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[Intervention Review]

Eradication therapy for peptic ulcer disease in *Helicobacter pylori*-positive people

Alexander C Ford[1], Kurinchi Selvan Gurusamy[2], Brendan Delaney[3], David Forman[4], Paul Moayyedi[5]

[1]Leeds Gastroenterology Unit, St. James's University Hospital, Leeds, UK. [2]Department of Surgery, Royal Free Campus, UCL Medical School, London, UK. [3]Division of Health and Social Care Research, King's College London, London, UK. [4]International Agency for Research on Cancer, Lyon, France. [5]Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, Canada

Contact address: Kurinchi Selvan Gurusamy, Department of Surgery, Royal Free Campus, UCL Medical School, Royal Free Hospital, Rowland Hill Street, London, NW3 2PF, UK. k.gurusamy@ucl.ac.uk.

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ABSTRACT

Background

Peptic ulcer disease is the cause of dyspepsia in about 10% of people. Ninety-five percent of duodenal and 70% of gastric ulcers are associated with *Helicobacter pylori*. Eradication of *H. pylori* reduces the relapse rate of ulcers but the magnitude of this effect is uncertain. This is an update of Ford AC, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori*-positive patients. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD003840. DOI: 10.1002/14651858.CD003840.pub4.

Objectives

To assess the proportion of peptic ulcers healed and the proportion of participants who remained free from relapse with eradication therapy against placebo or other pharmacological therapies in *H. pylori*-positive people.

To assess the proportion of participants that achieved complete relief of symptoms and improvement in quality of life scores.

To compare the incidence of adverse effects/drop-outs (total number for each drug) associated with the different treatments.

To assess the proportion of participants in whom successful eradication was achieved.

Search methods

In this update, we identified trials by searching the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE (1950 to March 2016) and Ovid EMBASE (1980 to March 2016). To identify further relevant trials, we handsearched reference lists from trials selected by electronic searching, and published abstracts from conference proceedings from the United European Gastroenterology Week (published in *Gut*) and Digestive Disease Week (published in *Gastroenterology*). The search was last updated in March 2016. We contacted members of Cochrane Upper GI and Pancreatic Diseases, and experts in the field and asked them to provide details of outstanding clinical trials and any relevant unpublished materials.

Selection criteria

We analysed randomised controlled trials of short- and long-term treatment of peptic ulcer disease in *H. pylori*-positive adults. Participants received at least one week of *H. pylori* eradication compared with ulcer healing drug, placebo or no treatment. Trials were included if they reported assessment from two weeks onwards.

Data collection and analysis

We collected data on ulcer healing, recurrence, relief of symptoms and adverse effects. We calculated the risk ratio (RR) with 95% confidence intervals (CI) using both fixed-effect and random-effects models with Review Manager software (RevMan 5.3) based on intention-to-treat analysis as far as possible.

Main results

A total of 55 trials were included for one or more outcomes for this review.

In duodenal ulcer healing, eradication therapy was superior to ulcer healing drug (UHD) (34 trials, 3910 participants, RR of ulcer persisting = 0.66, 95% confidence interval (CI) 0.58 to 0.76; 381/2286 (adjusted proportion: 12.4%) in eradication therapy plus UHD versus 304/1624 (18.7%) in UHD; low quality evidence) and no treatment (two trials, 207 participants, RR 0.37, 95% CI 0.26 to 0.53; 30/125 (adjusted proportion: 21.7%) in eradication therapy versus 48/82 (58.5%) in no treatment; low quality evidence).

In gastric ulcer healing, the differences were imprecise between eradication therapy and UHD (15 trials, 1974 participants, RR 1.23, 95% CI 0.90 to 1.68; 220/1192 (adjusted proportion: 16.0%) in eradication therapy plus UHD versus 102/782 (13.0%) in UHD; very low quality evidence). In preventing duodenal ulcer recurrence the differences were imprecise between maintenance therapy with *H.pylori* eradication therapy and maintenance therapy with UHD (four trials, 319 participants, RR of ulcer recurring 0.73; 95% CI 0.42 to 1.25; 19/159 (adjusted proportion: 11.9%) in eradication therapy versus 26/160 (16.3%) in UHD; very low quality evidence), but eradication therapy was superior to no treatment (27 trials 2509 participants, RR 0.20, 95% CI 0.15 to 0.26; 215/1501 (adjusted proportion: 12.9%) in eradication therapy versus 649/1008 (64.4%) in no treatment; very low quality evidence).

In preventing gastric ulcer recurrence, eradication therapy was superior to no treatment (12 trials, 1476 participants, RR 0.31, 95% CI 0.22 to 0.45; 116/697 (adjusted proportion: 16.3%) in eradication therapy versus 356/679 (52.4%) in no treatment; very low quality evidence). None of the trials reported proportion of people with gastric ulcer not healed after initial therapy between *H.pylori* eradication therapy and no active treatment or the proportion of people with recurrent gastric ulcer or peptic ulcers during maintenance therapy between *H.pylori* eradication therapy and ulcer healing drug therapy.

Authors' conclusions

Adding a one to two-week course of *H. pylori* eradication therapy is an effective treatment for people with *H. pylori*-positive duodenal ulcer when compared to ulcer healing drugs alone and no treatment. *H. pylori* eradication therapy is also effective in preventing recurrence of duodenal and gastric ulcer compared to no treatment. There is currently no evidence that *H. pylori* eradication therapy is an effective treatment in people with gastric ulcer or that it is effective in preventing recurrence of duodenal ulcer compared to ulcer healing drug. However, confidence intervals were wide and significant benefits or harms of *H. pylori* eradication therapy in acute ulcer healing of gastric ulcers compared to no treatment, and in preventing recurrence of duodenal ulcers compared to ulcer healing drugs cannot be ruled out.

PLAIN LANGUAGE SUMMARY

Antibiotics for people with peptic ulcers caused by *Helicobacter pylori* infection

Review question

Are antibiotics useful for the treatment of peptic ulcer (ulcers in the stomach or upper small intestine) in people with *Helicobacter pylori* (*H. pylori*) infection?

Background

Peptic ulcers are caused by acidic stomach juices damaging the lining of the stomach (gastric ulcer) or upper small intestine (duodenal ulcer). This causes pain, indigestion and sometimes, bleeding. Ulcers can return after being healed, especially if the person is infected with *Helicobacter pylori* (a lifelong infection unless treated). *H. pylori* causes most peptic ulcers. It is not clear whether eradicating *H.pylori* by treating with antibiotics as part of a combination of drugs (*H.pylori* eradication therapy) is helpful in the treatment of people with peptic ulcers compared to no treatment or other medical treatments. This is an update of a previous Cochrane review published in 2006.

Study characteristics

Fifty-five studies provided information for the review. Thirty-four studies compared *H. pylori* eradication therapy plus ulcer-healing drug against ulcer-healing drug alone in the healing of duodenal ulcer. Two studies compared *H. pylori* eradication therapy against no treatment in the healing of duodenal ulcer. Fifteen studies compared *H. pylori* eradication therapy plus ulcer-healing drug against ulcer-healing drug alone in the healing of gastric ulcer. Three studies compared *H. pylori* eradication therapy plus ulcer-healing drug against ulcer-healing drug alone in the healing of peptic ulcer (gastric or duodenal ulcer). One study compared *H. pylori* eradication therapy against no treatment in the healing of peptic ulcer (gastric or duodenal ulcer). Four studies compared *H. pylori* eradication therapy against ulcer-healing drug in preventing the recurrence of duodenal ulcer after initial ulcer had been healed. Twenty-seven studies compared *H. pylori* eradication therapy against no treatment in preventing the recurrence of duodenal ulcer after initial ulcer had been healed. Twelve studies compared *H. pylori* eradication therapy against no treatment in preventing the recurrence of gastric ulcer after initial ulcer had been healed, while

one study compared *H. pylori* eradication therapy against no treatment in preventing the recurrence of peptic ulcer (gastric or duodenal ulcer) after initial ulcer had been healed. Four studies compared *H. pylori* eradication therapy plus ulcer-healing drug versus comparison regimen in the relief of symptoms from peptic ulcer (gastric or duodenal ulcer). There were no studies comparing *H. pylori* eradication therapy against no treatment in the healing of gastric ulcer, *H. pylori* eradication therapy against ulcer-healing drug as maintenance therapy in preventing the recurrence of gastric ulcer after initial ulcer had been healed, or *H. pylori* eradication therapy plus ulcer-healing drug against no treatment or ulcer-healing drug in the relief of symptoms in people with peptic ulcer. Some trials provided information for more than one comparison. The evidence is current until March 2016.

Key results

Adding a one to two-week course of *H. pylori* eradication therapy speeds up ulcer healing for people with *H. pylori*-positive duodenal ulcer when compared to ulcer-healing drugs alone and no treatment. *H. pylori* eradication therapy is also effective in preventing recurrence of duodenal and gastric ulcer (ulcer returning after initial healing) compared to no treatment. There is currently no evidence that *H. pylori* eradication therapy is an effective treatment in people with gastric ulcer or that it is effective in preventing recurrence of duodenal ulcer compared to ulcer-healing drugs. However, because of the small number of studies included for the last two comparisons, significant benefits or harms of *H. pylori* eradication therapy in acute ulcer healing of gastric ulcers compared to no treatment and in preventing recurrence of duodenal ulcers compared to ulcer healing drugs cannot be ruled out.

Quality of the evidence

The quality of evidence was low or very low because most of the studies had errors in study design. As a result, there is a lot of uncertainty regarding the results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Additional *Helicobacter pylori* eradication therapy for acute ulcer healing in people with *Helicobacter pylori*-positive peptic ulcer

Additional *Helicobacter pylori* eradication therapy for acute ulcer healing in people with *Helicobacter pylori*-positive peptic ulcer

Patient or population: people with *Helicobacter pylori-positive* peptic ulcer
Settings: secondary and tertiary care
Intervention: Additional *Helicobacter pylori* eradication therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Additional Helicobacter pylori eradication therapy			
Proportion of people with duodenal ulcer not healed after initial therapy					
H. pylori eradication therapy plus ulcer healing drug versus ulcer healing drug alone	**187 per 1000**	**124 per 1000** (109 to 142)	**RR 0.66** (0.58 to 0.76)	3910 (34 studies)	⊕⊕⊖⊖ **low** [1,2]
H. pylori eradication therapy versus no active treatment	**585 per 1000**	**217 per 1000** (152 to 310)	**RR 0.37** (0.26 to 0.53)	207 (2 studies)	⊕⊕⊖⊖ **low** [1,3]
Proportion of people with gastric ulcer not healed after initial therapy					
H. pylori eradication therapy plus ulcer healing drug versus ulcer healing drug alone	**130 per 1000**	**160 per 1000** (117 to 219)	**RR 1.23** (0.9 to 1.68)	1974 (15 studies)	⊕⊖⊖⊖ **very low** [1,2,4,5]
Proportion of people with peptic ulcer (gastric or duodenal ulcer) not healed after initial therapy					
H. pylori eradication therapy plus ulcer healing drug versus ulcer healing drug alone	**247 per 1000**	**129 per 1000** (77 to 210)	**RR 0.52** (0.31 to 0.85)	287 (3 studies)	⊕⊕⊖⊖ **low** [1,3]
H. pylori eradication therapy versus no active treatment	**800 per 1000**	**120 per 1000** (40 to 360)	**RR 0.15** (0.05 to 0.45)	40 (1 study)	⊕⊕⊖⊖ **low** [1,3]

None of the trials reported proportion of people with gastric ulcer not healed after initial therapy between *H.pylori* eradication therapy and no active treatment.

*The basis for the **assumed risk** is the control group risk. 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] The risk of bias in trial(s) was high.
[2] Possible small study effect/publication bias as suggested by funnel plot and tests for funnel plot asymmetry (Begg 1994; Egger 1997).
[3] The sample size was small.
[4] There was moderate to significant heterogeneity as measured by I^2 (Higgins 2003).
[5] The confidence intervals were wide.

Summary of findings 2. Additional Helicobacter pylori eradication therapy for prevention of recurrence in people with Helicobacter-positive peptic ulcer

Additional *Helicobacter* pylori eradication therapy for prevention of recurrence in people with Helicobacter-positive peptic ulcer

Patient or population: prevention of recurrence in people with *Helicobacter pylori*-positive peptic ulcer
Settings:
Intervention: Additional *Helicobacter pylori* eradication therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Additional Helicobacter pylori eradication therapy			
Proportion of people with duodenal ulcer with recurrence after maintenance therapy					
H. pylori eradication therapy versus ulcer healing drug alone	**162 per 1000**	**119 per 1000** (68 to 203)	**RR 0.73** (0.42 to 1.25)	319 (4 studies)	⊕⊖⊖⊖ **very low** [1,2,3]
H. pylori eradication therapy versus no active treatment	**644 per 1000**	**129 per 1000** (97 to 167)	**RR 0.2** (0.15 to 0.26)	2509 (27 studies)	⊕⊖⊖⊖ **very low** [1,4,5]
Proportion of people with gastric ulcer with recurrence after maintenance therapy					

H. pylori eradication therapy versus no active treatment	**524 per 1000**	**163 per 1000** (115 to 236)	**RR 0.31** (0.22 to 0.45)	1476 (12 studies)	⊕⊖⊖⊖ **very low** [1,4,5]
Proportion of people with peptic ulcer (gastric or duodenal ulcer) with recurrence after maintenance therapy					
H. pylori eradication therapy versus no active treatment	**333 per 1000**	**77 per 1000** (30 to 197)	**RR 0.23** (0.09 to 0.59)	103 (1 study)	⊕⊕⊖⊖ **low** [1,2]

None of the trials reported proportion of people with recurrent gastric ulcer or peptic ulcers during maintenance therapy between *H.pylori* eradication therapy and ulcer-healing drug therapy.

*The basis for the **assumed risk** is the control group risk across studies. 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] The risk of bias in trial(s) was high.
[2] The sample size was small.
[3] The confidence intervals were wide.
[4] There was moderate to significant heterogeneity as measured by I^2 (Higgins 2003).
[5] Possible small study effect/publication bias as suggested by funnel plot and tests for funnel plot asymmetry (Begg 1994; Egger 1997).

BACKGROUND

Description of the condition

Peptic ulcer disease is common, with some 10% of the population of Western countries likely to suffer a duodenal or gastric ulcer during their lifetime (Dobrilla 1993). The annual estimated national costs were USD 3.1 billion in United States, USD 29 to USD 94 million in Sweden in 1998 and USD 522 million in France in 1987 (Barkun 2010). Those suffering from peptic ulcer disease can be troubled by recurrent bouts of pain, in addition to more serious consequences such as haemorrhage or perforation (Penston 1993).

Until the recognition of the major role played by *Helicobacter pylori*, the most important factors in the pathogenesis of peptic ulcer disease were thought to be acid and pepsin damaging the epithelial cells of the stomach and duodenum (Peterson 1990).

Description of the intervention

Triple therapy regimens (acid suppressing therapy combined with two antibiotics aimed at eradicating *H. pylori*) given for one week are said to achieve rapid symptom relief and healing rates of approximately 90% of duodenal ulcers and 85% of gastric ulcers, with studies suggesting this is more effective than antisecretory drugs alone (Penston 1996). Furthermore, people receiving successful *H. pylori* eradication had a relapse rate of approximately 5% compared with 80% of those healed on histamine-2 receptor antagonists (H2RAs) (Penston 1996).

Initially triple therapy was instituted using bismuth salts and antibiotics, but subsequent trials replaced the bismuth with proton pump inhibitors (PPI) and discovered that this was better tolerated, and achieved similar rates of eradication of *H. pylori* (Hunt 1997). Despite these advances, and numerous narrative reviews on *H. pylori* eradication in peptic ulcer disease, we were not aware of a recent systematic review evaluating duodenal and gastric ulcers separately.

How the intervention might work

In the 1970s and 1980s therapy was mainly aimed at reducing acid secretion, achieved by the use of H2RAs and PPIs (Feldman 1995). However in the late 1980s and early 1990s the importance of *H. pylori* in ulcer development and recurrence was confirmed, and it was postulated that this could be prevented by eradication of this organism (Tytgat 1998), which is implicated in 90% to 95% of duodenal and approximately 70% of gastric ulcers.

Why it is important to do this review

The aim of this review was to conduct a systematic review of randomised controlled trials to obtain a more precise estimate of the efficacy of eradication therapy in the short- and long-term treatment of *H. pylori*-positive individuals with peptic ulcer disease. This is an update of a previous Cochrane review (Ford 2006). The previous version concluded that a one to two-week course of *H. pylori* eradication therapy is an effective treatment for *H. pylori*-positive peptic ulcer disease. Since the search was outdated, it is important to provide up-to-date evidence.

OBJECTIVES

To assess the proportion of peptic ulcers healed and the proportion of participants who remained free from relapse with eradication therapy against placebo or other pharmacological therapies in *H. pylori*-positive people.

To assess the proportion of participants that achieved complete relief of symptoms and improvement in quality of life scores.

To compare the incidence of adverse effects/drop-outs (total number for each drug) associated with the different treatments.

To assess the proportion of participants in whom successful eradication was achieved.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials looking at the short- and long-term treatment of peptic ulcer disease were eligible for inclusion in this review. We also included the first period of cross-over trials.

Types of participants

All participants recruited in the trials analysed were adults who had peptic ulcer diagnosed at endoscopy or on barium meal and who had *H. pylori* status confirmed positive on either serology, CLO test, urease breath test, biopsy or a combination of these tests.

Types of interventions

The tested drug had to fall within the following drug class 1, the comparison regimen also had to be one of 2 to 9 from the list below.

1. Efficacious eradication therapy: we defined this as a regimen reported in the literature that usually achieves at least a 50% eradication rate, and this included;
   a. PPI dual therapy (PPI plus either amoxicillin or clarithromycin)
   b. PPI triple therapy (PPI plus two of the following; amoxicillin, macrolide, 5 nitroimidazole)
   c. H2RA triple therapy (H2RA plus two of the following; amoxicillin, macrolide, 5 nitroimidazole)
   d. Bismuth triple therapy (bismuth salt and 5 nitroimidazole with either amoxicillin or tetracycline)
   e. Bismuth quadruple therapy (as bismuth triple therapy, but PPI in addition)
   f. Ranitidine bismuth citrate dual/triple therapy (as for PPI)
   g. Clarithromycin monotherapy
2. PPIs: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.
3. H2RAs: cimetidine, famotidine, nizatidine, ranitidine.
4. Bismuth salts.
5. Sucralfate.
6. Regular antacid.
7. Antacid as needed (PRN).
8. Placebo.
9. No treatment.

Participants had to have had at least one week of therapy.

Types of outcome measures

Trials were included if they reported evidence of assessment from two weeks onwards.
The following outcomes were included in this review.

Primary outcomes

1. Proportion of peptic ulcers healed after initial therapy.
2. Proportion of participants with peptic ulcer that remained free from relapse following successful ulcer healing.
3. Proportion of participants that achieved complete relief from symptoms of peptic ulcer.

Secondary outcomes

1. Recording of adverse effects of the pharmacological interventions.
2. *H. pylori* eradication rates.
3. Improvement in quality of life (QoL) scores.

Search methods for identification of studies

We conducted searches to identify all published and unpublished randomised controlled trials. Articles published in any language were included.

Electronic searches

We identified trials by searching the Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley (Appendix 1), MEDLINE (1950 to March 2016) via OvidSP (Appendix 2) and EMBASE (1980 to March 2016) via OvidSP (Appendix 3). We did not confine our search to English language publications. Searches in all databases were updated in September 2003, November 2004, November 2005, July 2008, August 2010, January 2015, and March 2016. The Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE, sensitivity-maximising version, Ovid format (Lefebvre 2011) was combined with search terms to identify randomised controlled trials in MEDLINE (Appendix 2). The MEDLINE search strategy (please see Appendix 2) was adapted for use in the other databases searched.

Searching other resources

We handsearched reference lists from trials selected by electronic searching to identify further relevant trials.

Abstracts

We handsearched Digestive Disease Week (DDW) (published in *Gastroenterology*) and United European Gastroenterology Week (UEGW) (published in *Gut*) abstract books between 1994 and 2003. We contacted authors of trial reports published only as abstracts and asked them to contribute full data sets or completed papers.

Correspondence

We contacted experts in the field registered with the Cochrane Upper GI and Pancreatic Diseases (UGPD) review group for leads on unpublished studies. In addition, we contacted the following pharmaceutical companies - Abbott-Knoll, Astra-Zeneca, Eisai, Glaxo-Smithkline, Lilly and Wyeth and asked them to supply details of any outstanding clinical trials and relevant unpublished materials.

We contacted the following experts in the field:

1. Dr. Franco Bazzoli, Università di Medicina Interna e Gastroenterologica, Bologna, Italy
2. Dr. Cathy Bennett, North Yorkshire Cancer Registry, Leeds, UK
3. Dr. Xavier Calvet, Corporacio Sanitaria del Park Tau, Sabell, Spain
4. Dr. Naoki Chiba, Guelph, Canada
5. Dr. C Fallone, McMaster University Medical Centre, Hamilton, Canada
6. Dr. Lori Fischbach, University of Texas, Dallas, USA
7. Dr. Javier P Gisbert, University Hospital de la Princesa, Madrid, Spain
8. Dr. Adam Harris, Kent and Sussex Hospitals, Tunbridge Wells, UK
9. Professor Richard Hunt, McMaster University Medical Centre, Hamilton, Canada
10. Dr. J Huang, McMaster University Medical Centre, Hamilton, Canada
11. Professor Ernst J Kuipers, Free University Hospital, Amsterdam, Netherlands
12. Dr. Robert Laheij, Dept. of Gastroenterology, Nijmegen, Netherlands
13. Professor Francis Megraud, Hôpital Pellegrin, Bordeaux, France
14. Dr. D Palli, Epidemiology Unit CSPO, Florence, Italy
15. Dr. V Savarino, Università di Genova, Genova, Italy
16. Dr. P Unge, Gävle, Sweden

Data collection and analysis

Selection of studies

The lead review author screened titles and trial abstracts that had been identified by the search strategy for articles that could possibly be eligible for the review. A second review author independently checked a sample of this selection process.

The lead review author then screened the full article of selected trials to confirm eligibility, using pre-designed eligibility forms. A second review author, masked to the initial assessment, also evaluated all full articles for eligibility. A third review author adjudicated any discrepancies and a consensus view was taken.

Data extraction and management

Data were extracted by the lead review author and recorded onto specially developed forms. There was an unblinded check on this by a second review author. We also double-checked data entry into RevMan (RevMan 2014).

The following characteristics were recorded for each trial

1. Setting: primary or secondary care
2. Country of origin
3. Inclusion and exclusion criteria used
4. Baseline comparability between treatment groups
5. Treatments compared and number of participants in each arm
6. Drop-outs reported and their reasons
7. Site of ulcer
8. Ulcer healing rates
9. Ulcer recurrence rates

10. Complication rates
11. Eradication rates
12. Type of eradication regimen
13. Names, dosage, and schedule of drugs
14. Adverse events: the total and individual numbers reported
15. Quality of life
16. Global symptoms cured or recurred

We extracted data as intention-to-treat analyses, where we considered that the treatment had failed in all participants who were excluded from analysis.

Assessment of risk of bias in included studies

Two review authors assessed the risk of bias for each study independently using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and resolved any disagreement by discussion. We assessed the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants, personnel and outcome assessors;
4. incomplete outcome data;
5. selective outcome reporting;
6. other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed.

Measures of treatment effect

We combined risk ratios (RR) for binary outcomes. We calculated the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) as the inverse of the risk difference from the meta-analysis.

Dealing with missing data

Completeness of follow-up and intention-to-treat analysis

Where possible, we recorded completeness of follow-up, intention-to-treat analysis and drop-out rates by group.

Assessment of heterogeneity

We explored reasons for heterogeneity according to the following predefined criteria.

1. Multi-centre versus single-centre
2. Country of origin
3. Mean age of participants included in the study
4. Method of randomisation
5. Method of concealment of allocation
6. Masking versus no masking
7. Type of eradication regimen
8. *H. pylori* eradication rate
9. Duration of treatment
10. Completeness of follow-up

We used the I^2 statistic to measure heterogeneity among the trials in each analysis (Higgins 2003).

Assessment of reporting biases

If we were able to pool more than 10 trials, we created and examined a funnel plot to explore possible publication biases. We used Egger's test (Egger 1997) and Begg's test (Begg 1994) to determine the statistical significance of the reporting bias. A P value of less than 0.10 was considered statistically significant reporting bias.

Data synthesis

For binary outcomes, such as peptic ulcer healing, peptic ulcer recurrence and absence of symptoms, we expressed the impact of interventions as risk ratios (RR) together with 95% confidence intervals (CI). We analysed the data for gastric ulcer and duodenal ulcer, and for short- and long-term treatment, separately wherever possible. We also analysed the comparison regimens separately.

There was sufficient data for the generation of a meta-analysis for this review.

Subgroup analysis and investigation of heterogeneity

Where significant ($P < 0.1$) heterogeneity was detected, we investigated possible explanations informally, and summarised the data using a random-effects analysis.

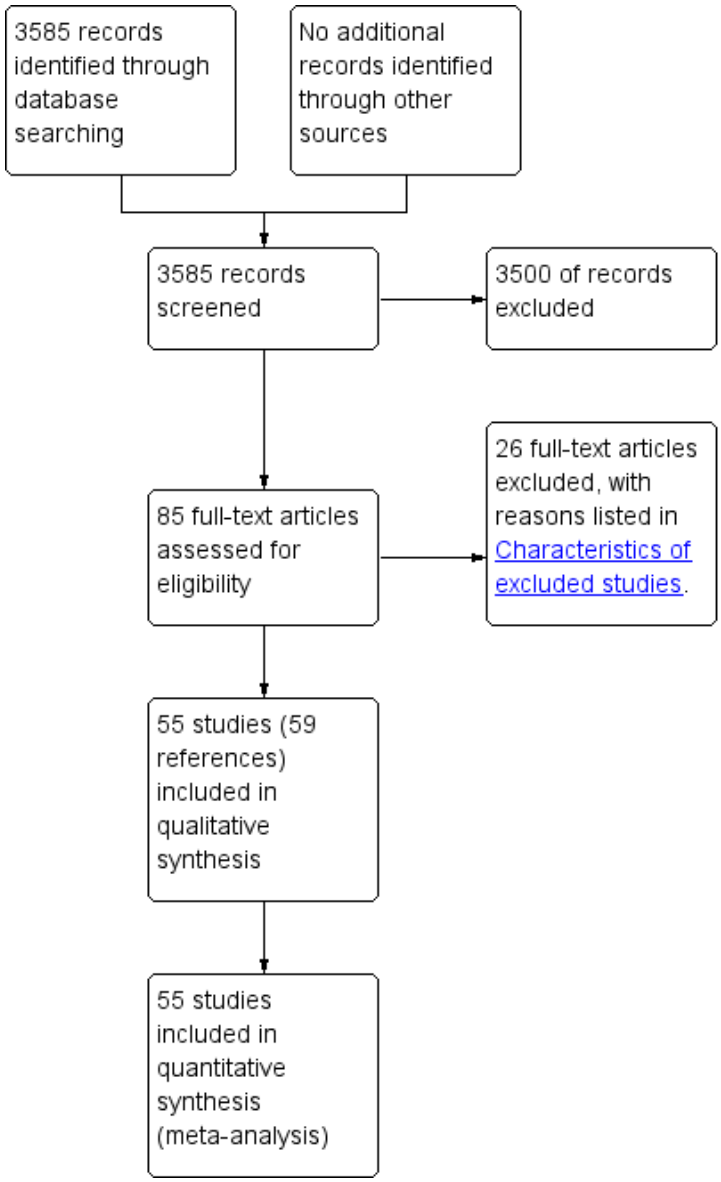
RESULTS

Description of studies

Results of the search

In total, we identified 3585 citations using the search strategy outlined above. We reviewed the titles and abstracts and selected 85 papers which compared a recognised *H. pylori* eradication regimen against placebo or other pharmacological therapies in *H. pylori*-positive peptic ulcer disease. Twenty-five studies (26 reports) did not meet the eligibility criteria and were excluded (Characteristics of excluded studies). A total of 55 trials (59 references) provided data for one or more comparisons and outcomes for this review (see Effects of interventions). The reference flow is shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

Please see Characteristics of included studies.

H. pylori eradication therapy plus ulcer-healing drug versus ulcer-healing drug alone in the healing of duodenal ulcer

Thirty-four RCTs (Asaka 2001; Avsar 1996; Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; Bianchi Porro 1993; Bianchi Porro 1996; Carpintero 1997; Figueroa 1996; Furuta 1995; Graham 1991; Graham 1998; Harford 1996; Hentschel 1993; Hosking 1992; Kato 1996; Katoh 1995; Kepecki 1999; Lin 1994; Logan 1995; Mantzaris 1993; Mones 2001; O'Morain 1996; Parente 1996; Pinero 1995; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Sobhani 1995; Spinzi 1994; Van Zanten 1999; Wang 1993; Wong 1999) with a total of 3910 participants which comprised:

- nine RCTs (Bayerdorffer 1992; Bayerdorffer 1995; Furuta 1995; Harford 1996; Kato 1996; Katoh 1995; Logan 1995; O'Morain 1996; Spinzi 1994) comparing PPI dual therapy with ulcer-healing drug alone;
- eight RCTs (Avsar 1996; Bianchi Porro 1993; Graham 1991; Lin 1994; Mantzaris 1993; Pinero 1995; Rauws 1990; Wang 1993) comparing bismuth triple therapy with ulcer-healing drug alone;
- five RCTs (Asaka 2001; Bianchi Porro 1996; Kepecki 1999; Mones 2001; Van Zanten 1999) comparing PPI triple therapy with ulcer-healing drug alone;
- three RCTs (Hentschel 1993; Shirotani 1996; Sobhani 1995) comparing H2RA triple therapy with ulcer-healing drug alone;
- three RCTs (Bardhan 1997; Graham 1998; Pounder 1997) comparing ranitidine bismuth citrate dual therapy with ulcer-healing drug alone;
- two RCTs (Figueroa 1996; Hosking 1992) comparing bismuth quadruple therapy with ulcer-healing drug alone;
- one RCT (Parente 1996) comparing bismuth quadruple therapy and PPI dual therapy with ulcer-healing drug alone;

- one RCT (Carpintero 1997) comparing bismuth triple therapy and H2RA triple therapy with ulcer-healing drug alone;
- one RCT (Schwartz 1998) comparing PPI triple and dual therapy with ulcer-healing drug alone;
- one RCT (Wong 1999) comparing clarithromycin monotherapy with ulcer-healing drug alone.

There were 14 multi-centre trials. The smallest RCT included 32 participants. The largest RCT included 352 participants.

H. pylori eradication therapy versus no treatment in the healing of duodenal ulcer

Two RCTs (Graham 1998; Lam 1997) with a total of 207 participants which comprised:

- one multi-centre RCT (Graham 1998) comparing ranitidine bismuth citrate dual therapy with no treatment;
- one RCT (Lam 1997) comparing clarithromycin monotherapy with no treatment.

H. pylori eradication therapy plus ulcer-healing drug versus ulcer-healing drug alone in the healing of gastric ulcer

Fifteen RCTs (Asaka 2001; Axon 1997; Bayerdorffer 1996; Befrits 2004; Fukuda 1995a; Fukuda 1995b; Furuta 1995; Higuchi 2003; Kato 1996; Katoh 1995; Lazzaroni 1997; Malfertheiner 1999; Meining 1998; Sung 1995; Tulassay 2008) with a total of 1974 participants which comprised:

- eight RCTs (Axon 1997; Fukuda 1995a; Fukuda 1995b; Furuta 1995; Kato 1996; Katoh 1995; Lazzaroni 1997; Meining 1998) comparing PPI dual therapy with ulcer-healing drug alone;
- two RCTs (Bayerdorffer 1996; Sung 1995) comparing bismuth triple therapy with ulcer-healing drug alone;
- five RCTs (Asaka 2001; Befrits 2004; Higuchi 2003; Malfertheiner 1999; Tulassay 2008) comparing PPI triple therapy with ulcer-healing drug alone.

There were seven multi-centre trials. The smallest trial included 27 participants. The largest trial included 402 participants.

H. pylori eradication therapy versus no treatment in the healing of gastric ulcer

No RCTs were identified.

H. pylori eradication therapy plus ulcer-healing drug versus ulcer-healing drug alone in the healing of peptic ulcer

Three RCTs (Arkkila 2005; Suarez 1999; Wang 1996) with a total of 287 participants which comprised:

- one RCT (Arkkila 2005) comparing bismuth quadruple therapy, PPI triple therapy, and PPI dual therapy with ulcer-healing drug alone;
- one RCT (Wang 1996) comparing bismuth triple therapy and PPI dual therapy with ulcer-healing drug alone;
- one RCT (Suarez 1999) comparing bismuth triple therapy with ulcer-healing drug alone.

H. pylori eradication therapy versus no treatment in the healing of peptic ulcer

One single-centre RCT (Feng 2005) with a total of 40 participants comparing PPI triple therapy with no treatment.

H. pylori eradication therapy versus ulcer-healing drug as maintenance therapy in preventing the recurrence of duodenal ulcer (after initial ulcer had been healed)

Four RCTs (Kepecki 1999; Mones 2001; Sobhani 1995; Wong 1999) with a total of 319 participants which comprised:

- two RCTs (Kepecki 1999; Mones 2001) comparing PPI triple therapy with ulcer-healing drug alone;
- one RCT (Sobhani 1995) comparing H2RA triple therapy with ulcer-healing drug alone;
- one RCT (Wong 1999) comparing clarithromycin monotherapy with ulcer-healing drug alone.

There were two multi-centre trials: the smallest trial included 73 participants, the largest trial included 119 participants.

H. pylori eradication therapy versus no treatment in preventing the recurrence of duodenal ulcer (after initial ulcer had been healed)

Twenty-seven RCTs (Avsar 1996; Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; Bianchi Porro 1996; Carpintero 1997; Chen 1995; Figueroa 1996; Graham 1992; Hentschel 1993; Hosking 1992; Kato 1996; Kim 2002; Lin 1994; Logan 1995; Mantzaris 1993; O'Morain 1996; Pinero 1995; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Spinzi 1994; Tomita 2002; Unge 1993; Van Zanten 1999; Wang 1993) with a total of 2509 participants which comprised:

- eight RCTs (Avsar 1996; Chen 1995; Graham 1992; Lin 1994; Mantzaris 1993; Pinero 1995; Rauws 1990; Wang 1993) comparing bismuth triple therapy with no treatment;
- seven RCTs (Bayerdorffer 1992; Bayerdorffer 1995; Kato 1996; Logan 1995; O'Morain 1996; Spinzi 1994; Unge 1993) comparing PPI dual therapy with no treatment;
- four RCTs (Bianchi Porro 1996; Kim 2002; Tomita 2002; Van Zanten 1999) comparing PPI triple therapy with no treatment;
- two RCTs (Hentschel 1993; Shirotani 1996) comparing H2RA triple therapy with no treatment;
- two RCTs (Bardhan 1997; Pounder 1997) comparing ranitidine bismuth citrate dual therapy with no treatment;
- two RCTs (Figueroa 1996; Hosking 1992) comparing bismuth quadruple therapy with no treatment;
- one RCT (Schwartz 1998) comparing PPI triple and dual therapy with no treatment;
- one RCT (Carpintero 1997) comparing bismuth triple therapy and H2RA triple therapy with no treatment.

There were nine multi-centre trials: the smallest trial contained 20 participants, the largest trial contained 233 participants.

H. pylori eradication therapy versus ulcer-healing drug as maintenance therapy in preventing the recurrence of gastric ulcer (after initial ulcer had been healed)

No RCTs were identified.

H. pylori eradication therapy versus no treatment in preventing the recurrence of gastric ulcer (after initial ulcer had been healed)

Twelve RCTs (Axon 1997; Bayerdorffer 1996; Befrits 2004; Fukuda 1995b; Graham 1992; Kato 1996; Lazzaroni 1997; Malfertheiner 1999; Meining 1998; Sung 1995; Tomita 2002; Tulassay 2008) with a total of 1476 participants which comprised:

- five RCTs (Axon 1997; Fukuda 1995b; Kato 1996; Lazzaroni 1997; Meining 1998) comparing PPI dual therapy with no treatment;
- three RCTs (Bayerdorffer 1996; Graham 1992; Sung 1995) comparing bismuth triple therapy with no treatment;
- four RCTs (Befrits 2004; Malfertheiner 1999; Tomita 2002; Tulassay 2008) comparing PPI triple therapy with no treatment.

There were six multi-centre trials. The smallest trial contained 59 participants. The largest trial contained 372 participants.

H. pylori eradication therapy versus ulcer-healing drug as maintenance therapy in preventing the recurrence of peptic ulcer (after initial ulcer had been healed)

No RCTs were identified.

H. pylori eradication therapy versus no treatment in preventing the recurrence of peptic ulcer (after initial ulcer had been healed)

One RCT (Arkkila 2005) with a total of 103 participants comparing bismuth quadruple therapy, PPI triple therapy, and PPI dual therapy with no treatment.

H. pylori eradication therapy plus ulcer-healing drug versus comparison regimen in the relief of symptoms from peptic ulcer

Four RCTs (Higuchi 2003; Lam 1997; Pounder 1997; Suarez 1999) with a total of 368 participants which comprised:

- one RCT (Higuchi 2003) comparing PPI triple therapy with ulcer-healing drug alone
- one RCT (Lam 1997) comparing clarithromycin monotherapy with no treatment
- one RCT (Pounder 1997) comparing ranitidine bismuth citrate dual therapy with no treatment
- one RCT (Suarez 1999) comparing bismuth triple therapy with ulcer-healing drug alone

H. pylori eradication therapy plus ulcer-healing drug versus comparison regimen and improvement in quality of life scores in people with peptic ulcer patients

No RCTs were identified.

Excluded studies

Please see Characteristics of excluded studies.

We excluded:

- seven studies because they were non-randomised studies (Kohli 1995; Nakata 1995; O'Riordan 1990; Parente 1998; Shimoyama 1995; Sugiyama 1995; Xia 1995);
- two studies since not all participants were *H. pylori*-positive, and separate data was not available for *H. pylori*-positive participants (Bytzer 2000; Peterson 1996);
- one study because participants in control arm were *H. pylori* -negative (Dogan 1997);
- two studies since not all participants had documented peptic ulcer disease (Prach 1998; Veldhuyzen Van Zanten 2000);
- two studies (three references) since the participants did not have peptic ulcer disease (Dumbleton 2015; Tham 1996);
- one study since the eradication regimen used was not a recognised regimen (Rune 1993);
- one study since there was no comparison arm (Hosking 1994);
- nine studies since there was no ulcer healing or recurrence data (Al-Assi 1995; Gisbert 2000; Labenz 1993; Laine 2000; Lind 1996; Malfertheiner 2002a; Sonnenberg 1998; Sonnenberg 1999; Tavakoli 1999).

Risk of bias in included studies

Two authors undertook an assessment of the risk of bias of each eligible study independently. Methods of randomisation, concealment, and masking were assessed (Higgins 2011). A summary of the risk of bias may be found in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

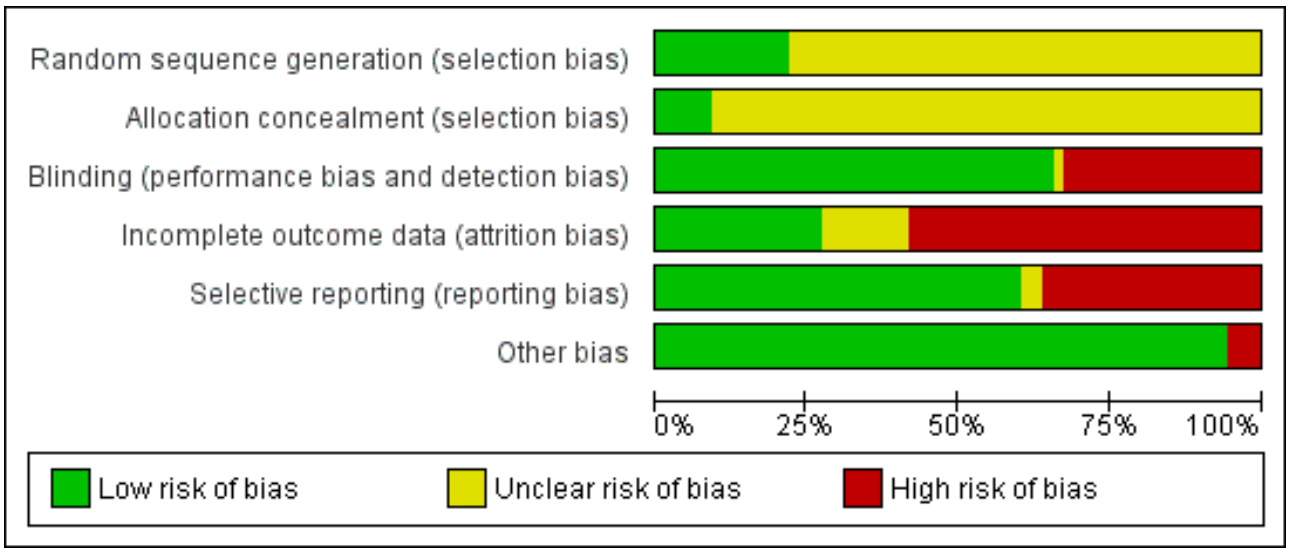


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

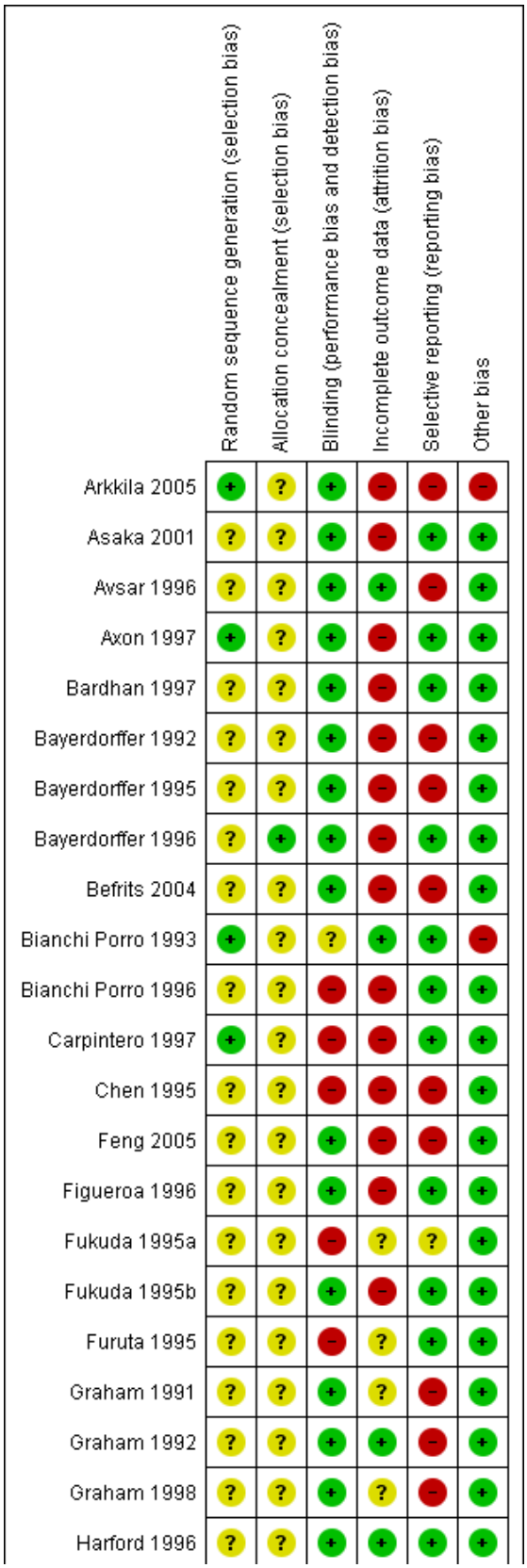


Figure 3. (Continued)

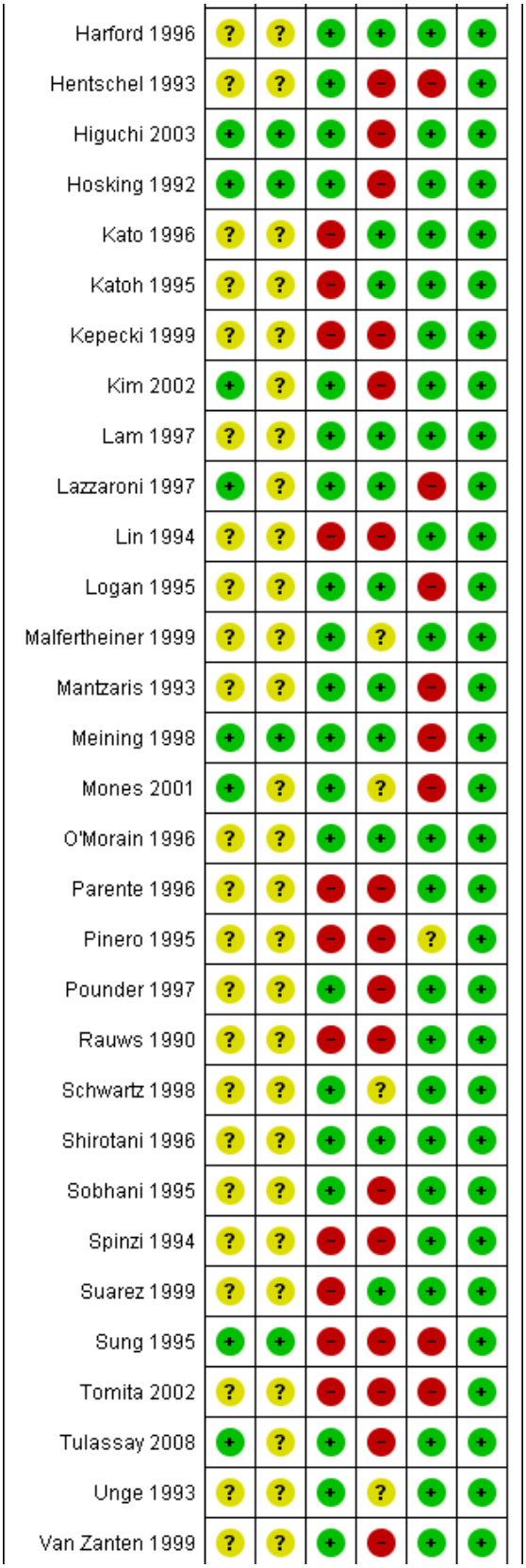
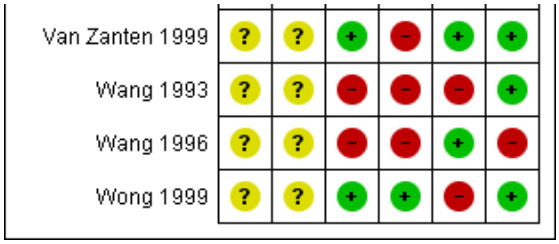


Figure 3. (Continued)



Allocation

Twelve trials stated the method of random sequence generation (Arkkila 2005; Axon 1997; Bianchi Porro 1993; Carpintero 1997; Higuchi 2003; Hosking 1992; Kim 2002; Lazzaroni 1997; Meining 1998; Mones 2001; Sung 1995; Tulassay 2008) and five trials reported the method of allocation concealment (Bayerdorffer 1996; Higuchi 2003; Hosking 1992; Meining 1998; Sung 1995). Four trials reported the random sequence generation and allocation concealment and were free from selection bias (Higuchi 2003; Hosking 1992; Meining 1998; Sung 1995).

Blinding

Blinding was performed in 36 trials (Arkkila 2005; Asaka 2001; Avsar 1996; Axon 1997; Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; Bayerdorffer 1996; Befrits 2004; Feng 2005; Figueroa 1996; Fukuda 1995b; Graham 1991; Graham 1992; Graham 1998; Harford 1996; Hentschel 1993; Higuchi 2003; Hosking 1992; Kim 2002; Lam 1997; Lazzaroni 1997; Logan 1995; Malfertheiner 1999; Mantzaris 1993; Meining 1998; Mones 2001; O'Morain 1996; Pounder 1997; Schwartz 1998; Shirotani 1996; Sobhani 1995; Tulassay 2008; Unge 1993; Van Zanten 1999; Wong 1999) and were free from performance bias and detection bias.

Incomplete outcome data

Fifteen trials included all participants in the analysis and were free from attrition bias (Avsar 1996; Bianchi Porro 1993; Graham 1992; Harford 1996; Kato 1996; Katoh 1995; Lam 1997; Lazzaroni 1997; Logan 1995; Mantzaris 1993; Meining 1998; O'Morain 1996; Shirotani 1996; Suarez 1999; Wong 1999).

Selective reporting

Thirty-three trials reported the outcomes collected and were free from selective outcome reporting bias (Asaka 2001; Axon 1997; Bardhan 1997; Bayerdorffer 1996; Bianchi Porro 1993; Bianchi Porro 1996; Carpintero 1997; Figueroa 1996; Fukuda 1995b; Furuta 1995; Harford 1996; Higuchi 2003; Hosking 1992; Kato 1996; Katoh 1995; Kepecki 1999; Kim 2002; Lam 1997; Lin 1994; Malfertheiner 1999; O'Morain 1996; Parente 1996; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Sobhani 1995; Spinzi 1994; Suarez 1999; Tulassay 2008; Unge 1993; Van Zanten 1999; Wang 1996).

Other bias

Fifty-two trials were free from other bias (Asaka 2001; Avsar 1996; Axon 1997; Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; Bayerdorffer 1996; Befrits 2004; Bianchi Porro 1996; Carpintero 1997; Chen 1995; Feng 2005; Figueroa 1996; Fukuda 1995a; Fukuda 1995b; Furuta 1995; Graham 1991; Graham 1992; Graham 1998; Harford 1996; Hentschel 1993; Higuchi 2003; Hosking 1992; Kato 1996; Katoh 1995; Kepecki 1999; Kim 2002; Lam 1997; Lazzaroni 1997; Lin 1994; Logan 1995; Malfertheiner 1999; Mantzaris 1993; Meining 1998; Mones 2001; O'Morain 1996; Parente 1996; Pinero 1995; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Sobhani 1995; Spinzi 1994; Suarez 1999; Sung 1995; Tomita 2002; Tulassay 2008; Unge 1993; Van Zanten 1999; Wang 1993; Wong 1999).

Effects of interventions

See: **Summary of findings for the main comparison** Additional *Helicobacter pylori* eradication therapy for acute ulcer healing in people with *Helicobacter pylori*-positive peptic ulcer; **Summary of findings 2** Additional Helicobacter pylori eradication therapy for prevention of recurrence in people with Helicobacter-positive peptic ulcer

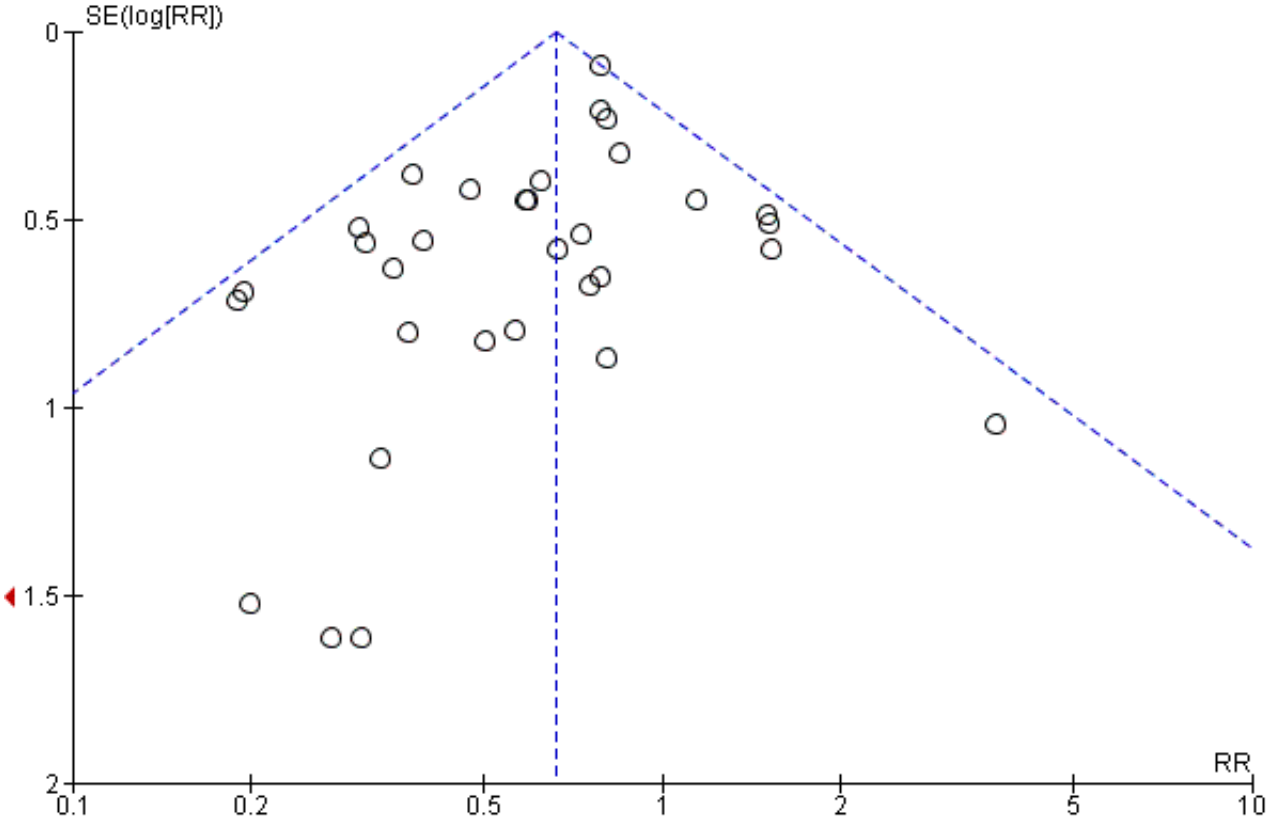
In dealing with the results obtained in this review we will, for the sake of clarity, consider them in the following order; firstly ulcer healing, secondly prevention of ulcer recurrence after initial healing, thirdly relief of symptoms of peptic ulcer, and finally side effects.

Ulcer healing

H. pylori eradication therapy plus ulcer-healing drug versus ulcer-healing drug alone in the healing of duodenal ulcer

Thirty-four RCTs (Asaka 2001; Avsar 1996; Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; Bianchi Porro 1993; Bianchi Porro 1996; Carpintero 1997; Figueroa 1996; Furuta 1995; Graham 1991; Graham 1998; Harford 1996; Hentschel 1993; Hosking 1992; Kato 1996; Katoh 1995; Kepecki 1999; Lin 1994; Logan 1995; Mantzaris 1993; Mones 2001; O'Morain 1996; Parente 1996; Pinero 1995; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Sobhani 1995; Spinzi 1994; Van Zanten 1999; Wang 1993; Wong 1999) reported a dichotomous duodenal ulcer healing outcome evaluating 3910 participants, between one and four months. Overall 17% of duodenal ulcers remained unhealed in the *H. pylori* eradication group compared with 19% in the ulcer-healing drug group. There was no statistically significant heterogeneity between the trial results (heterogeneity test (32 degrees of freedom) Chi^2 statistic = 36.30, P = 0.27). There was a small but statistically significant benefit of *H. pylori* eradication therapy plus ulcer-healing drug compared to ulcer-healing drug alone in the healing of duodenal ulcer (relative risk of ulcer persisting with *H. pylori* eradication therapy plus ulcer-healing drug versus ulcer-healing drug alone (RR 0.66, 95% CI 0.58 to 0.76; Analysis 1.1) (NNTB = 14; 95% CI 11 to 20). Egger test revealed funnel plot asymmetry (P = 0.02) with a preponderance of trials with few events showing large effects when 1/standard error was used as a measure of study size (Figure 4).

Figure 4. Funnel plot of comparison: 1 *H. pylori* eradication + ulcer-healing drug vs. ulcer-healing drug alone: duodenal ulcer acute healing, outcome: 1.1 Proportion not healed.



H. pylori eradication therapy versus no treatment in the healing of duodenal ulcer

Two RCTs (Graham 1998; Lam 1997) reported a dichotomous duodenal ulcer healing outcome evaluating 207 participants, between two and three months. Overall 24% of duodenal ulcers remained unhealed in the *H. pylori* eradication group compared with 58.5% in the no treatment group. There was no statistically significant heterogeneity between the trial results (heterogeneity test (1 degree of freedom) Chi^2 statistic = 0.02, P = 0.88). There was a statistically significant benefit of *H. pylori* eradication therapy plus ulcer-healing drug compared to no treatment in the healing of duodenal ulcer (RR 0.37, 95% CI 0.26 to 0.53; Analysis 2.1) (NNTB 2.5; 95% CI 2 to 4).

H. pylori eradication therapy plus ulcer-healing drug versus ulcer-healing drug alone in the healing of gastric ulcer

Fifteen RCTs (Asaka 2001; Axon 1997; Bayerdorffer 1996; Befrits 2004; Fukuda 1995a; Fukuda 1995b; Furuta 1995; Higuchi 2003; Kato 1996; Katoh 1995; Lazzaroni 1997; Malfertheiner 1999; Meining 1998; Sung 1995; Tulassay 2008) reported a dichotomous gastric ulcer healing outcome evaluating 1974 participants, between one and three months. Overall 18% of gastric ulcers remained unhealed in the *H. pylori* eradication group compared with 13% in the ulcer-healing drug group. There was statistically significant heterogeneity between the trial results (heterogeneity test (14 degrees of freedom) Chi^2 statistic = 22.93, P = 0.06) and a random-effects model was used. There was no statistically significant benefit of *H. pylori* eradication therapy plus ulcer-healing drug compared to ulcer-healing drug alone in the healing of gastric ulcer (RR 1.23, 95% CI 0.90 to 1.68; Analysis 3.1). There was no evidence of funnel plot asymmetry (Egger test P = 0.39). Metaregression was performed to evaluate whether length of treatment in the control group, duration of eradication therapy, eradication rate, length of follow-up, number of centres, method of randomisation, concealment of allocation, blinding, intention-to-treat analysis and completeness of follow-up had any impact on the result that could explain some of the heterogeneity observed. This suggested that multi-centre studies (log RR 1.52; 95% CI 0.87 to 2.18. P < 0.001), absence of blinding (log RR = 3.17; 95% CI 1.53 to 4.82. P < 0.001), and a greater than 10% difference in follow-up between trial arms (log RR = 3.09; 95% CI 0.82 to 5.37. P = 0.008) increased the effect size whereas performing an intention-to-treat analysis (log RR = -1.55; 95% CI -0.38 to -2.72. P = 0.01), and increasing completeness of follow-up (log RR = -8.79; 95% CI -4.31 to -13.26. P < 0.001) reduced the effect size.

H. pylori eradication therapy plus ulcer-healing drug versus ulcer-healing drug alone in the healing of peptic ulcer

Three RCTs (Arkkila 2005; Suarez 1999; Wang 1996) reported a dichotomous peptic ulcer healing outcome evaluating 287 participants, between one and two months. Overall 12% of peptic ulcers remained unhealed in the*H. pylori* eradication group compared with 25% in the ulcer-healing drug group. There was

no statistically significant heterogeneity between trial results (heterogeneity test (2 degrees of freedom) Chi^2 statistic = 3.31, P = 0.19). There was a statistically significant benefit of *H. pylori* eradication therapy plus ulcer-healing drug compared to ulcer-healing drug alone in the healing of peptic ulcer (RR 0.52, 95% CI 0.31 to 0.85; Analysis 4.1) (NNTB = 8; 95% CI 4.5 to 50).

H. pylori eradication therapy versus no treatment in the healing of peptic ulcer

One RCT (Feng 2005) reported a dichotomous peptic ulcer healing outcome evaluating 40 participants, at 1 month. Overall 12% of peptic ulcers remained unhealed in the *H. pylori* eradication therapy group compared with 80% in the no treatment group. There was a statistically significant benefit of *H. pylori* eradication therapy group compared to no treatment in the healing of peptic ulcer (RR 0.15; 95% CI 0.05 to 0.45; Analysis 5.1) (NNTB = 1.5; 95% CI 1.1 to 2.3).

Preventing ulcer recurrence after initial ulcer healing

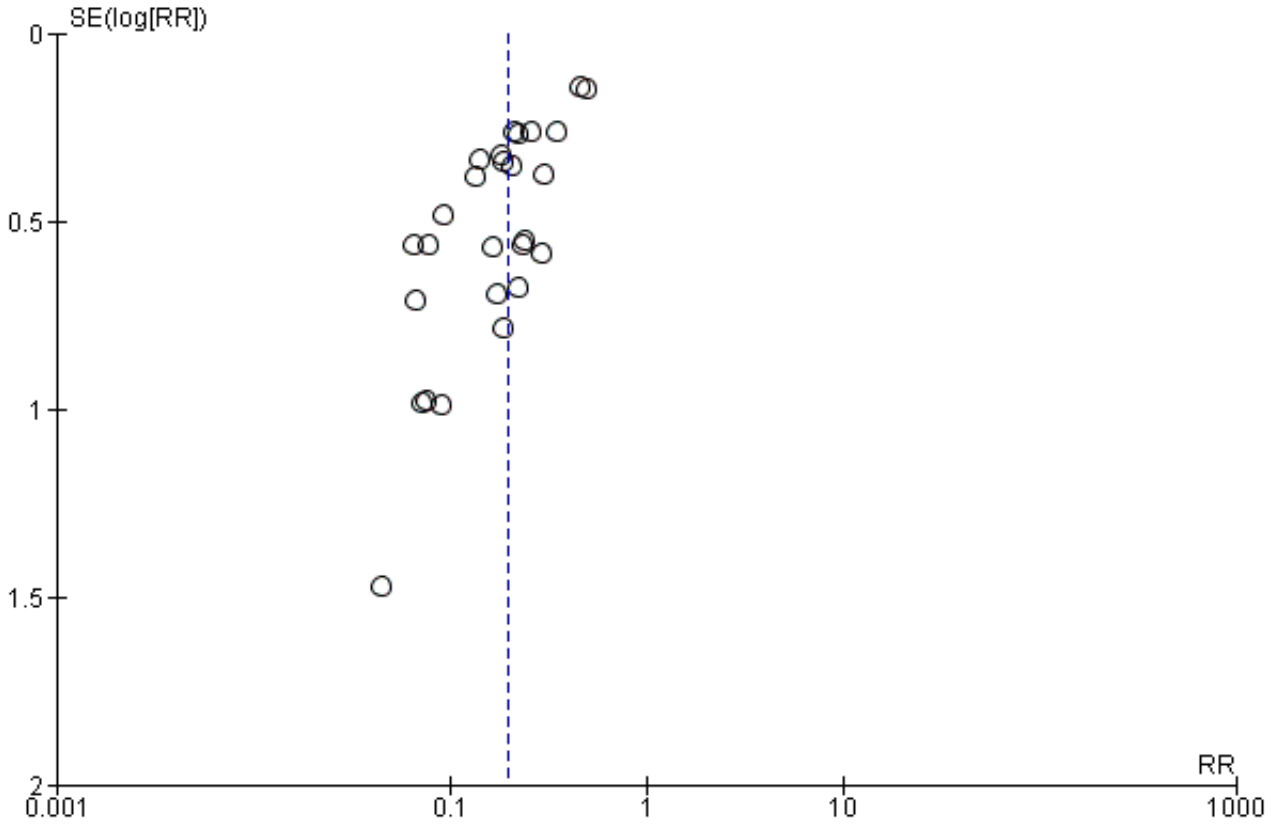
H. pylori eradication therapy versus ulcer-healing drug as maintenance therapy in preventing the recurrence of duodenal ulcer (after initial ulcer had been healed)

Four RCTs (Kepecki 1999; Mones 2001; Sobhani 1995; Wong 1999) reported a dichotomous duodenal ulcer recurrence outcome evaluating 319 participants, between six months and two years. Overall 12% of duodenal ulcers recurred in the *H. pylori* eradication group compared with 16% in the ulcer-healing drug as maintenance group. There was no statistically significant heterogeneity between trial results (heterogeneity test (3 degrees of freedom) Chi^2 statistic = 3.22, P = 0.36). There was no statistically significant benefit of *H. pylori* eradication therapy compared to ulcer-healing drug as maintenance therapy in the prevention of duodenal ulcer recurrence (relative risk of ulcer recurring after *H. pylori* eradication therapy versus maintenance anti-secretory therapy (RR 0.73; 95% CI 0.42 to 1.25; Analysis 6.1).

H. pylori eradication therapy versus no treatment in preventing the recurrence of duodenal ulcer (after initial ulcer had been healed)

Twenty-seven RCTs (Avsar 1996; Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; Bianchi Porro 1996; Carpintero 1997; Chen 1995; Figueroa 1996; Graham 1992; Hentschel 1993; Hosking 1992; Kato 1996; Kim 2002; Lin 1994; Logan 1995; Mantzaris 1993; O'Morain 1996; Pinero 1995; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Spinzi 1994; Tomita 2002; Unge 1993; Van Zanten 1999; Wang 1993) reported a dichotomous duodenal ulcer recurrence outcome evaluating 2509 participants, between two months and five years. Overall 14% of duodenal ulcers recurred in the *H. pylori* eradication group compared with 64% in the no treatment group. There was statistically significant heterogeneity between trial results (heterogeneity test (26 degrees of freedom) Chi^2 statistic = 85.11, P < 0.00001) and a random-effects model was used. There was a statistically significant benefit of *H. pylori* eradication therapy compared to no treatment in the prevention of duodenal ulcer recurrence (RR 0.20; 95% CI 0.15 to 0.26; Analysis 7.1) (NNTB = 2; 95% CI 1.6 to 2.2). Egger test revealed funnel plot asymmetry (P < 0.001) with a preponderance of trials with few events showing large effects when 1/standard error was used as a measure of study size (Figure 5). This statistically significant asymmetry was less marked if the sample size was used as the measure of study size (P = 0.04). Metaregression was performed to evaluate whether length of treatment in the control group, duration of eradication therapy, eradication rate, length of follow-up, number of centres, method of randomisation, concealment of allocation, blinding, intention-to-treat analysis and completeness of follow-up had any impact on the result that could explain some of the heterogeneity observed. This revealed that the relative risk of recurrence reduced with increasing eradication rate (log RR = -1.80; 95% CI -0.81 to -2.80. P < 0.001) and duration of eradication therapy (log RR = -0.38; 95% CI -0.27 to -0.50. P < 0.001) and increased with increasing length of follow-up (log RR = 0.006; 95% CI 0.001 to 0.010. P = 0.02) and when an intention-to-treat analysis was performed by the review authors (log RR = 0.31; 95% CI 0.11 to 0.52. P = 0.003).

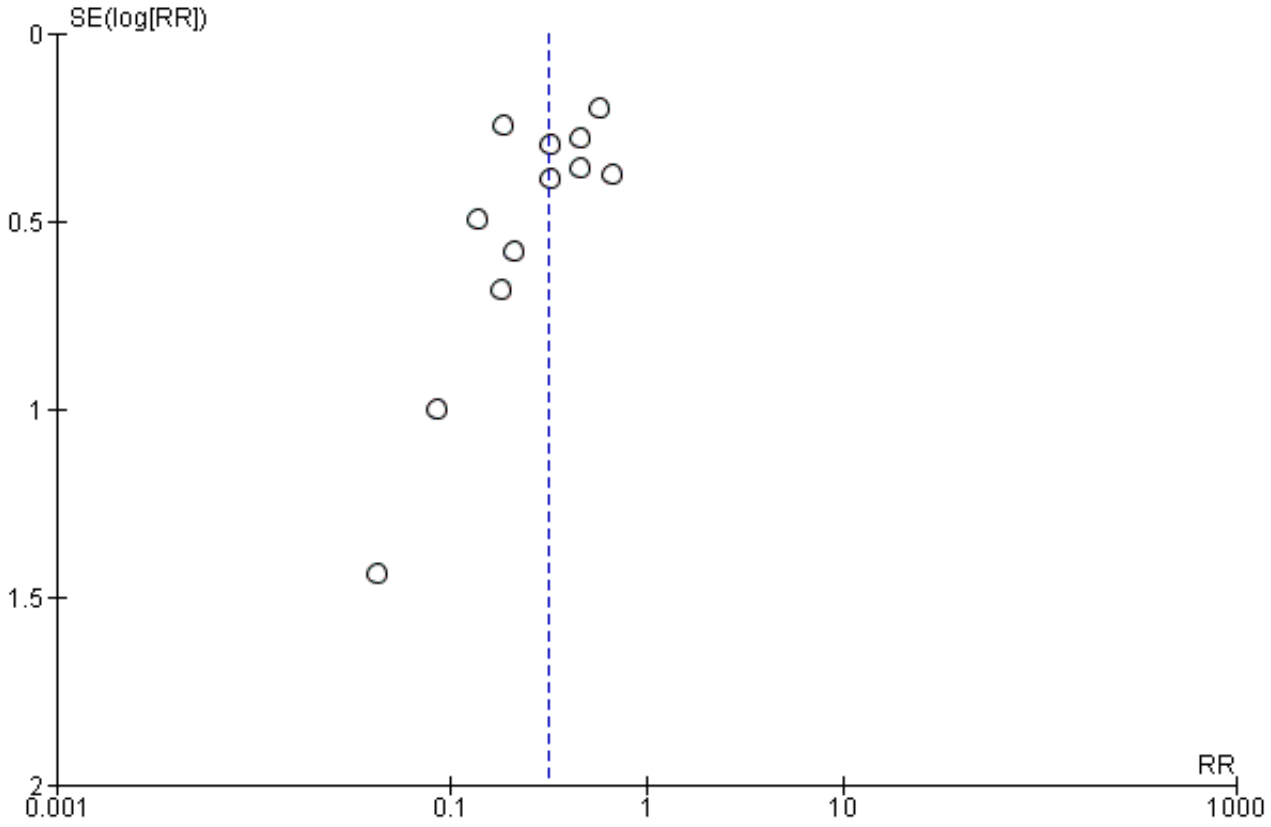
Figure 5. Funnel plot of comparison: 7 *H. pylori* eradication vs. no treatment (after initial ulcer healing): duodenal ulcer recurrence, outcome: 7.1 Proportion recurred.



***H. pylori* eradication therapy versus no treatment in preventing the recurrence of gastric ulcer (after initial ulcer had been healed)**

Twelve RCTs (Axon 1997; Bayerdorffer 1996; Befrits 2004; Fukuda 1995b; Graham 1992; Kato 1996; Lazzaroni 1997; Malfertheiner 1999; Meining 1998; Sung 1995; Tomita 2002; Tulassay 2008) reported a dichotomous gastric ulcer recurrence outcome evaluating 1476 participants, between three months and five years. Overall 15% of gastric ulcers recurred in the *H. pylori* eradication group compared with 52% in the no treatment group. There was statistically significant heterogeneity between trial results (heterogeneity test (11 degrees of freedom) Chi^2 statistic = 29.09, P = 0.002) and a random effects model was used. There was a statistically significant benefit of *H. pylori* eradication therapy compared to no treatment in the prevention of gastric ulcer recurrence (RR 0.31; 95% CI 0.22 to 0.45; Analysis 8.1) (NNTB = 3; 95% CI 2 to 5). Egger test revealed a trend towards funnel plot asymmetry (P = 0.07) with a preponderance of trials with few events showing large effects when 1/standard error was used as a measure of study size (Figure 6). Metaregression was performed to evaluate whether length of treatment in the control group, duration of eradication therapy, eradication rate, length of follow-up, number of centres, method of randomisation, concealment of allocation, blinding, intention-to-treat analysis and completeness of follow-up had any impact on the result that could explain some of the heterogeneity observed. This revealed that only concealment of allocation had any impact on effect size (RR of recurrence increased if concealment of allocation present (log RR = 0.52; 95% CI 0.28 to 0.77 P < 0.001)).

Figure 6. Funnel plot of comparison: 8 Gastric ulcer recurrence with *H. pylori* eradication vs. no treatment (after initial ulcer healing), outcome: 8.1 Proportion recurred.



***H. pylori* eradication therapy versus no treatment in preventing the recurrence of peptic ulcer (after initial ulcer had been healed)**

One RCT (Arkkila 2005) reported a dichotomous peptic ulcer recurrence outcome evaluating 103 participants at one year. Overall 8% of peptic ulcers recurred in the *H. pylori* eradication group compared with 33% in the no treatment group. There was a statistically significant benefit of *H. pylori* eradication therapy compared to no treatment in the prevention of peptic ulcer recurrence (RR 0.23; 95% CI 0.09 to 0.59; Analysis 9.1) (NNTB = 4; 95% CI 2 to 17).

Relief of symptoms from peptic ulcer

***H. pylori* eradication therapy plus ulcer-healing drug versus ulcer healing drug alone**

Two RCTs (Higuchi 2003; Suarez 1999) reported a dichotomous relief of symptoms from peptic ulcer evaluating 180 participants, between four and six weeks. Overall 49% of symptoms resolved in the *H. pylori* eradication group compared to 32% with ulcer healing drug alone. There was statistically significant heterogeneity between trial results (heterogeneity test (1 degree of freedom) Chi^2 statistic = 5.07, P = 0.02) and a random-effects model was used. There was no statistically significant benefit of *H. pylori* eradication therapy compared to ulcer-healing drug in the relief of symptoms from peptic ulcer (relative risk of symptoms persisting with *H. pylori* eradication therapy compared to ulcer-healing drug (RR 0.86; 95% CI 0.42 to 1.74; Analysis 10.1).

***H. pylori* eradication therapy versus no treatment in the relief of symptoms from peptic ulcer**

Two RCTs (Lam 1997; Pounder 1997) reported a dichotomous relief of symptoms from peptic ulcer evaluating 188 participants at four weeks. Overall 21% of symptoms resolved in the *H. pylori* eradication group compared to 42% with no treatment. There was statistically significant heterogeneity between trial results (heterogeneity test (1 degree of freedom) Chi^2 statistic = 4.19, P = 0.04) and a random-effects model was used. There was no statistically significant benefit of *H. pylori* eradication therapy compared to no treatment in the relief of symptoms from peptic ulcer (relative risk of symptoms persisting with *H. pylori* eradication therapy compared to no treatment (RR 1.27; 95% CI 0.83 to 1.93; Analysis 10.2).

Side effect profile

Total number of adverse events

Forty-three trials (Arkkila 2005; Asaka 2001; Avsar 1996; Axon 1997; Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; Bayerdorffer 1996; Befrits 2004; Bianchi Porro 1996; Carpintero 1997; Chen 1995; Fukuda 1995a; Fukuda 1995b; Graham 1991; Graham 1998; Harford 1996; Hentschel 1993; Higuchi 2003; Hosking 1992; Kato 1996; Lam 1997; Lazzaroni 1997; Lin 1994; Logan 1995; Malfertheiner 1999; Mantzaris 1993; Meining 1998; O'Morain 1996; Parente 1996;

Pinero 1995; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Sobhani 1995; Spinzi 1994; Suarez 1999; Sung 1995; Tomita 2002; Tulassay 2008; Wang 1996; Wong 1999) reported overall numbers of adverse events as a dichotomous outcome in 6093 participants. In total 22% of participants in the *H. pylori* eradication group experienced side-effects of therapy compared with 8% in the comparison regimen group. There was statistically significant heterogeneity between trial results (heterogeneity test (40 degrees of freedom) Chi^2 statistic = 80.47, P = 0.0002) and a random-effects model was used. There was a statistically significant higher number of adverse events with *H. pylori* eradication therapy over comparison regimens (relative risk of adverse events with *H. pylori* eradication therapy compared to comparison regimen (RR 2.30; 95% CI 1.77 to 2.99; Analysis 11.1) (NNTH = 10; 95% CI 8 to 14).

Diarrhoea

Thirty trials (Arkkila 2005; Asaka 2001; Bardhan 1997; Bayerdorffer 1995; Bayerdorffer 1996; Bianchi Porro 1996; Carpintero 1997; Chen 1995; Graham 1991; Graham 1998; Harford 1996; Hentschel 1993; Kato 1996; Lam 1997; Lazzaroni 1997; Lin 1994; Logan 1995; Malfertheiner 1999; Meining 1998; O'Morain 1996; Parente 1996; Pounder 1997; Rauws 1990; Shirotani 1996; Sobhani 1995; Sung 1995; Tulassay 2008; Van Zanten 1999; Wang 1996; Wong 1999) reported occurrence of diarrhoea as a dichotomous outcome in 4590 participants. Overall 8% of participants in the *H. pylori* eradication group reported diarrhoea compared with 2% in the comparison regimen group. There was no statistically significant heterogeneity between trial results (heterogeneity test (29 degrees of freedom) Chi^2 statistic = 18.13, P = 0.94). There was a statistically significant higher number of participants reporting diarrhoea with *H. pylori* eradication therapy over comparison regimens (relative risk of diarrhoea with *H. pylori* eradication therapy compared to comparison regimen (RR 2.86; 95% CI 2.11 to 3.88; Analysis 11.2) (NNTH = 24; 95% CI 17 to 37).

Nausea and/or vomiting

Fifteen trials (Bayerdorffer 1995; Bayerdorffer 1996; Carpintero 1997; Chen 1995; Graham 1991; Graham 1998; Lazzaroni 1997; Lin 1994; Mantzaris 1993; Rauws 1990; Shirotani 1996; Suarez 1999; Sung 1995; Van Zanten 1999; Wang 1996) reported occurrence of nausea or vomiting, or both as a dichotomous outcome in 1533 participants. Overall 5% of participants in the *H. pylori* eradication group reported nausea and/or vomiting compared with 0.5% in the comparison regimen group. There was no statistically significant heterogeneity between trial results (heterogeneity test (14 degrees of freedom) Chi^2 statistic = 3.72, P = 1). There was a statistically significant higher number of participants reporting nausea and/or vomiting with *H. pylori* eradication therapy over comparison regimens (relative risk of nausea and/or vomiting with *H. pylori* eradication therapy compared to comparison regimen (RR 3.76; 95% CI 1.91 to 7.37; Analysis 11.3) (NNTH = 25; 95% CI 17 to 50).

Skin rash

Eighteen trials (Arkkila 2005; Bayerdorffer 1996; Bianchi Porro 1996; Carpintero 1997; Chen 1995; Harford 1996; Hentschel 1993; Higuchi 2003; Kato 1996; Lam 1997; Logan 1995; Malfertheiner 1999; Meining 1998; Pounder 1997; Rauws 1990; Suarez 1999; Tomita 2002; Wang 1996) reported occurrence of skin rash as a dichotomous outcome in 2385 participants. Overall 2% of participants in the *H. pylori* eradication group reported skin rash compared with 1% in the comparison regimen group. There was no statistically significant heterogeneity between trial results (heterogeneity test (17 degrees of freedom) Chi^2 statistic = 10.60, P = 0.88). There was no statistically significant higher number of participants reporting skin rash with *H. pylori* eradication therapy over comparison regimens (relative risk of skin rash with *H. pylori* eradication therapy compared to comparison regimen (RR 1.36; 95% CI 0.78 to 2.37; Analysis 11.4).

Headache

Fourteen trials (Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; Bayerdorffer 1996; Carpintero 1997; Chen 1995; Graham 1998; Harford 1996; Logan 1995; Pinero 1995; Pounder 1997; Sobhani 1995; Tulassay 2008; Van Zanten 1999) reported occurrence of headache as a dichotomous outcome in 2292 participants. Overall 3% of participants in the *H. pylori* eradication group reported headache compared with 3% in the comparison regimen group. There was no statistically significant heterogeneity between trial results (heterogeneity test (13 degrees of freedom) Chi^2 statistic = 7.27, P = 0.89). There was no statistically significant higher number of participants reporting headache with *H. pylori* eradication therapy over comparison regimens (relative risk of headache with *H. pylori* eradication therapy compared to comparison regimen (RR 1.11; 95% CI 0.70 to 1.75; Analysis 11.5).

Epigastric pain

Eleven trials (Bayerdorffer 1995; Bayerdorffer 1996; Bianchi Porro 1996; Carpintero 1997; Chen 1995; Logan 1995; Pounder 1997; Sobhani 1995; Sung 1995; Van Zanten 1999; Wong 1999) reported occurrence of epigastric pain as a dichotomous outcome in 1491 participants. Overall 5% of participants in the *H. pylori* eradication group reported epigastric pain compared with 0.6% in the comparison regimen group. There was no statistically significant heterogeneity between trial results (heterogeneity test (10 degrees of freedom) Chi^2 statistic = 4.94, P = 0.9). There was a statistically significant higher number of participants reporting epigastric pain with *H. pylori* eradication therapy over comparison regimens (relative risk of epigastric pain with *H. pylori* eradication therapy compared to comparison regimen (RR 4.09; 95% CI 1.90 to 8.82; Analysis 11.6) (NNTH = 25; 95% CI 20 to 50).

Altered taste

Thirteen trials (Arkkila 2005; Asaka 2001; Bayerdorffer 1996; Carpintero 1997; Fukuda 1995b; Logan 1995; Malfertheiner 1999; Mantzaris 1993; O'Morain 1996; Pinero 1995; Pounder 1997; Tulassay 2008; Van Zanten 1999) reported occurrence of altered taste as a dichotomous outcome in 2299 participants. Overall 7% of participants in the *H. pylori* eradication group reported altered taste compared with 0.4% in the comparison regimen group. There was no statistically significant heterogeneity between trial results (heterogeneity test (12 degrees of freedom) Chi^2 statistic = 6.16, P = 0.91). There was a statistically significant higher number of participants reporting altered taste with*H. pylori* eradication therapy over comparison regimens (relative risk of altered taste with *H. pylori* eradication therapy compared to comparison regimen (RR 8.85; 95% CI 4.38 to 17.90; Analysis 11.7) (NNTH = 15; 95% CI 10 to 30).

Stomatitis

Eight trials (Arkkila 2005; Bayerdorffer 1996; Bianchi Porro 1996; Carpintero 1997; Lazzaroni 1997; Shirotani 1996; Sobhani 1995; Suarez 1999) reported occurrence of stomatitis as a dichotomous outcome in 838 participants. Overall 2.5% of participants in the *H. pylori* eradication group reported stomatitis compared to 0.3% in the comparison regimen group. There was no statistically significant heterogeneity between trial results (heterogeneity test (seven degrees of freedom) Chi^2 statistic = 1.24, P = 0.99). There was no statistically significant higher number of participants reporting stomatitis with *H. pylori* eradication therapy over comparison regimens (relative risk of stomatitis with *H. pylori* eradication therapy compared to comparison regimen (RR 2.65; 95% CI 0.94 to 7.48; Analysis 11.8).

DISCUSSION

Summary of main results

The most important finding of this review concerns the ulcer recurrence rate of people with duodenal or gastric ulcer treated with *H. pylori* eradication therapy compared to those given a short-term course of ulcer-healing drug. There was a significant relative risk reduction of 80% in the recurrence of duodenal ulcer, and a slightly smaller but still significant risk ratio reduction of 69% for gastric ulcer. The difference in results between duodenal and gastric ulcer probably reflects the lower control relapse rate seen in the latter disease. In addition, one week of *H. pylori* eradication therapy appears to be at least as effective as maintenance therapy with ulcer-healing drug in the recurrence of duodenal ulcer. This review also finds that *H. pylori* eradication therapy has a small benefit over ulcer-healing drug, and a larger benefit over no treatment or placebo in the healing of duodenal ulcer. This does not appear to be the case in the healing of gastric ulcer, where our results show a slight increase in healing rates with ulcer-healing drug alone. Overall *H. pylori* eradication rate in all trials was 68%. Finally, there appears to be no significant improvement in relief of symptoms of peptic ulcer disease with *H. pylori* eradication therapy over comparison regimen, although the number of trials that report this outcome is small. There are also no studies that have evaluated symptoms beyond six weeks, and it is the long-term effect of *H. pylori* eradication on peptic ulcer disease symptoms that is important. These advantages are offset by an increased incidence of short-term side effects. People receiving eradication therapy report a higher incidence of side effects, with a greater than two-fold increase in the risk of adverse events in people assigned to comparison regimen rather than *H. pylori* eradication therapy. Although these unwanted effects are only short-term they may be significant (Moayyedi 2000).

Overall completeness and applicability of evidence

Further trials comparing *H. pylori* eradication therapy with placebo in the healing of gastric ulcer disease are required. In addition, more trials reporting the effect of eradication therapy on symptoms arising from peptic ulcer are required.

Quality of the evidence

Only a small proportion of all trials identified were of high quality, in terms of their reporting of the methods used to generate the randomisation sequence and conceal treatment allocation. In addition, a significant number did not report losses to follow-up completely and could not be judged to be free from selective reporting. Details of these issues are provided in the 'Summary of findings' tables.

Potential biases in the review process

We have explored reasons for heterogeneity in the results using metaregression. These results need to be interpreted with caution as metaregression evaluates the average of patient characteristics within each trial and is open to giving spurious results due to the ecological fallacy (Lau 1998). Nevertheless the finding that effects size was reduced in trials with adequate concealment of allocation in the long term gastric ulcer recurrence trials, and effect size increased with absence of blinding in short term gastric ulcer healing trials, is consistent with previous reports of the general systematic review literature (Moher 1999). The reduction of effect size with intention-to-treat analysis in the long-term duodenal and gastric ulcer recurrence trials is also consistent with this literature (Moher 1999) and the increase in effect size with increasing eradication rate is biologically plausible.

Agreements and disagreements with other studies or reviews

These findings support the recommendations of the European *Helicobacter pylori* Study Group (EHPSG) and the American Gastroenterological Association, both of which recommend a recognised course of *H. pylori* eradication therapy for the treatment of *H. pylori*-positive peptic ulcer disease (Howden 1998; Malfertheiner 2002b). This approach is also advocated from a health economic perspective from models (Briggs 1996; Imperiale 1995) and also a randomised controlled trial (Sonnenberg 1998), all of which show a reduced use of ulcer-related health care resources compared to conventional ulcer-healing drug therapy in subsequent follow-up.

Two systematic reviews have previously been conducted in this area (Leodolter 2001; Moore 1994). Both these reviews reported a greater benefit from*H. pylori* eradication therapy in peptic ulcer disease than our review. In the earlier of these studies (Moore 1994), ulcer-healing rates of 90% to 95% with*H. pylori* eradication therapy were reported, compared to 75% to 85% in our review, and ulcer-recurrence rates of less than 10%, compared to 12% to 15%. The more recent (Leodolter 2001) quoted healing rates of 87% to 93% and recurrence rates of 2% to 3%. This could be accounted for by our use of intention-to-treat data. We assumed all participants lost to follow-up in the trials were treatment failures, whereas the authors of the two previous studies only used intention-to-treat data where reported.

The study by Moore was performed in 1994 and there has been considerable information published in the interim period. In addition, the study author did not perform a separate analysis for duodenal and gastric ulcers, but amalgamated results into an overall healing and recurrence rate for peptic ulcers. The later meta-analysis, Leodolter 2001 has several differences from our review. Firstly, it was designed to reveal the efficacy of eradication therapy in healing and preventing recurrence of duodenal ulcer compared to gastric ulcer. This means that articles were only eligible for inclusion if they contained data for both duodenal and gastric ulcer healing or recurrence, reported separately. Secondly, in order to 'limit' the number of studies eligible for inclusion in the healing analysis only trials that used PPI-based eradication regimens were

used. Finally, there were several non-randomised or uncontrolled studies, or both included in the analysis. Neither of these two previous reviews reported data for symptom relief or adverse events. We have addressed all these issues in our review.

AUTHORS' CONCLUSIONS

Implications for practice

Adding a one to two-week course of *H. pylori* eradication therapy is an effective treatment for people with *H. pylori*-positive duodenal ulcer when compared to ulcer-healing drugs alone and no treatment. *H. pylori* eradication therapy is also effective in preventing recurrence of duodenal and gastric ulcer compared to no treatment. There is currently no evidence that *H. pylori* eradication therapy is an effective treatment in people with gastric ulcer or that it is effective in preventing recurrence of duodenal ulcer compared to ulcer-healing drug. However, confidence intervals were wide and significant benefits or harms of *H. pylori* eradication therapy in acute ulcer healing of gastric ulcers compared to no treatment and in preventing recurrence of duodenal ulcers compared to ulcer healing drugs cannot be ruled out.

Implications for research

This review has identified some directions for further research. In the future, papers should state the method of randomisation, allocation of concealment, and masking more clearly. More trials are needed to evaluate *H. pylori* eradication therapy in the healing of gastric ulcer disease, particularly comparing antibiotic therapy with placebo. Finally, there has been little data on symptom relief and quality of life changes and this should be addressed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Arkkila 2005

Methods	Multi-centre RCT Double-blinded
Participants	Finland 115 people with peptic ulcer
Interventions	Bi quadruple therapy (2 weeks colloidal bismuth subcitrate 120 mg qds, lansoprazole 30 mg bd, tetracycline 500 mg qds, and metronidazole 400 mg qds) PPI triple therapy (2 weeks lansoprazole 30 mg bd,

Arkkila 2005 *(Continued)*

	amoxicillin 500 mg qds, and clarithromycin 500 mg tds) PPI dual therapy (lansoprazole 30 mg bd and amoxicillin 500 mg qds) versus PPI (lansoprazole 30 mg bd for 2 weeks, then 30 mg od for 2 weeks)
Outcomes	Ulcer healing Ulcer recurrence *H. pylori* eradication rates
Notes	Eradication rates: Bi quadruple therapy 89% PPI triple therapy 100% PPI dual therapy 80% PPI 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment groups were determined by a list of random numbers generated by computer
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Endoscopists were blinded for the treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Collected serology for *H. pylori* status but did not record these data
Other bias	High risk	Participants in placebo arm had *H. pylori* eradication at 8 weeks so 12 month follow-up not randomised

Asaka 2001

Methods	Multi-centre RCT Double-blinded
Participants	Japan 536 people with gastric or duodenal ulcer
Interventions	PPI triple therapy (5 weeks (DU)/7 weeks (GU) lansoprazole 30 mg bd, 1 week amoxicillin 750 mg bd and clarithromycin 200 mg/400 mg bd) versus PPI (5 weeks (DU)/7 weeks (GU) lansoprazole 30 mg bd)
Outcomes	Ulcer healing *H. pylori* eradication rates
Notes	Eradication rates: PPI triple therapy group 76.9% PPI group 1.89%

Risk of bias

Asaka 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Avsar 1996

Methods	Single-centre RCT Single-blinded
Participants	Turkey 45 people with duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120 mg qds, 2 weeks tetracycline 250 mg qds and metronidazole 250 mg tds) versus PPI (8 weeks omeprazole 40 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy group 78.3% PPI group 36.4%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"Endoscopies were performed by one of the authors, who was blinded to the clinical data, bacteriological findings and treatment regimen"
Incomplete outcome data (attrition bias)	Low risk	20/45 (44%) lost to follow up

Avsar 1996 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported in sufficient detail
Other bias	Low risk	There was no other bias

Axon 1997

Methods	Multi-centre RCT Double-blinded
Participants	UK and Republic of Ireland 129 people with gastric ulcer
Interventions	PPI dual therapy (8 weeks omeprazole 40mg od and 2 weeks amoxicillin 750 mg bd) versus PPI (8 weeks omeprazole 40 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy group 48.3% PPI group 4.8%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation... From a computer generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind, double dummy design"
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Bardhan 1997

Methods	Multi-centre RCT Double-blinded

Bardhan 1997 *(Continued)*

Participants	Multi-national 232 people with duodenal ulcer
Interventions	RBC dual therapy (2 weeks RBC 400 mg/800 mg bd and clarithromycin 250 mg qds, then 2 weeks RBC 400 mg bd) versus RBC (4 weeks RBC 400 mg bd)
Outcomes	Ulcer healing Ulcer recurrence at 28 weeks *H. pylori* eradication rates
Notes	Eradication rates: RBC dual therapy 76.6% RBC 1.4%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind,double dummy"
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Bayerdorffer 1992

Methods	Multi-centre RCT Single-blinded
Participants	Germany 58 people with duodenal ulcer
Interventions	PPI dual therapy (10 days omeprazole 40 mg bd and amoxicillin 1 g bd, then 4 1/2 weeks omeprazole 20 mg od) versus PPI (10 days omeprazole 40 mg bd then 4 1/2 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 75.9% PPI 0%

Bayerdorffer 1992 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"investigator blinded clinical trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Endoscopy performed if symptoms recurred but this data not given
Other bias	Low risk	There was no other bias

Bayerdorffer 1995

Methods	Multi-centre RCT Double-blinded
Participants	Germany 264 people with duodenal ulcer
Interventions	PPI dual therapy (2 weeks omeprazole 40 mg tds and amoxicillin 750 mg tds, then 4 weeks omeprazole 20 mg od) versus PPI (2 weeks omeprazole 40 mg tds then 4 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 88.9% PPI 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind" "placebo treatment"

Bayerdorffer 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Highlighted differences in pretreatment with omeprazole but it is hard to believe that this was the only subgroup analysed
Other bias	Low risk	There was no other bias

Bayerdorffer 1996

Methods	Multi-centre RCT Single-blinded
Participants	Germany 130 people with gastric ulcer
Interventions	Bi triple therapy (8 weeks bismuth subsalicylate 600 mg tds, 10 days amoxicillin 500 mg bd and tinidazole 1 g bd) versus PPI (8 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 18 months *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 66.1% PPI 7.7% If ulcer not healed at 8 weeks Bi/PPI continued for a further 4 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Low risk	"Randomisation was carried out by a central study secretariat"
Blinding (performance bias and detection bias) All outcomes	Low risk	"investigator blinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Befrits 2004

Methods	Multi-centre RCT Double-blinded
Participants	Sweden 103 people with gastric ulcer
Interventions	PPI triple therapy (1 week omeprazole 20 mg bd, metronidazole 400 mg bd, clarithromycin 250 mg bd) versus PPI (1 week omeprazole 20 mg bd then 3 weeks 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 5 years *H. pylori* eradication rates
Notes	Eradication rates: PPI triple therapy 64% PPI 2%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind? Using placebo of the same size and appearance as conventional metronidazole and clarithromycin tablets"
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported in sufficient detail
Other bias	Low risk	There was no other bias

Bianchi Porro 1993

Methods	Single-centre RCT Double-blinded
Participants	Italy 183 people with duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120 mg qds, 1 week amoxicillin 1 g tds and tinidazole 500 mg bd) versus sucralfate (4 weeks 1 g qds)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates

Bianchi Porro 1993 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"allocated, according to a randomised list"
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	This information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported according to *H. pylori* status for 12 month data rather than randomised groups
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	High risk	Reported data according to *H. pylori* status rather than ITT

Bianchi Porro 1996

Methods	Single-centre RCT Unblinded
Participants	Italy 32 people with duodenal ulcer
Interventions	PPI triple therapy (4 weeks omeprazole 20 mg od, 2 weeks metronidazole 250 mg qds and amoxicillin 1 g tds) versus PPI (4 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at one year *H. pylori* eradication rates
Notes	If the ulcer did not heal, participants crossed over to other therapy, therefore we were unable to extract eradication rates

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias)	High risk	Blinding was not performed

Bianchi Porro 1996 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Carpintero 1997

Methods	Single-centre RCT Unblinded
Participants	Spain 122 people with duodenal ulcer
Interventions	Bi triple therapy (6 weeks colloidal bismuth subcitrate 120 mg qds, 12 days amoxicillin 500 mg tds and metronidazole 500 mg bd) or H2RA triple therapy (6 weeks ranitidine 300 mg qds, 12 days amoxicillin 500 mg tds and metronidazole 500 mg bd) versus H2RA (6 weeks ranitidine 300 mg qds)
Outcomes	Ulcer healing Ulcer recurrence at 18 months *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 86.8% H2RA triple therapy 25% H2RA 0%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"treatment assignments were determined by a list of random numbers generated by computer"
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	Data only on group A 39/44, Group B 38/40 and group C 34/38 at 12 months
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Chen 1995

Methods	Single-centre RCT Single-blinded
Participants	Taiwan 62 people with duodenal ulcer
Interventions	Bi triple therapy (1 or 2 weeks colloidal bismuth subcitrate 120 mg qds, amoxicillin 500 mg tds and metronidazole 500 mg tds) versus no treatment
Outcomes	Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 93.9% No treatment 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Dyspepsia symptoms obtained but not reported
Other bias	Low risk	There was no other bias

Feng 2005

Methods	Single-centre RCT Double-blinded
Participants	China 75 people with peptic ulcer
Interventions	PPI triple therapy (10 days lansoprazole 30 mg qds, clarithromycin 250 mg bd, amoxicillin 500 mg bd) versus 'killing' quadruple therapy (10 days lansoprazole 30 mg qds, clarithromycin 250 mg bd, amoxicillin 500 mg bd and 4 weeks *H. pylori* 'killing' capsule 6 bd) versus placebo
Outcomes	Ulcer healing at 4 weeks Ulcer recurrence at 5 years

Feng 2005 *(Continued)*

	H. pylori eradication rates
Notes	Eradication rates: PPI triple therapy 94% PPI 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind", The medicine, starch or placebo (gastropine) was packed in gelatin capsules of similar appearance. The investigators did not know what medicines were given to patients, and the patients did not know what medicines they had taken"
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 5 participants not reported on at one year
Selective reporting (reporting bias)	High risk	Dyspepsia symptoms data obtained but not reported (only that upper abdominal pain was significantly less ($P < 0.05$) in group B)
Other bias	Low risk	There was no other bias

Figueroa 1996

Methods	Single-centre RCT Unblinded
Participants	Chile 113 people with duodenal ulcer
Interventions	Bi quadruple therapy (4 weeks omeprazole 20 mg qds, bismuth subsalicylate 524 mg qds, amoxicillin 500 mg tds and metronidazole 250 mg tds) versus PPI (4 weeks omeprazole 20nmg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Bi quadruple therapy 82.5% PPI 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available

Figueroa 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"single blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Fukuda 1995a

Methods	Single-centre RCT Unblinded
Participants	Japan 65 people with gastric ulcer
Interventions	PPI dual therapy (8 weeks lansoprazole 30 mg od and 2 weeks clarithromycin 200 mg tds) versus PPI (8 weeks omeprazole 20 mg od or lansoprazole 30 mg od)
Outcomes	Ulcer healing *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 62.5% PPI 24.2% All participants received 4 weeks' ranitidine 150 mg od after initial therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This information was not available
Selective reporting (reporting bias)	Unclear risk	This information was not available

Fukuda 1995a *(Continued)*

Other bias	Low risk	There was no other bias

Fukuda 1995b

Methods	Single-centre RCT Single-blinded
Participants	Japan 86 people with gastric ulcer
Interventions	PPI dual therapy (8 weeks lansoprazole 30 mg qds and 2 weeks clarithromycin 200 mg tds/amoxicillin 500 mg tds) versus PPI (8 weeks omeprazole 20 mg qds or lansoprazole 30 mg qds)
Outcomes	Ulcer healing Ulcer recurrence at 40 weeks *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 48.6% PPI 12.2% All participants received 4 weeks ranitidine 150 mg od after initial therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"endoscopy was performed at 3 month intervals by a gastroenterologist who was kept uninformed of the details of the patients' past medical histories"
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 2 participants missing
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Furuta 1995

Methods	Single-centre RCT Unblinded
Participants	Japan 67 people with gastric or duodenal ulcer

Furuta 1995 *(Continued)*

Interventions	PPI dual therapy (6 weeks lansoprazole 30 mg qds and 2 weeks amoxicillin 1-2 g qds) versus PPI (6 weeks lansoprazole 30 mg qds)
Outcomes	Ulcer healing *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 62.5% PPI 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers not given at end of follow-up just percentages
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Graham 1991

Methods	Single-centre RCT Single-blinded
Participants	USA 105 people with duodenal ulcer
Interventions	Bi triple therapy (2 weeks bismuth subsalicylate 300 mg qds/150 mg tds + 300 mg nocte, tetracycline 500 mg qds and metronidazole 250 mg tds) versus H2RA (16 weeks ranitidine 300 mg od)
Outcomes	Ulcer healing *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 82.7% H2RA 0% All participants received 16 weeks H2RA

Risk of bias

Bias	Authors' judgement	Support for judgement

Graham 1991 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"results were not shared with the endoscopist"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Percentages rather than numbers given for follow-up data (6 lost to follow up in the eradication group)
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported
Other bias	Low risk	There was no other bias

Graham 1992

Methods	Single-centre RCT Single-blinded
Participants	USA 109 people with gastric or duodenal ulcer
Interventions	Bi triple therapy (2 weeks bismuth subsalicylate 300 mg qds/150 mg tds + 300 mg nocte, tetracycline 500 mg qds and metronidazole 250 mg tds) versus H2RA (16 weeks ranitidine 300 mg od)
Outcomes	Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 88.7% H2RA 0% All participants received 16 weeks H2RA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"the endoscopist was blinded to the treatment status of the patient"
Incomplete outcome data (attrition bias)	Low risk	83/112 (74%) with ulcer healing agreed to enter follow-up part of study

Graham 1992 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported
Other bias	Low risk	There was no other bias

Graham 1998

Methods	Multi-centre RCT Double-blinded
Participants	USA and Puerto Rico 153 people with duodenal ulcer
Interventions	RBC dual therapy (4 weeks RBC 400 mg bd, 2 weeks amoxicillin 500 mg qds) versus Bi (4 weeks RBC 400 mg bd) and placebo
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: RBC dual therapy 40% RBC 0% Placebo 0%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind" placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	24-week data reported as percentage not absolute numbers
Selective reporting (reporting bias)	High risk	24-week data according to *H. pylori* status not randomised groups
Other bias	Low risk	There was no other bias

Harford 1996

Methods	Multi-centre RCT

Harford 1996 *(Continued)*

	Double-blinded
Participants	USA 196 people with duodenal ulcer
Interventions	PPI dual therapy (2 weeks lansoprazole 30 mg bd/tds and amoxicillin 1 g tds) versus PPI (2 weeks lansoprazole 30 mg tds)
Outcomes	Ulcer healing *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 55.1% PPI 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebos were supplied to maintain the double-blind nature of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Ulcer data missing on 50/262 (19%) subjects
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Hentschel 1993

Methods	Two centre RCT Double-blinded
Participants	Austria 104 people with duodenal ulcer
Interventions	H2RA triple therapy (6 weeks ranitidine 300 mg od, 12 days amoxicillin 750 mg tds and metronidazole 500 mg tds) versus H2RA (6 weeks ranitidine 300 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: H2RA triple therapy 88.5% H2RA 1.9%

Hentschel 1993 *(Continued)*

	If ulcer not healed at 6 weeks ranitidine continued for a further 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical appearing placebos"
Incomplete outcome data (attrition bias) All outcomes	High risk	1/104 dropped out (from eradication group)
Selective reporting (reporting bias)	High risk	Histology taken but not reported
Other bias	Low risk	There was no other bias

Higuchi 2003

Methods	Two-centre RCT Single-blinded
Participants	Japan 120 people with gastric ulcer
Interventions	PPI triple therapy (1 week lansoprazole 30 mg od or rabeprazole 20 mg od plus amoxicillin 1.5 g od and clarithromycin 800 mg od) versus PPI (lansoprazole 30 mg od or rabeprazole 20 mg od)
Outcomes	Ulcer healing Global symptoms cured *H. pylori* eradication rates
Notes	Eradication rates: PPI triple therapy 83.6% PPI 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a table of random numbers was used to generate the randomisation sequence"
Allocation concealment (selection bias)	Low risk	"using sealed opaque envelopes numbered sequentially and containing the assignment"
Blinding (performance bias and detection bias)	Low risk	"Patients and their physicians were aware of the treatment assignment, but endoscopists and pathologists were not"

Higuchi 2003 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	109/120 (91%) completed trial
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Hosking 1992

Methods	Single-centre RCT Single-blinded
Participants	Hong Kong 155 people with duodenal ulcer
Interventions	Bi quadruple therapy (4 weeks omeprazole 40 mg qds, 1 week colloidal bismuth subcitrate 120 mg qds, tetracycline 500 mg qds and metronidazole 400 mg qds) versus PPI (4 weeks omeprazole 40 mg qds)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Bi quadruple therapy 89.7% PPI 3.9%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised by instructions"
Allocation concealment (selection bias)	Low risk	"randomised in consecutively numbered sealed opaque envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"staff performing the endoscopic and bacteriologic assessments were unaware of the drugs the patient had been taking"
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Kato 1996

Methods	Single-centre RCT Unblinded
Participants	Japan 119 people with gastric or duodenal ulcer
Interventions	PPI dual therapy (6 weeks (DU)/8 weeks (GU) lansoprazole 30 mg od and 2 weeks amoxicillin 500 mg qds) versus PPI (6 weeks (DU)/8 weeks (GU) lansoprazole 30 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 36.5% PPI 1.8%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	99/119 (83%) completed 1 year follow up
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Katoh 1995

Methods	Single-centre RCT Unblinded
Participants	Japan 133 people with gastric or duodenal ulcer
Interventions	PPI dual therapy (6 weeks (DU)/8 weeks (GU) lansoprazole 30 mg od and 2 weeks amoxicillin 500 mg qds) versus PPI (6 weeks (DU)/8 weeks (GU) lansoprazole 30mg od)
Outcomes	Ulcer healing *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 38.8%

Katoh 1995 *(Continued)*

	PPI 9.4%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Kepecki 1999

Methods	Single-centre RCT Unblinded
Participants	Turkey 73 people with duodenal ulcer
Interventions	PPI triple therapy (1 week omeprazole 20 mg bd, amoxicillin 1 g bd and metronidazole 500 mg tds, then 3 weeks omeprazole 20 mg od) versus PPI (1 week omeprazole 20 mg bd then 3 weeks 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 2 years *H. pylori* eradication rates
Notes	Eradication rates: PPI triple therapy 82% PPI 0% PPI group received long-term famotidine 20 mg od

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available

Kepecki 1999 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Kim 2002

Methods	Single-centre RCT Single-blinded
Participants	South Korea 53 people with duodenal ulcer
Interventions	PPI triple therapy (1 week omeprazole 20 mg bd, amoxicillin 1 g bd and clarithromycin 500 mg bd) versus no treatment
Outcomes	Ulcer recurrence at 30 months *H. pylori* eradication rates
Notes	Eradication rates: PPI triple therapy 83.3% No treatment 0% Participants with ulcers not eradicated with triple therapy received Bi quadruple therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomised?.using a computer generated list"
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"two experienced endoscopists, who were blind to the clinical data"
Incomplete outcome data (attrition bias) All outcomes	High risk	"no patient was lost to follow up"
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Lam 1997

Methods	Single-centre RCT Double-blinded
Participants	Hong Kong 97 people with duodenal ulcer
Interventions	Clarithromycin monotherapy (2 weeks clarithromycin 250 mg qds) versus placebo
Outcomes	Ulcer healing Global symptoms cured *H. pylori* eradication rates
Notes	Eradication rates: Clarithromycin monotherapy 70.8% Placebo 10.2% Clarithromycin participants also received amoxicillin and metronidazole

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"placebo capsules were identical in appearance and taste"
Incomplete outcome data (attrition bias) All outcomes	Low risk	81/97 (83%) completed the trial
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Lazzaroni 1997

Methods	Single-centre RCT Double-blinded
Participants	Italy 59 people with gastric ulcer
Interventions	PPI dual therapy (4 weeks omeprazole 20 mg bd and 2 weeks amoxicillin 1 g tds) versus PPI (4 weeks omeprazole 20 mg bd)
Outcomes	Ulcer healing Ulcer recurrence at 1 year

Lazzaroni 1997 *(Continued)*

	H. pylori eradication rates
Notes	Eradication rates: PPI dual therapy 62.1% PPI 6.7%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"allocated according to a computer generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind" placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	15/59 (25%) lost to follow up
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported in sufficient detail
Other bias	Low risk	There was no other bias

Lin 1994

Methods	Single-centre RCT Unblinded
Participants	Taiwan 42 people with duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120 mg qds, 1 week metronidazole 250 mg qds and amoxicillin 500 mg qds) versus H2RA (4 weeks famotidine 20 mg bd)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 100% H2RA 4.8%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available

Lin 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	3/42 (7%) lost to follow up at 12 months
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Logan 1995

Methods	Multi-centre RCT Double-blinded
Participants	UK 148 people with duodenal ulcer
Interventions	PPI dual therapy (4 weeks omeprazole 40 mg od and 2 weeks clarithromycin 500 mg tds) versus PPI (4 weeks omeprazole 40 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 81.4% PPI 1.3%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically appearing placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"17 clarithromycin treated patients lost to follow up"
Selective reporting (reporting bias)	High risk	Symptom data not reported at one year

Logan 1995 *(Continued)*

Other bias	Low risk	There was no other bias

Malfertheiner 1999

Methods	Multi-centre RCT Double-blinded
Participants	Germany, Hungary and Poland 145 people with gastric ulcer
Interventions	PPI triple therapy (1 week omeprazole 20 mg bd, amoxicillin 1 g bd and clarithromycin 500 mg bd or 1 week omeprazole 20 mg bd, metronidazole 400 mg bd and clarithromycin 250 mg bd) versus PPI (1 week omeprazole 20 mg bd)
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: PPI triple therapy 82.4% PPI 4.2% PPI given until ulcer healing in control arm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical tablets/capsules containing active drug or placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number lost to follow up at 6 months not stated
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Mantzaris 1993

Methods	Single-centre RCT Single-blinded
Participants	Greece 33 people with duodenal ulcer

Mantzaris 1993 *(Continued)*

Interventions	Bi triple therapy (8 weeks colloidal bismuth subcitrate 120 mg qds, 2 weeks tetracycline 500 mg qds and metronidazole 500 mg tds) versus Bi (8 weeks colloidal bismuth subcitrate 120 mg qds)
Outcomes	Ulcer healing Ulcer recurrence at 18 months *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 58.8% Bi 6.3%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"Endoscopies were all performed by the same physician who was unaware of the patient's treatment category"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/12 in *H. pylori* eradication arm withdrew because of side effects
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported in sufficient detail
Other bias	Low risk	There was no other bias

Meining 1998

Methods	Multi-centre RCT Double-blinded
Participants	Germany 185 people with gastric ulcer
Interventions	PPI dual therapy (2 weeks omeprazole 40 mg bd and amoxicillin 750 mg tds then 2 weeks omeprazole 20 mg od) versus PPI (2 weeks omeprazole 40 mg bd then 2 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 3 months *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 61% PPI 5.9%

Risk of bias

Meining 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Each centre had its own randomisation list"
Allocation concealment (selection bias)	Low risk	"Randomisation was carried out by a central study secretariat"
Blinding (performance bias and detection bias) All outcomes	Low risk	"amoxicillin-placebo" "double-blind trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	23/185 (12%) missed follow up
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported
Other bias	Low risk	There was no other bias

Mones 2001

Methods	Multi-centre RCT Double-blinded
Participants	Spain 85 people with duodenal ulcer
Interventions	PPI triple therapy (1 week omeprazole 20 mg bd, amoxicillin 1 g bd and clarithromycin 500 mg bd then 3 weeks omeprazole 20 mg od) versus PPI (1 week omeprazole 20 mg bd then 3 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: PPI triple therapy 76.2% PPI 0% PPI participants given 1 year of ranitidine 150 mg od

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using a computerized randomisation program"
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind" "antibiotic matching placebo"

Mones 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This information was not available
Selective reporting (reporting bias)	High risk	Dyspepsia symptoms obtained but not reported
Other bias	Low risk	There was no other bias

O'Morain 1996

Methods	Multi-centre RCT Double-blinded
Participants	Republic of Ireland, Germany and New Zealand 208 people with duodenal ulcer
Interventions	PPI dual therapy (2 weeks omeprazole 40 mg od and clarithromycin 500 mg tds, then 2 weeks omeprazole 20 mg od) versus PPI (2 weeks omeprazole 40 mg od then 2 weeks 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 62.7% PPI 0.9%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind" "identically appearing placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	33/208 (16%) did not have follow up endoscopy
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Parente 1996

Methods	Single-centre RCT Unblinded
Participants	Italy 96 people with duodenal ulcer
Interventions	PPI dual therapy (4 weeks lansoprazole 30 mg bd and 2 weeks amoxicillin 1 g tds) and Bi quadruple therapy (4 weeks lansoprazole 30 mg od, 2 weeks bismuth 240 mg bd, amoxicillin 1 g tds and tinidazole 500 mg bd) versus PPI (4 weeks lansoprazole 30 mg od)
Outcomes	Ulcer healing *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 51.6% Bi quadruple therapy 81.3% PPI 3%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Pinero 1995

Methods	Single-centre RCT Unblinded
Participants	Venezuela 60 people with duodenal ulcer
Interventions	Bi triple therapy (2 weeks colloidal bismuth subcitrate 120 mg qds, amoxicillin 500 mg tds and metronidazole 500 mg tds) versus PPI (4 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 3 months *H. pylori* eradication rates

Pinero 1995 *(Continued)*

Notes	Eradication rates: Bi triple therapy 63.3% PPI 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Unclear risk	This information was not available
Other bias	Low risk	There was no other bias

Pounder 1997

Methods	Multi-centre RCT Double-blinded
Participants	Multi-national 91 people with duodenal ulcer
Interventions	RBC dual therapy (2 weeks RBC 400 mg/800 mg bd and clarithromycin 250 mg qds, then 2 weeks RBC 400 mg bd) versus RBC (4 weeks 400 mg bd)
Outcomes	Ulcer healing Ulcer recurrence at 2 months Global symptoms cured *H. pylori* eradication rates
Notes	Eradication rates: RBC dual therapy 57.4% RBC 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available

Pounder 1997 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"blinded study" "placebo capsules"
Incomplete outcome data (attrition bias) All outcomes	High risk	10/95 (11%) lost to follow up
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Rauws 1990

Methods	Single-centre RCT Single-blinded
Participants	Netherlands 66 people with duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120 mg qds and amoxicillin 375 mg tds, 10 days metronidazole 500 mg tds) versus Bi (4 weeks colloidal bismuth subcitrate 120 mg qds)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 62.5% Bi 7.7% All participants received a further 4 weeks ranitidine 150 mg od

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	"open study"
Incomplete outcome data (attrition bias) All outcomes	High risk	5/24 on triple therapy withdrew due to side effects, 11 others lost to follow up

Rauws 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Schwartz 1998

Methods	Multi-centre RCT Double-blinded
Participants	USA 352 people with duodenal ulcer
Interventions	PPI dual therapy (2 weeks lansoprazole 30 mg bd and clarithromycin 500 mg bd/tds or 2 weeks lansoprazole 30 mg bd/tds and amoxicillin 1 g tds) and triple therapy (2 weeks lansoprazole 30 mg bd, amoxicillin 1 g bd and clarithromycin 500 mg bd) versus PPI (2 weeks lansoprazole 30 mg tds)
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 65.5% PPI triple therapy 93.6% PPI 1.9%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"all study medication was matched with placebo to maintain the double-blind nature of the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This information was not available
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Shirotani 1996

Methods	Single-centre RCT Single-blinded

Shirotani 1996 *(Continued)*

Participants	Japan 50 people with duodenal ulcer
Interventions	H2RA triple therapy (6 weeks cimetidine 400 mg bd, 2 weeks amoxicillin 300 mg tds and metronidazole 250 mg tds) versus H2RA (6 weeks cimetidine 400 mg bd)
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: H2RA triple therapy 56% H2RA 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"endoscopic examinations were ultimately judged by an experienced endoscopist who was also not informed of the treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/50 (16%) were lost to follow up
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Sobhani 1995

Methods	Multi-centre RCT Double-blinded
Participants	France 119 people with duodenal ulcer
Interventions	H2RA triple therapy (6 weeks famotidine 40 mg od, 1 week amoxicillin 500 mg qds and tinidazole 500 mg tds) versus H2RA (6 weeks famotidine 40 mg od then 20 weeks 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: H2RA triple therapy 42.4% H2RA 1.7%

Sobhani 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind, double dummy"
Incomplete outcome data (attrition bias) All outcomes	High risk	9/97 (9%) of healed ulcer participants were lost to follow up over 6 months
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Spinzi 1994

Methods	Multi-centre RCT Unblinded
Participants	Italy 53 people with duodenal ulcer
Interventions	PPI dual therapy (4 weeks omeprazole 20 mg od, 2 weeks amoxicillin 1 g bd) versus PPI (4 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 41.7% PPI 6.9%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed

Spinzi 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	3/53 (6%) dropped out
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Suarez 1999

Methods	Single-centre RCT Unblinded
Participants	Cuba 60 people with gastric and duodenal ulcer
Interventions	Bi triple therapy (6 weeks colloidal bismuth subcitrate 240 mg bd, 10 days metronidazole 500 mg tds and tetracycline 500 mg tds/amoxicillin 750 mg bd) versus Bi (6 weeks colloidal bismuth subcitrate 240 mg bd)
Outcomes	Ulcer healing Global symptoms cured *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 22.5% Bi 0%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/60 (12%) drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Sung 1995

Methods	Single-centre RCT Unblinded
Participants	Hong Kong 96 people with gastric ulcer
Interventions	Bi triple therapy (1 week colloidal bismuth subcitrate 120 mg qds, tetracycline 500 mg qds and metronidazole 400 mg qds) versus PPI (4 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 80.4% PPI 11.1% If no healing at 4 weeks triple therapy participants received antacids and PPI participants received further PPI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	treatment assignments were determined with a list of random numbers generated by computer
Allocation concealment (selection bias)	Low risk	"randomly assigned to one of two treatment groups with the use of sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	85/100 (85%) completed the trial
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported in sufficient detail
Other bias	Low risk	There was no other bias

Tomita 2002

Methods	Single-centre RCT Unblinded
Participants	Japan 445 people with gastric or duodenal ulcer
Interventions	PPI triple therapy (6 weeks (DU) / 8 weeks (GU) lansoprazole 30 mg od or omeprazole 20 mg od, 2 weeks amoxicillin 1.5 g od and clarithromycin 400 mg od) versus PPI (6 weeks (DU) / 8 weeks (GU) lansoprazole 30 mg od or omeprazole 20 mg od) or H2RA (6 weeks (DU) / 8 weeks (GU) famotidine 40 mg od or cimetidine 800 mg od)
Outcomes	Ulcer recurrence at 5 years

Tomita 2002 *(Continued)*

	H. pylori eradication rates
Notes	Eradication rates: PPI triple therapy 81.9% PPI / H2RA 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	32/445 (7%) loss to follow up
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported
Other bias	Low risk	There was no other bias

Tulassay 2008

Methods	Multi-centre RCT Double-blinded
Participants	Bulgaria, Czech Republic, Germany, Hong Kong, Hungary, Philippines, Poland, Romania, and Slovakia 402 people with gastric ulcer
Interventions	PPI triple therapy (1 week esomeprazole 20 mg bd, amoxicillin 1 g bd, clarithromycin 500 mg bd followed by either 3 weeks of esomeprazole 20 mg od or placebo) versus PPI (1 week of esomeprazole 20 mg bd followed by 3 weeks of esomeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 12 months *H. pylori* eradication rates
Notes	Eradication rates: PPI triple therapy 79.2% PPI 9.5%

Risk of bias

Tulassay 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised according to a computer-generated list"
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"to maintain blinding, the active and placebo tablets were identical in terms of appearance, taste and smell, as well as packaging and labelling"
Incomplete outcome data (attrition bias) All outcomes	High risk	14/480 (3%) no primary end point data
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Unge 1993

Methods	Multi-centre RCT Double-blinded
Participants	Sweden 233 people with duodenal ulcer
Interventions	PPI dual therapy (4 weeks omeprazole 40 mg od and 2 weeks amoxicillin 750 mg bd) versus PPI (4 weeks omeprazole 40 mg od)
Outcomes	Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: PPI dual therapy 53.5% PPI 3.9%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"double blind and used a single placebo technique"
Incomplete outcome data (attrition bias)	Unclear risk	This information was not available

Unge 1993 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Van Zanten 1999

Methods	Multi-centre RCT Double-blinded
Participants	Canada 146 people with duodenal ulcer
Interventions	PPI triple therapy (1 week omeprazole 20 mg bd, amoxicillin 1 g bd and clarithromycin 500 mg bd or 1 week omeprazole 20 mg bd, metronidazole 400 mg bd and clarithromycin 250 mg bd then 3 weeks omeprazole 20 mg od) versus PPI (4 weeks omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication
Notes	Eradication rates: PPI triple therapy 81.6% PPI 0%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was performed
Incomplete outcome data (attrition bias) All outcomes	High risk	17/146 (12%) loss to follow up (n = 9) or not included in ulcer relapse analysis (n = 8)
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	Low risk	There was no other bias

Wang 1993

Methods	Single-centre RCT

Wang 1993 *(Continued)*

	Unblinded
Participants	Taiwan 59 people with duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120 mg qds, 2 weeks tetracycline 500 mg qds and metronidazole 250 mg qds) versus H2RA (4 weeks ranitidine 150 mg bd) and Bi (4 weeks colloidal bismuth subcitrate 120 mg qds)
Outcomes	Ulcer healing Ulcer recurrence at 6 months *H. pylori* eradication rates
Notes	Eradication rates: Bi triple therapy 82.6% H2RA 0% Bi 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	H2RA given until ulcers healed but these data were not given
Other bias	Low risk	There was no other bias

Wang 1996

Methods	Single-centre RCT Unblinded
Participants	Taiwan 112 people with gastric and duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 300 mg qds, 1 week amoxicillin 750 mg bd and metronidazole 500 mg tds) and PPI dual therapy (4 weeks omeprazole 20 mg bd/qds and 10 days amoxicillin 750 mg bd) versus PPI (4 weeks omeprazole 20 mg qds) and H2RA (4 weeks nizatidine/ranitidine 150 mg bd)
Outcomes	Ulcer healing *H. pylori* eradication rates

Wang 1996 *(Continued)*

Notes	Eradication rates: Bi triple therapy 68% PPI dual therapy 50% PPI 4.5% H2RA 0% All participants received 4 weeks H2RA after initial therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Collected data was reported
Other bias	High risk	Reported according to *H. pylori* status and not randomised groups

Wong 1999

Methods	Single-centre RCT Single-blinded
Participants	Hong Kong 114 people with duodenal ulcer
Interventions	Clarithromycin monotherapy (2 weeks 250 mg qds) versus PPI (1 year omeprazole 20 mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year *H. pylori* eradication rates
Notes	Eradication rates: Clarithromycin monotherapy 66.7% PPI 7% Clarithromycin participants also received 4 weeks sucralfate 1 g qds and 2 weeks metronidazole 300 mg qds

Risk of bias

Bias	Authors' judgement	Support for judgement

Wong 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	This information was not available
Allocation concealment (selection bias)	Unclear risk	This information was not available
Blinding (performance bias and detection bias) All outcomes	Low risk	"the endoscopists were blinded to the treatment type and any clinical information related to the patients"
Incomplete outcome data (attrition bias) All outcomes	Low risk	15/114 (13%) drop-outs
Selective reporting (reporting bias)	High risk	Symptom data collected but not reported
Other bias	Low risk	There was no other bias

bd: twice per day
od: once per day
qds: four times per day
tds: three times per day
Bi quadruple therapy: Bismuth quadruple therapy
PPI: proton pump inhibitor

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Assi 1995	No ulcer healing or recurrence data
Bytzer 2000	Not all participants were *H. pylori* positive, and no way of extracting data for just the *H. pylori*-positive participants
Dogan 1997	Control arm of the trial were all *H. pylori* negative
Dumbleton 2015	Not participants with peptic ulcer disease
Gisbert 2000	No ulcer healing or recurrence data
Hosking 1994	No comparative intervention
Kohli 1995	Not truly randomised
Labenz 1993	No ulcer healing or recurrence data
Laine 2000	No ulcer healing or recurrence data
Lind 1996	No ulcer healing or recurrence data
Malfertheiner 2002a	No ulcer healing or recurrence data
Nakata 1995	Not truly randomised

Study	Reason for exclusion
O'Riordan 1990	Not truly randomised
Parente 1998	Not truly randomised
Peterson 1996	Not all participants were *H. pylori*-positive, and no way of extracting data for just the *H. pylori*-positive participants
Prach 1998	Not all participants had documented peptic ulcer disease
Rune 1993	Not a recognised eradication regimen
Shimoyama 1995	Not truly randomised
Sonnenberg 1998	No ulcer healing or recurrence data
Sonnenberg 1999	No ulcer healing or recurrence data
Sugiyama 1995	Not truly randomised
Tavakoli 1999	No ulcer healing or recurrence data
Tham 1996	Not participants with peptic ulcer disease
Veldhuyzen Van Zanten 2000	Not all participants had documented peptic ulcer disease
Xia 1995	Not truly randomised

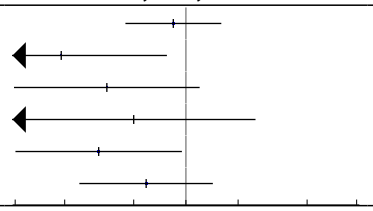
DATA AND ANALYSES

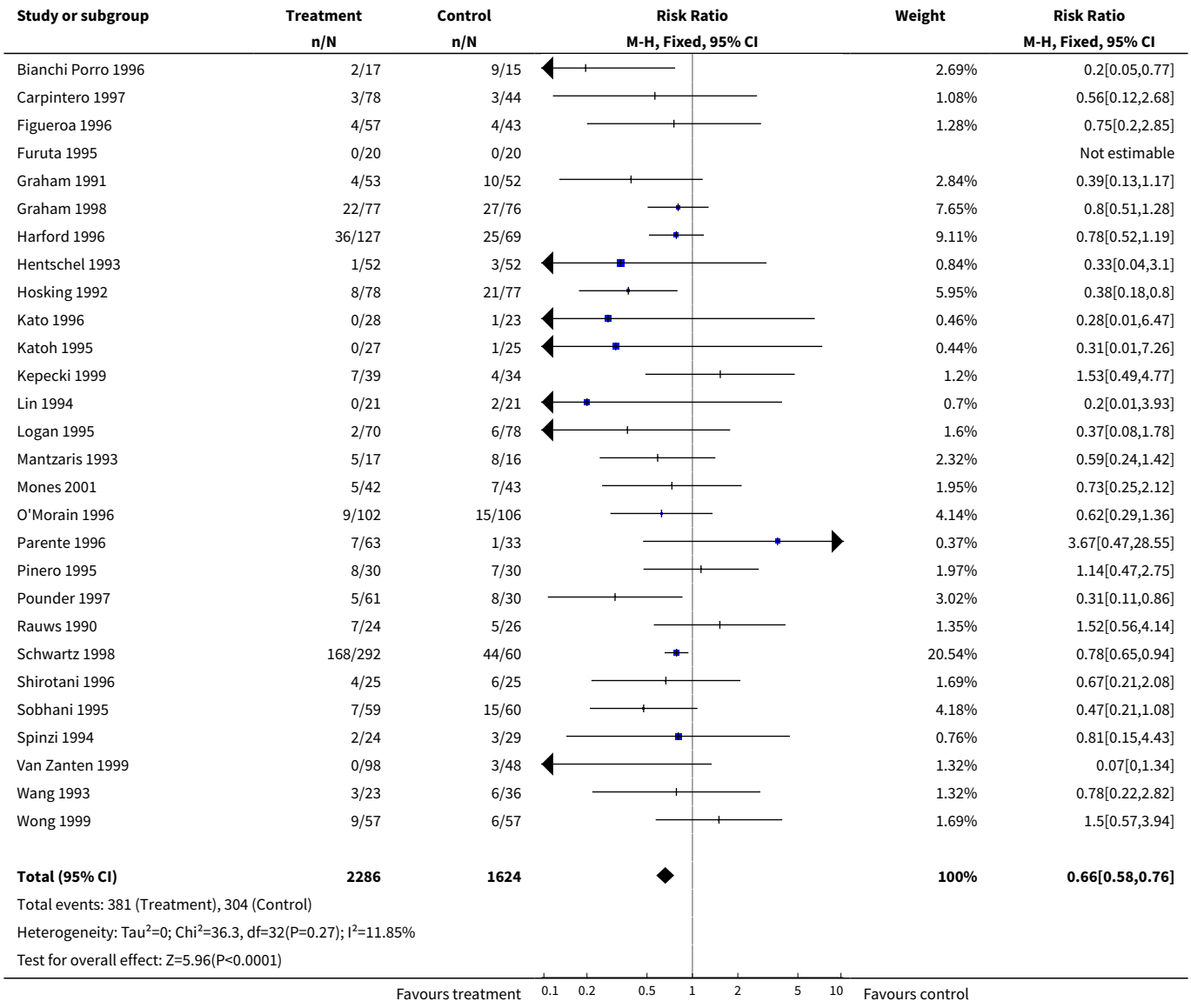
Comparison 1. *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone: duodenal ulcer acute healing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion not healed	34	3910	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.58, 0.76]

Analysis 1.1. Comparison 1 *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone: duodenal ulcer acute healing, Outcome 1 Proportion not healed.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asaka 2001	34/205	10/51		4.51%	0.85[0.45,1.6]
Avsar 1996	2/23	10/22		2.88%	0.19[0.05,0.78]
Bardhan 1997	4/141	6/74		2.21%	0.35[0.1,1.2]
Bayerdorffer 1992	2/29	4/29		1.13%	0.5[0.1,2.52]
Bayerdorffer 1995	4/136	12/128		3.48%	0.31[0.1,0.95]
Bianchi Porro 1993	7/91	12/92		3.36%	0.59[0.24,1.43]



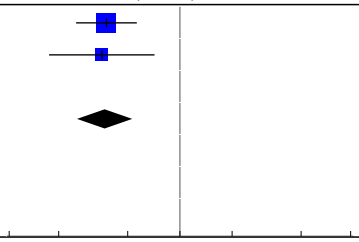


Comparison 2. *H. pylori* eradication vs. no treatment/placebo: duodenal ulcer acute healing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion not healed	2	207	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.26, 0.53]

Analysis 2.1. Comparison 2 *H. pylori* eradication vs. no treatment/ placebo: duodenal ulcer acute healing, Outcome 1 Proportion not healed.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Graham 1998	22/77	25/33		60.59%	0.38[0.25,0.56]
Lam 1997	8/48	23/49		39.41%	0.36[0.18,0.71]
Total (95% CI)	**125**	**82**		**100%**	**0.37[0.26,0.53]**
Total events: 30 (Treatment), 48 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=5.35(P<0.0001)					

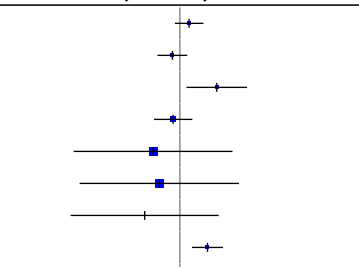


Comparison 3. *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone: gastric ulcer acute healing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion not healed	15	1974	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.90, 1.68]

Analysis 3.1. Comparison 3 *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone: gastric ulcer acute healing, Outcome 1 Proportion not healed.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Asaka 2001	65/225	11/55		12.06%	1.44[0.82,2.55]
Axon 1997	20/87	13/42		11.63%	0.74[0.41,1.34]
Bayerdorffer 1996	13/65	3/65		5.02%	4.33[1.3,14.49]
Befrits 2004	10/56	11/47		9.12%	0.76[0.36,1.64]
Fukuda 1995a	0/32	1/33		0.93%	0.34[0.01,8.13]
Fukuda 1995b	0/37	1/49		0.93%	0.44[0.02,10.47]
Furuta 1995	0/12	2/15		1.07%	0.25[0.01,4.69]
Higuchi 2003	31/61	10/59		11.25%	3[1.62,5.55]
Kato 1996	5/35	3/33		4.23%	1.57[0.41,6.06]
Katoh 1995	7/40	3/39		4.6%	2.28[0.63,8.17]
Lazzaroni 1997	0/29	2/30		1.03%	0.21[0.01,4.13]
Malfertheiner 1999	20/97	10/48		10.34%	0.99[0.5,1.95]
Meining 1998	23/100	15/85		11.8%	1.3[0.73,2.33]
Sung 1995	6/51	7/45		6.44%	0.76[0.27,2.08]
Tulassay 2008	20/265	10/137		9.56%	1.03[0.5,2.15]
Total (95% CI)	**1192**	**782**		**100%**	**1.23[0.9,1.68]**
Total events: 220 (Treatment), 102 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=22.93, df=14(P=0.06); I^2=38.94%					
Test for overall effect: Z=1.29(P=0.2)					

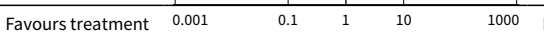


Comparison 4. *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone: peptic ulcer acute healing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion not healed	3	287	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.31, 0.85]

Analysis 4.1. Comparison 4 *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone: peptic ulcer acute healing, Outcome 1 Proportion not healed.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Arkkila 2005	3/85	6/30		28.96%	0.18[0.05,0.66]
Suarez 1999	11/40	8/20		34.83%	0.69[0.33,1.43]
Wang 1996	9/69	9/43		36.21%	0.62[0.27,1.45]
Total (95% CI)	**194**	**93**		**100%**	**0.52[0.31,0.85]**
Total events: 23 (Treatment), 23 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.31, df=2(P=0.19); I^2=39.53%					
Test for overall effect: Z=2.59(P=0.01)					

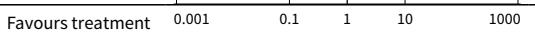


Comparison 5. *H. pylori* eradication vs. no treatment/placebo: peptic ulcer acute healing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion not healed	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 *H. pylori* eradication vs. no treatment/placebo: peptic ulcer acute healing, Outcome 1 Proportion not healed.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Feng 2005	3/25	12/15		0.15[0.05,0.45]

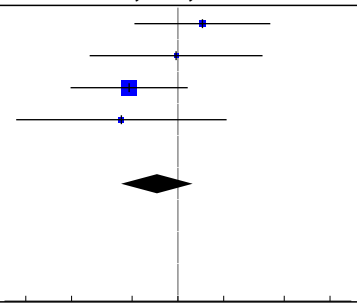


Comparison 6. *H. pylori* eradication vs. ulcer healing drug alone (after initial ulcer healing): duodenal ulcer recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion recurred	4	319	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.42, 1.25]

Analysis 6.1. Comparison 6 *H. pylori* eradication vs. ulcer healing drug alone (after initial ulcer healing): duodenal ulcer recurrence, Outcome 1 Proportion recurred.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kepecki 1999	7/29	5/30		18.84%	1.45[0.52,4.05]
Mones 2001	4/37	4/36		15.54%	0.97[0.26,3.6]
Sobhani 1995	6/45	12/43		47.04%	0.48[0.2,1.16]
Wong 1999	2/48	5/51		18.58%	0.43[0.09,2.09]
Total (95% CI)	**159**	**160**		**100%**	**0.73[0.42,1.25]**
Total events: 19 (Treatment), 26 (Control)					
Heterogeneity: Tau²=0; Chi²=3.22, df=3(P=0.36); I²=6.71%					
Test for overall effect: Z=1.15(P=0.25)					

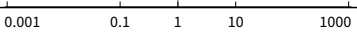


Comparison 7. *H. pylori* eradication vs. no treatment (after initial ulcer healing): duodenal ulcer recurrence

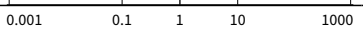
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion recurred	27	2509	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.15, 0.26]

Analysis 7.1. Comparison 7 *H. pylori* eradication vs. no treatment (after initial ulcer healing): duodenal ulcer recurrence, Outcome 1 Proportion recurred.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Avsar 1996	3/17	6/10		3.07%	0.29[0.09,0.92]
Bardhan 1997	10/133	25/63		4.78%	0.19[0.1,0.37]
Bayerdorffer 1992	6/26	19/25		4.51%	0.3[0.15,0.63]
Bayerdorffer 1995	15/132	51/116		5.41%	0.26[0.15,0.43]
Bianchi Porro 1996	8/71	52/66		4.8%	0.14[0.07,0.28]
Carpintero 1997	31/72	34/39		6.26%	0.49[0.37,0.66]
Chen 1995	10/31	27/29		5.41%	0.35[0.21,0.58]
Figueroa 1996	3/53	34/39		3.18%	0.06[0.02,0.2]
Graham 1992	6/47	34/36		4.45%	0.14[0.06,0.29]
Hentschel 1993	4/50	42/49		3.71%	0.09[0.04,0.24]
Hosking 1992	2/61	22/45		2.43%	0.07[0.02,0.27]
Kato 1996	3/27	12/18		3.15%	0.17[0.05,0.51]
Kim 2002	2/36	5/17		2.14%	0.19[0.04,0.88]
Lin 1994	1/18	11/18		1.52%	0.09[0.01,0.63]
Logan 1995	3/51	47/62		3.18%	0.08[0.03,0.23]
Mantzaris 1993	2/12	6/8		2.58%	0.22[0.06,0.84]
O'Morain 1996	8/78	41/82		4.69%	0.21[0.1,0.41]
Pinero 1995	3/19	13/20		3.24%	0.24[0.08,0.72]
Pounder 1997	0/56	4/22		0.78%	0.04[0,0.8]
Rauws 1990	1/17	16/21		1.55%	0.08[0.01,0.52]



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Schwartz 1998	19/124	11/16		5.37%	0.22[0.13,0.38]
Shirotani 1996	2/18	9/14		2.5%	0.17[0.04,0.68]
Spinzi 1994	3/22	15/26		3.2%	0.24[0.08,0.71]
Tomita 2002	11/55	20/20		5.41%	0.21[0.13,0.35]
Unge 1993	48/157	50/76		6.27%	0.46[0.35,0.62]
Van Zanten 1999	10/98	25/45		4.89%	0.18[0.1,0.35]
Wang 1993	1/20	18/26		1.53%	0.07[0.01,0.5]
Total (95% CI)	**1501**	**1008**		**100%**	**0.2[0.15,0.26]**
Total events: 215 (Treatment), 649 (Control)					
Heterogeneity: Tau^2=0.28; Chi^2=85.11, df=26(P<0.0001); I^2=69.45%					
Test for overall effect: Z=11.74(P<0.0001)					



Comparison 8. *H. pylori* eradication vs. no treatment (after initial ulcer healing): gastric ulcer recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion recurred	12	1476	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.22, 0.45]

Analysis 8.1. Comparison 8 *H. pylori* eradication vs. no treatment (after initial ulcer healing): gastric ulcer recurrence, Outcome 1 Proportion recurred.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Axon 1997	16/72	17/35		11.56%	0.46[0.26,0.79]
Bayerdorffer 1996	4/52	34/62		7.42%	0.14[0.05,0.37]
Befrits 2004	10/42	24/33		11.23%	0.33[0.18,0.58]
Fukuda 1995b	3/36	19/48		6.17%	0.21[0.07,0.66]
Graham 1992	2/15	8/11		5%	0.18[0.05,0.7]
Kato 1996	8/28	11/26		9.53%	0.68[0.32,1.41]
Lazzaroni 1997	6/28	16/24		9.27%	0.32[0.15,0.69]
Malfertheiner 1999	12/97	13/48		9.88%	0.46[0.23,0.92]
Meining 1998	0/77	10/70		1.5%	0.04[0,0.73]
Sung 1995	1/22	12/23		2.82%	0.09[0.01,0.62]
Tomita 2002	14/83	156/172		12.35%	0.19[0.12,0.3]
Tulassay 2008	40/245	36/127		13.27%	0.58[0.39,0.86]
Total (95% CI)	**797**	**679**		**100%**	**0.31[0.22,0.45]**
Total events: 116 (Treatment), 356 (Control)					
Heterogeneity: Tau^2=0.22; Chi^2=29.09, df=11(P=0); I^2=62.19%					
Test for overall effect: Z=6.27(P<0.0001)					

Comparison 9. *H. pylori* eradication vs. no treatment (after initial ulcer healing): peptic ulcer recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion recurred	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 *H. pylori* eradication vs. no treatment (after initial ulcer healing): peptic ulcer recurrence, Outcome 1 Proportion recurred.

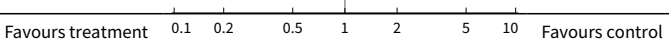
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Arkkila 2005	6/79	8/24		0.23[0.09,0.59]

Comparison 10. Global symptoms persisting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone	2	180	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.42, 1.74]
2 *H. pylori* eradication vs. no treatment	2	188	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.83, 1.93]

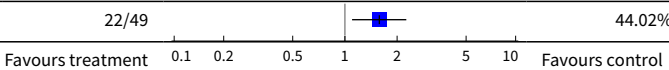
Analysis 10.1. Comparison 10 Global symptoms persisting, Outcome 1 *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone.

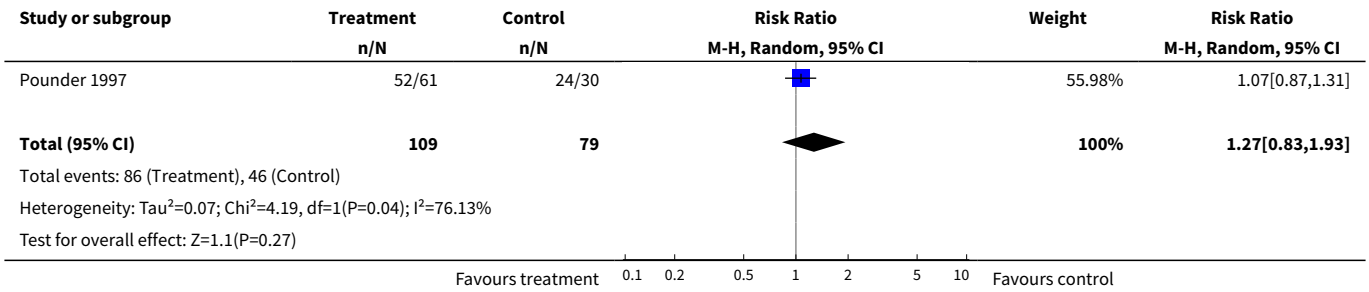
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Higuchi 2003	29/61	45/59		55.39%	0.62[0.46,0.84]
Suarez 1999	23/40	9/20		44.61%	1.28[0.74,2.22]
Total (95% CI)	**101**	**79**		**100%**	**0.86[0.42,1.74]**
Total events: 52 (Treatment), 54 (Control)					
Heterogeneity: Tau^2=0.21; Chi^2=5.07, df=1(P=0.02); I^2=80.28%					
Test for overall effect: Z=0.42(P=0.67)					



Analysis 10.2. Comparison 10 Global symptoms persisting, Outcome 2 *H. pylori* eradication vs. no treatment.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Lam 1997	34/48	22/49		44.02%	1.58[1.1,2.26]

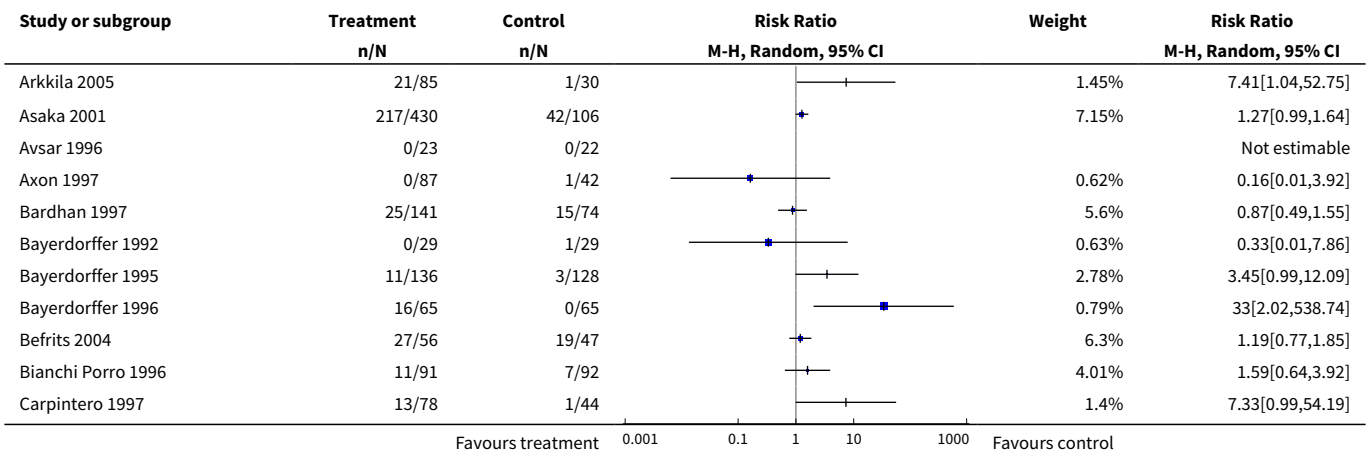




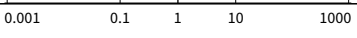
Comparison 11. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall, proportion occurred	43	6093	Risk Ratio (M-H, Random, 95% CI)	2.30 [1.77, 2.99]
2 Diarrhoea, proportion occurred	30	4590	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [2.11, 3.88]
3 Nausea/vomiting, proportion occurred	15	1533	Risk Ratio (M-H, Fixed, 95% CI)	3.76 [1.91, 7.37]
4 Skin rash, proportion occurred	18	2385	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.78, 2.37]
5 Headache, proportion occurred	14	2292	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.70, 1.75]
6 Epigastric pain, proportion occurred	11	1491	Risk Ratio (M-H, Fixed, 95% CI)	4.09 [1.90, 8.82]
7 Altered taste, proportion occurred	13	2299	Risk Ratio (M-H, Fixed, 95% CI)	8.85 [4.38, 17.90]
8 Stomatitis, proportion occurred versus not occurred	8	838	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [0.94, 7.48]

Analysis 11.1. Comparison 11 Adverse events, Outcome 1 Overall, proportion occurred.



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chen 1995	24/49	0/29		0.8%	29.4[1.85,465.97]
Fukuda 1995a	0/32	0/33			Not estimable
Fukuda 1995b	1/37	0/49		0.63%	3.95[0.17,94.23]
Graham 1991	6/53	0/52		0.76%	12.76[0.74,220.88]
Graham 1998	7/77	7/109		3.6%	1.42[0.52,3.87]
Harford 1996	24/127	5/69		3.95%	2.61[1.04,6.53]
Hentschel 1993	8/52	1/52		1.35%	8[1.04,61.71]
Higuchi 2003	11/61	1/59		1.38%	10.64[1.42,79.85]
Hosking 1992	6/78	6/77		3.3%	0.99[0.33,2.93]
Kato 1996	4/63	0/56		0.74%	8.02[0.44,145.66]
Lam 1997	2/48	0/49		0.69%	5.1[0.25,103.58]
Lazzaroni 1997	4/29	2/30		1.95%	2.07[0.41,10.44]
Lin 1994	5/21	0/21		0.77%	11[0.65,187.17]
Logan 1995	28/70	23/78		6.26%	1.36[0.87,2.12]
Malfertheiner 1999	12/97	6/48		3.95%	0.99[0.4,2.48]
Mantzaris 1993	3/17	0/16		0.74%	6.61[0.37,118.73]
Meining 1998	23/100	5/85		3.93%	3.91[1.55,9.84]
O'Morain 1996	38/102	13/106		5.63%	3.04[1.72,5.36]
Parente 1996	6/63	0/33		0.76%	6.91[0.4,118.94]
Pinero 1995	2/30	0/30		0.7%	5[0.25,99.95]
Pounder 1997	21/61	7/30		4.78%	1.48[0.71,3.08]
Rauws 1990	5/24	0/26		0.76%	11.88[0.69,204.05]
Schwartz 1998	80/292	9/60		5.31%	1.83[0.97,3.43]
Shirotani 1996	4/25	0/25		0.75%	9[0.51,158.85]
Sobhani 1995	10/59	3/60		2.82%	3.39[0.98,11.7]
Spinzi 1994	1/24	0/29		0.63%	3.6[0.15,84.54]
Suarez 1999	11/40	3/20		3.07%	1.83[0.58,5.84]
Sung 1995	5/51	0/45		0.75%	9.73[0.55,171.24]
Tomita 2002	3/138	0/192		0.71%	9.72[0.51,186.66]
Tulassay 2008	79/315	13/164		5.7%	3.16[1.82,5.51]
Wang 1996	13/69	0/43		0.79%	16.97[1.03,278.36]
Wong 1999	6/57	1/57		1.31%	6[0.75,48.26]
Total (95% CI)	**3582**	**2511**		**100%**	**2.3[1.77,2.99]**
Total events: 793 (Treatment), 195 (Control)					
Heterogeneity: Tau^2=0.23; Chi^2=80.47, df=40(P=0); I^2=50.29%					
Test for overall effect: Z=6.22(P<0.0001)					

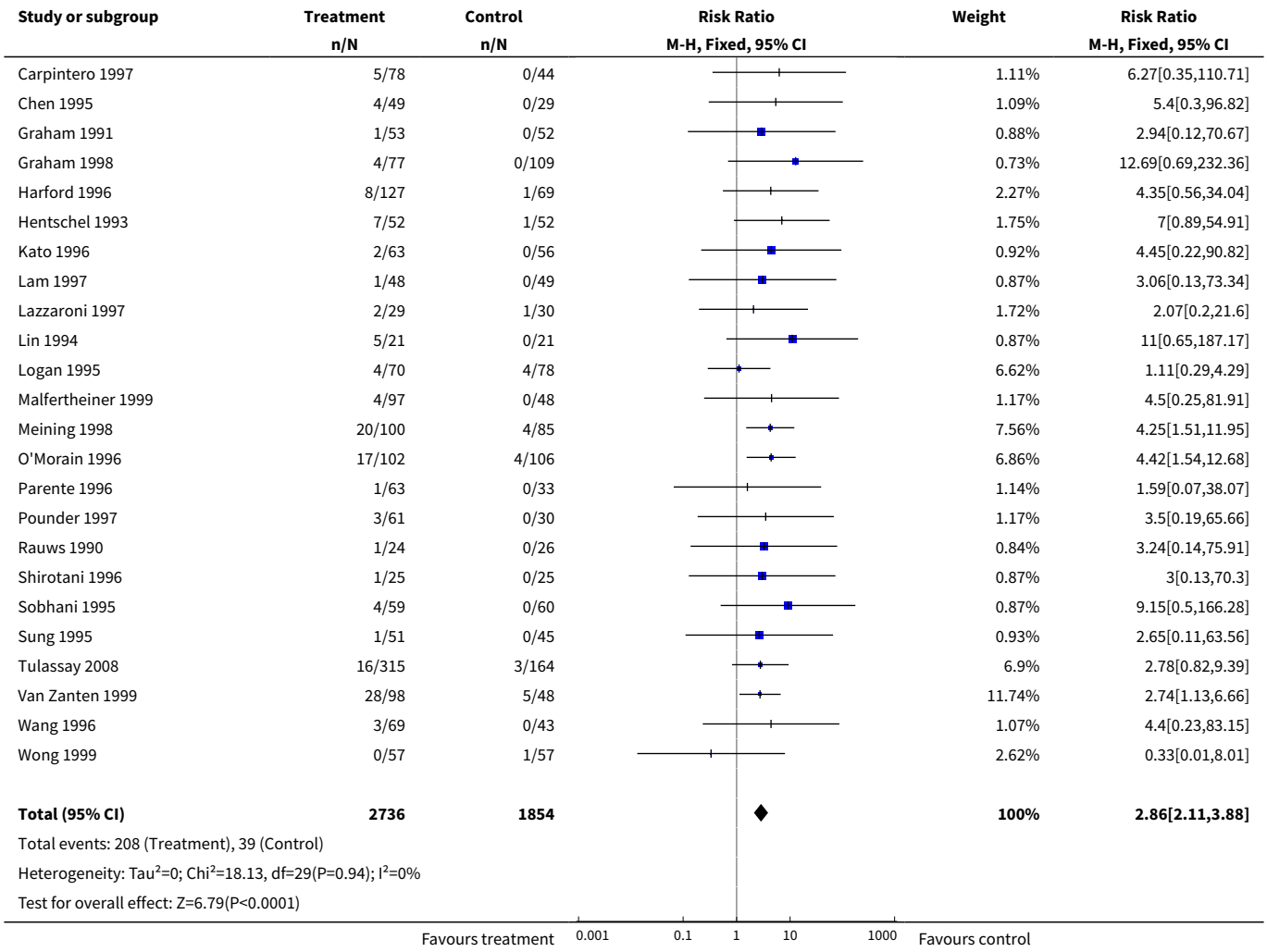


Favours treatment — Favours control

Analysis 11.2. Comparison 11 Adverse events, Outcome 2 Diarrhoea, proportion occurred.

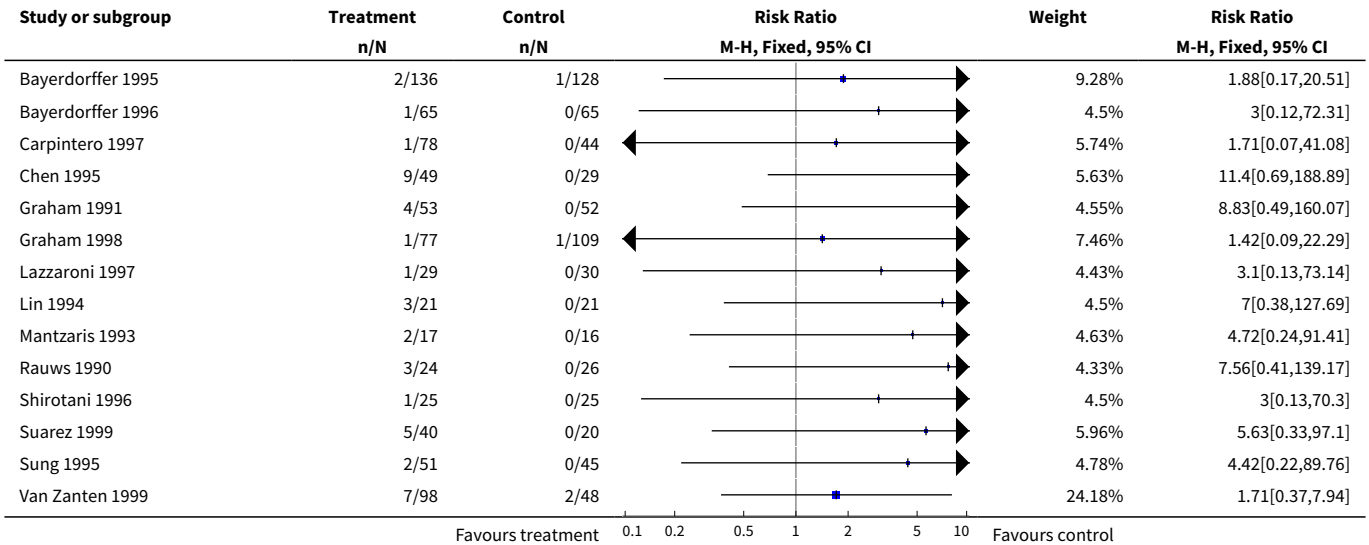
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Arkkila 2005	7/85	0/30		1.29%	5.41[0.32,91.91]
Asaka 2001	38/430	7/106		19.64%	1.34[0.61,2.91]
Bardhan 1997	9/141	3/74		6.88%	1.57[0.44,5.64]
Bayerdorffer 1995	3/136	1/128		1.8%	2.82[0.3,26.8]
Bayerdorffer 1996	6/65	0/65		0.87%	13[0.75,226.12]
Bianchi Porro 1996	3/91	4/92		6.96%	0.76[0.17,3.29]

Favours treatment — Favours control

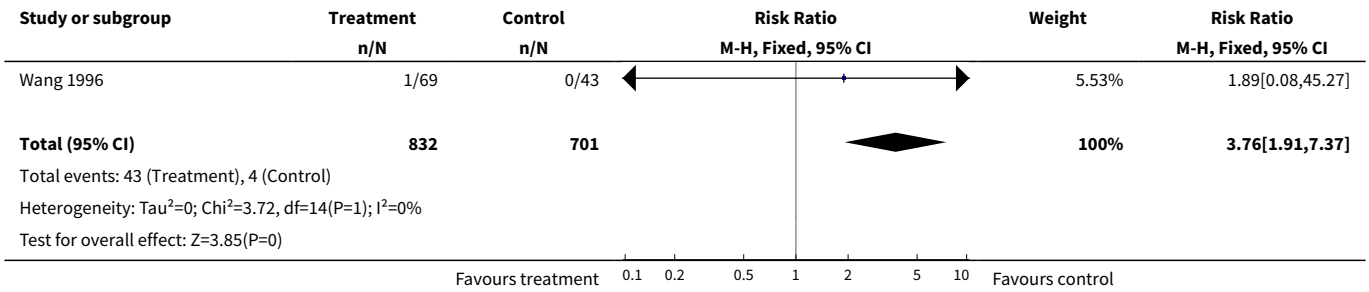


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Carpintero 1997	5/78	0/44		1.11%	6.27[0.35,110.71]
Chen 1995	4/49	0/29		1.09%	5.4[0.3,96.82]
Graham 1991	1/53	0/52		0.88%	2.94[0.12,70.67]
Graham 1998	4/77	0/109		0.73%	12.69[0.69,232.36]
Harford 1996	8/127	1/69		2.27%	4.35[0.56,34.04]
Hentschel 1993	7/52	1/52		1.75%	7[0.89,54.91]
Kato 1996	2/63	0/56		0.92%	4.45[0.22,90.82]
Lam 1997	1/48	0/49		0.87%	3.06[0.13,73.34]
Lazzaroni 1997	2/29	1/30		1.72%	2.07[0.2,21.6]
Lin 1994	5/21	0/21		0.87%	11[0.65,187.17]
Logan 1995	4/70	4/78		6.62%	1.11[0.29,4.29]
Malfertheiner 1999	4/97	0/48		1.17%	4.5[0.25,81.91]
Meining 1998	20/100	4/85		7.56%	4.25[1.51,11.95]
O'Morain 1996	17/102	4/106		6.86%	4.42[1.54,12.68]
Parente 1996	1/63	0/33		1.14%	1.59[0.07,38.07]
Pounder 1997	3/61	0/30		1.17%	3.5[0.19,65.66]
Rauws 1990	1/24	0/26		0.84%	3.24[0.14,75.91]
Shirotani 1996	1/25	0/25		0.87%	3[0.13,70.3]
Sobhani 1995	4/59	0/60		0.87%	9.15[0.5,166.28]
Sung 1995	1/51	0/45		0.93%	2.65[0.11,63.56]
Tulassay 2008	16/315	3/164		6.9%	2.78[0.82,9.39]
Van Zanten 1999	28/98	5/48		11.74%	2.74[1.13,6.66]
Wang 1996	3/69	0/43		1.07%	4.4[0.23,83.15]
Wong 1999	0/57	1/57		2.62%	0.33[0.01,8.01]
Total (95% CI)	**2736**	**1854**		**100%**	**2.86[2.11,3.88]**
Total events: 208 (Treatment), 39 (Control)					
Heterogeneity: Tau²=0; Chi²=18.13, df=29(P=0.94); I²=0%					
Test for overall effect: Z=6.79(P<0.0001)					

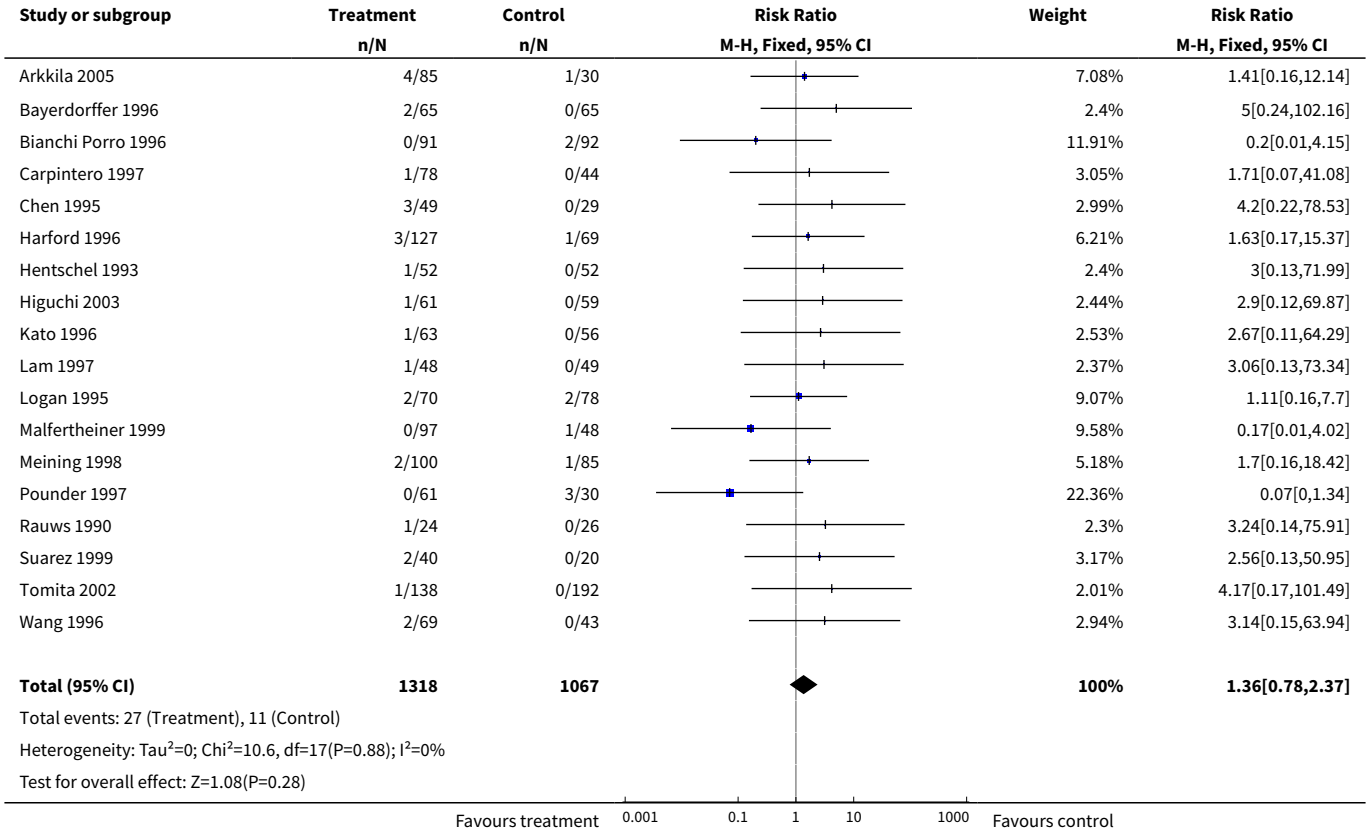
Analysis 11.3. Comparison 11 Adverse events, Outcome 3 Nausea/vomiting, proportion occurred.



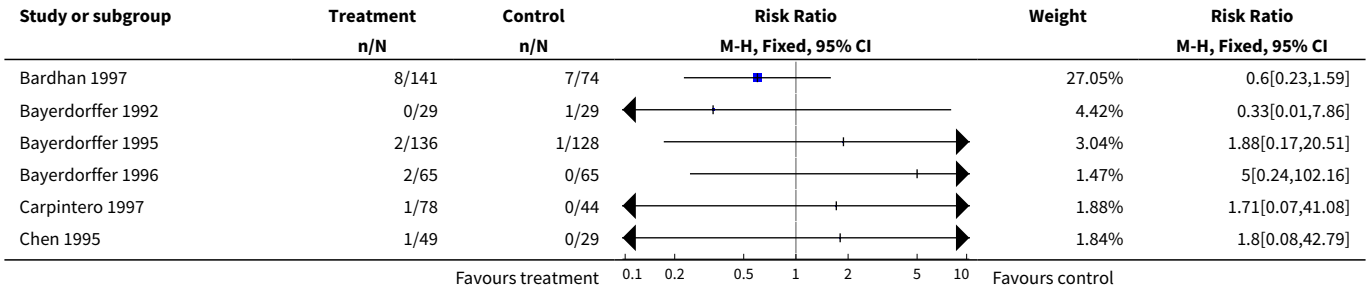
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bayerdorffer 1995	2/136	1/128		9.28%	1.88[0.17,20.51]
Bayerdorffer 1996	1/65	0/65		4.5%	3[0.12,72.31]
Carpintero 1997	1/78	0/44		5.74%	1.71[0.07,41.08]
Chen 1995	9/49	0/29		5.63%	11.4[0.69,188.89]
Graham 1991	4/53	0/52		4.55%	8.83[0.49,160.07]
Graham 1998	1/77	1/109		7.46%	1.42[0.09,22.29]
Lazzaroni 1997	1/29	0/30		4.43%	3.1[0.13,73.14]
Lin 1994	3/21	0/21		4.5%	7[0.38,127.69]
Mantzaris 1993	2/17	0/16		4.63%	4.72[0.24,91.41]
Rauws 1990	3/24	0/26		4.33%	7.56[0.41,139.17]
Shirotani 1996	1/25	0/25		4.5%	3[0.13,70.3]
Suarez 1999	5/40	0/20		5.96%	5.63[0.33,97.1]
Sung 1995	2/51	0/45		4.78%	4.42[0.22,89.76]
Van Zanten 1999	7/98	2/48		24.18%	1.71[0.37,7.94]

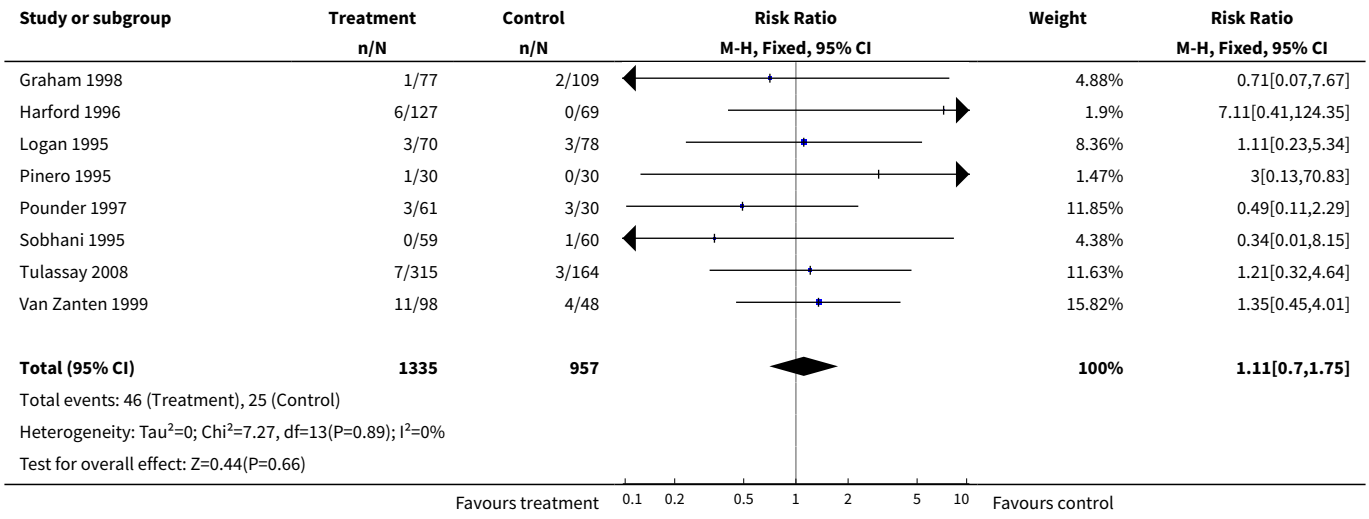


Analysis 11.4. Comparison 11 Adverse events, Outcome 4 Skin rash, proportion occurred.

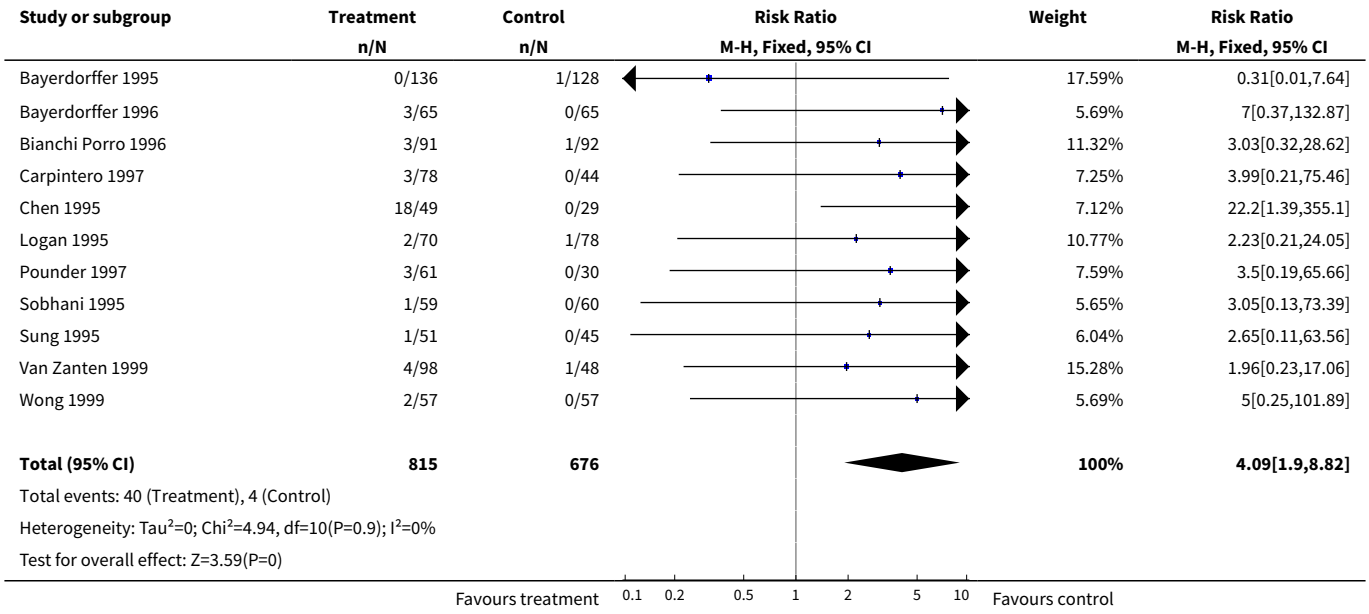


Analysis 11.5. Comparison 11 Adverse events, Outcome 5 Headache, proportion occurred.

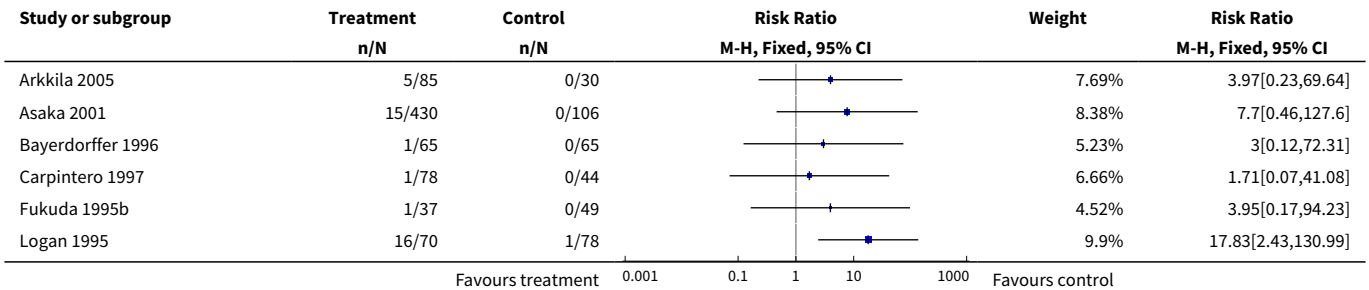


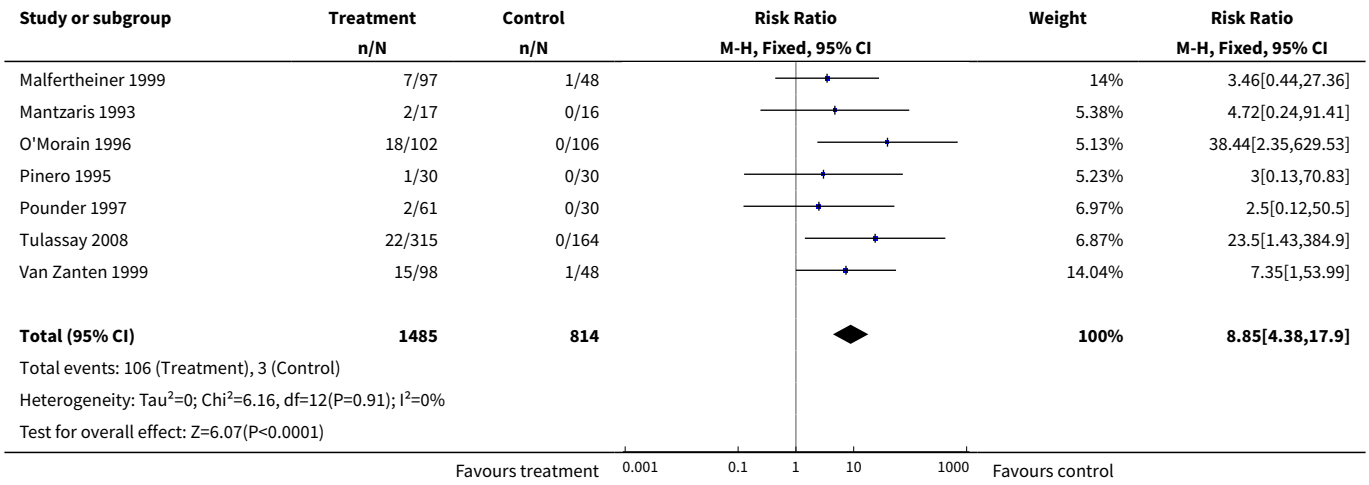


Analysis 11.6. Comparison 11 Adverse events, Outcome 6 Epigastric pain, proportion occurred.

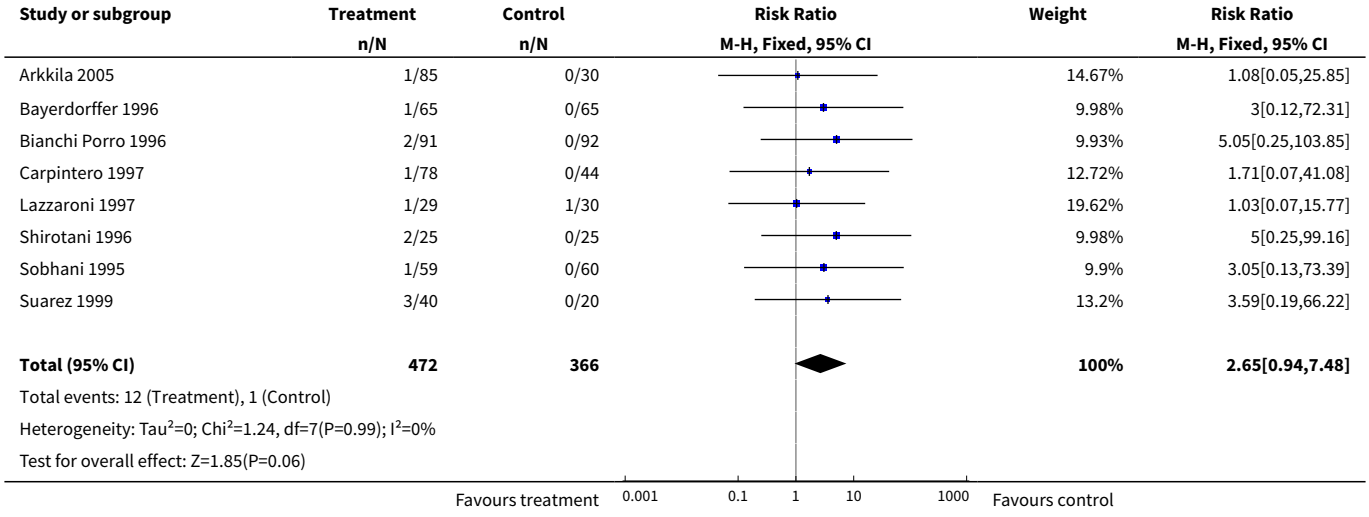


Analysis 11.7. Comparison 11 Adverse events, Outcome 7 Altered taste, proportion occurred.





Analysis 11.8. Comparison 11 Adverse events, Outcome 8 Stomatitis, proportion occurred versus not occurred.



APPENDICES

Appendix 1. CENTRAL search strategy

Via Wiley

#1 MeSH descriptor: [Peptic Ulcer] explode all trees

#2 MeSH descriptor: [Peptic Ulcer Hemorrhage] explode all trees

#3 MeSH descriptor: [Peptic Ulcer Perforation] explode all trees

#4 MeSH descriptor: [Duodenal Ulcer] explode all trees

#5 MeSH descriptor: [Stomach Ulcer] explode all trees

#6 (pep* near/5 ulcer*)

#7 (stomach near/5 ulcer*)

#8 (duoden* near/5 ulcer*)

#9 (gastr* near/5 ulcer*)

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#11 MeSH descriptor: [Dyspepsia] explode all trees

#12 MeSH descriptor: [Eructation] explode all trees

#13 MeSH descriptor: [Flatulence] explode all trees

#14 MeSH descriptor: [Heartburn] explode all trees

#15 MeSH descriptor: [Gastroparesis] explode all trees

#16 MeSH descriptor: [Gastric Emptying] explode all trees

#17 MeSH descriptor: [Gastritis] explode all trees

#18 dyspep*

#19 (acid near/5 reflux)

#20 belch*

#21 bloat*

#22 burp*

#23 (early near/5 satiety)

#24 eructation

#25 flatu*

#26 heartburn

#27 indigestion

#28 pyro*

#29 hiatus hernia

#30 (stomach near/5 paresis)

#31 gastritis

#32 (gastric near/5 acid near/5 secretion)

#33 (stomach near/5 acid near/5 secretion)

#34 (gastric near/5 erosion*)

#35 (gastric near/5 emptying near/5 disorder*)

#36 (stomach near/5 emptying near/5 disorder*)

#37 gastroparesis

#38 (bleed* near/5 ulcer*)

#39 (rebleed* near/5 ulcer*)

#40 (recurrent near/5 bleed* near/5 ulcer*)

#41 (acute near/5 bleed* near/5 ulcer*)

#42 (gastrointestinal near/5 bleed*)

#43 (gastrointestinal near/5 rebleed*)

#44 (gastrointestinal near/5 hemorrhag*)

#45 (gastrointestinal near/5 haemorrhag*)

#46 (ulcer near/5 hemorrhag*)

#47 (ulcer near/5 haemorrhag*)

#48 (mucos* near/5 injur*)

#49 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48

#50 MeSH descriptor: [Anti-Ulcer Agents] explode all trees

#51 MeSH descriptor: [Omeprazole] explode all trees

#52 omeprazole

#53 lansoprazole

#54 pantoprazole

#55 rabeprazole

#56 esomeprazole

#57 MeSH descriptor: [Histamine H2 Antagonists] explode all trees

#58 MeSH descriptor: [Cimetidine] explode all trees

#59 cimetidine

#60 MeSH descriptor: [Ranitidine] explode all trees

#61 ranitidine

#62 MeSH descriptor: [Famotidine] explode all trees

#63 famotidine

#64 MeSH descriptor: [Nizatidine] explode all trees

#65 nizatidine

#66 (histamine near/3 H2 near/3 antagonist*)

#67 (antiulcer near/5 agent*)

#68 (H2 near/5 receptor near/5 antagonist*)

#69 (proton near/3 pump near/3 inhibitor*)

#70 MeSH descriptor: [Bismuth] explode all trees

#71 MeSH descriptor: [Antacids] explode all trees

#72 MeSH descriptor: [Alginates] explode all trees

#73 MeSH descriptor: [Aluminum Hydroxide] explode all trees

#74 MeSH descriptor: [Magnesium Hydroxide] explode all trees

#75 MeSH descriptor: [Magnesium Oxide] explode all trees

#76 MeSH descriptor: [Calcium Carbonate] explode all trees

#77 (magnesium near/5 carbonate)

#78 MeSH descriptor: [Magnesium Hydroxide] explode all trees

#79 MeSH descriptor: [Magnesium Oxide] explode all trees

#80 MeSH descriptor: [Magnesium Silicates] explode all trees

#81 MeSH descriptor: [Carbenoxolone] explode all trees

#82 MeSH descriptor: [Misoprostol] explode all trees

#83 MeSH descriptor: [Sucralfate] explode all trees

#84 MeSH descriptor: [Muscarinic Antagonists] explode all trees

#85 MeSH descriptor: [Dicyclomine] explode all trees

#86 MeSH descriptor: [Pirenzepine] explode all trees

#87 MeSH descriptor: [Propantheline] explode all trees

#88 algicon

#89 alginates

#90 (alumin?um near/5 hydroxide)

#91 (calcium near/5 carbonate)

#92 gaviscon

#93 hydrotalcite

#94 maalox

#95 (magnesium near/5 hydroxide)

#96 (magnesium near/5 oxide)

#97 (magnesium near/5 trisilicate)

#98 (sodium near/5 bicarbonate)

#99 (sodium near/5 carbonate)

#100 (mucosal near/5 protecting near/5 agent*)

#101 carbenoxolone

#102 misoprostol

#103 sucralfate

#104 antimuscarinic*

#105 (muscarinic near/5 receptor near/5 antagonist*)

#106 dicyclomine

#107 pirenzepine

#108 propantheline

#109 MeSH descriptor: [Macrolides] explode all trees

#110 macrolides

#111 MeSH descriptor: [Nitroimidazoles] explode all trees

#112 nitroimidazole*

#113 MeSH descriptor: [Tetracyclines] explode all trees

#114 tetracyclines

#115 MeSH descriptor: [Penicillins] explode all trees

#116 penicillin*

#117 MeSH descriptor: [Bismuth] explode all trees

#118 bismuth*

#119 de-nol

#120 MeSH descriptor: [Clarithromycin] explode all trees

#121 clarithromycin*

#122 MeSH descriptor: [Amoxicillin] explode all trees

#123 amoxycillin*

#124 amox?cillin*

#125 MeSH descriptor: [Metronidazole] explode all trees

#126 metronidazole*

#127 MeSH descriptor: [Tinidazole] explode all trees

#128 tinidazole*

#129 MeSH descriptor: [Tetracyclines] explode all trees

#130 tetracycline*

#131 MeSH descriptor: [Anti-Bacterial Agents] explode all trees

#132 #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129 or #130 or #131

#133 MeSH descriptor: [Helicobacter pylori] explode all trees

#134 (campylobacter near/1 pylori*)

#135 (h near/1 pylori)

#136 (pylori* near/250 eradicat*)

#137 #133 or #134 or #135 or #136

#138 #10 and #49

#139 #10 or #138

#140 #132 and #139

#141 #137 and #140

#142 #141 Publication Year from 2015 to 2016

Appendix 2. MEDLINE search strategy

Via OVIDSP

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized controlled trials.sh.

4. random allocation.sh.

5. double blind method.sh.

6. single-blind method.sh.

7. or/1-6

8. (animal not human).sh.

9. 7 not 8

10. clinical trial.pt.

11. exp clinical trial/

12. (clin$ adj25 trial$).ti,ab.

13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 blind$).mp. or mask$.ti,ab. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

14. placebos.sh.

15. placebo$.ti,ab.

16. random$.ti,ab.

17. research design.sh.

18. or/10-17

19. 18 not 8

20. 19 not 9

21. comparative study.sh.

22. exp evaluation studies/

23. follow up studies.sh.

24. prospective studies.sh.

25. (control$ or prospectiv$).mp. or volunteer$.ti,ab. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

26. or/21-25

27. 26 not 8

28. 27 not (9 or 20)

29. 9 or 20 or 28

30. exp peptic ulcer/

31. exp peptic ulcer hemorrhage/

32. exp peptic ulcer perforation/

33. exp duodenal ulcer/

34. exp stomach ulcer/

35. (pep$ adj5 ulcer$).tw.

36. (stomach adj5 ulcer$).tw.

37. (duoden$ adj5 ulcer$).tw.

38. (gastr$ adj5 ulcer$).tw.

39. or/30-38

40. exp dyspepsia/

41. exp eructation/

42. exp flatulence/

43. exp heartburn/

44. exp gastroparesis/

45. exp gastric emptying/

46. exp gastritis/

47. dyspep$.tw.

48. (acid adj5 reflux).tw.

49. belch$.tw.

50. bloat$.tw.

51. burp$.tw.

52. (early adj5 satiety).tw.

53. eructation.tw.

54. flatu$.tw.

55. heartburn.tw.

56. indigestion.tw.

57. pyro$.tw.

58. hiatus hernia.tw.

59. (stomach adj5 paresis).tw.

60. gastritis.tw.

61. (gastric adj5 acid adj5 secretion).tw.

62. (stomach adj5 acid adj5 secretion).tw.

63. (gastric adj5 erosion$).tw.

64. (gastric adj5 emptying adj5 disorder$).tw.

65. (stomach adj5 emptying adj5 disorder$).tw.

66. gastroparesis.tw.

67. (bleed$ adj5 ulcer$).tw.

68. (rebleed$ adj5 ulcer$).tw.

69. (recurrent adj5 bleed$ adj5 ulcer$).tw.

70. (acute adj5 bleed$ adj5 ulcer$).tw.

71. (gastrointestinal adj5 bleed$).tw.

72. (gastrointestinal adj5 rebleed$).tw.

73. (gastrointestinal adj5 hemorrhag$).tw.

74. (gastrointestinal adj5 haemorrhag$).tw.

75. (ulcer adj5 hemorrhag$).tw.

76. (ulcer adj5 haemorrhag$).tw.

77. (mucos$ adj5 injur$).tw.

78. or/40-77

79. exp anti-ulcer agents/

80. exp omeprazole/

81. omeprazole.tw.

82. lansoprazole.tw.

83. pantoprazole.tw.

84. rabeprazole.tw.

85. esomeprazole.tw.

86. exp histamine H2 antagonists/

87. exp cimetidine/

88. cimetidine.tw.

89. exp ranitidine/

90. ranitidine.tw.

91. exp famotidine/

92. famotidine.tw.

93. exp nizatidine/

94. nizatidine.tw.

95. (histamine adj3 H2 adj3 antagonist$).tw.

96. (antiulcer adj5 agent$).tw.

97. (H2 adj5 receptor adj5 antagonist$).tw.

98. (proton adj3 pump adj3 inhibitor$).tw.

99. exp bismuth/

100. exp antacids/

101. exp alginates/

102. Aluminum hydroxide/

103. exp magnesium hydroxide/

104. exp magnesium oxide/

105. exp calcium carbonate/

106. (magnesium adj5 carbonate).tw.

107. exp magnesium hydroxide/

108. exp magnesium oxide/

109. Magnesium silicates/

110. exp carbenoxolone/

111. exp misoprostol/

112. exp sucralfate/

113. exp muscarinic antagonists/

114. exp dicyclomine/

115. exp pirenzepine/

116. exp propantheline/

117. algicon.tw.

118. alginates.tw.

119. (alumin?um adj5 hydroxide).tw.

120. (calcium adj5 carbonate).tw.

121. gaviscon.tw.

122. hydrotalcite.tw.

123. maalox.tw.

124. (magnesium adj5 hydroxide).tw.

125. (magnesium adj5 oxide).tw.

126. (magnesium adj5 trisilicate).tw.

127. (sodium adj5 bicarbonate).tw.

128. (sodium adj5 carbonate).tw.

129. (mucosal adj5 protecting adj5 agent$).tw.

130. carbenoxolone.tw.

131. misoprostol.tw.

132. sucralfate.tw.

133. antimuscarinic$.tw.

134. (muscarinic adj5 receptor adj5 antagonist$).tw.

135. dicyclomine.tw.

136. pirenzepine.tw.

137. propantheline.tw.

138. exp macrolides/

139. macrolides.tw.

140. exp nitroimidazoles/

141. nitroimidazole$.tw.

142. exp tetracyclines/

143. tetracyclines.tw.

144. exp penicillins/

145. penicillin$.tw.

146. exp bismuth/

147. bismuth$.tw.

148. de-nol.tw.

149. exp clarithromycin/

150. clarithromycin$.tw.

151. exp amoxicillin/

152. amoxycillin$.tw.

153. amox?cillin$.tw.

154. exp metronidazole/

155. metronidazole$.tw.

156. exp tinidazole/

157. tinidazole$.tw.

158. exp tetracyclines/

159. tetracycline$.tw.

160. anti-bacterial agents/[RS1]

161. or/79-160

162. exp helicobacter pylori/

163. (campylobacter adj1 pylori$).tw.

164. (h adj1 pylori).tw.

165. (pylori$ adj250 eradicat$).tw.

166. or/162-165

167. 39 and 78

168. 39 or 167

169. 161 and 168

170. 166 and 169

171. 170 and 29

172. randomized controlled trial.pt.

173. controlled clinical trial.pt.

174. randomized.ab.

175. placebo.ab.

176. drug therapy.fs.

177. randomly.ab.

178. trial.ab.

179. groups.ab.

180. or/172-179

181. exp animals/ not humans.sh.

182. 180 not 181

183. 170 and 182

184. 183 not 171

185. limit 184 to yr="2015 - 2016"

Appendix 3. EMBASE search strategy

Via OVIDSP

1. exp randomized controlled trial/

2. randomized controlled trial.mp.

3. randomized controlled trial$.tw.

4. exp randomization/

5. exp single blind method/

6. exp double blind method/

7. or/1-6

8. animal.hw.

9. human.hw.

10. 8 not (8 and 9)

11. 7 not 10

12. exp clinical trial/

13. clinical trial.mp.

14. (clin$ adj3 (stud$ or trial$)).ti,ab,tw.

15. (clin$ adj3 trial$).ti,ab,tw.

16. ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$)).ti,ab,tw.

17. exp placebo/

18. placebo$.ti,ab,tw.

19. random.ti,ab,tw.

20. (crossover$ or cross-over$).ti,ab,tw.

21. or/12-20

22. 21 not 10

23. 22 not 11

24. exp comparative study/

25. exp evaluation studies/

26. exp prospective studies/

27. exp controlled study/

28. (control$ or prospective$ or volunteer$).ti,ab,tw.

29. or/24-28

30. 29 not 10

31. 30 not (11 or 23)

32. 11 or 23 or 31

33. exp peptic ulcer/

34. exp peptic ulcer hemorrhage/

35. exp peptic ulcer perforation/

36. exp duodenal ulcer/

37. exp stomach ulcer/

38. (pep$ adj5 ulcer$).tw.

39. (stomach adj5 ulcer$).tw.

40. (duoden$ adj5 ulcer$).tw.

41. (gastr$ adj5 ulcer$).tw.

42. or/33-41

43. exp dyspepsia/

44. exp eructation/

45. exp flatulence/

46. exp heartburn/

47. exp gastroparesis/

48. exp gastric emptying/

49. exp gastritis/

50. dyspep$.tw.

51. (acid adj5 reflux).tw.

52. belch$.tw.

53. bloat$.tw.

54. burp$.tw.

55. (early adj5 satiety).tw.

56. eructation.tw.

57. flatu$.tw.

58. heartburn.tw.

59. indigestion.tw.

60. pyro$.tw.

61. hiatus hernia.tw.

62. (stomach adj5 paresis).tw.

63. gastritis.tw.

64. (gastric adj5 acid adj5 secretion).tw.

65. (stomach adj5 acid adj5 secretion).tw.

66. (gastric adj5 erosion$).tw.

67. (gastric adj5 emptying adj5 disorder$).tw.

68. (stomach adj5 emptying adj5 disorder$).tw.

69. gastroparesis.tw.

70. (bleed$ adj5 ulcer$).tw.

71. (rebleed$ adj5 ulcer$).tw.

72. (recurrent adj5 bleed$ adj5 ulcer$).tw.

73. (acute adj5 bleed$ adj5 ulcer$).tw.

74. (gastrointestinal adj5 bleed$).tw.

75. (gastrointestinal adj5 rebleed$).tw.

76. (gastrointestinal adj5 hemorrhag$).tw.

77. (gastrointestinal adj5 haemorrhag$).tw.

78. (ulcer adj5 hemorrhag$).tw.

79. (ulcer adj5 haemorrhag$).tw.

80. (mucos$ adj5 injur$).tw.

81. or/43-80

82. exp anti-ulcer agents/

83. exp omeprazole/

84. omeprazole.tw.

85. lansoprazole.tw.

86. pantoprazole.tw.

87. rabeprazole.tw.

88. esomeprazole.tw.

89. exp histamine H2 antagonists/

90. exp cimetidine/

91. cimetidine.tw.

92. exp ranitidine/

93. ranitidine.tw.

94. exp famotidine/

95. famotidine.tw.

96. exp nizatidine/

97. nizatidine.tw.

98. (histamine adj3 H2 adj3 antagonist$).tw.

99. (antiulcer adj5 agent$).tw.

100. (H2 adj5 receptor adj5 antagonist$).tw.

101. (proton adj3 pump adj3 inhibitor$).tw.

102. exp bismuth/

103. exp antacids/

104. exp alginates/

105. Aluminum hydroxide/

106. exp magnesium hydroxide/

107. exp magnesium oxide/

108. exp calcium carbonate/

109. (magnesium adj5 carbonate).tw.

110. exp magnesium hydroxide/

111. exp magnesium oxide/

112. Magnesium silicates/

113. exp carbenoxolone/

114. exp misoprostol/

115. exp sucralfate/

116. exp muscarinic antagonists/

117. exp dicyclomine/

118. exp pirenzepine/

119. exp propantheline/

120. algicon.tw.

121. alginates.tw.

122. (alumin?um adj5 hydroxide).tw.

123. (calcium adj5 carbonate).tw.

124. gaviscon.tw.

125. hydrotalcite.tw.

126. maalox.tw.

127. (magnesium adj5 hydroxide).tw.

128. (magnesium adj5 oxide).tw.

129. (magnesium adj5 trisilicate).tw.

130. (sodium adj5 bicarbonate).tw.

131. (sodium adj5 carbonate).tw.

132. (mucosal adj5 protecting adj5 agent$).tw.

133. carbenoxolone.tw.

134. misoprostol.tw.

135. sucralfate.tw.

136. antimuscarinic$.tw.

137. (muscarinic adj5 receptor adj5 antagonist$).tw.

138. dicyclomine.tw.

139. pirenzepine.tw.

140. propantheline.tw.

141. exp macrolides/

142. macrolides.tw.

143. exp nitroimidazoles/

144. nitroimidazole$.tw.

145. exp tetracyclines/

146. tetracyclines.tw.

147. exp penicillins/

148. penicillin$.tw.

149. exp bismuth/

150. bismuth$.tw.

151. de-nol.tw.

152. exp clarithromycin/

153. clarithromycin$.tw.

154. exp amoxicillin/

155. amoxycillin$.tw.

156. amox?cillin$.tw.

157. exp metronidazole/

158. metronidazole$.tw.

159. exp tinidazole/

160. tinidazole$.tw.

161. exp tetracycline/

162. tetracycline$.tw.

163. exp antibiotics, tetracycline/

164. or/82-163

165. exp helicobacter pylori/

166. (campylobacter adj1 pylori$).tw.

167. (h adj1 pylori).tw.

168. (pylori$ adj250 eradicat$).tw.

169. or/165-168

170. 42 and 81

171. 42 or 170

172. 164 and 171

173. 172 and 169

174. 173 and 32

175. Clinical trial/

176. Randomized controlled trial/

177. Randomization/

178. Single-Blind Method/

179. Double-Blind Method/

180. Cross-Over Studies/

181. Random Allocation/

182. Placebo/

183. Randomi?ed controlled trial$.tw.

184. Rct.tw.

185. Random allocation.tw.

186. Randomly allocated.tw.

187. Allocated randomly.tw.

188. (allocated adj2 random).tw.

189. Single blind$.tw.

190. Double blind$.tw.

191. ((treble or triple) adj blind$).tw.

192. Placebo$.tw.

193. Prospective study/

194. or/175-193

195. Case study/

196. Case report.tw.

197. Abstract report/ or letter/

198. or/195-197

199. 194 not 198

200. 173 and 199

201. 200 not 174

202. 174 or 200

203. limit 202 to yr="2015 - 2016"

WHAT'S NEW

Date	Event	Description
21 March 2016	New citation required and conclusions have changed	No new studies identified for inclusion. Results remain unchanged. Conclusions have changed.
18 March 2016	New search has been performed	The searches were re-run. Two references (one trial: Dumbleton 2015) were identified and excluded. The search results and reference flow were revised.
31 January 2015	New search has been performed	Review updated to incorporate results of updated literature search.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 4, 2003

Date	Event	Description
9 October 2008	Amended	Converted to new review format.
1 February 2006	New citation required and conclusions have changed	Substantive amendment
6 October 2003	New search has been performed	Minor update.

CONTRIBUTIONS OF AUTHORS

AF and PM wrote the protocol
AF assessed citations for initial eligibility
PM checked a sample of these
AF obtained the papers
AF and PM decided eligibility on papers obtained
BD adjudicated disagreements for eligibility
AF extracted data and entered into RevMan (RevMan 2014)
PM checked data extraction and entry into RevMan (RevMan 2014)
PM performed metaregression
AF and PM wrote the review

DF made revisions to the text of the review
KG re-ran the searches in March 2016 and made revisions to the review following copy editor comments and ensured that the review follows the current MECIR standards.

DECLARATIONS OF INTEREST

Kurinchi Gurusamy: receives funding from the National Institute for Health Research to perform systematic reviews (Sources of support) and from Wellcome Trust UK and Cancer Research UK for unrelated projects.

Alex Ford: none.

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INDEX TERMS

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*Helicobacter pylori; Anti-Bacterial Agents [therapeutic use]; Anti-Ulcer Agents [therapeutic use]; Drug Therapy, Combination; Duodenal Ulcer [*drug therapy] [microbiology]; Helicobacter Infections [*drug therapy]; Randomized Controlled Trials as Topic; Stomach Ulcer [*drug therapy] [microbiology]

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