; unknown in 4 (0.8%)	Grade C: 467 (89.1%) Grade D: 57 (10.9%)	

Table III[C]: (GERD) E vs R - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Severity (LA Grades) (n, %)***	**Other**
Laine 2011 Study 2	E40 (ITT= 537/540)	342 (63.7%)	49.1	BMI≤30: 324 (60.3%)	White: 480 (89.4%) Black or African American: 30 (5.6%) Asian: 30 (5.6%) Other: 13 (2.4%)	NR	NR	1 (0.2%); unknown in 1 (0.2%)	Grade C: 477 (88.8%) Grade D: 60 (11.2%)	
	R50 (ITT= 528/529)	349 (66.1%)4	51.0	BMI≤30: 299 (56.6%)	White: 469 (88.8%) Black or African American: 17 (3.2%) Asian: 28 (5.3%) Other: 14 (2.7%)	NR	NR	1 (0.2%); unknown in 1 (0.2%)	Grade C: 460 (87.1%) Grade D: 68 (12.9%)	
Maiti 2011	E40 (n=30)	17 (56.7%)	35.3	NR	NR	NR	NR	14 (46.7%)	Grade A: 18 (60%) Grade B: 12 (40%)	Overall GERD symptom scoring: 4.7 (SD2.2) Overall QOLRAD scoring: 35.1 (SD12.8)
	R40 (n=30)	19 (63.3%)	38	NR	NR	NR	NR	12 (40%)	Grade A: 22 (73.3%) Grade B: 8 (17.7%)	Overall GERD symptom scoring: 4.6 (SD1.8) Overall QOLRAD scoring: 38.7 (SD14.8)

ABBREVIATIONS: GERD, Gastroesophageal reflux disease; OD, once daily; R, Rabeprazole; E, Esomeprazole; BMI, Body Mass Index; QOLRAD, Quality of Life in Reflux and Dyspepsia; NR, Not Reported; SD, Standard Deviation; ITT, Intention-to-treat

* Savary Miller classifications (I-IV); LA classification (A-D)

Table III[D]: (GERD) E vs R - Summary of Patient Disposition						
Author, Year, Trial Name	**Treatment**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for WD**	**Additional Details Provided**
Fock 2005	E20	67 randomized; 66 treated	NR	NR	NR for all WD 1 withdrew before taking medication; 1 withdrew consent; 1 withdrew due to AE	
	R10	67 randomized; 63 treated	NR	NR	NR for all WD 4 withdrew before taking medication	
Eggleston 2009	E20	459	400 (87.1%)	59 (12.9%)	AE (n=16), lost to follow-up (n=20); Subject choice (n=21); other (n=2)	
	E40	469	406 (86.6%)	63 (13.4%)	AE (n=27), lost to follow-up (n=19); Not eligible (n=1); Subject choice (n=13); other (n=3)	
	R20	464	395 (85.1%)	69 (14.9%)	AE (n=22), lost to follow-up (n=29); Investigator decision (n=1); Subject choice (n=15); other (n=2)	
Laine 2011 Study 1	E40	534 randomized; 531 treated	491 (92.5%)	40 (7.5%)	AE (n=5); lost to follow-up (n=14); patient choice (n=8); administrative/other (n=13)	
	R50	527 randomized; 524 treated	479 (91.4%)	45 (8.6%)	AE (n=7); lost to follow-up (n=22); patient choice (n=6); administrative/other (n=10)	
Laine 2011 Study 2	E40	540 randomized; 537 treated	495 (92.2%)	42 (7.8%)	AE (n=4); lost to follow-up (n=17); patient choice (n=6); administrative/other (n=15)	
	R50	529 randomized; 528 treated	485 (91.9%)	43 (8.1%)	AE (n=6); lost to follow-up (n=18); patient choice (n=4); administrative/other (n=15)	
Maiti 2011	E40	30	26 (86.7%)	4 (13.3%)	AE (n=1), lost to follow up (n=2), reasons not provided (n=1)	
	R40	30	25 (83.3%)	5 (16.7%)	Lost to follow up (n=4), reasons not provided (n=1)	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; R, Rabeprazole; E, Esomeprazole; NR, Not Reported; AE; Adverse Events; WD, Withdrawals						

Table III[E]: (GERD) E vs R - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Recurrence or relapse**	**Ssubgroup analysis**
Fock 2005	E20 (n=67 randomised)	Complete heartburn relief @ 4 weeks (day-time): 18/67 (26.9%) (night-time): 16/67 (23.9%) ** Complete relief defined as no episodes of heartburn during evaluation week.* Median time to first 24 hour symptom free interval: Heartburn =9.0 days; Regurgitation =7.5 days % patients achieving 24 hour symptom free interval Heartburn = 90.0%; Regurgitation = 67.9 %	Not applicable (NERD patients)	NA	NA	Subgroup analyses in patients who experienced heartburn and/or regurgitation prior to start of study (no extractable data for meta-analysis) No statistically significant differences were observed in analyses of regurgitation (data not provided for meta-analysis)
	R10 (n=67 randomised)	Complete heartburn relief @ 4 weeks (day-time): 26/67 (38.8%); (night-time): 20/67 (29.9%) Median time to first 24hr symptom free interval: Heartburn =8.5 days; Regurgitation =6.0 days (P=NS) % patients achieving 24 hour symptom free interval for Heartburn = 84.4%; Regurgitation = 60.9% (P=NS)		NA	NA	
Eggleston 2009	E20 (N=459)	Complete resolution @ week 4 Heartburn: 209/459 (45.5%) Regurgitation: 203/459 (44.2%) Median time to complete resolution(Kaplan-Maier):	NA	SF-36 scores improved significantly from baseline for all domains	NA	"A post hoc logistic regression for complete heartburn response found that a baseline heartburn symptom score of 0 (none) was a significant predictor

Table III[E]: (GERD) E vs R - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Recurrence or relapse**	**Ssubgroup analysis**
		Heartburn symptoms = 12days Regurgitation = 13 days Mean percentage of 24-h periods free of symptoms Heartburn: 56.1% Regurgitation: 57.5%		for all treatment groups with no significant differences observed among treatment groups. Change from baseline of SF-36 scores shown graphically (Data not extracted)		(P < 0.0001) for achieving complete heartburn resolution. The proportion of patients with a heartburn score of 0 at baseline was significantly higher in the E40 mg group than in the R20 mg group (16.4% vs. 11.0%, P = 0.02). No adjustments for baseline scores were made for this study"
	E40 (N=469)	Complete resolution @ week 4 Heartburn: 229/469 (48.8%) Regurgitation: 218/469 (46.5%) Median time to complete resolution (Kaplan-Maier): Heartburn symptoms =9 days Regurgitation =11 days Mean percentage of 24-h periods free of symptoms Heartburn: 63.4% Regurgitation: 61.6%	NA		NA	
	R20 (N=464)	Complete resolution @ week 4 Heartburn: 195/464 (42.0%) Regurgitation: 206/464 (44.4%) Median time to complete resolution: Heartburn symptoms: 11 days Regurgitation 9 days Mean percentage of 24-h periods free of symptoms Heartburn: 56.3% (p=0.696 vs E40) Regurgitation: 60%	NA		NA	

Table III[E]: (GERD) E vs R - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Recurrence or relapse**	**Ssubgroup analysis**
Laine 2011 Study 1	E40 (ITT= 531/534)	Diary recorded sustained resolution of heartburn @ 4 weeks, defined as ≥7 days consecutive heartburn-free days: 256/531 (48.2%)	@ 4 weeks: 267 /531 (50.3%) @ 8 weeks: 398/531 (75%)	NA	NA	Sustained resolution at week 4: Grade C: 228/466 Grade D: 28/65 Healing @ 4 weeks: Grade C: 247/466 Grade D: 20/65 Healing @ 8 weeks: Grade C: 358/466 Grade D: 40/65
	R50 (ITT= 524/527)	Diary recorded sustained resolution of heartburn @ 4 weeks, defined as ≥7 days consecutive heartburn-free days: 253/524 (48.3%)	@ 4 weeks: 287/524 (54.8%) @ 8 weeks: 419/524 (80%)	NA	NA	Sustained resolution @ week 4: Grade C : 225/467 Grade D: 28/57 Healing @ 4 weeks: Grade C: 259/467 Grade D: 28/57 Healing @ 8 weeks: Grade C: 376/467 Grade D: 43/57
Laine 2011 Study 2	E40 (ITT= 537/540)	Diary recorded sustained resolution of heartburn @ 4 weeks, defined as ≥7 days consecutive heartburn-free days: 282/537 (52.5%)	@ 4 weeks: 272/537 (50.7%) @ 8 weeks: 421/537 (78.4%)	NA	NA	Sustained heartburn resolution at week 4: Grade C: 260/477 Grade D: 22/60 Healing @ 4 weeks: Grade C : 255/477 Grade D: 17/60 Healing @ 8 weeks: Grade C: 387/477 Grade D: 34/60

Table III[E]: (GERD) E vs R - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Recurrence or relapse**	**Ssubgroup analysis**
	R50 (ITT= 528/529)	Diary recorded sustained resolution of heartburn @ 4 weeks, defined as ≥7 days consecutive heartburn-free days: 281/528 (53.2%)	@ 4 weeks: 269/528 (50.9%) @ 8 weeks: 409/528 (77.5%)	NA	NA	Sustained heartburn resolution at week 4: Grade C: 251/460 Grade D: 30/68 Healing @ 4 weeks: Grade C: 245/460 Grade D: 24/68 Healing @ 8 weeks: Grade C: 365/460 Grade D: 44/68
Maiti 2011	E40 (n=30)	% patients with symptomatic relief not reported. Overall symptom scoring: Baseline: 4.4 (SD2.2) @ 4 week: 3.3 (SD1.6) Change: -25%; p<0.001	@ 4 weeks: 9/30 (30%)	Overall symptom scoring: Baseline: 34.5 (SD13.4) @ 4 week: 38.9 (SD12.5) Change: 12.8%; p<0.001	NA	
	R40 (n=30)	% patients with symptomatic relief not reported. Overall symptom scoring: Baseline: 4.5 (SD1.8) @ 4 week: 2.8 (SD1.4) Change from baseline : -38.8%; p<0.001 significantly lowered symptom scoring compared to Esomeprazole group (P=0.01)	@ 4 weeks: 15/30 (50%)	Overall QOLRAD scoring: Baseline: 38.0 (SD13.6) @ 4 week: 53.7 (SD14.4) Change:	NA	

Table III[E]: (GERD) E vs R - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Recurrence or relapse**	**Ssubgroup analysis**
				41.3%; p<0.001 Significantly lower than Esomeprazole group (P=0.01) Significantly improved QOLARD scoring compared to Esomeprazole group (P=0.01)		
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; R, Rabeprazole; E, Esomeprazole; QoL; Quality of Life; NERD, Nonerosive reflux disease; NA, Not applicable; QOLRAD , QOLRAD, Quality of Life in Reflux and Dyspepsia; ITT, Intention-to-treat						

Table III[F]: (GERD) E vs R - Harm Outcomes						
Author, Year, Trial Name	Treatment group	Mortality & Reasons (n/N)	SAES & Reasons Most Common SAEs	WDAE and reasons	Subjects with >0 AE, N (%)	Most common AEs (n/N)
Fock 2005	E20 (N=66 treated)	NR	NR	Total WDAE not reported; 1 WDAE due to persistent headache	Total AE: Not reported Patients with 'study medication related AE': 18.2%	Reported AE Elevation of ALT: 4 Elevation of AST: 2
	R10 (N=63 treated)	NR	NR	Total WDAE not reported	Total AE: Not reported Patients with study medication related AE: 22%	Reported AE Elevation of ALT: 1 Elevation of AST: 1

Table III[F]: (GERD) E vs R - Harm Outcomes						
Author, Year, Trial Name	Treatment group	Mortality & Reasons (n/N)	SAES & Reasons Most Common SAEs	WDAE and reasons	Subjects with >0 AE, N (%)	Most common AEs (n/N)
Eggleston 2009	E20 (N=459)	NR	Total: NR 8 hospitalizations	16	158	GI signs and symptoms: 77 GI motility and defecation conditions: 40 Headaches: 32 Infections-unspecified pathogen:29
	E40 (N=469)	NR	Total: NR 1 hospitalizations	27	155	GI signs and symptoms: 80 GI motility and defecation conditions: 32 Headaches: 30 Infections-unspecified pathogen:10
	R20 (N=464)	NR	Total: NR 4 hospitalizations	22	151	GI signs and symptoms: 86 GI motility and defecation conditions: 26 Headaches: 22 Infections-unspecified pathogen:22
Laine 2011 Study 1	Not provided separately					
Laine 2011 Study 2	Not provided separately					
Laine 2011 Study 1 and Study 2 combined (data could not be used in meta-analysis)	E40 (n= NR for safety analysis)	0	7 serious adverse events by 7patients (0.7%)	1% of patients in each group discontinued study treatment due to adverse events.	"A total of 2105 patients [out of the 2120 who took study medication] were included in the safety analyses for the two studies. Treatment-emergent adverse events were reported by 289 (28%) patients in the Rabeprazole-ER group and 282 (27%) patients in the Esomeprazole group"	Diarrhoea (1.5%)
	R50 (n= NR for safety analysis)	2 (acute coronary syndrome; head injury)	8 serious adverse events were reported by 7 patients (0.7%)	1% of patients in each group discontinued study treatment due to adverse events.		The most frequently reported (≥2.0%) adverse event was diarrhoea (2.4%)

Table III[F]: (GERD) E vs R - Harm Outcomes						
Author, Year, Trial Name	Treatment group	Mortality & Reasons (n/N)	SAES & Reasons Most Common SAEs	WDAE and reasons	Subjects with >0 AE, N (%)	Most common AEs (n/N)
Maiti 2011	E40 (n=30)	NR	0	1 (moderate, persistent headache)	Total not clearly reported.	Headache: 2 Nausea: 1 Diarrhea: 1 Borderline increase in serum AST/ALT: 2
	R40 (n=30)	NR	0	0	4	Headache: 2 Dizziness: 1 Borderline increase in serum AST/ALT: 1
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; E, Esomeprazole; R, Rabeprazole; NR. Not reported; AE. Adverse event; WDAE, Withdrawals due to adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GI, Gastrointestinal						

IV. Comparison 4: Lansoprazole vs. Omeprazole (12 RCTs)

Table IV[A]: (GERD) L vs O - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention /Comparator and dosage**	**Study Duration**	**Outcome(s)**
Hatlebakk 1993	DBRCT	9 Scandinavian hospitals	L30: 116 O20: 113	229 patients with grade 1 and 2 esophagitis	L 30 mg OD O 20 mg OD	4-8 weeks (4 weeks plus 4 additional weeks if patient not healed week 4 (defined as absence of endoscopic criteria for reflux esophagitis)	Main efficacy variables: healing of endoscopic changes, relief of reflux symptoms Patient diary recording heartburn and antacids use; Adverse Events
Castell 1996	DBRCT	Multicenter USA	L30: 422 L15: 218 O20: 431 Placebo: 213	1284 patients with endoscopically diagnosed erosive reflux esophagitis	L 30 mg OD L 15 mg OD O 20 mg OD Placebo	8 weeks	Endoscopic healing at weeks 2, 4, 6, and 8; symptoms assessment at each treatment visit (investigator-elicited; diary recorded symptoms; percentage of days/nights with heartburn; safety
Mee 1996	DBRCT	Multicentre in UK and Ireland	L30:300 O20: 304	604 patients with endoscopically proven reflux esophagitis (Savary Miller grades I-IV) and a recent history of at least mild heartburn	L 30 mg OD O 20 mg OD	4-8 weeks (4 weeks plus 4 additional weeks if esophagitis was still present or patient was still symptomatic at week 4)	Patient assessment of symptom relief (Daily record of symptoms of day-and night-time epigastric pain and heartburn by scoring symptoms on Visual Analog Scale); healing of esophagitis at week 4 and week 8; clinical assessment of symptoms at week 1, 4, 8
Mulder 1996	DBRCT	29 centres in Netherlands	L30: 106 O40: 105	211 patients with moderate (Savary-Miller grade II) as well as severe reflux oesophagitis (grade III/IVa).	L 30 mg OD O 40 mg OD	4-8 weeks (4 weeks plus 4 additional weeks if patient not healed at week 4 (defined as complete re-epithelialization	Endoscopy healing at week 4 (and 8); symptom assessment at week 4 (and 8) for heartburn, retrosternal pain, regurgitation, dysphagia and abdominal distension; Adverse events; haematological and biochemical parameters at week 4 (and 8).
Fass 2000	Open label RCT	3 centres; USA	L60: 46 O40: 50	96 patients with severe symptomatic GERD who failed a	L 30 mg BD O 40 mg OD	6 weeks	Symptom control: daytime heartburn, night time heartburn and acid regurgitation (improvement in

Table IV[A]: (GERD) L vs O - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention /Comparator and dosage**	**Study Duration**	**Outcome(s)**
				standard dose of Lansoprazole (30 mg once daily for at least 3 months)			symptom score; symptom severity change during first 7 days;
Richter 2001b	DBRCT	Multicentre (Authors from USA)	L30: 1754 O20: 1756	3510 patients with erosive esophagitis and at least one episode of moderate to very severe daytime and/or night-time heartburn during the 3 days immediately before the screening visit	L30 mg OD O20 mg OD	8 weeks	Frequency and severity of daytime and night time heartburn experienced by patients on day 1 of treatment and during days 1–3 (primary), week 1, week 1 and 2, and the entire 8 week of treatment (reported in patient diaries); Time to sustained resolution of heartburn defined as 7 consecutive days with no heartburn; % of heartburn-free patients and % of heartburn-free days and nights; adverse events
Mulder 2002	DBRCT	31 centres in Netherlands	L30: 156 O20: 151 P40: 154	461 adults with grade I–IV symptomatic reflux esophagitis (modified Savary–Miller)	L30 mg OD O20 mg OD P40 mg OD	4 or 8 weeks (4 weeks plus 4 additional weeks if patient is not satisfied at week 4) *Data after 8 weeks (treated with open O 40 mg) will not be discussed in this review.*	Primary outcomes: Symptom relief, patient satisfaction and quality of life Other outcomes: severity of reflux esophagitis symptoms (heartburn, regurgitation, dysphagia) using the Likert Scale at each visit; patient satisfaction at each visit; Change in proportion of patients suffering from constipation at week 4; Any adverse event
Adachi 2003	RCT	Multicentre Japan	L30: 25 O20: 30 R20: 30	85 patients with erosive reflux esophagitis	L 30 mg OD O 20 mg OD R 20 mg OD	8 weeks	Primary endpoint : rapid symptom relief (heartburn and acid reflux symptoms) in the first week of drug administration and Endoscopy at week 8

Table IV[A]: (GERD) L vs O - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention /Comparator and dosage**	**Study Duration**	**Outcome(s)**
Pilotto 2007	Open RCT	Single centre, Italy	L30: 80 O20: 80 P40: 80 R20: 80	320 patients over 65 years of age with endoscopically diagnosed esophagitis (grade I–IV)	L 30 mg OD O 20 mg OD P 40 mg OD R 20 mg OD	8 weeks	Primary outcome: Esophagitis healing rates at week 8 Other outcomes: Symptom disappearance at week 8 (Interview question: Absent or Presence of Acid regurgitation, heartburn, epigastric pain, dysphagia, vomiting and anaemia)
Zheng 2009	RCT	China	L30: 69 O20: 68 E40: 68 P40: 69	274 adults with endoscopically proven reflux esophagitis	L 30 mg OD O 20 mg OD E 40 mg OD P 40 mg OD	8 weeks	Primary outcome: rapid symptom relief in the first week of drug administration Other outcomes: Endoscopic healing at week 8; severity of symptoms during the first 7 days of PPI administration (symptom diary)
Maintenance studies							
Carling 1998	DBRCT	23 centres in Denmark, Finland and Sweden	L30: 126 O20: 122	248 patients with healed Grade II, III, or IV esophagitis after 8-12 weeks of L30 mg OD treatment and reported no severe symptoms of heartburn, regurgitation or dysphagia	L 30 mg OD O 20 mg OD	48 weeks maintenance	Primary efficacy: Time to endoscopic (Grade II esophagitis or single erosions or worse) and/or symptomatic relapse (severe symptoms of heartburn, regurgitation or dysphagia) Endoscopy at week 12, 24, and 48; symptom assessment (heartburn, dysphagia or regurgitation) at week 12, 24, 36, 48; safety

Table IV[A]: (GERD) L vs O - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention /Comparator and dosage**	**Study Duration**	**Outcome(s)**
Jaspersen 1998	RCT	Germany	30 of the 36 patients randomised were included in the maintenance phase. L30: 10 O20: 10 P40: 10	30 patients with reflux esophagitis and stricture confirmed by endoscopy who responded to O 20mg BD. (healing of esophagitis and relief from all reflux symptoms and dysphagia achieved)	L 30 mg BD O 20 mg BD P 40 mg BD	4 weeks maintenance	Primary outcome: Maintenance of remission at week 4, defined as absence of esophagitis and stricture at repeat endoscopy after 4 weeks, and absence of symptoms Relapse: defined as one or more of the following a) recurrence of dysphagia, b) need for re-dilatation c) recurrence of reflux symptoms and d) relapse of esophagitis.
ABBREVIATIONS: DB, Double-blind; RCT, Randomized controlled trial; GERD, Gastroesophageal reflux disease; OD, once daily; BD, twice daily; R, Rabeprazole; E, Esomeprazole; P, Pantoprazole; O, Omeprazole; E, Esomeprazole							

Table IV[B]: (GERD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
Hatlebakk 2003	Patients presenting with grade 1 and 2 oesophagitis (Grade 1: red streaks or spots along the ridge of the folds in the distal oesophagus, covered or not by fibrinous exudate; Grade 2: broader lesions, each involving the entire width of a fold or coalescing into fields of erythema, covered or not with fibrinous exudate)	Patients with grade 3 lesions or Barrett's oesophagus (defined as metaplasia extending more than 3 cm proximal from the cardia) were, excluded from the study. Patients with active peptic ulcer disease, inflammatory bowel disease, malignant disease in any organ or previous surgery of the upper gastrointestinal tract or active biliary or pancreatic disease. Treatment with H2-receptor antagonists, Omeprazole, sucralfate, or prokinetic or anti-cholinergic drugs during the last 6 days before endoscopy was reason for exclusion, as was ongoing treatment with non-steroidal anti-inflammatory drugs or glucocorticosteroids.	Only antacids were allowed
Castell 1996	Adult patients with erosive reflux esophagitis ≥ grade 2 were enrolled in	Barrett's esophagus displaying dysplastic changes, esophagitis due to a coexisting systemic disease, Zollinger-Ellison	Antacids (Gelusil tablets, Warner Wellcome, Morris

Table IV[B]: (GERD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
	the study if no coexisting duodenal ulcer and/or gastric ulcer ≥ 3 mm in diameter was observed; Free from other uncontrolled clinical disease, had no active bleeding at the time of the screening endoscopic evaluation, and had clinically acceptable laboratory results.	syndrome, esophageal varices, or malignancy necessitating active treatment (except basal cell carcinoma), a history of gastric, duodenal, or esophageal surgery (except simple ulcer oversew), esophageal stricture necessitating dilation, or a history of stricture dilation within the previous 12 wk. The following also resulted in exclusion: current alcohol abuse, illegal drug use, or drug abuse within the past 12 months, chronic use of any ulcerogenic drug within 30 days before the screening endoscopy, chronic anticoagulant therapy, consumption of Omeprazole or participation in any other experimental drug study within the previous 12 wk, or participation in any other Lansoprazole study.	Plains, NJ) were supplied to all patients and used as needed. During the treatment period, patients were not to take any non-study antiulcer medication. Continuous treatment with theophylline derivatives, hydantoin, or digoxin was allowed, with monitoring of serum drug concentrations. The initiation of new courses of chronic tricyclic antidepressant therapy was not permitted during the study.
Mee 1996	Patients aged between 18 and 80 years, with endoscopically proven reflux esophagitis (Savary Miller grades I-IV) and a recent history of at least mild heartburn	Barrett's oesophagus and / or oesophageal ulcer; Patients with concomitant peptic ulcer, major co-existent disease, pregnant or lactating women and those who had taken an H2-receptor antagonist within 3 days entry or a proton pump inhibitor within 7 days or trial entry were excluded from the study.	Patients were not permitted to take corticosteroids, phenytoin, anticoagulants or NSAIDs during the study. For additional symptom relief, antacid tablets were provided.
Mulder 1996	Patients presenting with reflux oesophagitis grade I (longitudinal, confluent, non-circumferential erosions), III (longitudinal, confluent, circumferential erosions that bleed easily) or Iva (one or several ulcerations in the mucosal transition zone, which can be accompanied by stricture or metaplasia) according to the classification of Savary and Miller.	Patient with a bleeding ulcer, a stricture requiring more than one dilatation, Barrett's esophagus without erosions and ulcers above the Barrett segment (grade IVb), coexisting duodenal or gastric ulcer, Zollinger-Ellison syndrome, concurrent malignant disease (except basal cell carcinoma), previous gastrectomy, vagotomy or operation on the oesophagogastric junction. Patients with evidence of uncontrolled, clinically significant cardiovascular, pulmonary, renal, hepatobiliary, pancreatic, metabolic, neurological, endocrine or other system disease were excluded. Use of a proton pump inhibitor (PPI) or any investigational drug within 4 weeks of initiating study treatment was reason for exclusion, as was evidence of current alcohol abuse, illicit drug use, drug abuse, demonstrated intolerance for PPIs, ongoing treatment with any other anti-	Patients requiring constant treatment with NSAIDs, tricyclic antidepressants, reserpine, phenytoin, p-mimetic drugs, cholinergic and anti-cholinergic drugs were excluded, although acute treatment for some days was accepted in the month preceding inclusion and during the course of the trial.

Table IV[B]: (GERD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
		ulcer medication, corticosteroids and anticoagulants. Pregnant or lactating women were not included.	
Fass 2000	Patients who remained symptomatic on a standard dose of Lansoprazole (30 mg) after a trial of therapy for at least 3 months were recruited into the study. Therapeutic failure of standard dose Lansoprazole was considered if patients continued to experience heartburn episodes more than once a week.	Patients were excluded if they were allergic to one of the proton pump inhibitors, were unable or unwilling to sign an inform consent, unable to complete all symptom diaries or all stages of the study.	Mylanta tablets were provided for treatment rescue (when heartburn symptoms recur)
Richter 2001b	Patients aged >=18 yrs of age with endoscopically confirmed erosive esophagitis of grade 2 or higher; had at least one episode of moderate to very severe daytime and/or night-time heartburn during the 3 days immediately before the screening visit (assessed by a retrospective heartburn questionnaire).	Patients were excluded from study participation if they had active duodenal or gastric ulcers of ≥3 mm in diameter; coexisting systemic disease affecting the esophagus (*e.g.*, scleroderma); esophageal stricture requiring dilation; a history of GI bleeding or gastric, duodenal, or esophageal surgery; clinically significant abnormal laboratory values or disease; chronic use of ulcerogenic drugs, including nonsteroidal anti-inflammatory drugs or systemic corticosteroids or >325 mg/day of aspirin; or evidence of current alcohol or drug abuse. Women who were pregnant or lactating were excluded from study participation.	Patients receiving proton pump inhibitor or histamine-2 receptor antagonist therapy discontinued use of the antisecretory agent 2 wk or within 1 day, respectively, of study initiation.
Mulder 2002	Patients (aged 18–80 years) with symptomatic reflux esophagitis grade I–IV according to the modified Savary–Miller classification, verified by endoscopy within 10 days prior to inclusion, were included (grade I, linear, non-confluent erosions; grade II, longitudinal, confluent, non-circumferential erosions; grade III, longitudinal, confluent, circumferential	Patients with gastric and/or duodenal ulcers or erosive bulbitis; previous gastro-oesophageal surgery; pregnancy or lactation; concurrent disease or therapy that may complicate the evaluation of the drug (e.g. gastrointestinal disorders that may impair drug absorption; significant cardiovascular, renal or liver disease; endocrine disease; suspected or confirmed malignancy; use of cytotoxic drugs); use of a PPI during the month preceding the endoscopy; contraindication to use of Omeprazole, Lansoprazole and/or Pantoprazole; participation in clinical study or treatment with unregistered drug during the	Antacid allowed

Table IV[B]: (GERD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
	erosions that bleed easily; grade Iva, one or several ulcerations in the mucosal transition zone, which can be accompanied by stricture or metaplasia; grade IV b, with the presence of a stricture but without indications of erosions or ulcerations).	previous month; Clinically significant abnormalities; chronic alcoholism, drug abuse or other conditions associated with poor compliance and requirement of an interpreter were excluded.	
Adachi 2003	Patients with endoscopically proven reflux esophagitis	Active peptic ulcer, upper gastrointestinal cancers, malignant diseases of other organs, severe cardiac active peptic ulcer, upper gastrointestinal cancers, malignant diseases of other organs, severe cardiac, hepatic, or renal diseases, anemia (haemoglobin concentration < 10 g/dL), or who were pregnant and/or lactating.	Subjects were not permitted to take H2RA or prokinetic drugs during the study period. Antacids (aluminium hydroxide suspensions) were allowed as rescue medication for the relief of symptoms, if necessary)
Pilotto 2007	The inclusion criteria were: (1) age 65 years or over and (2) endoscopic diagnosis of esophagitis grade I to IV according to the Savary-Miller Classification. Patients with Barrett's esophagus were not included unless erosive esophagitis was also present.	Major exclusion criteria were: history of Zollinger-Ellison syndrome, pyloric stenosis, previous surgery of the esophagus and/or gastrointestinal tract (except for appendectomy and cholecystectomy), and gastrointestinal malignancy. Patients were excluded if they had received antacids, sucralfate, prokinetics, H2-blockers, and/or PPIs for more than 7 days in the four weeks prior to the start of the study. Patients with diffuse erythema and/or fragility of the lower esophagus were not included.	*H. pylori* positive patients were treated with the PPI plus two antibiotics i.e., amoxicillin 1g twice daily and clarithromycin 250 mg twice daily or metronidazole 250 mg four times daily for 7 day
Zheng 2009	Patients with endoscopically proven reflux esophagitis in the Affiliated Hospital of Yanbian University from January, 2006 to September, 2007 and the Affiliated Hospital of Hainan Medical College from October, 2007 to November, 2008	Subjects with active peptic ulcer, upper gastrointestinal cancers, malignant diseases of other organs, severe cardiac, hepatic, or renal diseases, anemia (concentration < 10 g/dL), or who were pregnant and/or lactating, were excluded.	Subjects were not permitted to take H_2RA antagonists or prokinetic drugs during the study period.

Table IV[B]: (GERD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
Maintenance studies			
Carling 1998	Patients aged 18-80 years, with esophagitis Grade 0 and I (without erosions) after an initial Grade II, III or IV esophagitis (Savary-Miller grading scale) treated with L 30 mg OD for 8-12 weeks and who reported no severe symptoms of heartburn, regurgitation or dysphagia	Patients who were pregnant or lactating, had undergone previous upper gastrointestinal surgery (except simple perforation closure), had a malignancy of the upper gastrointestinal tract, or severe oesophageal disease (e.g. stricture needing dilation, Barrett's oesophagus) or other gastrointestinal disease which was likely to complicate evaluation of esophagitis; taking H2 receptor antagonists, prokinetic agents, proton pump inhibitors, anticholinergics, sucralfate, colloidal bismuth, corticosteroids, anticoagulants or continuous NSAID therapy.	NR
Jaspersen 1998	Patients (>=18 years) with Grade 4 esophagitis according to the Savary-Miller classification (esophagitis with multiple circumferential erosions and stricture) and one or more of four symptoms (heartburn, pain, regurgitation and solid food dysphagia). These patients were then treated with Omeprazole BD until healing of esophagitis and relief from all reflux symptoms and dysphagia. Patient who responded (absence of esophagitis and stricture, and absence of symptoms) were then included in the randomisation phase.	Pregnancy; malignant oesophageal stenosis; esophago-gastric surgery; serious renal, cardiac, hepatic or pulmonary disease; expected poor compliance with treatment. Patients not responding to Omeprazole BD.	NR
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; O, Omeprazole; OD, once daily; BD, twice daily; NSAID, Non-steroidal anti-inflammatory drug			

Table IV[C]: (GERD) L vs O - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Severity (n, %)***	**Other**
Hatlebakk 1993	L30 (n=116)	77 (66.4%)	54.3	Weight: 79.7 kg	NR	24 (20.7%)	65 (56.0%)	NR	Grades** 1: 75 (64.7%) 2: 41 (35.3%)	Heartburn Grade 0: 2.6%
	O20 (n=113)	74 (65.5%)	55.4	Weight: 78.3 kg	NR	33 (29.2%)	61 (54.0%)	NR	1: 72 (63.7%) 2: 41 (36.7%)	Heartburn Grade 0: 2.7%
Castell 1996	L15 (n=218)	145 (66.5%	45.8	NR	Approximately 85% were white, 9% black, and 5% Hispanic.	63 (28.9%)	95 (43.6%)	NR	Grades** 2: 63.3% 3: 28.9% 4: 7.8%	Barrett's esophagus: 8.7%
	L30 (n=421/422)	288 (68.4%)	48.6	NR		90 (21.4%)	202 (47.9%)	NR	2: 61.0% 3: 30.2% 4: 8.8%	Barrett's esophagus: 8.1%
	O20 (n=431)	260 (60.3%)	47.5	NR		104 (24.1%)	210 (48.7%)	NR	2: 66.6% 3: 26.7% 4: 6.7%	Barrett's esophagus: 6.5%
Mee 1996	L30 (n=282/300)	186 (66%)	Median age: 53.4	NR	NR	79 (28%)	220 (78%)	NR	I: 112 (40%) II: 124 (44%) III: 39 (14%) IV: 7 (2%)	
	O20 (n=283/304)	190 (67%)	Median age: 52.4	NR	NR	54 (19%)	218 (77%)	NR	I: 109 (38%) II: 126 (45%) III: 43 (15%) IV: 5 (2%)	
Mulder 1996	L30 (n=106)	73 (68.9%)	54.4	Weight: 80.5 kg (n=104)	NR	25 (23.6%)	NR	NR	I: 0 II: 77 (72.6%) III: 23 (21.7%) IVa: 6 (5.7%)	Barrett's oesophagus 7 (6.6%)
	O40 (n=105)	75 (71.4%)	55.5	Weight: 77.8 kg	NR	32 (30.5%)	NR	NR	I: 1 (1.0%) II: 67 (63.8%) III: 27 (25.7%) IVa: 10 (9.5%)	Barrett's oesophagus 8 (7.6%)

Table IV[C]: (GERD) L vs O - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Severity (n, %)***	**Other**
Fass 2000	L60 (n=44/46)	40 (90.9%)	57.8	NR	Caucasian: 32 (72.7%) African American: 5 (11.4%) Hispanic: 1 (2.3%) Asian: 0 Unknown: 6 (13.6%)	14 (31.8%)	10 (22.7%)	NR	NR	
	O40 (n=46/50)	44 (95.7%)	57.8	NR	Caucasian: 34 (73.9%) African American: 7 (15.2%) Hispanic: 2 (4.4%) Asian: 1 (2.2%) Unknown: 2 (4.4%)	10 (21.7%)	8 (17.4%)	NR	NR	
Richter 2001b	L30 (n=1754)	1007 (57%)	47.8	NR	White: 88% African American: 5% Other 7%	437 (25%)	973 (55%)	508/1752 (89%)	Grades** 0: 1 (<1%) 1: 0 2: 1176 (67%) 3: 447 (26%) 4: 130 (7%)	Mean % of days with heartburn: 90% Mean % of nights with heartburn: 84%
	O20 (n=1756)	984 (56%)	46.9	NR	White: 88% African American: 5% Other 8%	497 (28%)	983 (56%)	488/1754 (28%)	0: 0 1: 0 2: 1206 (69%) 3: 440 (25%) 4: 110 (6%)	Mean % of days with heartburn: 90% Mean % of nights with heartburn: 82%

Table IV[C]: (GERD) L vs O - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Severity (n, %)***	**Other**
Mulder 2002 *Data for Pantoprazole group not reported in this table*	L30 (n=156)	90 (58%)	50.8	27.0	NR	NR	NR	28% positive	Grade I: 94 (60%) Grade II: 46 (29%) Grade III: 10 (6%) Grade IVa: 6 (4%) Grade IVb: 0	Severity of heartburn – none 3%, mild 21%, moderate 41%, severe 35%; Mean GSRS score of 2.8
	O20 (n=151)	88 (58%)	51.6	26.9	NR	NR	NR	22% positive	Grade I: 87 (58%) Grade II: 45 (30%) Grade III: 11 (7%) Grade IVa: 8 (5%) Grade IVb: 0	Severity of heartburn – none 3%, mild 25%, moderate 46%, severe 26%; Mean GSRS score of 2.9
Adachi 2003 *Data for Rabeprazole group not reported in*	L30 (n=25)	13 (52%)	65.2	NR	NR	NR	NR	9 (36%)	A: 2 B: 14 C: 8 D: 1	Heartburn: 21 (84%) Acid regurgitation: 15 (60%) No symptom: 1 (4%)
	O20 (n=30)	15 (50%)	67.3	NR	NR	NR	NR	13 (43.3%)	A: 9 B: 15 C: 6 D: 0	Heartburn: 23 (76.7%) Acid regurgitation: 12 (40%) No symptom: 6 (20%)

Table IV[C]: (GERD) L vs O - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Severity (n, %)***	**Other**
Pilotto 2007 *Data for Pantoprazole and for Rabeprazole group not reported in this table*	L30 (n=80)	36 (45%)	77.8	NR	NR	NR	NR	61/76 (80.3%)	Grade I: 26 (32.5%) Grade II: 33 (41.3%) Grade III-IV: 21 (26.2%)	In 301 completers: Heartburn: 131 (43.5%) Regurgitation: 39 (13.0%) Epigastric pain: 143 (47.5%) Dysphagia: 10 (3.3%) Vomiting: 60 (19.9%) Anaemia: 28 (9.3%)
	O20 (n=80)	44 (55%)	77.9	NR	NR	NR	NR	52/76 (68.4%)	Grade I: 34 (42.5%) Grade II: 27 (33.8%) Grade III-IV (19 (23.8%)	
Zheng 2009 *Data for Esomeprazole and for Pantoprazole group not reported in this table*	L30 (n=69)	35 (50.7%)	58.1	NR	NR	NR	NR	31 (44.9%)	Grade A: 20 (28.9%) Grade B: 26 (37.7%) Grade C: 21 (30.4%) Grade D: 2 (2.9%)	Heartburn: 91.3% Acid reflux: 50.7% No symptoms: 7.2%
	O20 (n=68)	33 (48.5%)	57.9	NR	NR	NR	NR	29 (%)	Grade A: 20 (29.4%) Grade B: 26 (38.2%) Grade C: 20 (29.4%) Grade D: 2 (2.9%)	Heartburn: 89.7% Acid reflux: 48.5% No symptoms: 11.8%

Table IV[C]: (GERD) L vs O - Baseline characteristics of patients in included studies										
Trial name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Age (Yrs)**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Severity (n, %)***	**Other**
Maintenance Studies										
Carling 1998	L30 (n=126)	72 (57%)	55.4	Height: 170.8cm Weight: 79.5 kg	NR	31 (25%)	NR	NR	Grade 0 or I without erosions	
	O20 (n=122)	81 (66%)	56.0	Height: 173.2cm Weight: 79.5 kg	NR	31 (25%)	NR	NR	Grade 0 or I without erosions	
Jaspersen 1998 *Data for Pantoprazole group not reported in this table*	L30 (n=10)	5 (50%)	57.0	NR	NR	NR	NR	NR	In remission (healing of oesophagitis and relief from all reflux symptoms and dysphagia)	
	O20 (n=10)	6 (60%)	59.6	NR	NR	NR	NR	NR		

ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; O; Omeprazole; BMI, Body Mass Index; NR, Not Reported; SD, Standard Deviation; GSRS; Gastrointestinal Symptom Rating Scale

* Savary Miller classifications (I-IV); LA classification (A-D);

** See Appendix 5 for grading scales

Table IV[D]: (GERD) L vs O - Summary of Patient Disposition						
Author, Year, Trial Name	**Treatment**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for WD**	**Additional Details Provided**
Hatlebakk 1993	L30	116	NR	NR	NR	
	O20	113	NR	NR	NR	
Castell 1996	L15	218	NR	NR	NR	
	L30	422	NR	NR	NR	
	O20	431	NR	NR	NR	

Table IV[D]: (GERD) L vs O - Summary of Patient Disposition						
Author, Year, Trial Name	**Treatment**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for WD**	**Additional Details Provided**
Mee 1996	L30	300	NR	NR	NR	
	O20	304	NR	NR	NR	
Mulder 1996	L30	106	103	3	2 lost to follow-up 1 refused endoscopy and was withdrawn	
	O40	105	101	4	1 lost to follow-up 2 lack of efficacy 1 received double dose during first 4 weeks	
Fass 2000	L60	46	44	2	1 WDAE in O40 group (angina pectoris) Reasons for other 5 WD: 2 unable to complete all diaries; 2 requested to be removed from study; 1 lost to follow-up	
	O40	50	46	4		
Richter 2001b	L30	1754	1679	75	AE (n=40), lack of symptom relief (n=10), loss to follow-up (n=11), personal reason (n=5), other (n=9)	
	O20	1756	1678	78	AE (n=30), lack of symptom relief (n=15), loss to follow-up (n=12), personal reason (n=5), other (n=16)	
Mulder 2002 *Data for Pantoprazole group not reported*	L30	156	145	11	AE (n=3), lack of symptom improvement (n=1), unwillingness to continue (n=3), and loss to follow-up (n=4)	
	O20	151	144	7	AE (n=2), lack of symptom improvement (n-4), and loss to follow-up (n=1)	
Adachi 2003 *Data for Rabeprazole group not reported*	L30	25	NR	NR	NR	
	O20	30	NR	NR	NR	
Pilotto 2007 *Data for Pantoprazole and for Rabeprazole group not reported*	L30	80	75	5	AE (n=2), low compliance (n=11), refusal of endoscopy after 2 months of treatment (n=6)	
	O20	80	74	6		

Table IV[D]: (GERD) L vs O - Summary of Patient Disposition						
Author, Year, Trial Name	**Treatment**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for WD**	**Additional Details Provided**
Zheng 2009 *Data for Esomeprazole and for Pantoprazole group not reported*	L30	69	69	0	No Withdrawals	
	O20	68	68	0	No Withdrawals	
Maintenance Studies						
Carling 1998	L30	126	NR	NR	NR	
	O20	122	NR	NR	NR	
Jaspersen 1998 *Data for Pantoprazole group not reported*	L30	10	10	0	No Withdrawals	
	O20	10	10	0	No Withdrawals	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; O, Omeprazole; NR, Not Reported; AE; Adverse Events; WD, Withdrawals						

Table IV[E]: (GERD) L vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Remission**	**Subgroup analysis performed**
Hatlebakk 1993	L30 (n=116)	No quantitative data provided for extraction. It was reported that at 4 and 8 weeks, there is no statistically significant difference in relief of heartburn, regurgitation and dysphagia.	@ 4 weeks: 71/113 (62.8%) @ 8 weeks: 95/112 (84.8%)	NA	NA	"Grade of oesophagitis and, alcohol consumption were the only significant determinants. At both 4 and 8 weeks, and irrespective of treatment, healing rates were higher for patients with grade 1 reflux oesophagitis than for patients with grade 2 ($p<0.01$), and lower for consumers of alcohol than for non-consumers ($p<0.01$)"
	O20 (n=113)		@ 4 weeks: 73/112(65.2%) @ 8 weeks: 96/111 (86.5%)	NA	NA	

Table IV[E]: (GERD) L vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Remission**	**Subgroup analysis performed**
Castell 1996	L15 (n=218)	Data not provided for meta-analysis. "no statistically significant differences between active treatment groups in producing relief of the primary symptoms of day and night heartburn, belching, gastroesophageal regurgitation, and painful swallowing, except that O20 was significantly better (p<0.05) than L15 at alleviating painful swallowing"	@ 4 weeks: 157/218 (72.0%) @ 6 weeks: 167/218 (76.6%) @ 8 weeks: 164/218 (75.2%)	NA	NA	(Not an ITT analysis) @ week 4: Grade II: 109/131 (83.2%) Grade III/IV: 44/74 (59.5%) @ week 8: Grade II: 115/131 (87.8%) Grade III/IV: 45/72 (62.5%)
	L30 (n= 421/422) *1 patient had grade 0 at baseline		@ 4 weeks: 335/421 (79.6%) @ 6 weeks: 360/421 (85.5%) @ 8 weeks: 367/421 (87.2%)	NA	NA	@ week 4: Grade II: 219/245 (89.4%) Grade III/IV: 111/151 (73.5%) @ week 8: Grade II: 231/245 (94.3%) Grade III/IV: 128/150 (85.3%)
	O20 (n=431)		@ 4 weeks: 343/431 (79.6%) @ 6 weeks: 370/431 (85.8%) @ 8 weeks: 375/431 (87.0%)	NA	NA	@ week 4: Grade II: 240/272 (88.2%) Grade III/IV: 97/139 (69.8%) @ week 8: Grade II: 251/274 (91.6%) Grade III/IV: 118/133 (88.7%)
Mee 1996	L30 (n=300)	Total or individual symptomatic relief not reported.	@ 4 weeks: 186/300 (62%) @ 8 weeks: 226/300 (75%)	NA	NA	Not provided for ITT population. Healing of esophagitis by baseline grade provided for per-protocol analysis: Baseline grade of esophagitis significantly affect the overall healing rates, whereby the lower the grade, the greater the chance of being healed. The odds ratio of healing on L compared with O was found to be 1.46 (95% CI = 0.87 – 2.45)

Table IV[E]: (GERD) L vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Remission**	**Subgroup analysis performed**
						Healing of esophagitis by baseline grade (per-protocol population) <u>@ week 4</u> Grade I: 71/90 (79%) Grade II: 74/103 (72%) Grade III: 15/33 (45%) Grade IV: 3/7 (43%) <u>@ week 8 (cumulative)</u> Grade I: 79/86 (92%) Grade II: 87/101 (88%) Grade III: 24/33 (73%) Grade IV: 2/4 (50%)
	O20 (n=304)	Total or individual symptomatic relief not reported.	@ 4 weeks: 172/304 (57%) @ 8 weeks: 216/304 (71%)		NA	Healing of oesophagitis by baseline grade (per-protocol population) <u>@ week 4</u> Grade I: 61/90 (68%) Grade II: 67/108 (62%) Grade III: 21/37 (57%) Grade IV: 3/5 (60%) <u>@ week 8 (cumulative)</u> Grade I: 74/85 (87%) Grade II: 83/103 (81%) Grade III: 26/36 (72%) Grade IV: 1/2 (50%)
Mulder 1996	L30 (n=106)	@ 4 weeks (for those with symptoms at baseline) Heartburn: 84/95 (88.4%) Retrosternal Pain: 69/87 (79.3%) Regurgitation: 49/62 (79.0%) Dysphagia: 30/34 (88.2%) Abdominal distension: 33/43 (76.7%)	@ 4 weeks: 91/104 (87.5%) Overall 8 weeks: 99/103 (96.1%)	NA	NA	Healing rates @ 4 week Grade II: 90.8% Grade III/IVa: 81.5% Overall @ 8 weeks: Grade II: 97.4% Grade III/IVa: 92.6%

Table IV[E]: (GERD) L vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Remission**	**Subgroup analysis performed**
		Overall symptoms for those reporting at week 4: 78/105 (74.3%) "Because of the low number of patients not healed at 4 analysis of symptoms was not performed at 8 weeks" Median time to first episode of 3 consecutive days of heartburn-free interval: 3 days				Note: Only percentages were reported in the article. The number of patients included in the analysis was not clearly reported. (data not used for meta-analysis)
	O40 (n=105)	@ 4 weeks (for those with symptoms at baseline) Heartburn: 80/89 (89.9%) Retrosternal Pain: 67/86 (77.6%) Regurgitation: 53/60 (88.3%) Dysphagia: 35/37 (94.6%) Abdominal distension: 32/42 (76.2%) Overall symptoms for those reporting at week 4: 75/103 (72.8%) Median time to first episode of 3 consecutive days of heartburn-free interval: 3 days	@ 4 weeks: 83/103 (80.6%) Overall 8 weeks: 95/102 (93.1%)	NA	NA	Healing rates @ 4 week Grade II: 88.1% Grade III/IVa: 70.6% Overall @ 8 weeks: Grade II: 98.5% Grade III/IVa: 85.3% "Overall, the healing percentages of patients with grade **II** did not differ significantly from those of grade III/IVa"
Fass 2000	L60 (n=46)	@ 6 weeks <u>Daytime heartburn</u> Complete relief: 10/44 (22.7%) Average time for complete resolution: 17.3 days	NA	NA	NA	

Table IV[E]: (GERD) L vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Remission**	**Subgroup analysis performed**
		Nighttime heartburn Complete relief: 10/44 (22.7%) Average time for complete resolution: 24.5 days Acid regurgitation Complete relief: 9/44 (20.5%) Average time for complete resolution: 20.3 days				
	O40 (n=50)	@ 6 weeks Daytime heartburn Complete relief: 8/46 (17.4%) Average time for complete resolution: 14.3 days Nighttime heartburn Complete relief: 12/46 (26.1%) Average time for complete resolution: 22.1 days Acid regurgitation Complete relief: 8/46 (17.6%) Average time for complete resolution: 17.3 days	NA	NA	NA	
Richter 2001b	L30 (n=1754)	Cumulative % of patients with sustained heartburn relief @ 4 weeks: 1351/1750 (77.2%) @ 8 weeks: 1475/1750 (84.3%) During the entire 8 week, significantly higher percentages	NA	NA	NA	Because there were differences in the baseline parameters of tobacco smoking and the number of nights with heartburn between the treatment groups, all efficacy data were analyzed after stratification for these baseline differences. Results of these analyses

Table IV[E]: (GERD) L vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Remission**	**Subgroup analysis performed**
		of patients in the Lansoprazole group (13-14%) recorded not having a single episode of daytime or nighttime heartburn as compared to the Omeprazole group (11-12%) (data presented graphically only; p<0.05)				were similar to those observed for all patient (data not shown)
	O20 (n=1756)	Sustained heartburn relief @ 4 weeks: 1333 /1749 (76.2%) @ 8 weeks: 1452/1749 (83.0%)	NA	NA	NA	
Mulder 2002 *Data for Pantoprazole group not reported in this table*	L30 (n=156)	Heartburn relief @ 4 weeks: 122/156 (78%) @ 8 weeks: 126/156 (81%) Total GSRS score given graphically only. Difference between L and O group is not statistically or clinically significant.	NA	Patient satisfaction @ 4 weeks: 76% @8 weeks: 86%	Not assessed at this randomised phase	
	O20 (n=151)	Heartburn relief @ 4 weeks: 127/151 (84%) @ 8 weeks: 131/151 (87%)	NA	@ 4 weeks: 79% @8 weeks: 89%		
Adachi 2003 *Data for Rabeprazole group not reported in this table*	L30 (n=25)	Symptom score only provided daily for first 7 days (reported graphically only). NA at week 4 or week 8 Heartburn score was significantly lower in Rabeprazole group after 2 days than in Omeprazole and	@ 8 weeks: 17/25 (68.0%)	NA	NA	Subgroup by *H. pylori* status for healing rate (cannot extract for each treatment groups)
	O20 (n=30)		@ 8 weeks: 24/30 (80%)	NA	NA	

Table IV[E]: (GERD) L vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Remission**	**Subgroup analysis performed**
		Lansoprazole groups (p=0.045). Differences disappeared after day 5. No significant differences in acid reflux scores between groups.				
Pilotto 2007 *Data for Pantoprazole and for Rabeprazole group not reported in this table*	L30 (n=80)	Heartburn@ 8 weeks : 66/80 (82.4%) Relief of Acid regurgitation@ 8 weeks : 60/80 (75%) Epigastric pain @ 8 weeks : 66/80 (82.6%) Dysphagia@ 8 weeks : 80/80 (100%) Vomiting@ 8 weeks : 80/80 (100%) Anemia@ 8 weeks : 80/80 (100%)	@ 8 week: 68/80 (85.0%)	NA	NA	Subgroup data for grade I, Grade II, Grade III-IV, *H. pylori*, Healing of esophagitis Grade 1 L = 25/25 and O= 27/33 Grade 2 L = 28/29 and O= 18/22 Grade 3 and 4 L = 15/21 and O= 15/19 By *H. pylori* + or –ve *H. pylori* positive L = 54/57 and O= 38/49 *H. pylori* negative L = 11/14 and O =19/22 By *H. pylori* cured or still positive *H. pylori* cured L = 43/46 and O = 24/32 *H. pylori* still positive L = 11/11 and O =14/17
	O20 (n=80)	Disappearance of symptoms at week 4: Heartburn: 70/80 (86.9%) Acid regurgitation: 80/80 (100%) Epigastric pain: 76/80 (95%) Dysphagia: 80/80 (100%) Vomiting: 80/80 (100%) Anemia: 80/80 (100%)	@ 8 week: 60/80 (75.0%)	NA	NA	

Table IV[E]: (GERD) L vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Remission**	**Subgroup analysis performed**
Zheng 2009 *Data for Esomeprazole and for Pantoprazole group not reported in this table*	L30 (n=69)	NA	@ 8 weeks: 60/69 (87%)	NA	NA	When the patients were divided into *H. pylori* positive and negative groups, the healing rate for reflux esophagitis at week 8 in *H. pylori* positive patients tended to be higher than that in negative subjects (92.4% *vs* 85.8%, *P* > 0.05, χ2 =2.95, by χ2 test).
	O20 (n=68)	NA	@ 8 weeks: 57/68 (83.8%)	NA	NA	
Maintenance Studies						
Carling 1998	L30 (n=126)	NA	NA	NA	Remission - Overall up to 48 weeks: 12/126 (9.5%) – 11 endoscopic and one symptomatic *symptomatic relapse is graded as severe "No difference between treatment groups with respect to time to relapse (P=0.95)" Subgroup analysis: Not performed	
	O20 (n=122)	NA	NA	NA	Remission - Overall up to 48 weeks: 11/122 (9.0%) – 9 endoscopic and 1 symptomatic and 1 both.	
Jaspersen 1998 *Data for Pantoprazole group not reported in this table*	L30 (n=10)	NA	NA	NA	Endoscopic recurrences or relapse @ 4 week: 8/10 (80%) Symptomatic recurrences or relapse@ 4 week: 6/10 (60%) Subgroup analysis: Not performed	
	O20 (n=10)	NA	NA	NA	Endoscopic recurrences or relapse @ 4 week: 1/10 (10%) Symptomatic recurrences or relapse@ 4 week: 1/10 (10%)	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; O, Omeprazole; QoL; Quality of Life; NA, Not applicable, GSRS, Gastrointestinal Symptom Rating Scale						

Table IV[F]: (GERD) L vs O - Harm Outcomes						
Author, Year, Trial Name	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N %)**	**Most common AEs (n/N)**
Hatlebakk 1993	L30 (n=116)	NR	NR	NR	38 (32.8%)	Diarrhoea: 9 (7.8%) Vertigo: 4 (3.4%) Dizziness: 1 (0.9%) Fatigue: 2 (1.7%) Headache: 0 Nausea: 3 (2.6%) Increased appetite: 2 (1.7%)
	O20 (n=113)	NR	NR	NR (At least 1 WDAE due to diarrhoea)	33 (29.2%)	Diarrhoea: 5 (4.4%) Vertigo: 2 (1.8%) Dizziness: 4 (3.5%) Fatigue: 2 (1.8%) Headache: 4 (3.5%) Nausea: 1 (0.9%) Increased appetite: 2 (1.8%)
Castell 1996	L15 (n=218)	NR	NR	7	97 (44.5%)	Headache: 9 (4.1%) Diarrhea: 9 (4.1%) Nausea: 8 (3.7%)
	L30 (n=422)	NR	NR	2	235 (55.7%)	Headache: 19 (4.5%) Diarrhea: 15 (3.5%) Nausea: 4 (0.9%)
	O20 (n=431)	NR	NR	9	230 (53.4%)	Headache: 17 (3.9%) Diarrhea: 17 (3.9%) Nausea: 3 (0.7%)
Mee 1996	L30 (n=300)	0	0	NR	308/604 (51%) Not reported separately	Headache: 36 (12%) Diarrhoea: 28 (9.4%) Nausea: 13 (4.3%)
	O20	0	2	NR		Headache: 33 (11%)

Table IV[F]: (GERD) L vs O - Harm Outcomes						
Author, Year, Trial Name	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N %)**	**Most common AEs (n/N)**
	(n=304)		(oesophageal cancer; vasovagal syncope and loose stools)		for each group.	Diarrhoea: 24 (8%) Nausea: 14 (4.7%)
Mulder 1996	L30 (n=106)	NR	3 (midsternal chest pain; hernia nuclei pulposi, bleeding urinary bladder)	0	20 (18.9%)	<u>Grouped by body system</u> Body as a whole: 6 (5.7%) Cardiovascular: 4 (3.8%) Digestive: 3 (2.9%) Musculoskeletal: 4 (3.8%) Nervous: 4 (3.8%)
	O40 (n=105)	NR	1 (pulmonary tumour	0	22 (21.0%)	Body as a whole: 7 (6.7%) Cardiovascular: 1 (1.0%) Digestive: 7 (6.7%) Musculoskeletal: 1 (1.0%) Nervous: 6 (5.7%)
Fass 2000	L60 (n=46)	NR	NR	0/44	14/44 (31.8%)	Diarrhoea: 4/44 (9.1%) Abdominal pain/discomfort: 4/44 (9.1%) Bloating/gas: 3/44 (6.8%) Vomiting: 3/44 (6.8%) Headache: 2/44 (4.6%) Dizziness: 2/44 (4.6%) Nausea: 2/44 (4.6%) Fatigue: 2/44 (4.6%) Constipation: 0

Table IV[F]: (GERD) L vs O - Harm Outcomes						
Author, Year, Trial Name	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N %)**	**Most common AEs (n/N)**
	O40 (n=50)	NR	NR	1/46 (developed angina pectoris due to coronary artery disease and patient requested to be withdrawn)	18/46 (39.1%)	Diarrhoea: 8/46 (17.4%) Abdominal pain/discomfort: 4/46 (8.7%) Bloating/gas: 5/46 (10.9%) Vomiting: 4/46 (8.7%) Headache: 3/46 (6.5%) Dizziness: 1/46 (2.2%) Nausea: 0 Fatigue: 0 Constipation: 2/46 (4.4%)
Richter 2001b	L30 (n=1754)	NR	NR	40 (8 of which is due to diarrhea)	772 (44%)	Diarrhoea: 174/1754 (10%) Increased appetite: 6/1754 (0.3%) Melena: 2/1754 (0.1%); Asthma: 7/1754 (0.4%)
	O20 (n=1756)	NR	NR	33 (3 of which is due to diarrhea) *Due to discrepancies in reporting, 33 was used instead of 30)	773 (44%)	Diarrhoea:131/1755 (8%) increased appetite: 0/1755 Melena: 13/1755 (0.7%) Asthma: 0/1755
Mulder 2002 *Data for Pantoprazole group not reported in this table*	L30 (n=156)	NR	In all 3 groups combined, 4 patients were hospitalized (one COPD exacerbation; one	3	In total, 73 (16%) patients reported one or more	Diarrhoea: 6 (3.8%) Headache: 5 (3.2%) Nausea: 6 (3.8%
	O20 (n=151)	NR		2		Diarrhoea: 5 (3.3%) Headache: 3 (2%) Nausea: 3 (2%)

Table IV[F]: (GERD) L vs O - Harm Outcomes						
Author, Year, Trial Name	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N %)**	**Most common AEs (n/N)**
			allergic reaction to soya; one venous thrombosis and pulmonary embolism; one ruptured cerebral aneurysm)		adverse events. NS between groups.	
Adachi 2003	L30 (n=25)	NR	NR	NR	NR	NR
Data for Rabeprazole group not reported	O20 (n=30)	NR	NR	NR	NR	NR
Pilotto 2007	L30 (n=80)	NR	NR	NR for each group; Total of 2 in all 4 treatment groups combined	1	In all 4 treatment groups combined: Utricaria, glossitis, nausea, and headache
Data for Pantoprazole and for Rabeprazole group not reported	O20 (n=80)	NR	NR		1	
Zheng 2009	L30 (n=69)	0	NR	NR	NR	NR
Data for Esomeprazole and for Pantoprazole group not reported	O20 (n=68)	0	NR	NR	NR	NR
Maintenance Studies						
Carling 1998	L30 (n=126)	NR	**0**	5 (1 eructation and fatigue; 1 abdominal pain, nausea and enzyme abnormality; 2 diarrhoea; 1	66 (52.3%)	

Table IV[F]: (GERD) L vs O - Harm Outcomes						
Author, Year, Trial Name	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N %)**	**Most common AEs (n/N)**
				abscess, dry mouth, diarrhoea and eczema)		
	O20 (n=122)	NR	**0**	4 (1 itching and itching; 1 constipation; 1 dizziness and muscle pain; 1 vertigo, headache, diarrhoea and tachycardia)	68 (55.7%)	
Jaspersen 1998 *Data for Pantoprazole group not reported in this table*	L30 (n=10)	0	NR	NR	NR	NR
	O20 (n=10)	0	NR	NR	NR	NR
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; O, Omeprazole; NR. Not reported; NS; Not significant; AE. Adverse event; WDAE, Withdrawals due to adverse event						

V. Comparison 5: Lansoprazole vs. Pantoprazole (5 RCTs)

Table V[A]: (GERD) L vs P - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (n)**	**Patient Type**	**Intervention /Comparator and dosage**	**Study Duration**	**Outcome(s)**
Jaspersen 1998	RCT	Germany	L60: 10 P80: 10 O40: 10	30 patients with reflux esophagitis and stricture confirmed by endoscopy who responded to O 20mg BD. (healing of esophagitis and relief from all reflux symptoms and dysphagia achieved)	L 30 mg BD P 40 mg BD O 20 mg BD	4 weeks maintenance	Primary outcome: Maintenance of remission at week 4, defined as absence of esophagitis and stricture at repeat endoscopy after 4 weeks, and absence of symptoms Relapse: defined as one or more of the following a) recurrence of dysphagia, b) need for re-dilatation c) recurrence of reflux symptoms and d) relapse of esophagitis.
Dupas 2001	DBRCT	72 centres in France	L30: 236 P40:225	461 adults with endoscopically confirmed grade II or grade III reflux esophagitis (new Savary-Miller)	L30 mg OD P40 mg OD	4 or 8 weeks (4 weeks plus 4 additional weeks if complete healing had not occurred at week 4)	Primary efficacy outcome: Endoscopy healing rate at week 4 Other: Cumulative endoscopy healing rate at week 8; symptom relief at week 4 (heartburn, acid regurgitation and pain on swallowing); rapidity of symptom relief and symptom resolution rates; safety

Mulder 2002	DBRCT	31 centres in Netherlands	L30: 156 P40: 154 O20: 151	461 adults with grade I–IV symptomatic reflux esophagitis (modified Savary–Miller)	L30 mg OD P40 mg OD O20 mg OD	4 or 8 weeks (4 weeks plus 4 additional weeks if patient is not **satisfied** at week 4) Data after 8 weeks (treated with open O 40 mg) will not be discussed in this review.	Primary outcomes: Symptom relief, patient satisfaction and quality of life Other outcomes: severity of reflux esophagitis symptoms (heartburn, regurgitation, dysphagia) using the Likert Scale at each visit; patient satisfaction at each visit; Change in proportion of patients suffering from constipation at week 4; Any adverse event
Pilotto 2007	Open RCT	Single centre, Italy	L30: 80 P40: 80 R20: 80 O20: 80	320 patients over 65 years of age with endoscopically diagnosed esophagitis (grade I–IV)	L 30 mg OD P 40 mg OD R 20 mg OD O 20 mg OD	8 weeks	Primary outcome: Esophagitis healing rates at week 8 Other outcomes: Symptom disappearance at week 8 (Interview question: Absent or Presence of Acid regurgitation, heartburn, epigastric pain, dysphagia, vomiting and anaemia)
Zheng 2009	RCT	China	L30: 69 E40: 68 P40: 69 O20: 68	274 adults with endoscopically proven reflux esophagitis	L 30 mg OD P 40 mg OD E 40 mg OD O 20 mg OD	8 weeks	Primary outcome: rapid symptom relief in the first week of drug administration Other outcomes: Endoscopic healing at week 8; severity of symptoms during the first 7 days of PPI administration (symptom diary)
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; DB, Double-blind; RCT, Randomized controlled trial; OD, once daily; BD, twice daily; R, Rabeprazole; E, Esomeprazole; P, Pantoprazole; O, Omeprazole; E, Esomeprazole; PPI, Proton-pump inhibitor							

Table V[B]: (GERD) L vs P - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant Medications**
Jaspersen 1998	Patients (>=18 years) with Grade 4 esophagitis according to the Savary-Miller classification (esophagitis with multiple circumferential erosions and stricture) and one or more of four symptoms (heartburn, pain, regurgitation and solid food dysphagia). These patients were then treated with Omeprazole BD until healing of esophagitis and relief from all reflux symptoms and dysphagia. Patient who responded (absence of esophagitis and stricture, and absence of symptoms) were then included in the randomisation phase.	Pregnancy; malignant oesophageal stenosis; esophago-gastric surgery; serious renal, cardiac, hepatic or pulmonary disease; expected poor compliance with treatment. Patients not responding to Omeprazole BD.	Not described.
Dupas 2001	Patients (≥ 18 years) if they have symptoms: heartburn, acid regurgitation, pain on swallowing and endoscopically confirmed grade II (multiple erosions affecting multiple folds, erosions may be confluent) and III (multiple circumferential erosions) reflux esophagitis according to Savary-Miller classification, performed 5 days prior to enrolment.	Duodenal or gastric ulcer; Zollinger-Ellison syndrome; Grades <II or >III esophagitis; Infectious, caustic or post-radiotherapy esophagitis; Surgical history of the esophagus, stomach or duodenum except for basal peptic ulcer suture; any serious, severe or malignant disease susceptible to interfere with the study outcome were excluded.	Concomitant therapy with anti-ulcer medications such as PPIs, H2receptor antagonists, prokinetic agents, sucralfate or mucosal protective agents (prostaglandins, antacids or alginates) was not allowed.
Mulder 2002	Patients (aged 18–80 years) with symptomatic reflux esophagitis grade I–IV according to the modified Savary–Miller classification, verified by endoscopy within 10 days prior to inclusion, were included (grade I, linear, non-confluent erosions; grade II, longitudinal, confluent, non-circumferential erosions; grade III, longitudinal, confluent, circumferential erosions that bleed easily; grade Iva, one or several ulcerations in the mucosal transition zone, which can be accompanied by stricture or metaplasia; grade IV b, with the presence of a stricture but without indications of erosions or ulcerations).	Patients with gastric and/or duodenal ulcers or erosive bulbitis; previous gastro-oesophageal surgery; pregnancy or lactation; concurrent disease or therapy that may complicate the evaluation of the drug (e.g. GI disorders that may impair drug absorption; significant cardiovascular, renal or liver disease; endocrine disease; suspected or confirmed malignancy; use of cytotoxic drugs); use of a PPI during the month preceding the endoscopy; contraindication to use of Omeprazole, Lansoprazole and/or Pantoprazole; participation in clinical study or treatment with unregistered drug during the previous month;	Antacid

		Clinically significant abnormalities; chronic alcoholism, drug abuse or other conditions associated with poor compliance and requirement of an interpreter were excluded.	
Pilotto 2007	The inclusion criteria were: (1) age 65 years or over and (2) endoscopic diagnosis of esophagitis grade I to IV according to the Savary-Miller Classification. Patients with Barrett's esophagus were not included unless erosive esophagitis was also present.	Major exclusion criteria were: history of Zollinger-Ellison syndrome, pyloric stenosis, previous surgery of the esophagus and/or GI tract (except for appendectomy and cholecystectomy), and GI malignancy. Patients were excluded if they had received antacids, sucralfate, prokinetics, H2-blockers, and/or PPIs for more than 7 days in the four weeks prior to the start of the study. Patients with diffuse erythema and/or fragility of the lower esophagus were not included.	*H. pylori* positive patients were treated with the PPI plus two antibiotics i.e., amoxicillin 1g twice daily and clarithromycin 250 mg twice daily or metronidazole 250 mg four times daily for 7 day
Zheng 2009	Patients with endoscopically proven reflux esophagitis in the Affiliated Hospital of Yanbian University from January, 2006 to September, 2007 and the Affiliated Hospital of Hainan Medical College from October, 2007 to November, 2008	Subjects with active peptic ulcer, upper GI cancers, malignant diseases of other organs, severe cardiac, hepatic, or renal diseases, anemia (concentration < 10 g/dL), or who were pregnant and/or lactating, were excluded.	Subjects were not permitted to take H_2RA antagonists or prokinetic drugs during the study period.
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; P, Pantoprazole; GI, Gastrointestinal; NSAID, Non-steroidal anti-inflammatory drug; BD, twice daily			

Table V[C]: (GERD) L vs P - Baseline characteristics of patients in included studies

Trial name	Treatment (Drug and mg/day)	Sex (Male %)	Age (Yrs)	BMI (kg/m^2)	Race (n, %)	Smoking (n, %)	Alcohol Consumption (n, %)	*H. pylori* positive (n, %)	Severity (n, %)*	Other
Jaspersen 1998	L60 (n=10)	5 (50%)	57.0	NR	NR	NR	NR	NR	All patients in remission	
Data for Omeprazole group not reported	P80 (n=10)	7 (70%)	62.1	NR	NR	NR	NR	NR	All patients in remission	

Dupas 2001	L30 (n=236)	178 (75%)	55	BMI: NR Height: 170cm Weight: 76kg	NR	56 (24%)	Daily 47 (20%)	NR	Grade II: 197 (83%) Grade III: 39 (17%)	Heartburn: 223 (94%) Acid regurgitation: 178 (75%) Pain on swallowing: 70 (30%)
	P40 (n=225)	165 (73%)	53	BMI: NR Height: 170cm Weight: 77kg	NR	45 (20%)	Daily 45 (20%)	NR	Grade II: 186 (83%) Grade III: 39 (17%)	Heartburn: 222 (90%) Acid regurgitation: 163 (72%) Pain on swallowing: 79 (35%)
Mulder 2002 *Data for Omeprazole group not reported*	L30 (n=156)	90 (58%)	50.8	27.0	NR	NR	NR	44 (28%) positive	Grade I: 94 (60%) Grade II: 46 (29%) Grade III: 10 (6%) Grade IVa: 6 (4%) Grade IVb: 0	Severity of heartburn – none 3%, mild 21%, moderate 41%, severe 35%; Mean GSRS score of 2.8
	P40 (n=154)	94 (61%)	51.2	26.7	NR	NR	NR	37 (24%) positive	Grade I: 93 (60%) Grade II: 42 (27%) Grade III: 16 (10%) Grade IVa: 3 (2%) Grade IVb: 0	Severity of heartburn – none 6%, mild 21%, moderate 48%, severe 25%; Mean GSRS score of 2.9
Pilotto 2007 *Data for Rabeprazole and for Omeprazole group not reported*	L30 (n=80)	36 (45%)	77.8	NR	NR	NR	NR	61/76 (80.3%)	Grade I: 26 (32.5%) Grade II: 33 (41.3%) Grade III-IV: 21 (26.2%)	
	P40 (n=80)	39 (49%)	76.8	NR	NR	NR	NR	51/77 (66.2%)	Grade I: 20 (25.0%) Grade II: 42 (52.5%) Grade III-IV: 18 (22.5%)	

Zheng 2009 *Data for Esomeprazole and for Omeprazole group not reported*	L30 (n=69)	35 (50.7%)	58.1	NR	NR	NR	NR	31 (44.9%)	Grade A: 20 (29%) Grade B: 26 (37.7%) Grade C: 21 (30.4%) Grade D: 2 (2.9%)	
	P40 (n=69)	34 (49.3%)	57.8	NR	NR	NR	NR	30 (43.5%)	Grade A: 20 (29%) Grade B: 28 (40.6%) Grade C: 20 (29%) Grade D: 1 (1.4%)	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; P, Pantoprazole; Body Mass Index; NR, Not Reported * Savary Miller classifications (I-IV); LA classification (A-D)										

Table V[D]: (GERD) L vs P - Summary of Patient Disposition

Author, Year, Trial Name	Treatment	Randomized and Treated	Completed	Discontinued	Reasons for WD	Additional Details Provided
Jaspersen 1998 *Data for Omeprazole group not reported*	L60	10	10	0	No Withdrawals	
	P80	10	10	0	No Withdrawals	
Dupas 2001	L30	236	NR	NR	NR	
	P40	225	NR	NR	NR	
Mulder 2002 *Data for Omeprazole group not reported*	L30	156	145	11	AE (n=3), lack of symptom improvement (n=1), unwillingness to continue (n=3), and loss to follow-up (n=4)	
	P40	154	149	5	AE (n=1), lack of symptom improvement (n=3), and unwillingness to continue (n=1)	
Pilotto 2007 *Data for Rabeprazole and for Omeprazole group not reported*	L30	80	75	5	NR for individual groups; In all 4 treatment groups combined: AE (n=2), low compliance (n=11), refusal of endoscopy after 2 months of treatment (n=6)	
	P40	80	77	3		
Zheng 2009 *Data for Esomeprazole and for Omeprazole group not reported*	L30	69	69	0	No Withdrawals	
	P40	69	69	0	No Withdrawals	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; P, Pantoprazole; NR, Not Reported; AE; Adverse Events; WD, Withdrawals						

Table V[E]: (GERD) L vs P - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Recurrences or Relapse**	**Subgroup analysis performed**
Jaspersen 1998 *Data for Omeprazole group not reported*	L60 (n=10)	NA	NA	NA	Endoscopic relapse @ 4 week: 8/10 (80%) Symptomatic relapse @ 4 week: 6/10 (60%)	
	P80 (n=10)	NA	NA	NA	Endoscopic relapse @ 4 week: 7/10 (70%) Symptomatic relapse @ 4 week: 6/10 (60%)	
Dupas 2001	L30 (n=236)	Total symptom relief (heartburn, acid regurgitation, pain on swallowing) @ 4 weeks: 196/235 (83%) Heartburn relief @ 4 weeks: 216/235 Acid regurgitation relief @ 4 weeks: 211/235 Pain on swallowing relief @ 4 weeks: 225/235	@ 4 weeks: 189/235 (80%) @ 8 weeks: 201/235 (86%)	NA	NA	Healing rates at week 4 lower in grade III than in grade II esophagitis (69 vs 89%, per-protocol analysis, P=0.0001). Data not provided to calculate percentages. NS according to age, gender, weight, smoking behavior, and previous replaces of reflux esophagitis
	P40 (n=225)	Total symptom relief (heartburn, acid regurgitation, pain on swallowing) @ 4 weeks: 188/226 (83%) Heartburn relief @ 4 weeks: 204/226	@ 4 weeks: 184/226 (81%) @ 8 weeks: 203/226 (90%)	NA	NA	

		Acid regurgitation relief @ 4 weeks: 205/226 Pain on swallowing relief @ 4 weeks: 217/226				
Mulder 2002 *Data for Omeprazole group not reported*	L30 (n=156)	Heartburn relief @ 4 weeks: 122/156 (78%) @ 8 weeks: 126/156 (81%) Total GSRS score given graphically only. Difference between L and P group is not statistically or clinically significant.	NA	Patient Satisfaction: @ 4 weeks: 76% @ 8 weeks: 86%	NA	
	P40 (n=154)	Heartburn relief @ 4 weeks: 129/154 (84%) @ 8 weeks: 137/154 (89%)	NA	@ 4 weeks: 79% @ 8 weeks: 91%	NA	
Pilotto 2007 Elderly patients 65 years or older up to 93 years of age *Data for Rabeprazole and for Omeprazole group not reported*	L30 (n=80)	Heartburn@ 8 weeks : 66/80 (82.4%) Relief of Acid regurgitation@ 8 weeks : 60/80 (75%) Epigastric pain @ 8 weeks : 66/80 (82.6%) Dysphagia@ 8 weeks : 80/80 (100%) Vomiting@ 8 weeks : 80/80 (100%) Anemia@ 8 weeks : 80/80 (100%)	@ 8 week: 68/80 (85.0%)	NA	NA	Subgroup Data can be extracted for grade I, Grade II, Grade III-IV, *H. pylori*, Healing of esophagitis Grade 1 L = 25/25 and P = 20/20 Grade 2 L = 28/29 and P = 36/40 Grade 3 and 4 L = 15/21 and P = 16/17 By *H. pylori* + or –ve

	P40 (n=80)	Heartburn: 80/80 (100%) Acid regurgitation: 74/80 (92.2%) Epigastric pain: 76/80 (95.2%) Dysphagia: 80/80 (100%) Vomiting: 80/80 (100%) Anemia: 80/80 (100%)	@ 8 week: 72/80 (90.0%)	NA	NA	*H. pylori* positive L = 54/57 and P = 45/48 *H. pylori* negative L = 11/14 and P =24/26 By *H. pylori* cured or still positive *H. pylori* cured L = 43/46 and P = 39/42 *H. pylori* still positive L = 11/11 and P =6/6
Zheng 2009 *Data for Esomeprazole and for Omeprazole group not reported*	L30 (n=69)	NA	@ 8 weeks: 60/69 (87%)	NA	NA	When the patients in all 4 groups were divided into *H. pylori* positive and negative groups, the healing rate for reflux esophagitis at week 8 in *H. pylori* positive patients tended to be higher than that in negative subjects (92.4% *vs* 85.8%, $P > 0.05$, $\chi 2 = 2.95$, by $\chi 2$ test). Data not provided for each treatment group separately.
	P40 (n=69)	NA	@ 8 weeks: 61/69 (88%)	NA	NA	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; P, Pantoprazole; QoL; Quality of Life; NA, Not applicable, GSRS, Gastrointestinal Symptom Rating Scale						

Table V[F]: (GERD) L vs P - Harm Outcomes						
Author, Year, Trial Name	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N (n, %)**	**Most common AEs (n/N)**
Jaspersen 1998 *Data for Omeprazole group not reported*	L60 (n=10)	0	NR	NR	NR	NR
	P80 (n=10)	0	NR	NR	NR	NR
Dupas 2001	L30 (n=236)	Total not reported (at least 1 due to traffic accident)	6 (thrombophlebitis, dyspnea, epigastric pain, bradycardia, supraventricular tachycardia and traffic accidental death)	6 Reasons NR	39 (17%)	Headache: 3 (1.3%) Diarrhea: 5 (2.1%) Abdominal pain 2 (0.8%) Skin disorders 4 (1.7%) Increase of ASAT/ALAT: 3 (1.3%)
	P40 (n=225)	Total not reported	5 (acute cholecystitis, thrombophlebitis, intrahepatic cholestasis, alcohol intoxication and lower limb edema)	3 Reasons NR	63 (28%)	Headache: 4 (1.8%) Diarrhea: 3 (1.3) Abdominal pain 4 (1.8) Skin disorders 0 Increase of ASAT/ALAT: 6 (2.7%)
Mulder 2002 *Data for Omeprazole group not reported*	L30 (n=156)	NR	Total in all 3 groups: 4 hospitalized (1 COPD exacerbation; 1 allergic reaction to soya; 1 venous thrombosis and pulmonary embolism; 1 ruptured cerebral aneurysm)	3	At 8 weeks, in total, 73 (16%) patients reported one or more adverse events. NS between groups.	Diarrhoea: 6 (3.8%) Headache: 5 (3.2%) Nausea: 6 (3.8%)
	P40 (n=154)	NR		1		Diarrhoea: 4 (2.6%) Headache: 3 (1.9%) Nausea: 1 (0.6%)
Pilotto 2007 *Data for Rabeprazole and for Omeprazole group not reported*	L30 (n=80)	NR	NR	NR for each group; Total of 2 in all 4 treatment groups combined	1 (1.3%)	In all 4 treatment groups combined: Utricaria, glossitis, nausea, and headache
	P40 (n=80)	NR	NR		1 (1.3%)	

Zheng 2009 *Data for Esomeprazole and for Omeprazole group not reported*	L30 (n=69)	0	NR	NR	NR	NR
	P40 (n=69)	0	NR	NR	NR	NR
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; P, Pantoprazole; NR. Not reported; AE. Adverse event; WDAE, Withdrawals due to adverse event; ASAT, Aspartate amino transferase; ALAT, Alanine amino transferase						

VI. Comparison 6: Lansoprazole vs. Rabeprazole (2 RCTs)

Table VI[A]: (GERD) L vs R - Description of trials meeting the inclusion criteria

Author, Year, Trial Name	Study Design	Location	Randomised sample size (n)	Patient Type	Intervention/Comparator and dosage	Study Duration	Outcome(s)
Adachi 2003	RCT	Multicentre, Japan	L: 25 R: 30 O: 30	85 patients with erosive reflux esophagitis	L 30 mg OD R 20 mg OD O 20 mg OD	8 weeks	Primary endpoint : rapid symptom relief (heartburn and acid reflux symptoms) in the 1st week of drug administration Endoscopy at week 8
Pilotto 2007	Open RCT	Single centre, Italy	L30: 80 P40: 80 R20: 80 O20: 80	320 patients over 65 years of age with endoscopically diagnosed esophagitis (grade I–IV)	L 30 mg OD P 40 mg OD R 20 mg OD O 20 mg OD	8 weeks	Primary outcome: Esophagitis healing rates at week 8 Other outcomes: Symptom disappearance at week 8 (Interview question: Absent or Presence of Acid regurgitation, heartburn, epigastric pain, dysphagia, vomiting and anaemia)

ABBREVIATIONS: GERD, Gastroesophageal reflux disease; RCT, Randomized controlled trial; OD, once daily; R, Rabeprazole; P, Pantoprazole; O, Omeprazole

Table VI[B]: (GERD) L vs R - Patient Inclusion and Exclusion Criteria from Included Studies

Author, Year	Inclusion Criteria	Exclusion Criteria	Concomitant Medications
Adachi 2003	Patients with endoscopically proven reflux esophagitis	Active peptic ulcer, upper GI cancers, malignant diseases of other organs, severe cardiac active peptic ulcer, upper gastrointestinal cancers, malignant diseases of other organs, severe cardiac, hepatic, or renal diseases, anemia (haemoglobin concentration < 10 g/dL), or who were pregnant and/or lactating.	Subjects were not permitted to take H2RA or prokinetic drugs during the study period. Antacids (aluminium hydroxide suspensions) were allowed as rescue medication for the relief of symptoms, if necessary)

Pilotto 2007	Age 65 years or over and endoscopic diagnosis of esophagitis grade I to IV according to the Savary-Miller classification. Patients with Barrett's esophagus were not included unless erosive esophagitis was also present.	Major exclusion criteria were: history of Zollinger-Ellison syndrome, pyloric stenosis, previous surgery of the esophagus and/or gastrointestinal tract (except for appendectomy and cholecystectomy), and gastrointestinal malignancy. Patients were excluded if they had received antacids, sucralfate, prokinetics, H2-blockers, and/or PPIs for more than 7 days in the four weeks prior to the start of the study. Patients with diffuse erythema and/or fragility of the lower esophagus were not included.	*H. pylori* positive patients were treated with the PPI plus two antibiotics i.e., amoxicillin 1g twice daily and clarithromycin 250 mg twice daily or metronidazole 250 mg four times daily for 7 day
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; R, Rabeprazole; GI, Gastrointestinal			

Table VI[C]: (GERD) L vs R - Baseline characteristics of patients in included studies

Trial name	Treatment (Drug and mg/day)	Sex (Male %)	Age (Yrs)	BMI (kg/m^2)	Race (n, %)	Smoking (n, %)	Alcohol (n, %)	*H. pylori* positive (n, %)	Severity (n, %)*	Other
Adachi 2003 *Data for Omeprazole group not reported in this table*	L30 (n=25)	13 (52%)	65.2	NR	NR	NR	NR	9 (36%)	A: 2 B: 14 C: 8 D: 1	Heartburn: 21 (84%) Acid regurgitation: 15 (60%) No symptom: 1 (4%)
	R20 (n=30)	15 (50%)	65.3	NR	NR	NR	NR	14 (46.7%)	A: 9 B: 16 C: 4 D: 1	Heartburn: 28 (93.3%) Acid regurgitation: 18 (60%) No symptom: 2 (6.6%)
Pilotto 2007 *Data for Pantoprazole and Omeprazole group not reported in this table*	L30 (n=80)	36 (45%)	77.8	NR	NR	NR	NR	61/76 (80.3%)	Grade I: 26 (32.5%) Grade II: 33 (41.3%) Grade III-IV: 21 (26.2%)	
	R20 (n=80)	39 (49%)	77.0	NR	NR	NR	NR	38/77 (49.3%)	Grade I: 16 (20.0%) Grade II: 50 (62.5%) Grade III-IV: 14 (27.6%)	

ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; R, Rabeprazole; BMI, Body Mass Index; QOLRAD, Quality of Life in Reflux and Dyspepsia; NR, Not Reported

* Savary Miller classifications (I-IV); LA classification (A-D)

Table VI[D]: (GERD) L vs R - Summary of Patient Disposition						
Author, Year, Trial Name	Treatment	Randomized and Treated	Completed	Discontinued	Reasons for WD	Additional Details Provided
Adachi 2003 *Data for Omeprazole group not reported in this table*	L30	25	NR	NR	NR	
	R20	30	NR	NR	NR	
Pilotto 2007 *Data for Pantoprazole and for Omeprazole group not reported in this table*	L30	80	75	5	NR for individual groups; In all 4 treatment groups combined: AE (n=2), low compliance (n=11), refusal of endoscopy after 2 months of treatment (n=6)	
	R20	80	75	5		
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; R, Rabeprazole; NR, Not Reported; AE; Adverse Events; WD, Withdrawals						

Table VI[E]: (GERD) L vs R - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Recurrences or relapse**	**Subgroup analysis performed**
Adachi 2003 *Data for Omeprazole group not reported*	L30 (n=25)	NA at week 4 or week 8. Symptom score only provided daily for first 7 days (reported graphically only) Heartburn score significantly lower in Rabeprazole group after 2 days than in Omeprazole and Lansoprazole groups (p=0.045). Differences disappeared after day 5. No significant differences in acid reflux scores between groups.	@ 8 weeks: 17/25 (68.0%)	NA	NA	Subgroup by *H.pylori* status for healing rate (cannot extract for each treatment group)
	R20 (n=30)		@ 8 weeks: 26/28 (86.7%)	NA	NA	

Table VI[E]: (GERD) L vs R - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment**	**Symptomatic relief (n/N)**	**Healing of esophagitis**	**QoL**	**Recurrences or relapse**	**Subgroup analysis performed**
Pilotto 2007 *Data for Pantoprazole and for Omeprazole group not reported*	L30 (n=80)	Heartburn: 66/80 (82.4%) Acid regurgitation: 60/80 (75%) Epigastric pain: 66/80 (82.6%) Dysphagia: 80/80 (100%) Vomiting: 80/80 (100%) Anemia: 80/80 (100%)	@ 8 week: 68/80 (85.0%)	NA	NA	Subgroup data can be extracted for grade I, Grade II, Grade III-IV, *H. pylori*, Healing of esophagitis Grade 1: L = 25/25 and R= 14/14 Grade 2: L = 28/29 and R= 46/48 Grade 3 and 4: L = 15/21 and R= 11/13 By *H. pylori* + or –ve *H. pylori* positive: L = 54/57 and R= 33/34 *H. pylori* negative: L = 11/14 and R =35/38 By *H. pylori* cured or still positive *H. pylori* cured: L = 43/46 and R = 28/29 *H. pylori* still positive: L = 11/11 and R =5/5
	R20 (n=80)	Heartburn: 80/80 (100%) Acid regurgitation: 72/80 (90.1%) Epigastric pain: 80/80 (100%) Dysphagia: 80/80 (100%) Vomiting: 80/80 (100%) Anemia: 80/80 (100%)	@ 8 week: 71/80 (88.8%)	NA	NA	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; R, Rabeprazole; QoL; Quality of Life; NA, Not applicable						

Table VI[F]: (GERD) L vs R - Harm Outcomes						
Author, Year, Trial Name	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N (%)**	**Most common AEs (n/N)**
Adachi 2003 *Data for Omeprazole group not reported in this table*	L30 (n=25)	NR	NR	NR	NR	NR
	R20 (n=30)	NR	NR	NR	NR	NR
Pilotto 2007 *Data for Pantoprazole and for Omeprazole group not reported in this table*	L30 (n=80)	NR	NR	NR for each group; Total of 2 in all 4 treatment groups combined	1	In all 4 treatment groups combined: Utricaria, glossitis, nausea, and headache
	R20 (n=80)	NR	NR		1	
ABBREVIATIONS: GERD, Gastroesophageal reflux disease; L, Lansoprazole; R, Rabeprazole; NR. Not reported; AE. Adverse event; WDAE, Withdrawals due to adverse event;						

Appendix 7: Details of PUD randomized trials meeting the inclusion criteria (TABLES)

VII. Comparison 7: Esomeprazole vs. Omeprazole (5RCTs)

Table VII[A]: (PUD) E vs O - Description of trials meeting the inclusion criteria

Author, Year, Trial Name	Study Design	Location	Randomised sample size (N)	Population	Intervention/ Comparator mg/day	Duration of follow up weeks	Outcome(s)
Van Zanten 2000	DBRCT	Europe and Canada	448 patients EAC = 224 OAC = 224	Adults patients with duodenal ulcer and *H. pylori* positive	E 40 mg BD, A 1g BD and C 500mg BD for duration of 1 week O 20 mg BD, A 1g BD and C 500mg BD for duration of 1 week	4 and 8 weeks	Primary outcome: *H. pylori* eradication (UBT negative at 4 and 8 weeks) Epigastric pain, heartburn; Severity of symptoms and adverse events
Tulassay 2001	DBRCT	Czech Republic, Hungary and Poland	446 patients EAC = 222 OAC = 224	Adult patients with active duodenal ulcer and *H. pylori*-positive	E40 mg BD, A 1g BD and C 500mg BD for duration of 1 week O 20 mg BD, A 1g BD and C 500mg BD for duration of 1 week 3 weeks' monotherapy with Omeprazole 20 mg OD in OAC group and placebo in EAC group	4 to 6 weeks after end of treatment	Primary outcome: *H. pylori* eradication (patients with both negative UBT and histological assessment at the final visit were considered *H. pylori* negative. The frequency and intensity of epigastric pain; heartburn Symptoms were Adverse events
Miehlke S 2003	Open label RCT	Germany	80 patients ECM = 42 OCM = 38	Adult patients testing positive for *H. pylori* by both culture and histology and susceptible to M and C	E 20 mg BD, C 500mg BD, M 800 mg BD for 7 days. O 20 mg BD, C 500mg BD, M 800 mg BD for 7 days	4-8 weeks	Primary outcome: *H. pylori* eradication (patients with two negative UBT and histological assessment at both 4 and 8 weeks after end of treatment)

Table VII[A]: (PUD) E vs O - Description of trials meeting the inclusion criteria							
Author, Year, Trial Name	**Study Design**	**Location**	**Randomised sample size (N)**	**Population**	**Intervention/ Comparator mg/day**	**Duration of follow up weeks**	**Outcome(s)**
Van Zanten 2003	DBRCT	Canada	379 patients EMC =190 OMC = 189	Adult patients with a minimum 3 month history of dyspepsia and confirmed *H. pylori* infection	E20mg BD, M 500 mg BD, and C 250 mg BD for 7 days O20 mg BD, M 500 mg BD, and C 250 mg BD for 7 days EMC group received placebo Esomeprazole BD and OMC group received Omeprazole 20mg BD for 3 additional weeks	4-week eradication phase and a 2-month follow-up phase	Primary outcome: *H. pylori* eradication (patients with two negative UBT and histological assessment at both 4 and 8 weeks after end of treatment)
Sheu BS 2005	Outcome assessor blinded RCT	Taiwan	200 patients EAC= 100 OAC = 100	Adult patients with dyspepsia and confirmed *H. pylori*-infection	E40mg BD, C 500mg BD A 1g BD for 7 days O 20mg BD, A1g BD and C 500mg BD for 7 days	6 weeks after end of treatment	Primary outcome: *H. pylori* eradication according to genotyping of CYP2C19
Abbreviations: PUD, peptic ulcer disease, BD, Twice daily; DB, Double blind; RCT, Randomized Clinical Trial; E, Esomeprazole; O, Omeprazole; A, Amoxicillin; C, Clarithromycin; M, Metronidazole							

Table VII[B]: (PUD) E vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Van Zanten 2000	Patients ≥ 18 years of age or older, with a history of at least one episode of endoscopically or radio logically documented duodenal ulcer disease and testing positive for *H. pylori* with a rapid Helicobacter urease test (HUT) were eligible for inclusion.	Current duodenal, gastric, prepyloric or pyloric ulcer, complications of duodenal ulcer disease (e.g. pyloric stenosis), treatment with medication for all acid related symptoms and/or peptic ulcer disease, e.g. antacids/anti-secretory drugs (any such treatment must be stopped at least 3 days before the UBT test at visit 1), history of oesophageal, gastric or duodenal surgery, pregnancy or lactation, inadequate contraception, contraindications to study drugs, treatment with amoxicillin, clarithromycin or bismuth-containing drugs during the month preceding the study, severe concurrent disease, malignancy and substance abuse. Concurrent treatment with drugs that might affect the efficacy and safety of study medication or regular use of non-steroidal or anti-inflammatory drugs (including aspirin at doses > 165 mg/day) were not allowed.	Not reported
Tulassay 2001	Patients aged ≥18 years with endoscopically confirmed active duodenal ulcer (> 5 mm diameter) and testing positive for *H. pylori* (rapid urease test) were eligible for inclusion.	Current gastric, pre-pyloric or pyloric ulcer, complications of duodenal ulcer disease (e.g. pyloric stenosis, bleeding or perforation), concomitant treatment for acid-related symptoms and/or peptic ulcer disease, a history of oesophageal, gastric or duodenal surgery, contraindications to study drugs, treatment with amoxicillin, clarithromycin or bismuth-containing drugs during the month preceding the study, severe concurrent disease, malignancy and substance abuse. Pregnant or lactating women, and women of childbearing potential who were not practising adequate contraception were also excluded. Concurrent treatment with drugs that might affect the efficacy and safety of study medication or regular use of non-steroidal or anti-inflammatory drugs (including aspirin at doses > 165 mg/day) were not allowed.	Not reported

Table VII[B]: (PUD) E vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Miehlke 2003	Patients (18 to 80 years old) had to be *H. pylori* positive by both culture and histology, and antimicrobial susceptibility testing had to be available showing susceptibility to both metronidazole and clarithromycin.	more than one previous attempt of *H. pylori* therapy, known or suspected intolerance against one of the study drugs, contraindication against biopsy taking, present complicated peptic ulcer (bleeding, perforation, stenosis), regular use of non-steroidal anti-inflammatory drugs, antibiotics or bismuth compounds within the 4 weeks prior to randomization, history of partial gastrectomy or proximal selective vagotomy, known malignant disease or other severe concomitant diseases (Karnofsky index <60)	Not reported
Van Zanten 2003	Patients $\geq$ 18 years or older, with a minimum 3-month history of dyspepsia with either continuous or intermittent symptoms and confirmed *H. pylori* infection by a 13C-urea breath test. One previous attempt to eradicate *H. pylori* was allowed, provided that the treatment had been completed for > 6 months prior to study inclusion.	Presence of alarm symptoms suggestive of serious underlying disease; a previous documented diagnosis of GERD; previous gastric surgery, including anti-reflux surgery; treatment with a proton pump inhibitor, antibiotics or bismuth-containing compounds in the 30 days or H2-receptor antagonists in the 14 days prior to visit 1; an ongoing need for acid suppressive therapy during the study; the need for the continuous use of any non-steroidal anti-inflammatory drug (NSAID) or aspirin (a daily dose of aspirin up to and including 325 mg/ day was allowed); pregnancy or lactation; inadequate contraception (applicable to women of child-bearing potential); and contraindications to the study drugs. Patients who had predominant symptoms of isolated heartburn or acid regurgitation without epigastric pain were not eligible.	Not reported
Sheu 2005	Patients with dyspepsia and *H. pylori*-infection with a positive result in either histology or culture.	Patients who had taken PPI, bismuth or antibiotics within 4 weeks of entry, an age of <20 years or > 70 years, concomitant severe disease, pregnancy or lactation, treatment with steroids or non-steroidal anti-inflammatory drugs and previous gastric surgery.	Not reported
Abbreviations: PUD, peptic ulcer disease; E, Esomeprazole; O, Omeprazole; NSAID, Non-steroidal anti-inflammatory drug			

Table VII[C]: (PUD) E vs O - Baseline characteristics of patients in included studies

Trial name	Treatment (Drug and mg/day)	Sex (Male %)	Mean age ± SD years	BMI (kg/ m^2)	Race (n, %)	Smoking (n, %)	Alcohol Consumption (n, %)	*H. pylori* positive (n, %)	Type of ulcer (%)	Other
Van Zanten 2000	EAC = 204	136 (67)	53 ± 14	NR	NR	NR	NR	100%	DU (100)	-
	OAC = 196	119 (61)	54 ± 15	NR	NR	NR	NR	100%	DU (100)	-
Tulassay 2001	EAC = 214	138 (65)	46 ± 13	NR	NR	122 (57)	NR	100%	DU (100)	-
	OAC = 219	132 (60)	45 ± 13	NR	NR	124 (57)	NR	100%	DU (100)	-
Van Zanten 2003	EMC= 190	72 (38)	48 (SD) not reported	NR	Caucasians 179 and 11 others	67 (35)	107 (56%)	100%	PUD (16)	-
	OMC = 189	96 (51)	49 (SD)	NR	Caucasians 175 and 14 others	57 (30)	121 (64%)	100%	PUD (22)	-
Miehlke 2003	EMC = 42	23 (57)	Median (range) 46 (18-83)	NR	NR	NR	NR	100%	PUD (43)	Dyspepsia 24(57%)
	OMC =38	24 (63)	Median (range) 39 (19-76)	NR	NR	NR	NR	100%	PUD (37)	Dyspepsia 24(63%)
Sheu 2005	EAC =100	49 (49)	42 (SD)	NR	NR	NR	NR	100%	GU(30) DU(40) Gastritis (30)	HomoEM: 46% HeteroEM: 33% PM : 21%
	OAC = 100	50 (50)	42 (SD) not reported	NR	NR	NR	NR	100%	GU: 30 DU: 41 Gastritis: 29	HomoEM 45% HeteroEM 32% PM 23%

Abbreviations: E, Esomeprazole; O, Omeprazole; A, amoxicillin; C, clarithromycin; M, metronidazole; GU: gastric ulcer; DU: duodenal ulcer; PUD, peptic ulcer disease; SD, standard deviation; PM, poor metabolizer; HomoEM, homologous extensive metabolizer; HeteroEM, heterologous extensive metabolizer of CYP2C19; BMI, Body Mass Index

Table VII-D: (PUD) E vs O - Summary of Patient Disposition						
Trial	**Treatment groups**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for withdrawal**	**Additional Details Provided**
Van Zanten 2000	EAC	224	220	4	16 due to adverse events, unwillingness to continue and loss to follow-up.	
	OAC	224	212	12		
Tulassay 2001	EAC	214	213	1	Adverse events, withdrawal of consent and loss to follow-up. 1 patient withdrew due to taste perversion/vomiting	
	OAC	219	215	4	One SAE (an episode of cerebral ischemia led to patient withdrawal) 3 patients withdrew (one patient due to rash, one due to allergic reaction and one due to dysmenorrhoea	
Miehlke 2003	EMC	42	39	3(7.1%)	3 patients due to denial of follow-up examination, untraceable	91% did follow-up endoscopy. One patient denied follow-up endoscopy but agreed to 13C-urea breath test.
	OMC	38	33	5 (13.2%)	5 due to denial of follow-up examination, untraceable	84% patients did follow-up endoscopy. One patient denied follow-up endoscopy but agreed to 13C-urea breath test
Van Zanten 2003	EMC	190	175	15 (8.6%)	Unwillingness to continue (4); Lost to follow-up (5); Adverse event (5); Other (1)	
	OMC	189	177	12 (6.3%)	Unwillingness to continue (6); Lost to follow-up (3); Adverse event (2); Due to eligibility criteria (1)	
Sheu 2005	EAC	100	97	3 (3%)	3 did not return for the follow-up	
	OAC	100	98	2 (2%)	2 did not return for the follow-up	
Abbreviations: PUD, peptic ulcer disease; E, Esomeprazole; O, Omeprazole; A, amoxicillin; C, clarithromycin; M, metronidazole						

Table VII[E]: (PUD) E vs O - Efficacy Outcomes						
Author, Year, Trial Name	**Treatment group**	***H. pylori* eradication (n/N) @ 4 or 8 weeks**	**Ulcer healing@ 4 weeks**	**Epigastric pain**	**Heart burn**	**Additional information**
Van Zanten 2000		@ 4 and 8 weeks				
	EAC= 224	183/204 (90%)	NR	Figure 2 has data 21/204 (10%)	Figure 4 has data 33/204 (16%)	48 patients excluded from the ITT analysis: 46 *H. pylori*-positive status was not verified by the ^{13}C-urea breath test (UBT) at the baseline and 2 for failure to take any study medication.
	OAC=224	172/196 (88%)	NR	Figure 2 has data 24/196 (10%)	Figure 4 has data 39/196 (20%)	
Tulassay 2001		@ 4 to 6weeks				
	EAC =214	184/209 (88%)	195/208 (93.8%)	Figure3 has data 18/214 (8%)	Figure 3 has data 27/214 (12.5%)	
	OAC = 219	192/213 (90%)	202/211 (96%)	Figure 3 has data 22/219 (10%)	Figure 3 has data 22/219 (10%)	
Miehlke 2003		@ 4 -8 weeks				
	ECM = 42	38/42 (90.4%)	NR	NR	NR	
	OCM = 38	31/38 (81.6%)	NR	NR	NR	
Van Zanten 2003		@ 4 and 8 weeks				
	EMC =190	144/190 (76%)	NR	NR	NR	
	OMC = 189	137/189(72%)	NR	NR	NR	
Sheu 2005		@ 6 weeks				
	EAC =100	86(86%)	NR	NR	NR	HomoEM 39/46 (84.8%) HeteroEM 28/33 (84.8%) PM 19/21 90.5%)
	OAC =100	79(79%)	NR	NR	NR	Homo EM 31/45 (68.9%) Hetero EM 27/32 (84.4%) PM 21/23 (91.3%)
Abbreviaytions: E, Esomeprazole; O, Omeprazole; A,amoxicillin; C, clarithromycin; M, metronidazole; GU, gastric ulcer; DU, duodenal ulcer; PUD, peptic ulcer disease; SD, standard deviation; PM, poor metabolizer; Homoem, homologous extensive metabolizer; Heteroem, heterlogous extensive metabolizer of CYP2C19; ITT, intention-to-treat analysis						

Table VII[F]: (PUD) E vs O - Harm Outcomes						
Trial	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons**	**WDAE and reasons**	**Subjects with ≥1 AE n/N (%)**	**Most common AEs (n/N)**
Van Zanten 2000	EAC =224	NR	None	diarrhoea (2); rash (1) diarrhoea/dizziness (1)	119/204 (58.5%)	Diarrhoea/loose stools 76(34%); Taste perversion 28 (12.5%); Headache 11(5%); Nausea 5(2%); Flatulence 5 (2%); Abdominal pain 4 (2%)
	OAC=222	NR	One stroke in one patient	diarrhoea/taste perversion (1); rash (1) anxiety/palpitations/ tinnitus (1); headache (1)	107/196 (54.5%)	Diarrhoea/loose stools 72(32%); Taste perversion 41 (18.5%); Headache 8 (4%); Nausea 7(3%); Flatulence 5(2%); Abdominal pain 4 (2%)
Tulassay 2001	EAC = 214	NR	0 SAE	4 patients due to adverse events (taste perversion and vomiting (1 patient)	71/214 (33%)	Diarrhoea/loose stools 20/222 (9%); Taste perversion 28/222 (13%); Dry mouth 9/222(4%); Headache 5/225(2%); Vomiting 5/222(2%)
	OAC = 219	NR	3 SAE (1 cerebral ischemia ; 1 haematuria and 1 appendicitis	3 due to SAEs listed and 3 additional patients one each due to rash, allergic reaction and dysmenorrhoea	67/219 (29.5%)	Diarrhoea/loose stools 21/224 (9%); Taste perversion 27/224 (12%); Dry mouth 5/224(2%); Headache 2/224(1%); Vomiting 2/224(1%)
Miehlke 2003	ECM = 42	none	none	WDAE = 0	9/42 (21.4%)	Diarrhoea 5; Taste perversion 3; Headache 4;l Nausea 0; Skin reaction 0
	OCM = 38	none	none	WDAE =0	6/38 (15.8%)	Diarrhoea 3; Taste perversion 1; Headache 1; Nausea 0; Skin reaction 2
Sheu 2003	EAC =100	NR	NR	WDAE = 0	28/100	Diarrhoea 5; Taste perversion 10; Constipation 3; Headache 4; Nausea 11; Vomiting 8
	OAC = 100	NR	NR	WDAE =0	26/100	Diarrhoea 6; Taste perversion 10; Constipation 2; Headache 7; Nausea 9; Vomiting 6
Van Zanten	EMC = 190	NR	2 in each	WDAE: 5/190	122/190 (64%)	Phase 1

Table VII[F]: (PUD) E vs O - Harm Outcomes						
Trial	**Treatment group**	**Mortality & Reasons (n/N)**	**SAES & Reasons**	**WDAE and reasons**	**Subjects with ≥1 AE n/N (%)**	**Most common AEs (n/N)**
2003			group (MI, colon cancer, worsening of migraine, Coronary artery disorder) One patient OMC group diagnosed with ovarian cancer during the run-in period			Diarrhoea 27 (14%); Taste perversion 20 (11%); Headache 12 (6%); Nausea 10 (5%); Increased ALT 9 (5%)
	OMC = 189	NR		WDAE: 2/189	138/189 (73%)	Phase 1 Diarrhoea 25 (13%); Taste perversion 14 (7%); Headache 19 (10%); Nausea 16 (9%); Increased ALT 11 (6%)
Abbreviations: PUD, peptic ulcer disease; E, Esomeprazole; O, Omeprazole; A, amoxicillin; C, clarithromycin; M, metronidazole						

VIII. Comparison 8: Esomeprazole vs. Pantoprazole (1 RCT)

Table VIII[A]: (PUD) E vs P - Description of trials meeting the inclusion criteria

Author, Year, Trial Name	Study Design	Location	Randomised sample size (N)	Population	Intervention/ Comparator mg/day	Duration of follow up weeks	Outcome(s)
Hsu 2005	Open label RCT Pilot study	Taiwan	200 patients EAC = 100 PAC = 100	Adults with endoscopically proven peptic ulcer or gastritis and *H. pylori* positive	E 40 mg BD, A 1g BD and C 500mg BD for 7 days P 40 mg BD, A 1g BD and C 500mg BD for 7 days Patients with peptic ulcers in initial endoscopy received an additional 3 weeks of monotherapy with Pantoprazole 40 mg OD and patients with gastritis only took 3 weeks of antacid following eradication therapy.	8 weeks after the end of eradication therapy	Primary outcome: *H. pylori* eradication at end of follow up. Eradication was defined as (1) negative results of both rapid urease test and histology, or (2) a negative result of urea breath test Adverse events (4 point scale -none; mild; moderate; or severe)

Abbreviations: PUD, peptic ulcer disease; A: amoxicillin; C: clarithromycin; E: Esomeprazole ; P: Pantoprazole; BD, Twice daily; OD, once-daily; DB, Double blind; RCT, Randomized Clinical Trial

Table VIII[B]: (PUD) E vs P - Patient Inclusion and Exclusion Criteria from Included Studies

Author, Year	Inclusion Criteria	Exclusion Criteria	Concomitant medication
Hsu 2005	Patients $\geq$ 18 years of age or older, with endoscopically documented peptic ulcer or gastritis and testing positive for *H. pylori* were eligible for inclusion.	Previous *H. pylori* eradication therapy; ingestion of antibiotics, bismuth, or PPIs within the prior 4 weeks; use of non-steroidal anti-inflammatory drugs within the prior 4 weeks; patients with allergic history to the medications used; patients with previous gastric surgery; the coexistence of serious concomitant illness (for example, decompensated liver cirrhosis, uremia); and pregnant women.	Not reported

Abbreviations: PUD, peptic ulcer disease; E: Esomeprazole ; P: Pantoprazole

Table VIII[C]: (PUD) E vs P - Baseline characteristics of patients in included studies

Trial name	Treatment (Drug and mg/day)	Sex (Male %)	Mean age ± SD in years	BMI (kg/ m^2)	Race (n, %)	Smoking (n, %)	Alcohol (n, %)	*H. pylori* positive (n, %)	Type of ulcer (n, %)	Comorbidity Underlying disease N (%) and history of peptic ulcer	Ingestion of Coffee (n, %) Tea (n, %)
Hsu 2005	EAC = 100	63 (63)	55.6 ± 15.5	NR	NR	27(27)	12(12)	100%	Gastritis 54 GU 54 DU 23 GU/DU 3	18(18) 36(36)	18(18) 25(25)
	PAC = 100	68 (68)	55.9 ± 13.1	NR	NR	26(26)	11(11)	100%	Gastritis 55 GU 18 DU 26 GU/DU 1	28(28) 46(46)	10(10) 24(24)

* Smoking was defined as consumption of cigarettes 1 pack or more per week. Coffee or tea consumption was defined as drinking 1 cup or more per day

Abbreviations: PUD, peptic ulcer disease; A: amoxicillin; C: clarithromycin; E: Esomeprazole ; P: Pantoprazole, DU, duodenal ulcer; GU, gastric ulcer; O, Omeprazole; P, Pantoprazole; SD, standard deviation; BMI, body mass index; NR, not reported

Table VIII[D]: (PUD) E vs P - Summary of Patient Disposition

Trial	Treatment groups	Randomized and Treated	Completed	Discontinued	Reasons for withdrawal	Additional Details Provided
Hsu 2005	EAC	100	98	2	abdominal cramping(1); Diarrhea and dizziness (1)	
	PAC	100	96	4	nausea/vomiting: 2; diarrhea: 1 dizziness: 1	

Abbreviations: PUD, peptic ulcer disease; A: amoxicillin; C: clarithromycin; E: Esomeprazole ; P: Pantoprazole

Table VIII[E]: (PUD) E vs P - Efficacy Outcomes						
Author, Year, Trial Name	Treatment group	*H. pylori* eradication (n/N) @ 8 weeks	Ulcer healing@ 8weeks	Epigastric pain	Heart burn	Additional information Eradication based on baseline characteristics all patients in both groups included
Hsu 2005	EAC= 100	94/100(94%)	36/40 (90%)	NR	NR	Age, sex, smoking, ingestion of coffee, tea, underlying disease, previous history of peptic ulcer no influence on eradication rate. Alcohol consumption, presence of ulcer, use of Omeprazole instead of Pantoprazole and poor compliance significantly reduced eradication rates.
	PAC= 100	82/100(82%)*	38/45 84.4%)	NR	NR	
Abbreviations: PUD, peptic ulcer disease; A: amoxicillin; C: clarithromycin; E: Esomeprazole ; P: Pantoprazole; NR, not reported						

Table VIII[F]: (PUD) E vs P - Harm Outcomes						
Trial	Treatment group	Mortality & Reasons (n/N)	SAES & Reasons	WDAE and reasons	Subjects with ≥1 AE n/N (%)	Most common AEs (n/N)
Hsu 2005	EAC =100	NR	NR	Two patients because of abdominal cramping pain (n = 1), diarrhea, and dizziness (n = 1).	15/100	N = 100 Abdominal pain 4; Constipation 2; Diarrhoea 5; Dizziness 3; Taste perversion 1; Headache 2; anorexia 0; Nausea/vomiting 3; Others 4
	PAC=100	NR	NR	four patients discontinued due to (nausea/vomiting: 2; diarrhea: 1 ; dizziness: 1	24/100	N = 100 Abdominal pain 3; Constipation 0; Diarrhoea 6; Dizziness 5; Taste perversion 2; Headache 2; anorexia 1; Nausea/vomiting 5; Others 9
Abbreviations: PUD, peptic ulcer disease; A: amoxicillin; C: clarithromycin; E: Esomeprazole ; P: Pantoprazole; SAE: Serious Adverse Events; AE: Adverse Events; NR, not reported						

IX. Comparison 9: Esomeprazole vs. Rabeprazole (No RCT identified)

X. Comparison 10: Lansoprazole vs. Omeprazole (15 RCTs)

Table X[A]: (PUD) L vs O - Description of trials meeting the inclusion criteria

Author, Year, Trial Name	Study Design location	Randomised sample size (N)	Patient Type	Intervention/ Comparator mg/day	Duration weeks	Outcome(s)
Ekstrom 1994	DBRCT 17 centres Sweden	279 patients L =143 O= 136	Patients aged 18-80 years with endoscopically confirmed duodenal ulcer(s) greater than 0.3 cm but less than 2.5 cm in diameter. *H. pylori* status was not determined at baseline.	L 30 mg OD O 20 mg OD	Duration of treatment was 4 weeks.	Primary outcome: endoscopically confirmed duodenal ulcer healing at week 2 and cumulative healing rate at week 4. Secondary outcomes: symptom relief (both physician and patient diary recording); antacid usage
Florent 1994	DBRCT Multi-centre	L = 60 O = 66	126 patients with single gastric ulcer > 5 mm in diameter diagnosed by endoscopy within 48 hours of hospitalization. *H. pylori* status not determined at study entry.	L 30 mg OD O 20 mg OD Half a dose of H_2RA was administered until eradication was assessed following the completion of eradication therapy	Duration of treatment was 4 weeks and prolonged for 4 additional weeks if the ulcer had not yet healed at the 4 week control endoscopy.	Primary outcome: endoscopic healing of gastric ulcer Secondary outcomes: Pain relief, history of daytime (6 am-l0 pm) and night-time (10 pm--6 am) ulcer pain. In addition, symptoms related to ulcer disease (nausea, vomiting, heartburn, acid reflux, flatulence, eructations and bowel disturbance) were recorded and graded for severity
Capurso 1995	DBRCT 12 centres Italy	107 patients L = 52 O = 55	Patients aged 18 to 75 years with active duodenal ulcer. *H. pylori* status was not determined at baseline.	L 30 mg OD O20 mg OD	Duration of treatment was a maximum of 42 days	Primary outcome: endoscopic healing of ulcer Secondary outcomes: symptomatic relief
Chang and Chiang 1995	Open label RCT Blinded Endpoint	111 patients L= 57 O= 54	Patients with endoscopically confirmed duodenal ulcer with a maximal	L 30 mg OD O 20 mg OD	Duration of treatment was 4 weeks	Primary outcome: endoscopic healing of ulcer Secondary outcomes: *Helicobacter*

Table X[A]: (PUD) L vs O - Description of trials meeting the inclusion criteria						
Author, Year, Trial Name	**Study Design location**	**Randomised sample size (N)**	**Patient Type**	**Intervention/ Comparator mg/day**	**Duration weeks**	**Outcome(s)**
	(PROBE) single centre Taiwan		diameter >5mm. *H. pylori* status not determined at study entry.			*pylori* clearance; ulcer related symptoms; adverse reactions
Chang and Lee 1995	Open label RCT (PROBE) single centre Taiwan	83 patients L = 42 O= 41	Patients with endoscopically confirmed duodenal ulcer with a maximal diameter >5mm. *H. pylori* status was not determined at baseline.	L 30 mg OD O 20 mg OD	Duration of treatment was 4 weeks	Primary outcome: fasting serum pepsinogen A level Secondary outcomes: endoscopic healing of ulcer (defined as the disappearance of any ulcer crater, leaving scars only); *Helicobacter pylori* clearance
Misiewicz 1997	Outcome assessor blind, RCT multi-centre	LAM = 131 OAM = 126 Other 2 treatment groups wrong comparators	508 patients with gastric ulcer, duodenal ulcer or both, who were *H. pylori* positive	LAM= L 30 mg BD, A 1 g BD and M 400mg BD OAM = O 20 mg BD, A 1 g BD and M 400mg BD Patients were not permitted to take H_2RA or any other ulcer healing drugs	Duration of treatment was 1 week and follow up at end of treatment and 4 week after completion of treatment	Primary outcome: eradication of *H. pylori* as determined by the results of 13C urea breath test at 28 days after completing treatment.
Spinzi 1998	Outcome assessor blind RCT multi-centre	LAC= 186 OAC = 170	356 patients with endoscopy proven gastric ulcer, duodenal ulcer who were *H. pylori* positive if both rapid urease test and histology were positive	LAC: L 30 mg BD, A 1 g BD, and C 500 mg BD OAC: O20 mg BD, A1 g BD, and C 500 mg BD	Duration of treatment was 1 week and follow up at end of treatment and 4 week after completion of treatment	Primary outcome: successful eradication of *H. pylori* (if both the rapid urease test and the histology were negative)

Table X[A]: (PUD) L vs O - Description of trials meeting the inclusion criteria						
Author, Year, Trial Name	**Study Design location**	**Randomised sample size (N)**	**Patient Type**	**Intervention/ Comparator mg/day**	**Duration weeks**	**Outcome(s)**
				Patients were not permitted to take H_2RA or any other ulcer healing drugs while receiving study medication	endoscopy was performed	
Dobrilla 1999	DBRCT 19 centres Italy	251 patients L 30= 167 O 40= 84	Patients aged 18 to 69 years with an endoscopic diagnosis of duodenal ulcer (DU) not treated for ≥1 month, or ulcer relapse. *H. pylori* positive status was not a necessary inclusion criterion.	L 30 mg OD O40 mg OD	Duration of treatment was 4 weeks.	Primary outcome: endoscopic healing of ulcer Secondary outcomes: symptomatic relief
Miwa 1999 317-321	Open label RCT single centre Japan	LAC = 73 O20AC = 76 O40AC = 75	224 *H. pylori* positive patients with peptic ulcer disease (N = 177) or non-ulcer dyspepsia (N = 47)	LAC = L 30 mg OD, A 500mg TDS, and C 200 mg BD O20AC = O20 mg OD, A 500mg TDS, and C 200 mg BD O40AC = O20mg BD, A500mg TDS, and C200 mg BD	Treatment for 7 days and follow up after 4 weeks.	Primary outcome: cure of infection was assessed by the [13C]-urea breath test 1 month after completion of therapy.
Miwa and Okura 1999 741-746 RAC = 72	Open label RCT single centre Japan	LAC = 74 OAC = 75	221 *H. pylori* positive patients with peptic ulcer disease	LAC = L 30 mg BD, A 500 mg TDS, C200 mg BD OAC = O 20 mg BD,	Treatment for 7 days and follow up after 4 weeks	Primary outcome: eradication of *H. pylori* as determined by the 13 C urea breath test 4 to 6 weeks after completion of treatment.

Table X[A]: (PUD) L vs O - Description of trials meeting the inclusion criteria						
Author, Year, Trial Name	**Study Design location**	**Randomised sample size (N)**	**Patient Type**	**Intervention/ Comparator mg/day**	**Duration weeks**	**Outcome(s)**
Rabeprazole 20mg BD, A 500 mg TDS, C 200 mg BD arm not included in this table				A 500 mg TDS, C 200 mg BD		
Eralp 2000	Open label RCT	LAC = 21 OAC = 21	42 patients with complaints of epigastric pain with *H. pylori* associated gastritis and peptic ulcer and *H. pylori* positive.	LAC = L 30 mg BD for one month, C 250 mg. TDS for 15 days and A 1g BD for 15 days OAC = O 20 mg BD for 1 month, C 250 mg. TDS for 15 days and A 1g BD for 15 days After this treatment, both groups received maintenance therapy of famotidine 40 mg OD for six weeks, followed by endoscopic examination	Duration of treatment was 1 month with PPI and 15 days with antibiotics followed by endoscopic examination at end of 6 weeks of treatment with famotidine	Primary outcome: eradication of *H. pylori* and decrease in gastric activity
Fanti 2001	Open label RCT	LCT = 25 OCT = 25	50 patients with endoscopically confirmed active or	L 30 mg for 1 to 4 weeks, C 250 mg BD and Tinidazole	1 week duration In patients with active ulcer 3	Primary outcome: eradication of *H. pylori* by endoscopy at 8 weeks. *H. pylori* was considered eradicated if

Table X[A]: (PUD) L vs O - Description of trials meeting the inclusion criteria						
Author, Year, Trial Name	**Study Design location**	**Randomised sample size (N)**	**Patient Type**	**Intervention/ Comparator mg/day**	**Duration weeks**	**Outcome(s)**
			scarred DU and *H. pylori* positive Active DU = 43 and Scarred ulcer = 7	500 mg BD for the first week O 20mg for 1 to 4 weeks, C 250 mg BD and Tinidazole 500 mg BD for the first week	more weeks of treatment. Follow up at 8 weeks and after 1 year	both histology and culture were negative. ^{13}C urea breath test was performed at 8 weeks and 12 months only in patients refusing to repeat endoscopic examination
Ungan M 2001 3 other treatment arms are wrong comparators and are not included in this table	Open label RCT Japan	LAC = 30 OAC = 30	145 treatment naïve patients with endoscopically confirmed DU and *H. pylori* positive	LAC: L 30 mg QD for 28 days, A1000 mg BD for 10 days, and C 500 mg BD for 10 days OAC: O 20 mg BD for 7 days, then 20 mg QD for 21 days, A1000 mg BD for 10 days, and C 500 mg BD for 10 days	4 weeks of therapy with PPI	Primary outcome: eradication of *H. pylori* Patient was considered cured only if both the urease and histology test results were negative for *H. pylori* after the first EGD (6 weeks post treatment)
Inaba 2002 RAC = 64 treatment arm is not included in this table	Open label RCT Japan	LAC = 60 OAC = 59	183 patients with peptic ulcer, and who were *H. pylori* positive.	L 30mg BD, A 500 mg TDS, C 200 mg TDS O 20mg BD, A 500 mg TDS, C 200 mg TDS	Duration of treatment was 1 week and follow up was 1 week.	Primary outcome: cure of infection and adverse events. Cure rates also provided based on CYP2C19 genetic polymorphism and PPI regimen.
Murakami 2008 RAM = 58 treatment arm	Open label RCT Japan	LAM = 56 OAM = 55 RAM = 58	169 patients with gastric ulcer, duodenal ulcer or gastritis who are *H. pylori* positive and had initial treatment failure	LAM = L 30 mg BD, A 750mg BD and M 250mg BD OAM = O 30 mg BD, A 750mg BD and M	Duration of treatment was 1 week and follow up at 4 week after completion of	Primary outcome: Bacteriologic response was assessed at least 4 weeks after completion of the 1-week eradication course. Treatment was considered successful

Table X[A]: (PUD) L vs O - Description of trials meeting the inclusion criteria						
Author, Year, Trial Name	**Study Design location**	**Randomised sample size (N)**	**Patient Type**	**Intervention/ Comparator mg/day**	**Duration weeks**	**Outcome(s)**
is not included in this table			with a PPI plus Amoxicillin and Clarithromycin	250mg BD After treatment, ½ dose of H_2RA were administered until assessment of eradication	treatment	if the results of the rapid urease test, culture, histologic examination, and the urea breath test (UBT) were all negative.
Abbreviations: PUD, peptic ulcer disease; A, amoxicillin; C, clarithromycin; E, Esomeprazole ; O, Omeprazole; L, Lansoprazole; T, Tinidazole; M, metronidazole; QD/OD, once daily; BD, Twice daily; TDS, three times daily; DB, Double blind; RCT, Randomized Clinical Trial;						

Table X[B]: (PUD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Ekstrom 1994	Patients between 18 and 80 years of age (inclusive) with endoscopically confirmed duodenal ulcer(s) greater than 0.3 cm but less than 2.5 cm in diameter, measured with an open biopsy forceps.	Patients were excluded from the study if they were women of child-bearing age not practising effective contraception or who were pregnant or lactating; unable to cooperate with the trial requirements; found to have malignancy of the oesophagus or stomach; previously operated on in the oesophagus or stomach except for simple closure of a perforation; found to have concomitant gastrointestinal pathologic findings such as reflux esophagitis, gastric ulcer, pyloric stenosis, oesophageal varices, or active biliary/pancreatic disease; abusers of alcohol or drugs; or found to have serious concurrent illness such as cardiac, renal, or hepatic disorders. Patients were not considered eligible for the study if they had taken healing doses of H2-receptor antagonists, anticholinergics, antimuscarinics, sucralfate, or prokinetic drugs within 3 days or Omeprazole within 3 months before trial entry.	Not reported
Florent 1994	Adult patients (18 to 75 years) with a single gastric ulcer over 5 mm in diameter, diagnosed by endoscopy within 48 h of hospitalization were eligible. They were included if only	Exclusion criteria included the presence of a concomitant, severe, progressive or unstable disease, particularly hepatic, renal, cardiovascular or malignant disease, Zollinger-Ellison syndrome or oesophageal varices. Patients with complications such as perforation, stenosis or bleeding requiring blood transfusion, had undergone gastric or duodenal surgery, pregnant and breast-feeding women were excluded.	The concomitant use of antacid drugs was not allowed.

Table X[B]: (PUD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
	one gastric ulcer was observed at endoscopy, without duodenal, pyloric or pre-pyloric ulceration. Five to ten biopsy specimens were systematically taken from the ulcer wall and base to exclude malignancy. *Helicobacter pylori* status was not determined for patient inclusion in the study.	Patients requiring any of the following treatments during the study were excluded: corticosteroids, non-steroidal anti-inflammatory drugs or aspirin, tricyclic antidepressants, reserpine, phenytoin, warfarin, theophylline, beta blockers or diazepam. In addition, patients who had received gastric anti-secretory agents or another anti-ulcer treatment for more than 2 days before the study were not eligible. Finally, patients with proven intolerance to proton pump inhibitors were not included.	
Capurso 1995	Patients whose age was between 18 and 75 years old with active duodenal ulcer. General conditions and laboratory biochemical and haematological parameters had to be normal and clinically acceptable according to the investigator's judgment.	Patients were excluded on the basis of the following parameters: endoscopic (concomitant ulcer localization, peptic oesophagitis, pyloric stenosis, bleeding ulcer); anamnestical (upper GI surgery, unhealed ulcer despite full doses H2 receptor antagonist, pregnant or breast feeding, hepatic/renal/heart/pulmonary diseases, tumors, chronic alcoholism, drug abuse, Zollinger Ellison syndrome, hyperplasia or hyperfunction of antral gastrin cells); and previous treatment (antisecretory drugs prior entering trial, PPI intolerance, continuous treatment with: warfarin, diazepam, beta blockers, theophylline, phenytoin, reserpine, or antidepressants).	Not reported.
Chang and Chiang 1995	Duodenal ulcer outpatients diagnosed by endoscopy, aged 21-75 years, and with an active ulcer in the duodenal bulb with a maximal diameter over 5 mm, were recruited to the study after having given their informed written consent. The dimension of the ulcer crater was measured with a counting device (M2-4KY Olympus, Tokyo, Japan).	Exclusion criteria for the study included pregnancy, channel ulcer, concomitant gastric or prepyloric ulcer, gastric outlet obstruction, recent peptic ulcer related bleeding, clinical suspicion of gastrinoma, an inability to suspend any ulcerogenic drugs, ingestion of any specific anti-ulcer medication with the exception of antacids within one week prior to inclusion in the study, and a history of chronic renal disease or surgery on the upper gastrointestinal tract.	In order to relieve undesirable epigastric pain, antacid tablets were allowed in the event of severe ulcer pain. Neither antibiotics nor bismuth preparations could be consumed during the period **of** study.

Table X[B]: (PUD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Chang and Lee 1995	Duodenal ulcer outpatients diagnosed by endoscopy, aged 21-75 years, and with an active ulcer in the duodenal bulb with a maximal diameter over 5 mm, were recruited to the study after having given their informed written consent. The dimension of the ulcer crater was measured with a counting device (M2-4KY Olympus, Tokyo, Japan).	Exclusion criteria for the study included pregnancy, channel ulcer, concomitant gastric or prepyloric ulcer, gastric outlet obstruction, recent peptic ulcer related bleeding, clinical suspicion of gastrinoma, an inability to suspend any ulcerogenic drugs, ingestion of any specific anti-ulcer medication with the exception of antacids within one week prior to inclusion in the study, and a history of chronic renal disease or surgery on the upper gastrointestinal tract.	Antacids were allowed.
Misiewicz 1997	Adult patients between 18–80 years, with a duodenal ulcer or gastritis, or both, who were *H. pylori* positive were invited to undergo a 13C urea breath test to confirm *H. pylori* status	Any patients who had a negative 13C urea breath test were not eligible to enter the study. Other exclusion criteria were treatment with PPI, compounds containing bismuth, sucralfate or antibiotics within the 2 weeks before study entry, and allergy to any of the study drugs. Additionally, patients were excluded if they had already participated in the study, were participating in another study, or had significant gastrointestinal, renal, hepatic, cardiovascular, metabolic, or haematological disease.	Not reported.
Spinzi 1998	Patients with endoscopy proven gastric ulcer, duodenal ulcer who were *H. pylori* positive if both rapid urease test and histology were positive. Those patients initially classified as *H. pylori*-positive on the basis of the rapid urease test were reclassified as negative if the result of the urease test was not confirmed by positive histology.	Patients were excluded < 18 years of age, had been enrolled in previous studies, had had prior gastric resection surgery, were on continuous treatment with NSAIDs (for more than 50% of the days in the month before the enrolment), if they required a continuous treatment with NSAIDs during the study or were allergic to the protocol drugs. Patients were also excluded in cases of pregnancy or if fertile but without effective contraception, if they had received eradication treatment in the 6 months before the enrolment and in cases of any kind of serious diseases, including digestive bleeding, in the previous 4 weeks.	Not reported.

Table X[B]: (PUD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Dobrilla 1999	Two hundred fifty-one patients (165 men and 86 women), aged 18 to 69 years (mean age, 45 years), with an endoscopic diagnosis of duodenal ulcer not treated for ≥1 month, or ulcer relapse, were recruited. *H. pylori* status could be positive or negative at baseline.	Patients were excluded from the study if they had reflux esophagitis, DU with a diameter >2 cm, pyloric stenosis, or any other mechanical obstruction. Patients who had used non -steroidal anti-inflammatory drugs, corticosteroids, or anti secretory therapy within 4 weeks before endoscopy were also excluded.	Not reported.
Miwa 1999	Patients (17 to 74 years) with peptic ulcer disease or non-ulcer dyspepsia and *H. pylori* positive assessed with 2 positive tests using histology, the rapid urease test (CLO test) or the [13C]-urea breath test.	Not specified.	Not reported.
Miwa and Okura 1999	Patients with endoscopically confirmed peptic ulcer disease and *H. pylori* positive diagnosed by at least 2 positive results: rapid-urea breath test; by histology, serology or 13C-urea breath test or culture.	Patients receiving previous curative therapy at the same clinic or other clinic; having past history of drug allergy to PPI, amoxicillin or clarithromycin; or being suspected of being pregnant; and having a severe complication such as malignancy or hepatic or renal failure.	Not reported.
Eralp 2000	Patients with complaints of epigastric pain with *H. pylori* associated gastritis and peptic ulcer were included in the study.	Not reported.	Not reported.

Table X[B]: (PUD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Fanti 2001	Patients with endoscopically proven active (at least 5 mm in diameter) or scarred duodenal ulcer diagnosed by endoscopy were consecutively enrolled in the study. During endoscopy, four biopsies, two from the antrum and two from the corpus, were taken for histologic examination and one additional specimen from the antrum for rapid urease test. *H. Pylori* was judged to be present if both histology and rapid urease test were positive.	Patients in whom a previous therapeutic attempt failed to cure *H. pylori* or who had been treated with PPIs, bismuth compounds, or antibiotics in the 30 days before endoscopy were excluded. Additional exclusion criteria were current complications of peptic ulcer disease, age below 18 years or above 75 years, allergy to one of the drugs administered, pregnancy or lactation, severe systemic illness, manifest clotting disorders, or use of anticoagulant therapy.	Not reported.
Ungan 2001	Patients with duodenal ulcer who had never received any *H. pylori* eradication protocol containing PPIs and antibiotics (according to the records and/or interview with the physician) were eligible for the study. The duodenal ulcer diagnosis was verified by endoscopy and presence of *H. pylori* infection was confirmed using the rapid urease test	Exclusion criteria were age < 16 years, ulcer not related to *H. pylori* infection (e.g., induced by non-steroidal anti-inflammatory drugs [NSAIDs]), history of allergy to antibiotics, use of any antibiotic within 30 days before endoscopy, other systemic diseases (coronary artery disease, heart failure, upper and lower respiratory tract diseases, bleeding disorders), and active bleeding.	Not reported.
Inaba 2002	Patients with endoscopically confirmed peptic ulcer, and who were *H. pylori* positive confirmed by culture, histological examination and a	Patients were excluded if they had previously undergone treatment for eradication of *H. pylori* or gastrectomy; were pregnant; had an allergy to penicillin; had used a PPI, H 2 receptor antagonist, adrenocortical steroids, or non-steroidal anti-inflammatory drugs within the month preceding the study; or were taking anticoagulants.	Not reported.

Table X[B]: (PUD) L vs O - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
	rapid urease test were included. In addition antibiotic sensitivity testing to determine the minimum inhibitory concentrations of amoxicillin, clarithromycin, and metronidazole was done.		
Murakami 2008	Patients with endoscopically determined gastric ulcers, duodenal ulcers, and gastritis and *H. pylori* positive assessed by the rapid urease test. Patients had failed triple therapy for 1 week with a PPI plus amoxicillin and clarithromycin at an interval of more than 6 months. During the period of retreatment, subjects were given the usual or half the dosage of H2-receptor antagonist.	Not specified.	After treatment, half doses of H2-receptor antagonists were administered until assessment of eradication.
Abbreviations: PUD, Peptic Ulcer Disease; PPI, Proton-pump inhibitor; L, Lansoprazole; O, Omeprazole; NSAID, Non-steroidal anti-inflammatory drug			

Table X[C]: (PUD) L vs O - Baseline characteristics of patients in included studies										
Author , Year, Trial Name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Mean age ± SD in years**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Type of ulcer (n, %)**	**Other**
Ekstrom 1994	L 30mg = 143	86 (60%)	54.4	NR	NR	69(48%)	63(44%)	NR	NR	
	O 20mg =136	85 (63%)	55.3	NR	NR	61(45%)	57(42%)	NR	NR	
Florent 1994	L 30mg = 60	NR	56 ± 14	Ht: 169 Wt: 68	NR	29(48%)	21(35%)	Not known	NR	Duration: 4 ± 10 months # relapses: 1.0 ± 1
	O 20mg = 66	NR	56 ± 15	Ht: 169 Wt: 67	NR	33(50%)	18(36%)	Not known	NR	Duration: 5 ± 17 months # relapses: 0.4 ± 1
Capurso 1995	L 30mg = 52	36(69%)	NR	NR	NR	NR	NR	NR	NR	
	O20mg = 55	35(64%)	NR	NR	NR	NR	NR	NR	NR	
Chang and Chiang 1995	L 30mg = 57	53(93%)	56.4 ± 13.9	23.4 ± 3.2	Taiwanese	28(49%)	18(32%)	90% positive	NR	
	O 20mg = 54	50(96%)	59.3 ± 12.8	23.2 ± 3.0	Taiwanese	25(46%)	20(37%)	96% positive	NR	
Chang and Lee 1995	L 30mg = 42	38(91%)	57.3 ± 14.7	23.4 ± 3.1	Taiwanese	20(48%)	NR	91% positive	NR	
	O 20mg = 41	36 (88%)	61.0 ± 11.9	23.2 ± 3.0	Taiwanese	19(46%)	NR	95% positive	NR	
Misiewicz 1997	LAM =131	94 (72%)	47.6 y	NR	NR	NR	NR	positive	DU: 49% Gastritis 51%	
	OAM = 126	88 (70%)	48.0 y	NR	NR	NR	NR	positive	DU: 60% Gastritis: 40%	
Spinzi 1998	LAC = 186	120 (65%)	50.1y	NR	NR	NR	NR	positive	GU = 15; DU = 154 GDU = 1	
	OAC = 170	109 (64%)	49.3y	NR	NR	NR	NR	positive	GU = 21; DU = 123 GDU = 2	
Dobrilla	L 30mg = 167	108 (65%)	43.5	NR	NR	82(49%)	59(35%)	92.5%	NR	

Table X[C]: (PUD) L vs O - Baseline characteristics of patients in included studies										
Author , Year, Trial Name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Mean age ± SD in years**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Type of ulcer (n, %)**	**Other**
1999								positive		
	O 40mg = 84	57 (68%)	44.9	NR	NR	48(57%)	26(31%)	94.0% positive	NR	
Miwa 1999	LAC = 73	54 (74%)	50.6 $\pm$ 1.2 y	NR	NR	NR	NR	positive	GU: 41%) DU: 16% GDU: 23% NUD: 19%	
	O20AC = 76	59(78%)	48.4 $\pm$ 1.3 y	NR	NR	NR	NR	positive	GU: 29% DU: 32% GDU: 21% NUD: 18%	
	O40AC = 75	49(65%)	48.7 $\pm$ 1.4 y	NR	NR	NR	NR	Positive	GU: 33% DU: 25% GDU: 16% NUD: 25%	
Miwa and Okura 1999 RAC not reported in this table	LAC = 74	56(76%)	50.2 $\pm$ 1.2 y	NR	NR	NR	NR	Positive	GU: 41% DU: 38% GDU: 22%	84 with gastric ulcer, 87 with duodenal ulcer and 50 with gastro duodenal ulcer; 184 men and 37 women with mean age 50.8 years.
	OAC = 75	61(81%)	52.7 $\pm$ 1.4 y	NR	NR	NR	NR	positive	GU: 39% DU: 37% GDU: 24%	
Eralp 2000	LAC = 21	11(52%)	46 $\pm$ 12	NR	NR	NR	NR	Positive	Gastritis = 22 PUD = 20	
	OAC = 21	NR	NR	NR	NR	NR	NR	positive		
Fanti 2001	LCT = 25	15(86%)	Median age 48.4	NR	NR	13(52%)	15(60%)	100% positive	NR	
	OCT = 25	19(76%)	Median age 46.8	NR	NR	15(60%)	12(48%)	100% positive	NR	
Ungan M 2001	LAC = 30	A total of 145 patients (mean SD age, 37 $\pm$ 13 years; range, 18-64 years) were included in the study-79 (54.5%) men and 66 (45.5%) women. Thirty-four (23.4%) were smokers. Five patients (3.4%) consumed alcohol >5 days per week. The place of longest settlement for 124 patients (85.5%) was Ankara. No								
	OAC = 30									

Table X[C]: (PUD) L vs O - Baseline characteristics of patients in included studies										
Author , Year, Trial Name	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Mean age ± SD in years**	**BMI (kg/m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Type of ulcer (n, %)**	**Other**
		significant difference was observed between treatment groups in the distribution of studied variables (age, sex, smoking, alcohol consumption, place of longest settlement) *(*P > 0.05). Forty-nine patients (33.8%) had 2 1 relative with a history of peptic ulcer disease or dyspepsia.								
Inaba 2002 RAC not reported in this table	LAC = 60	47(78%)	52	NR	Japanese	11/60	NR	100% +	NR	
	OAC = 59	48(81%)	56	NR	Japanese	10/59	NR	100% +	NR	
Murakami 2008 RAC treatment arm is not reported in this table	LAM = 56	30(54%)	51.8 ± 5.2 y	NR	Japanese	NR	NR	positive	GU = 16 DU = 4 GDU= 19	
	OAM = 55	28(51%)	52.4± 8.1 y	NR	Japanese	NR	NR	positive	GU = 14; DU = 3 GDU= 20	
Abbreviations: L, Lansoprazole; O, Omeprazole; A, amoxicillin; C, clarithromycin; T, Tinidazole; M, metronidazole; GU, gastric ulcer; DU, duodenal ulcer; PUD, peptic ulcer disease; GDU, Gastro-duodenal ulcer; NUD, non-ulcer dyspepsia; SD: standard deviation; BMI: Body Mass Index; NR, not reported										

Table X[D]: (PUD) L vs O - Summary of Patient Disposition						
Author , Year, Trial Name	Treatment groups	Randomized and Treated	Completed	Discontinued	Reasons for WD	Additional Details Provided
Ekstrom 1994	L 30mg	143	NR	NR	NR	
	O 20 mg	136	NR	NR	NR	
Florent 1994	L 30mg	60	56	4	2 lost to follow-up; 2 patients withdrew as biopsy was diagnosed as malignancy	
	O 20mg	66	56	10	5 lost to follow-up; 2 patients refused to continue the study after first visit; 2 patients withdrew as biopsy was diagnosed as malignancy; 1 patient lost due to ulcer complication who died later	
Capurso 1995	L 30mg	52	51	1	NR	
	O 20mg	55	54	1	NR	

Table X[D]: (PUD) L vs O - Summary of Patient Disposition						
Author , Year, Trial Name	Treatment groups	Randomized and Treated	Completed	Discontinued	Reasons for WD	Additional Details Provided
Chang and Chiang 1995	L 30 mg	57	51	6	2 lost to follow-up; 1 never returned; 1 refused second endoscopy	
	O 20 mg	54	47	7	3 lost to follow-up; 2 never returned; 1 withdrew due to gout	
Chang and Lee 1995	L 30 mg	42	42	0	NR	
	O 20 mg	41	41	0	NR	
Misiewicz 1997	LAM	131	130	1	1 due to adverse event	
	OAM	126	122	4	All 4 due to adverse event	
Spinzi 1998	LAC	186	170 (91%)	16	Refusal of follow-up examination because they felt well (7 patients); inter current serious diseases (one for myocardial infarction and one for stroke) and protocol violations not thought to be related to the study medication (seven cases).	
	OAC	170	146 (86%)	24	Refusal of follow-up examination because they felt well (14 patients); side-effects (four patients; see below); and protocol violations not thought to be related to the study medication (six cases).	
Miwa 1999	L AC	73	NR	8 (3.6%)	NR	
	O20AC	76	NR		NR	
	O40AC	75	NR		NR	
Miwa and Okura 1999 RAC not reported in this table	L AC	74	NR	37 (25%) withdrew from the study	NR	
	OAC	75	NR		NR	
Eralp 2000	LAC	21	NR	NR	NR	
	OAC	21	NR	NR	NR	
Fanti 2001	LCT	25	24	1	Total AE: NR One patient with mild diarrhea	2 patients, one from each group, who failed to complete the follow-up, were excluded from analysis

Table X[D]: (PUD) L vs O - Summary of Patient Disposition						
Author , Year, Trial Name	Treatment groups	Randomized and Treated	Completed	Discontinued	Reasons for WD	Additional Details Provided
	OCT	25	24	1	Total AE: NR One patient with stomatitis	
Ungan M 2001	LAC	30	NR	NR	One patient developed nausea, vomiting, and hypotension (systolic blood pressure <90 mm Hg, diastolic blood pressure < 50 mm Hg) on the first day of treatment.	
	OAC	30	NR	NR	One patient experienced a skin rash within the first 24 hours of treatment, with eruptions and vesicles in all parts of the body, including the scalp. *Taste disturbance, diarrhea, and nausea were the most frequent side effects in all groups. There was no significant difference in the incidence of side effects between the 5 regimens* ***(P >*** *0.05).*	
Inaba T et al 2002 RAC not reported in this table	LAC	60	58	2	2 lost to follow up	All 60 completed treatment regimen
	OAC	59	58	1	1 lost to follow up	All 59 completed treatment regimen
Murakami 2008 RAC not reported in this table	LAM	56	55	1	No visit	
	OAM	55	53	2	No visits in both patients	
Abbreviations: PUD, Peptic Ulcer Disease; L, Lansoprazole; O, Omeprazole; A, amoxicillin; C, clarithromycin; T, Tinidazole; M, metronidazole; WD, withdrawal; AE, adverse event; NR, not reported						

Table X[E]: (PUD) L vs O - Efficacy Outcomes						
Author, Year	**Treatment groups**	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**	**Other Outcomes**
Ekstrom 1994		Healing rate (ITT) @ 2 weeks	Healing rate (ITT) @ 4 weeks			
	L 30mg = 143	119/138 (86.2%)	136/140 (97.1%)			
	O 20mg = 136	110/134 (82.1%)	128/133 (96.2%)			
Florent 1994		Healing rate of GU(ITT) @ 4 weeks	Healing rate of GU (ITT) @ 8 weeks	After completion of treatment daytime ulcer pain relief (ITT)	After completion of treatment nocturnal pain relief (ITT)	Other
	L 30mg = 60	49/60 (82%)	56/60 (93%)	52/60 (86%)	60/60 (100%)	Delay for daytime pain relief was 6.6 days (p = 0.066); Delay for night time pain relief was NR
	O 20mg = 66	45/66 (68%)	54/66 (82%)	40/66 (60%)	46/66 (70%)	Delay for daytime pain relief was 11.0 days; Delay for night time pain relief was NR
Capurso 1995		Healing rate @ 14 days	Healing rate @ 28 days	Healing rate @ 42 days		
	L 30mg = 52	29/50 (58.0%)	47/50 (94.0%)	47/50 (94.0%)		
	O 20mg = 55	30/53 (56.6%)	50/53 (94.3%)	50/53 (94.3%)		
Chang and Chiang 1995		Healing rate (ITT) @ 4 weeks	*H. pylori* clearance (ITT) @ 4 weeks			
	L 30mg = 57	51/57 (89.5%)	36/49 (73.5%)			
	O 20mg = 54	45/54 (83.3%)	40/50 (80.0%)			
Chang and Lee 1995		Healing rate @ 4 weeks	*H. pylori* clearance @ 4 weeks			
	L 30mg = 42	40/42 (95.2%)	30/38 (78.9%)			
	O 20mg = 41	38/41 (92.7%)	32/39 (82.1%)			

Table X[E]: (PUD) L vs O - Efficacy Outcomes						
Author, Year	**Treatment groups**	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**	**Other Outcomes**
Misiewicz 1997		*H. pylori* eradication @ 4 weeks	*H. pylori* eradication Metronidazole sensitive @ 4 weeks	*H. pylori* eradication Metronidazole resistant @ 4 weeks	Other	
	LAM = 131	87/131 (66.4%)	60/68 (88.2%)	19/41 (46.3%)	Patient's sex, age, smoking status, alcohol consumption, diagnosis (duodenal ulcer *v* gastritis), treatment with H2 receptor antagonists in the month before study entry, or the duration of the patient's disease had no significant effect (p > 0.05) on the eradication of *H. pylori*.	
	OAM = 126	94/126 (74.6%)	62/66 (93.9%)	20/32(62.5%)		
Spinzi 1998		*H. pylori* eradication overall (ITT) @ 4 weeks	Ulcer healing overall (ITT) @ 4 weeks		Other	
	L AC = 186	134/186 (72%)	166/186 (89%)		The interval elapsed from start of therapy to second endoscopy was 45.7 (range 38–90) days for the LAC group and 45.1 (range 38–70) days for the OAC group (*P* = 0.80).	
	OAC = 170	105/170 (62%)	139/170 (82%) P =0.050			
Dobrilla 1999		Healing rate (ITT) @ 4 weeks				
	L 30mg = 167	154/164 (93.9%)	Before treatment, epigastric pain was present in 96.4% of both Lansoprazole and Omeprazole-treated patients. As assessed on a 4-point scale by patients, grade 2 (moderate) pain predominated in both groups; at the end of the acute phase, a combination of moderate and severe symptoms was present in 1.2% of patients receiving Lansoprazole and 2.5% of patients receiving Omeprazole. After 4 weeks of therapy, epigastric pain was present in 12.1% and 12.6% of L30- and 040-treated patients, respectively. There were no significant differences in pain between treatment groups at any time, but pain was significantly ameliorated within groups from baseline to the end of the acute phase (P < 0.05).			
	O 40mg = 84	77/79 (97.5%)				
Miwa 1999		*H. pylori* eradication overall (ITT) @ 4 weeks	Other			
	LAC = 73	60/73 (82.2%)	There were 12 patients in the borderline group, that is, whose Δ 13C value of the breath test at 1 month was between five and 10‰ (6.6 ± 0.3; mean ± SEM, range 5.1–9.1‰). Among the			
	O20AC = 76	57/76 (75%)				

Table X[E]: (PUD) L vs O - Efficacy Outcomes						
Author, Year	**Treatment groups**	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**	**Other Outcomes**
	O40AC = 75	60/75 (80%)	seven of those 12 patients who underwent a second breath test, four were judged to be cured, as their Δ 13C value for the second breath test was lower than 5‰; the remaining three were treated as failed-to-be cured, as the Δ 13C value of the second test was greater than 5‰.The five patients who did not take the second breath test were regarded as treatment failure patients.			
Miwa and Okura 1999 RAC treatment not reported in this table		*H. pylori* eradication overall (ITT) @ 4 weeks	Other			
	LAC = 74	62/74 (83.8%)	There were 17 patients in the borderline group as the Δ 13C value of the breath test at one month was between 5 and 10% (6.9 ± 0.4; mean ± SEM; range 5.1–9.7%). 16 of these, seventeen patients underwent a second breath test, of which seven were judged to be cured and nine were not. The remaining patients were regarded as treatment-failure patients since they did not take the second breath test.			
	OAC = 75	64/75 (85.3%)				
Eralp 2000		*H. pylori* eradication overall (ITT) @ 6 weeks end of treatment	Decrease in gastric activity from baseline		Other	
	LAC = 21	14/21 (67%)	In 14 patients with treatment success B = 2.7 ± 1.4; End of Rx = 0.7 ± 0.9 In 7 patients without treatment success B = NR; End of Rx = Reported as no change in activity		Reactive lymphoid hyperplasia showed a significant decrease in patients with *H. pylori* eradication (p<0.05).	
	OAC = 21	16/21 (76%)	In 16 patients with treatment success B = 3.4 ± 0.8; End of Rx = 0.9 ± 1.3 In 5 patients without treatment success B = 3.4 ± 0.8; End of Rx = 1.8 ± 1.6			
Fanti 2001		*H. pylori* eradication overall (ITT) @ 8 weeks	Healing of Ulcer in those with active ulcer at baseline @ 8 weeks	Follow up at 1 year	Other	
	LCT = 25	23/24	21/21 (100%)	**6** months later all patients (44 *H. pylori*	1 patient lost in each group and was not accounted for in the analysis.	
	OCT = 25	21/24	22/22 (100%)			

Table X[E]: (PUD) L vs O - Efficacy Outcomes						
Author, Year	**Treatment groups**	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**	**Other Outcomes**
				negative and 4 *H. pylori* positive) felt well and were asymptomatic. At month 12 all patients were symptom free. No recurrence of DU was observed in the 42 patients submitted to endoscopy and in 2 were assessed by urea breath test.	*H. pylori* eradication**,** defined as negative bacterial findings in both culture and histology, at least 4 weeks after cessation of treatment**,** was confirmed in 43/48 patients. In the remaining patient of group 1, who refused repeat endoscopy, eradication was confirmed by urea breath test.	
Ungan 2001		*H. pylori* eradication overall (ITT) @ 6 weeks	*H. pylori* eradication overall (ITT) @ 6 months	Other		
	LAC = 30	27/30 (90%)	26/30 (86.7%)	At 6 months, 9 more patients tested positive for *H. pylori* compared with the sixth week. These 9 patients were *H. pylori*-negative in the 6 week assessment and were therefore considered reinfection or recurrence cases. Patients belonged to which of the 5 treatment groups is not reported.		
	OAC = 30	28/30 (93.3%)	25/30 (83.3%)			
Inaba 2002 RAC treatment arm is not reported in this table		*H. pylori* eradication overall (ITT) @ 1 week	*H. pylori* eradication Homozygous extensive metabolizers(PPI)	*H. pylori* eradication Heterozygous extensive metabolizers (PPI)	*H. pylori* eradication Poor metabolizers	Other
	LAC = 60	52/60 (86.7%)	18/20 (90%	26/29 (89.7%)	8/9 (88.9%)	
	OAC = 59	49/59 (83.1%)	16/21 (76.2%)	24/27 (88.9%)	9/10 (90%)	

Table X[E]: (PUD) L vs O - Efficacy Outcomes						
Author, Year	**Treatment groups**	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**	**Other Outcomes**
Murakami K 2008 RAC treatment arm is not reported in this table			*H. pylori* eradication overall (ITT) @ 4 weeks	*H. pylori* eradication overall in CAM sensitive and resistant (ITT) @ 4 weeks	*H. pylori* eradication overall in MTZ Sensitive and MTZ resistant (ITT) @ 4 weeks	
	LAM = 56		51/56 (91.1%)	CAM S =11/13 (84.6%) CAM R = 37/40 (92.5%)	MTZ S = 47/49 (96.1%) MTZ R = 2/4 MTZ unknown = 2/2	
	OAM = 55		50/55 (90.9%)	CAM S =10/11 (90.9%) CAM R =40/42 (95.2%)	MTZ S = 48/50 (96%) MTZ R = 2/3 MTZ unknown = 0	
Abbreviations: PUD, Peptic Ulcer Disease; L, Lansoprazole; O, Omeprazole; A, amoxicillin; C, clarithromycin; T, Tinidazole; M, metronidazole; WD, withdrawal; AE, adverse event; NR, not reported; ITT, intention-to-treat analysis						

Table X[F]: (PUD) L vs O - Harm Outcomes					
Author, Year	Treatment groups	Mortality & Reasons (n/N)	SAES & Reasons Most Common SAEs	WDAE and reasons	Subjects with >O AE, N (%)Most common AEs (n/N)
Ekstrom 1994	L 30mg = 143	NR	NR	NR	AE: 23/143 (16.9%) Specific AE were NR
	O 20mg = 136	NR	NR	NR	AE: 34/136 (23.8%) Specific AE were NR
Florent 1994	L 30mg = 60	None	NR	0	Minor AE: 8 (Diarrhoea: 2; Asthenia: 1; Hot flushes (severe): 1; Renal colic (severe) 1: Paraesthesia moderate: 1; Others 2
	O 20mg = 66	Dramatic ulcer haemorrhage on day 5 in 1 patient and required gastrectomy. This	NR	0	Minor AE: 15 (Diarrhoea: 3; Asthenia: 1; Headache: 3; Dyspepsia: 2; Constipation: 1; Dry mouth severe: 1;

Table X[F]: (PUD) L vs O - Harm Outcomes					
Author, Year	Treatment groups	Mortality & Reasons (n/N)	SAES & Reasons Most Common SAEs	WDAE and reasons	Subjects with >O AE, N (%)Most common AEs (n/N)
		patient had undiagnosed hepatic cirrhosis and died 2 days later of hepatic and renal failure.			Others 3.
Capurso 1995	L 30mg = 52	0/52	0/52	0/52	Headache: 1; confusion: 1
	O 20mg = 55	0/55	0/55	0/55	Fecal mucus: 1; abdominal pain: 1; salivation: 1
Chang and Chiang 1995	L 30mg = 57	0/57	0/57	0/57	Reversible skin rash: 2
	O 20mg = 54	0/54	0/54	0/54	Reversible skin rash: 1; constipation: 2
Chang and Lee 1995	L 30mg = 42	0/42	0/42	0/42	NR
	O 20mg = 41	0/41	0/41	0/41	NR
Misiewicz 1997	LAM = 131	NR	5 SAEs 4 (pancreatic carcinoma, abnormal ECG, oesophageal carcinoma, and arteriosclerotic heart disease). One patient developed pseudo - membranous colitis successfully treated with vancomycin	1	75/132 (56.8%) Diarrhoea 12; Headache 10; Taste disturbance 7
	OAM = 126	NR		4	71/129 (55%) Diarrhoea 7; Headache 6; Taste disturbance 6
Spinzi 1998	LAC = 186	NR	2 (1 MI and 1 stroke)	16 Withdrew (refusal for FU examination; inter current serious disease (1 MI and 1 stroke) and	2 patients with diarrhea and stomatitis

Table X[F]: (PUD) L vs O - Harm Outcomes					
Author, Year	Treatment groups	Mortality & Reasons (n/N)	SAES & Reasons Most Common SAEs	WDAE and reasons	Subjects with >O AE, N (%)Most common AEs (n/N)
				protocol violations	
	OAC = 170	NR	NR	24 withdrew (14 refusal for FU examination; 4 due to side effects and 6 due to protocol violations	6 patients (4 nausea , diarrhea and abdominal discomfort causing WDAE; 1 mild diarrhea and one stomatitis)
Dobrilla 1999	L 30mg= 167	0/167	0/167	0/167	NR
	O 40mg = 84	0/84	0/84	0/84	NR
Miwa 1999	L 30mg = 73	NR	NR	NR	36/214 patients (16.1%), were not interviewed for adverse effects. Adverse effects were reported by 26.1% (49/188) of the interviewed patients. AE overall reported by 28/184 (15.2%) of interviewed patients. Over all AE: could not be calculated as denominator for each treatment group providing AE was not reported. Diarrhoea or soft stools (13.8%) and glossitis or taste disturbance (5.9%) were common adverse effects. Other such effects included skin rash or itching, dyspeptic symptoms, nausea and uncomfortable feeling in the chest. Adverse effects were observed equally among the three groups. There were no patients in whom adverse effects affected compliance.
	O 20mg = 76	NR	NR	NR	
	O 40mg = 75	NR	NR	NR	

Table X[F]: (PUD) L vs O - Harm Outcomes					
Author, Year	Treatment groups	Mortality & Reasons (n/N)	SAES & Reasons Most Common SAEs	WDAE and reasons	Subjects with >O AE, N (%)Most common AEs (n/N)
Miwa H and Okura 1999 RAC treatment arm is not reported in this table	LAC = 74	NR	NR	NR	AE overall reported by 28/184 (15.2%) of interviewed patients. Over all AE: in OAC 19/75 (25.3%), LAC 22/74 (29.7%) and RAC 24/72 (33.3%) respectively Most common AE: diarrhoea or soft stools (4.6%, 1.7% and 13.1% respectively); glossitis or taste disturbance (3.1%, 5.1% and 3.3% respectively); and skin rash (3.12%, 5.1% and 1.7% respectively); others (3.1%, 0% and 1.7% respectively. In 37/221 (16.7%) patients AE interview was not carried out as these patients withdrew from the study or visited other physicians who did not join this study.
	OAC = 75	NR	NR	NR	
Eralp 2000	LAC = 21	NR	NR	Both combination used did not cause major side-effects. All patients were able to complete treatment.	Reported side effects included slight abdominal pain, headache and metallic taste and occurred in 26.2% and 23% of the first and second groups respectively (p>0.05). Details for each group are not provided
	OAC = 21	NR	NR		
Fanti 2001	LCT = 25	NR	NR	NR	NR
	OCT = 25	NR	NR	NR	NR
Ungan M 2001	L AC = 30	NR	NR	NR	NR
	OAC = 30	NR	NR	NR	NR
Inaba T et al 2002 RAC treatment	LAC = 60	NR	NR	0	16/60 Diarrhoea and soft stools = 13; Glossitis and Pharyngitis = 2; Constipation = 1

Table X[F]: (PUD) L vs O - Harm Outcomes					
Author, Year	Treatment groups	Mortality & Reasons (n/N)	SAES & Reasons Most Common SAEs	WDAE and reasons	Subjects with >O AE, N (%)Most common AEs (n/N)
arm is not reported in this table	OAC = 59	NR	NR	0	20/59 Diarrhoea and soft stools = 16; Glossitis and Pharyngitis = 3; Constipation = 1
Murakami 2008 RAC treatment arm is not reported in this table	LAM = 56	NR	NR	NR	2 cases of diarrhoea
	OAM = 55	NR	NR	NR	2 cases of diarrhoea and 1 case of hives
Abbreviations: PUD, Peptic Ulcer Disease; L, Lansoprazole; O, Omeprazole; A, amoxicillin; C, clarithromycin; T, Tinidazole; M, metronidazole; WD, withdrawal; AE, adverse event; SAE, serious adverse event; NR, not reported; MI, myocardial infarction					

XI. Comparison 11: Lansoprazole vs. Pantoprazole (No RCT identified)

XII. Comparison 12: Lansoprazole vs. Rabeprazole (7 RCTs)

Table XII[A]: (PUD) L vs R - Description of trials meeting the inclusion criteria

Author, Year, Trial Name	Study Design location	Randomised sample size (N)	Patient Type	Intervention/ Comparator mg/day	Duration weeks	Outcome(s)
Miwa 1999	Open label RCT single centre Japan	LAC = 74 RAC = 72 OAC = 75	221 *H. pylori* positive patients with peptic ulcer disease	L30 mg BD, A500mg TDS, C200mg BD R20mg BD, A500mg TDS, C200mg BD O20 mg BD, A500mg TDS, C200mg BD	7 days	The primary end point was eradication of *H. pylori* as determined by the 13 C urea breath test 4 to 6 weeks after completion of treatment.
Miwa 2000	Open label RCT single centre Japan	LAC = 104 R1AC = 104 R2AC = 100	308 *H. pylori* positive patients with peptic ulcer disease and non-ulcer dyspepsia (NUD)	L 30 mg BD, A500mg TDS, C200mg BD R1 = R20mg BD, A500mg TDS, C200mg BD R2 = R10mg BD, A500mg TDS, C200mg BD	7 days	The primary end point was eradication of *H. pylori* as determined by the 13C urea breath test 4 weeks after completion of treatment.
Inaba 2002	Open label RCT Japan	LAC = 60 RAC = 64 OAC = 59	183 Patients with peptic ulcer, and who were *H. pylori* positive	L30mg BD, A500mg TDS, C200mg TDS R 10 mg BD, A500mg TDS, C200mg TDS O 20mg BD, A500mg TDS, C200mg TDS	7 days	The primary end points were eradication of *H. pylori* at 1 week and adverse events. [CYP2C19 genetic polymorphism cure rates]
Murakami and Sato 2002 R3 = R 20mg BD, A 750 mg BD and C 200mg BD (wrong comparator) so not reported in this table	Open label RCT Japan	LAC: 148 R1AC: 49 R2AC = 48 R3AC =50	295 patients with gastritis or gastric ulcer, or duodenal ulcer diagnosed by endoscopy who are *H. pylori* positive.	L 30mg BD, A 750 mg BD and C 200mg BD R1 =R 10mg BD, A 750 mg BD and C 200mg BD R2 = R 20mg BD, A 750 mg BD and C 200mg BD 1/2 dose of H_2RA until eradication was assessed	7 days	Primary outcome: Eradication of *H. pylori* was considered to be successful if culture, microscopic examination and urea breath tests all showed negative results.

Kawabata 2003	Open label RCT Japan	LAC = 87 RAC = 100	I87 patients with peptic ulcer and proven *H. pylori* infection	L 30 mg BD, A750mg BD, C 400mg BD R10 mg BD, A750mg BD, C 400mg BD	7 days	The primary end point was eradication of *H. pylori* at 6 weeks Adverse effects [CYP2C19 genotype and the pre-treatment susceptibility of *H. pylori* to antibiotics]
Murakami 2008	Open label RCT Japan	LAM = 56 RAM = 58 OAM= 55	169 patients with PUD or gastritis who had initial treatment failure with a PPI plus A and C and who are *H. pylori* positive	L30 mg BD, A 750mg BD and M 250mg BD R 10 mg BD, A 750mg BD and M 250mg BD O 30mg BD, A 750mg BD and M 250mg BD After treatment, half doses of H2-receptor antagonists were administered until assessment of eradication.	7 days	Primary outcome: *H. pylori* eradication at 4 weeks after completion of treatment. Treatment was considered successful if the results of the rapid urease test, culture, histologic examination, and the urea breath test (UBT) were all negative
Liu 2013	Open label RCT Taiwan	LAC =228 RAC= 222	426 peptic ulcer or gastritis patients who were *H. pylori*-positive	L 30 mg BD, A 1 g BD and C 500 mg BD R 20 mg BD, A 1 g BD and C 500 mg BD	1 week	Primary outcome: *H. pylori* eradication at 12 to 16 weeks after completion of treatment.
Abbreviations: PUD, peptic ulcer disease; BD, Twice daily; TDS, three times daily; DB, Double blind; RCT, Randomized Clinical Trial; A: amoxicillin; C: clarithromycin; R: Rabeprazole ; O: Omeprazole; L, Lansoprazole; M, metronidazole;						

Table XII[B]: (PUD) L vs R - Patient Inclusion and Exclusion Criteria from Included Studies

Author, Year	Inclusion Criteria	Exclusion Criteria	Concomitant medication
Miwa 1999	*H. pylori* positive patients with peptic ulcer disease diagnosed by at least 2 positive results of the following examinations: rapid-urea breath test; by histology (haematoxylin–eosin and Giemsa stain), serology (serum IgG antibody) or 13C-urea breath test or culture.	Patients receiving previous curative therapy; having past history of drug allergy to PPI, amoxicillin or clarithromycin; or being suspected of being pregnant; and having a severe complication such as malignancy or hepatic or renal failure were excluded.	Not reported.
Miwa 2000	*H. pylori* positive patients with peptic ulcer disease and non-ulcer dyspepsia were included. *H. pylori* infection	Not reported	Not reported.

Table XII[B]: (PUD) L vs R - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
	status was diagnosed by at least 2 positive results out of 5 tests for infection: by rapid-urea breath test; by histology (haematoxylin–eosin and Giemsa stain), serology (serum IgG antibody) or 13C-urea breath test or culture.		
Inaba 2002	Patients endoscopically diagnosed with peptic ulcer, and who were *H. pylori* positive on histological examination (Giemsa stain in addition to hematoxylin and eosin stain), and a rapid urease test (Helicocheck, Otsuka Pharmaceutical Co. Ltd, Tokyo, Japan) were included. Antibiotic sensitivity testing was performed.	Patients were excluded if they had previously undergone treatment for eradication of *H. pylori* or gastrectomy; were pregnant; had an allergy to penicillin; had used a PPI, H 2 receptor antagonist, adrenocortical steroids, or non-steroidal anti-inflammatory drugs within the month preceding the study; or were taking anticoagulants.	Not reported.
Murakami and Sato 2002	Patients with gastric ulcer, duodenal ulcer or gastritis diagnosed by endoscopy who were *H. pylori* positive. If patients were receiving a proton pump inhibitor as anti-ulcer treatment, it was changed to an H2-receptor antagonist (H_2RA), and the presence or absence of *H. pylori* was verified by rapid urease test after at least 1 month.	Patients who had previously received eradication treatment for *H. pylori*, those with drug allergies and those with serious complications, such as malignant tumours, cardiac disease, renal disease and hepatic disease, were excluded.	Not reported.
Kawabata H 2003	Patients with peptic ulcer and proven *H. pylori* infection. The CYP2C19 genotype (homozygous extensive metabolizer, heterozygous extensive metabolizer or poor metabolizer) was determined and antibiotic sensitivity testing was performed. Patients with active ulcer on initial endoscopy were treated with a proton pump inhibitor (Rabeprazole 10 mg OD, or Lansoprazole 30 mg OD) for a further 4 weeks after eradication therapy, but those with a peptic ulcer scar were not allowed any other ulcer healing drugs during the study.	Patients were excluded if they were an age of less than 20 years or greater than 80 years, concomitant severe disease, pregnancy or lactation, treatment with steroids or non-steroidal anti-inflammatory drugs, treatment with a proton pump inhibitor or antibiotics within 4 weeks of entry and previous gastric surgery.	Not reported.

Table XII[B]: (PUD) L vs R - Patient Inclusion and Exclusion Criteria from Included Studies			
Author, Year	**Inclusion Criteria**	**Exclusion Criteria**	**Concomitant medication**
Murakami 2008	Patients diagnosed with gastric ulcers, duodenal ulcers, and gastritis on endoscopic examination. Rapid urease test was used to identify *H. pylori* in biopsy specimens taken from the greater curvature of the gastric antrum and body, and this was judged to indicate patients for whom triple therapy for 1 week with a PPI plus amoxicillin and clarithromycin had resulted in failed eradication interval of more than 6 months.	Not specified.	After treatment, half doses of H2-receptor antagonists were administered until assessment of eradication.
Liu 2013	In patients with a complaint of epigastric discomfort EGD was performed and those diagnosed of non-ulcer dyspepsia (gastritis) or peptic ulcer with *H. pylori* infection were enrolled in this study.	EGD was performed and those diagnosed of non-ulcer dyspepsia (gastritis) or peptic ulcer with *H. pylori* infection were enrolled in this study.	Not reported.
Abbreviations: PUD, peptic ulcer disease; L, Lansoprazole; R, Rabeprazole; OD, once daily; EGD, esophagogastroduodenoscopy			

Table XII[C]: (PUD) L vs R - Baseline characteristics of patients in included studies									
Author, Year	**Treatment (Drug and mg/day)**	**Sex (Male %)**	**Mean age ± SD in years**	**BMI (kg/ m^2)**	**Race (n, %)**	**Smoking (n, %)**	**Alcohol (n, %)**	***H. pylori* positive (n, %)**	**Type of ulcer (n, %)**
Miwa 1999 OAC treatment arm is not reported in this table	LAC = 74	56 (76%)	50.2 $\pm$ 1.2 y	NR	NR	NR	NR	100% +	GU: 30 (41%); DU: 28 (38%); GDU: 16 (22%)
	RAC = 72	67 (93%)	49.3 $\pm$ 1.4 y	NR	NR	NR	NR	100% +	GU: 25 (35%); DU: 31 (43%); GDU: 16 (22%)
Miwa H 2000	LAC = 104	78 (75%)	49.8 $\pm$ 1.1y	NR	NR	46(50%)	29(31%)**	100% +	GU = 19 active & 19 scar stage DU = 16 active & 25 scar stage; GDU = 9 active & 9 scar stage; NUD = 7
	R10AC = 104	90 (87%)	48.2 $\pm$ 1.1y	NR	NR	49(49%)	48/ 104	100% +	GU = 17 active & 16 scar stage DU = 20 active & 19 scar stage; GDU = 14 active & 15 scar stage; NUD = 13
	R20AC = 100	68 (68%)	50.5 $\pm$ 1.2y	NR	NR	26(28%)	96/100	100% +	GU = 22 active & 17 scar stage DU = 12 active & 22 scar stage; GDU = 5 active & 4 scar

									stage; NUD = 18
Inaba 2002 OAC treatment arm is not reported in this table	LAC = 60	47(78%)	52	NR	Japanese	11/60	NR	100% +	NR
	RAC = 64	47(73%)	55	NR	Japanese	10/64	NR	100% +	NR
Murakami and Sato 2002 R3AC treatment arm is not reported in this table	LAC = 148	85(57%)	Mean + SE 51.3±4.3y	NR	NR	NR	NR	100% +	GU =56; DU=38 and Gastritis=34
	R10AC = 49	28(60%)	Mean + SE 49.5±9.2 y	NR	NR	NR	NR	100% +	GU =16; DU=22 and Gastritis=11
	R20AC = 48	29(60%)	Mean + SE 51.2±8.9 y	NR	NR	NR	NR	100% +	GU =18; DU=19and Gastritis=11
Kawabata 2003	LAC = 87	63(72%)	53.1 y	NR	Japanese	56/87	NR	100% +	GU= 48; DU =35; GDU = 4; Active ulcer 77 Ulcer history= 57
	RAC = 100	75(75)	50.8 y	NR	Japanese	55/100	NR	100% +	GU =55; DU=36; GDU=9; Active ulcer = 89; and Ulcer history: 71
Murakami 2008 OAC treatment arm is not reported in this table	LAM = 56	30(54)	51.8 ± 5.2 y	NR	Japanese	NR	NR	100% +	GU = 16; DU= 4 and GDU= 19
	RAM = 58	31(54)	50.8 ± 6.2 y	NR	Japanese	NR	NR	100% +	GU = 16; DU= 5 and GDU= 18
Liu 2013	LAC = 228	83(36%)	NR 54% were < 54y and 46% were > 54y	NR	NR	33(14.5)	19 (8.3)	100% +	Gastritis = 89; GU and DU= 139
	RAC = 222	94 (42%)	NR < 54y (53.2) > 54y (46.8)	NR	NR	32(14.8)	13 (6)	100% +	Gastritis = 77; GU and DU= 145

** Ex-smokers were considered non-smokers and social drinkers were considered as non-drinkers. Interview for daily habits was not done for several patients.

Abbreviations: A: amoxicillin; C: clarithromycin; R: Rabeprazole ; L, Lansoprazole; M, metronidazole; GU, gastric ulcer; DU, duodenal ulcer; PUD, peptic ulcer disease; GDU, Gastro-duodenal ulcer; NUD, non-ulcer dyspepsia; NR, not reported; SE, Standard error

Table XII[D]: (PUD) L vs R - Summary of Patient Disposition						
Author, Year	**Treatment groups**	**Randomized and Treated**	**Completed**	**Discontinued**	**Reasons for WD**	**Additional Details Provided**
Miwa 1999	LAC	74	NR	37/221 (16.7%)	NR	213 patients were included in ITT analysis. 5 patients were excluded from PP analysis as compliance was less than 80%.
	RAC	72	NR		NR	
Miwa 2000	LAC	104	99	5	Because they neither visited the hospital again nor took the breath test after the treatment.	
	R40AC	104	101	3		
	R20AC	100	97	3		
Inaba 2002 OAC treatment arm is not reported in this table	LAC	59	58	1	1 lost to follow up	All 59 completed treatment regimen
	RAC	64	63	1	1 due to AE	63 completed treatment regimen
Murakami and Sato 2002	LAC	148	144	4	3 due to AE urticaria (1), diarrhoea (2) and no revisits (1)	
	RAC	147	97	2	1 no revisit and 1 diarrhea	
Kawabata 2003	LAC	87	NR	NR	NR	
	RAC	100	NR	NR	NR	
Murakami 2008 OAC treatment arm is not reported in this table	LAM	56	55	1	No visit	
	RAM	58	58	0	Not applicable	
Liu 2013	LAC	226	212	14	NR	
	RAC	222	212	10	NR	
Abbreviations: PUD, peptic ulcer disease; A: amoxicillin; C: clarithromycin; R: Rabeprazole ; L, Lansoprazole; M, metronidazole; WD, withdrawal; AE, adverse event; ITT, intention-to-treat; NR, not reported						

Table XII[E]: (PUD) L vs R - Efficacy Outcomes						
Author, Year	Treatment groups	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Other Outcomes
Miwa 1999		*H. pylori* eradication overall (ITT) @ 4 weeks		Other		
	LAC = 74	63/74 (83.8%)		There were 17 patients in the borderline group as the Δ 13C value of the breath test at one month was between 5 and 10% (6.9 ± 0.4; mean ± SEM; range 5.1–9.7%). 16 of these, seventeen patients underwent a second breath test, of which seven were judged to be cured and nine were not. The remaining patients were regarded as treatment-failure patients since they did not take the second breath test.		
	RAC = 72	63(87.5%) N = 72				
Miwa 2000		*H. pylori* eradication @ 4 weeks	Border line case	Other		
	LAC = 104	86/104	5	11 patients in the borderline group (LAC regimen, 5; RAC regimen, 1; R1/2AC regimen, 1), as the Δ 13C value of the breath test at one month was between 5 and 10‰ (6.6 ± 0.4; mean ± SEM; range 5.5–9.3%). Of these, seven patients underwent a second breath test, of which five were judged to be cured and two were not. Another four patients were regarded as treatment-failure patients since they did not take the second breath test. Thus, five borderline patients were treated as treatment successes and the remaining six patients as treatment failures.		
	R40AC = 104	89/104	1			
	R20AC = 100	87/100	1			
Inaba 2002 OAC treatment arm is not reported in this table		*H. pylori* eradication overall (ITT) @ 1 week	*H. pylori* eradication Homozygous extensive metabolizers (PPI)	*H. pylori* eradication Heterozygous extensive metabolizers (PPI)	*H. pylori* eradication Poor metabolizers	Other
	LAC =60	52/60 (86.7%)	18/20 (90%	26/29 (89.7%)	8/9 (88.9%)	The overall cure rate was not significantly different among the three regimens but the impact of *CYP2C19* genetic polymorphism on the cure rate did not seem equal.
	RAC = 64	49/64 (76.6%)	15/24 (62.5%)	27/31 (87.1%)	7/8 (87.5%)	

Table XII[E]: (PUD) L vs R - Efficacy Outcomes						
Author, Year	Treatment groups	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Other Outcomes
Murakami and Sato 2002		*H. pylori* eradication overall (ITT) @ 4 weeks	*H. pylori* eradication C sensitive (ITT) @ 4 weeks	*H. pylori* eradication C resistant (ITT) @ 4 weeks	*H. pylori* eradication Unknown resistance	Other
	LAC = 148	116/148 (78%)	108/121 (89%)	0/13(0%)	8/10 (80%)	
	R1AC+R2AC= 97	85/97 (87.6%)	77/97 (79.4%)	1/8 (12.5%)	7/7 (100%)	
Kawabata 2003		*H. pylori* eradication overall (ITT)	*H. pylori* eradication C sensitive (ITT) Based on metabolizer type	*H. pylori* eradication C resistant (ITT) Based on metabolizer type	*H. pylori* eradication Unknown resistance	Other
	LAC = 87	60/87	Homozygous: 23/31 Heterozygous: 24/29 Poor: 10/10	Homozygous: 1/2 Heterozygous: 2/6 Poor: 0/2	NR	
	RAC = 100	75/100	Homozygous: 25/29 Heterozygous: 42/46 Poor: 6/7	Homozygous: 1/1 Heterozygous: 1/7 Poor: 0/3	NR	
Murakami 2008 OAC treatment arm is not reported in this table		*H. pylori* eradication overall (ITT) @ 4 weeks	*H. pylori* eradication overall in CAM sensitive and resistant (ITT) @ 4 weeks	*H. pylori* eradication overall in MTZ-S and MTZ-R (ITT) @ 4 weeks		
	LAM = 56	51/56 (91.1%)	CAM-S =11/13 (84.6%) CAM-R = 37/40 (92.5%)	MTZ-S = 47/49 (96.1%) MTZ-R = 2/4 MTZ unknown = 2/2		
	RAM = 58	50/55 (90.9%)	CAM-S=10/11 (90.9%) CAM-R =40/42 (95.2%)	MTZ-S = 48/50 (96%) MTZ-R = 2/3 MTZ unknown = 0		
Liu 2013		*H. pylori* eradication overall (ITT) @ 16 weeks				Univariate analysis of clinical factors on *H. pylori* eradication rates
	LAM =228	196/228 (86.0%)				Smokers vs non-smokers 65 (84.65) vs. 380 (87.1%)

Table XII[E]: (PUD) L vs R - Efficacy Outcomes						
Author, Year	Treatment groups	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Other Outcomes
	RAM = 222	195/222 (87.8%)				p =0.58 Alcohol consumption vs no consumption 32(84.3%) vs 413 (86.9%) p = 0.34 NSAID use vs non-use 73(76.7%) vs 373 (88.7%)
Abbreviations: PUD, peptic ulcer disease; A: amoxicillin; C: clarithromycin; R: Rabeprazole ; L, Lansoprazole; M, metronidazole; SEM: standard error of mean; ITT, intention-to-treat; NR, not reported; CAM-R indicates clarithromycin-resistant strains; CAM-S, clarithromycin-sensitive strains; MTZ-S, metronidazole-sensitive strains; MTZ-R, metronidazole-resistant strains; NSAID, Non-steroidal anti-inflammatory drug						

Table XII[F]: (PUD) L vs R - Harm Outcomes					
Author, Year	**Treatment groups**	**Mortality & Reasons (n/N)**	**SAES & reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N (%) Most common AEs (n/N)**
Miwa 1999	LAC = 74	NR	NR	NR	
	RAC = 72	NR	NR	NR	
Miwa 2000	LAC = 104	NR	NR	NR	38/104 (36.5%) Most common AEs were: Diarrhoea and soft stools: 3 (3.9%); glossitis or taste disturbance 4(5.3%); and skin rash 3(3.9%); others 0(0%). Compliance to treatment was affected in 2 patients. 1 due to skin rash; 1 due to diarrhoea.
	R1AC= 104	NR	NR	NR	40/104 (38.5%) Most common AEs were: Diarrhoea and soft stools: 14 (16.3%)*; glossitis or taste disturbance 3(3.5%); and skin rash 4(4.7%); others 1(1.2%). *P < 0.05 compared to other groups Compliance to treatment was affected in 2 patients due to diarrhoea and skin rash in both.
	R2AC= 100	NR	NR	No patients withdrew	38/100 (38%) Most common AEs were: Diarrhoea and soft stools:

Table XII[F]: (PUD) L vs R - Harm Outcomes					
Author, Year	**Treatment groups**	**Mortality & Reasons (n/N)**	**SAES & reasons Most Common SAEs**	**WDAE and reasons**	**Subjects with >O AE, N (%) Most common AEs (n/N)**
					4 (5.3%); glossitis or taste disturbance 8(10.7%); and skin rash 5(6.7%); others 0(0%). Compliance to treatment was affected in 2 patients. 1 due to diarrhoea and in other pharyngeal edema)
Inaba 2002 *OAC treatment arm is not reported in this table*	LAC = 60	NR	NR	0	16/60 (Diarrhoea and soft stools = 13; Glossitis and Pharyngitis = 2; Constipation = 1)
	RAC = 64	NR	NR	One patient in withdrew at approximately 20% compliance due to vomiting	17/64 (Diarrhoea and soft stools = 10; Glossitis and Pharyngitis =1; Vomiting = 2; Taste disturbance = 1; Abdominal pain = 1; Oral thirst = 1; Abdominal full sensation = 1)
Murakami K and Sato R 2002	LAC = 148	NR	NR	3 (1 urticarial) and 2 due to diarrhoea)	NR
	RAC = 97	NR	NR	1 (diarrhoea)	NR
Kawabata 2003	LAC = 87	NR	NR	Not reported	58% had AE. These included diarrhoea or soft stools (35%), nausea (14%), abdominal pain (13%), glossitis or taste disturbance (13%), constipation (12%), skin rash (4%) and headache (2%). Two patients in the LAC group had an abnormality on blood test just after eradication: elevation of transaminases (glutamic-oxaloacetic transaminase, 45 IU/L; glutamic-pyruvic transaminase, 50 IU/L) and a decrease in the white blood cell count (2900/mm^3), respectively.
	RAC = 100	NR	NR	Not reported	
Murakami 2008 *OAC treatment arm is not reported here*	LAM = 56	NR	NR	NR	2 cases of diarrhoea
	RAM = 58	NR	NR	NR	2 cases of diarrhoea and 1 case of hives
Liu 2013	LAC = 228	Not reported	Not reported	Not reported	13/202 (5.7%); Specific event rates not reported
	RAC = 222	Not reported	Not reported	Not reported	16/222 (7.2%); Specific event rates not reported
Abbreviations: PUD, peptic ulcer disease; A: amoxicillin; C: clarithromycin; R: Rabeprazole ; L, Lansoprazole; M, metronidazole; SAE, serious adverse event; AE, adverse event; NR, not reported, ITT					

Appendix 8: Summary of Findings Table

SoF Table 1: Comparison 1- Esomeprazole compared to Omeprazole for patients with GERD

Patient or population: 10 RCTs with 9638 patients with GERD
Intervention: Esomeprazole 20 or 40 mg OD
Comparison: Omeprazole 20 mg OD

Settings: Outpatient

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Omeprazole 20 mg OD	**Esomeprazole 20 or 40 mg OD**				
Total symptomatic relief	**Not reported**					
Relief of heartburn at 4 weeks	**Study population**		**RR 1.08** (1.05 to 1.12)	9365 (8 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
	599 per 1000	**647 per 1000** (623 to 665)				
Time to first resolution of symptoms	**Median days ranged from 1 to 4 days in both groups**					
Endoscopic healing rate of esophagitis at 4-8 weeks	**Study population**		**RR 1.07** (1.05 to 1.09)	6887 (6 studies)	⊕⊕⊖⊖ **low**[1,2]	
	818 per 1000	**875 per 1000** (858 to 891)				
Quality of life scores	**Not reported**					
Recurrence or relapse of symptoms	**Not reported**					
Mortality	**Study population**		**RR 0.69** (0.08 to 5.69)	4385 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,4]	
	1 per 1000	**0 per 1000**				

		(0 to 3)			
Serious adverse events	**Not reported**				
Withdrawal due to adverse event	**Study population**		**RR 1.2** (0.83 to 1.74)	6809 (5 studies)	⊕⊕⊖⊖ **low**[1,2]
	15 per 1000	**18 per 1000** (12 to 26)			
Patient with at least 1 adverse event	**Study population**		**RR 1** (0.92 to 1.09)	3621 (3 studies)	⊕⊕⊖⊖ **low**[1,2]
	376 per 1000	**376 per 1000** (346 to 410)			
Significant specific adverse event (Headache)	**Study population**		**RR 1.29** (1.08 to 1.54)	6809 (5 studies)	⊕⊕⊖⊖ **low**[1,2]
	63 per 1000	**81 per 1000** (68 to 96)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of selection and/or reporting bias

[2] High risk of performance and/or detection bias.
[3] Heterogeneity was significant.
[4] 95% CI is very wide.

SoF Table 2: Comparison 2 - Esomeprazole compared to Pantoprazole for GERD

Patient or population: 12 RCTs in 10,503 patients with GERD
Intervention: Esomeprazole 20 to 40 mg OD
Comparison: Pantoprazole 20 to 40 mg OD

Settings: Outpatient

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk **Pantoprazole**	Corresponding risk **Esomeprazole**	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Total symptom resolution at 4-12 weeks	**Study population**		**RR 0.94** (0.90 to 0.98)	2148 (5 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
	745 per 1000	**700 per 1000** (670 to 730)				
Relief of heart burn	**Study population**		**RR 0.99** (0.83 to 1.17)	217 (1 study)	⊕⊖⊖⊖ **very low** [2,3,4]	
	714 per 1000	**707 per 1000** (593 to 835)				
Time to first resolution of symptoms	**Median days = 2 for both groups**					
Endoscopic confirmed healing at 4-12 weeks	**Study population**		**RR 1.02** (1.00 to 1.04)	4865 (6 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
	885 per 1000	**903 per 1000** (885 to 920)				
Quality of life scores	**Not reported**					
Recurrence or relapse of symptoms	**Not reported**					
Mortality	**Study population**		**RR 0.55**	4069	⊕⊖⊖⊖	

	2 per 1000	**1 per 1000** (0 to 5)	(0.12 to 2.55)	(2 studies)	**very low**[1,2,3]
Serious adverse events	**Study population**		**RR 1.29** (0.84 to 1.97)	8424 (7 studies)	⊕⊕⊖⊖ **low**[1,2]
	9 per 1000	**11 per 1000** (7 to 17)			
Withdrawal due to adverse event	**Study population**		**RR 1.23** (0.93 to 1.63)	8363 (5 studies)	⊕⊕⊖⊖ **low**[1,2]
	20 per 1000	**24 per 1000** (18 to 32)			
Patient with at least one adverse event	**Study population**		**RR 1.05** (0.93 to 1.20)	3219 (5 studies)	⊕⊖⊖⊖ **very low**[1,2,3]
	215 per 1000	**226 per 1000** (200 to 258)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Included studies have high risk of selection bias and/or reporting bias.
[2] Included studies have high risk of attrition and/or detection bias.
[3] Small total sample size or wide 95% CI.
[4] Based on only 1 study.

SoF Table 3: Comparison 3 - Esomeprazole compared to Rabeprazole for patients with GERD

Patient or population: 5 RCTs in 3716 Patients with GERD
Intervention: Esomeprazole 20 to 40mg
Comparison: Rabeprazole 10 to 50mg
Settings: Outpatient

Outcomes^	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Rabeprazole**	Corresponding risk **Esomeprazole**				
Total symptomatic relief	**Not reported**					
Relief of heartburn at week 4	**Study population**		**RR 1.03** (0.96 to 1.11)	3512 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	
	481 per 1000	**495 per 1000** (462 to 534)				
Time to first resolution of symptoms	**Median days ranged from 8.5 to 9 days for heartburn and from 6 to 7.5 days for acid regurgitation**					
Healing of esophagitis at 4-8 weeks	**Study population**		**RR 0.97** (0.92 to 1.01)	2180 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	
	779 per 1000	**756 per 1000** (717 to 787)				
Quality of life scores	Not reported					
Recurrence or relapse of symptoms	Not reported					
Mortality	No mortality in 2 studies and not reported in 3 studies.					
Serious adverse events	No serious adverse event in Maiti 2011 study. Other 4 studies did not report data.					

Withdrawal due to adverse event	**Study population**	**RR 1.54** (0.89 to 2.65)	1452 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]
	33 per 1000	**50 per 1000** (29 to 87)		
Patient with at least one adverse event	**Study population**	**RR 1.03** (0.88 to 1.21)	1397 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]
	325 per 1000	**335 per 1000** (286 to 394)		

^ Non-significant individual symptom relief not reported in other comparisons are not presented in SoF table for this comparison

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Included studies have high risk of selection bias and/or selective reporting bias.

[2] Included studies have high risk of attrition bias and/or detection and performance bias.

[3] Wide 95% confidence interval

SoF Table 4: Comparison 4 - Lansoprazole compared to Omeprazole for patients with GERD

Patient or population: 12 RCTs in 6,648 patients with GERD
Intervention: Lansoprazole 30 to 60mg
Comparison: Omeprazole 20 to 40mg
Settings: Outpatient

Outcomes^	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Omeprazole**	Corresponding risk **Lansoprazole**				
Total symptomatic relief	**Not reported**					
Relief of heartburn at 4 to 8 weeks	**Study population**		**RR 1.01** (0.98 to 1.03)	4161 (4 studies)	⊕⊕⊖⊖ **low**[1,2]	
	835 per 1000	**843 per 1000** (818 to 860)				
Relief of acid regurgitation at 4 to 8 weeks	**Study population**		**RR 0.83** (0.75 to 0.93)	378 (3 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
	742 per 1000	**616 per 1000** (557 to 690)				
Relief of dysphagia at 4 to 8 weeks	**Study population**		**RR 0.98** (0.94 to 1.03)	231 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
	983 per 1000	**963 per 1000** (924 to 1000)				
Time to first resolution of symptoms	**Not reported**					
Endoscopic healing of esophagitis at 4-8 weeks	**Study population**		**RR 1.00** (0.96 to 1.04)	2466 (7 studies)	⊕⊕⊖⊖ **low**[1,2]	
	816 per 1000	**816 per 1000** (783 to 849)				
Quality of Life scores	**Not reported**					
Symptomatic relapse or recurrences at 48 weeks	**Study population**		**RR 0.48** (0.04 to 5.27)	248 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]	
	16 per 1000	**8 per 1000** (1 to 86)				
Mortality	Not reported in 9 RCTs. No deaths in 3					

	studies.				
Serious adverse events	**Study population**		**RR 1.00** (0.23 to 4.39)	911 (3 studies)	⊕⊖⊖⊖ **very low**[1,2,3]
	7 per 1000	**7 per 1000** (2 to 29)			
Withdrawal due to adverse event	**Study population**		**RR 1.05** (0.73 to 1.51)	5443 (6 studies)	⊕⊖⊖⊖ **very low**[1,2,3]
	20 per 1000	**21 per 1000** (15 to 31)			
Patient with at least 1 adverse event	**Study population**		**RR 1.00** (0.94 to 1.06)	5525 (7 studies)	⊕⊕⊖⊖ **low**[1,2]
	431 per 1000	**431 per 1000** (405 to 457)			
Significant specific adverse event Diarrhea	**Study population**		**RR 1.23** (1.02 to 1.48)	5581 (5 studies)	⊕⊕⊖⊖ **low**[1,2]
	69 per 1000	**85 per 1000** (70 to 102)			

^ Non-significant individual symptom relief not reported in other comparisons are not presented in SoF table for this comparison

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Included studies have a high risk of selective reporting bias and/or attrition bias/

[2] High risk of selection bias and/or performance and detection bias

[3] Small sample size and/or wide 95% confidence interval

SoF Table 5: Comparison 5 -Lansoprazole compared to Pantoprazole for patients with GERD

Patient or population: 5 RCTs in 1089 patients with GERD
Intervention: Lansoprazole 30 to 60 mg
Comparison: Pantoprazole 40 to 80 mg
Settings: Outpatient

Outcomes^	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Pantoprazole	Corresponding risk Lansoprazole				
Total Symptomatic relief at 4-8 weeks	**Study population**		**RR 0.96** (0.91 to 1.02)	771 (2 studies)	⊕⊕⊖⊖ **low**[1,2]	
	855 per 1000	**821 per 1000** (778 to 872)				
Relief of heartburn at 4-8 weeks	**Study population**		**RR 0.95** (0.90 to 0.99)	931 (3 studies)	⊕⊖⊖⊖ **very low**[1,2,,3]	
	915 per 1000	**869 per 1000** (824 to 906)				
Relief of acid regurgitation at 4-8 weeks	**Study population**		**RR 0.94** (0.89 to 1)	621 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,,3]	
	912 per 1000	**857 per 1000** (811 to 912)				
Relief of pain on swallowing at 4 weeks	**Study population**		**RR 1.00** (0.97 to 1.03)	621 (2 studies)	⊕⊕⊖⊖ **low**[1,2]	
	971 per 1000	**971 per 1000** (941 to 1000)				
Time to first resolution of symptoms	**Not reported**					
Endoscopic healing of esophagitis at 4-8 weeks	**Study population**		**RR 0.96** (0.91 to 1.01)	759 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	
	896 per 1000	**860 per 1000** (815 to 905)				
Quality of Life scores	Not reported					
Recurrence or relapse of symptoms	**Study population**		**RR 1.00** (0.49 to 2.05)	20 (1 study)	⊕⊖⊖⊖	

	600 per 1000	**600 per 1000** (294 to 1000)			**very low** [1,2,5]
Mortality	2 studies reported no mortality. Other 3 studies did not report data.				
Serious adverse events	**Study population**		**RR 1.14** (0.35 to 3.70)	461 (1 Study)	⊕⊖⊖⊖ **very low** [1,2,4]
	22 per 1000	**25 per 1000** (8 to 81)			
Withdrawal due to adverse event	**Study population**		**RR 2.17** (0.67 to 6.97)	771 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,,4]
	11 per 1000	**23 per 1000** (7 to 74)			
Patient with a least 1 adverse event	**Study population**		**RR 0.60** (0.42 to 0.85)	621 (2 studies)	⊕⊕⊖⊖ **low**[1,2]
	210 per 1000	**126 per 1000** (88 to 178)			

^ Non-significant individual symptom relief not reported in other comparisons are not presented in SoF table for this comparison

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] High risk of selection and/or detection or performance bias.

[2] High risk of selective reporting and /or attrition bias.

[3] Heterogeneity was significant.

[4] 95% CI was wide.

[5] Very small sample size.

SoF Table 6: Comparison 6 - Lansoprazole compared to Rabeprazole for patients with GERD

Patient or population: 2 RCTs in 215 patients with GERD
Intervention: Lansoprazole
Comparison: Rabeprazole
Settings: Outpatient

Outcomes^	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Rabeprazole	Corresponding risk Lansoprazole				
Total symptom relief	**Not reported**					
Relief of heart burn at week 8	**Study population**		**RR 0.83** (0.75 to 0.92)	160 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
	1000 per 1000	**830 per 1000** (750 to 920)				
Relief of acid regurgitation at week 8	**Study population**		**RR 0.83** (0.72 to 0.96)	160 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
	900 per 1000	**747 per 1000** (648 to 864)				
Relief of epigastric pain at week 8	**Study population**		**RR 0.83** (0.75 to 0.92)	160 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
	1000 per 1000	**830 per 1000** (750 to 920)				
Time to first resolution of symptoms	**Not reported**					
Endoscopic healing of esophagitis at week 8	**Study population**		**RR 0.90** (0.80 to 1.01)	213 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
	898 per 1000	**808 per 1000 (719 to 907)**				
Quality of Life scores	**Not reported**					
Mortality	**Not reported**					

Serious adverse events	**Not reported**				
Withdrawal due to adverse events	**Not reported**				
Patient with at least 1 adverse event	**Study population**		**RR 1.00** (0.06 to 15.71)	160 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4]
	12 per 1000	**13 per 1000** (1 to 204)			

^ Non-significant individual symptom relief not reported in other comparisons are not presented in SoF table for this comparison

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] High risk of selection bias

[2] High risk of detection and performance bias

[3] Small sample size

[4] Based only on one RCT

SoF Table 7: Comparison 7 - Esomeprazole compared to Omeprazole for patients with peptic ulcer

Patient or population: 5 RCTs in 1553 patients with peptic ulcer
Intervention: Esomeprazole
Comparison: Omeprazole
Settings: Outpatient

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Omeprazole	Corresponding risk Esomeprazole	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
***H. pylori* eradication at 6 to 8 weeks**	**Study population**		**RR 1.03** (0.98 to 1.07)	1481 (5 studies)	⊕⊖⊖⊖ **very low**[1,2,,3]	
	830 per 1000	**855 per 1000** (813 to 888)				
Total symptomatic relief	**Not reported**					
Relief of epigastric pain	**Study population**		**RR 0.84** (0.56 to 1.26)	833 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,,3,4]	
	111 per 1000	**93 per 1000** (62 to 140)				
Relief of heart burn	**Study population**		**RR 0.97** (0.70 to 1.35)	833 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,,3,4]	
	147 per 1000	**143 per 1000** (103 to 198)				
Time to first resolution of symptoms	**Not reported**					
Endoscopic healing of ulcer at 4 weeks	**Study population**		**RR 0.99** (0.93 to 1.05)	397 (1 study)	⊕⊖⊖⊖ **very low**[1,2,,3,4]	
	922 per 1000	**913 per 1000** (857 to 968)				
Recurrence or relapse of symptoms	**Not reported**					
Mortality	**1 RCT reported no deaths.**					

Serious adverse events	**Study population**		**RR 0.20** (0.02 to 1.73)	959 (3 studies)	⊕⊖⊖⊖ **very low**[1,2,,3,4]
	8 per 1000	**2 per 1000** (0 to 14)			
Withdrawal due to adverse event	**Study population**		**RR 1.01** (0.33 to 3.11)	812 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,,3,4,5]
	15 per 1000	**15 per 1000** (5 to 47)			
Patients with at least 1 adverse event	**Study population**		**RR 1.00** (0.9 to 1.11)	1492 (5 studies)	⊕⊖⊖⊖ **very low**[1,2,,3,4]
	464 per 1000	**464 per 1000** (418 to 515)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of selection bias
[2] High risk of attrition bias
[3] High risk of detection and/or performance bias
[4] High risk of selective reporting bias
[5] Wide 95% CI

SoF Table 8: Comparison 8 - Esomeprazole compared to Pantoprazole for patients with peptic ulcer

Patient or population: 1 RCT in 200 patients with peptic ulcer
Intervention: Esomeprazole
Comparison: Pantoprazole
Settings: Outpatient

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Pantoprazole	Corresponding risk Esomeprazole				
***H. pylori* eradication at 8 weeks**	**Study population**		**RR 1.15** (1.03 to 1.27)	200 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]	
	820 per 1000	**943 per 1000** (845 to 1000)				
Total symptomatic relief	**Not reported**					
Relief of individual symptoms	**Not reported**					
Time to first resolution of symptoms	**Not reported**					
Endoscopic healing of ulcer at 8 weeks	**Study population**		**RR 1.07** (0.91 to 1.25)	85 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]	
	844 per 1000	**903 per 1000** (768 to 1000)				
Quality of Life scores	**Not reported**					
Recurrence or relapse of symptoms	**Not reported**					
Mortality	**Not reported**					
Serious adverse events	**Not reported**					
Withdrawal due to adverse event	**Study population**		**RR 0.50** (0.09 to 2.67)	200 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
	40 per 1000	**20 per 1000** (4 to 107)				

Patient with at least 1 adverse event	**Study population**		**RR 0.62** (0.35 to 1.12)	200 (1 study)	⨁⊖⊖⊖ **very low**[1,2,3,4]
	240 per 1000	**149 per 1000** (84 to 269)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of detection and performance bias
[2] Based only on 1 RCT
[3] High risk of selection bias
[4] 95% CI confidence interval is wide

SoF Table 9: Comparison 10 - Lansoprazole compared to Omeprazole for patients with peptic ulcer

Patient or population: 15 RCT in 2265 patients with peptic ulcer
Intervention: Lansoprazole
Comparison: Omeprazole
Settings: Outpatient

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Omeprazole**	Corresponding risk **Lansoprazole**				
***H. pylori* eradication at 1 to 8 weeks**	**Study population**		**RR 1.03** (0.97 to 1.08)	1668 (12 studies)	⊕⊕⊖⊖ **low**[1]	
	763 per 1000	**786 per 1000** (740 to 824)				
Total symptomatic relief	**Not reported**					
Relief of individual symptoms	**Not reported**					
Time to first resolution of symptoms	**Not reported**					
Endoscopic healing of ulcer at 4 to 8 weeks	**Study population**		**RR 1.04** (1.01 to 1.07)	1610 (8 studies)	⊕⊕⊖⊖ **low**[1,2,3]	
	882 per 1000	**917 per 1000** (891 to 944)				
Quality of Life scores	**Not reported**					
Recurrence or relapse of symptoms	**Not reported**					
Mortality	**Study population**		**RR 0.37** (0.02 to 8.82)	678 (5 studies)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
	3 per 1000	**1 per 1000** (0 to 26)				
Serious adverse event	Reported in 4 RCTS no deaths		Not estimable	552 (4 studies)	⊕⊕⊖⊖ **low**[1,2,3]	
Withdrawal due to adverse	**Study population**		**RR 0.45**	858	⊕⊕⊖⊖	

events	**26 per 1000**	**12 per 1000** (4 to 33)	(0.16 to 1.27)	(4 studies)	**low**[1,2,3]
Patient with at least 1 adverse event	**Study population**		**RR 0.89** (0.75 to 1.07)	934 (5 studies)	⊕⊕⊖⊖ **low**[1,2,3]
	342 per 1000	**304 per 1000** (256 to 366)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of selection bias
[2] High risk of detection and performance bias
[3] High risk of selective reporting bias
[4] 95% CI is wide

SoF Table 10: Comparison 12 - Lansoprazole compared to Rabeprazole for patients with peptic ulcer

Patient or population: 7 RCTs in 1574 patients with Peptic ulcer
Intervention: Lansoprazole
Comparison: Rabeprazole
Settings: Outpatient

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Rabeprazole**	Corresponding risk **Lansoprazole**				
***H. pylori* eradication**	**Study population**		**RR 0.97** (0.93 to 1.01)	1571 (7 studies)	⊕⊕⊖⊖ **low**[1,2]	
	851 per 1000	**825 per 1000** (791 to 860)				
Total symptomatic relief	**Not reported**					
Relief of individual symptoms	**Not reported**					
Time to first resolution of symptoms	**Not reported**					
Endoscopic healing of ulcer	**Not reported**					
Quality of Life scores	**Not reported**					
Recurrence or relapse of symptoms	**Not reported**					
Mortality	**Not reported**					
Serious adverse events	**Not reported**					
Withdrawal due to adverse event	**Study population**		**RR 1.02** (0.23 to 4.47)	418 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
	14 per 1000	**14 per 1000** (3 to 63)				

Patient with at least 1 adverse event	**Study population** **240 per 1000** **226 per 1000** (180 to 283)	**RR 0.94** (0.75 to 1.18)	1002 (4 studies)	⊕⊕⊖⊖ **low**[1,2]
Significant specific adverse events Diarrhea	**Study population** **126 per 1000** **64 per 1000** (38 to 108)	**RR 0.51** (0.3 to 0.86)	577 (3 studies)	⊕⊕⊖⊖ **low**[1,2]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of selection bias
[2] High risk of detection and performance bias
[3] 95% CI is wide