Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients (Review)

Ford AC, Delaney B, Forman D, Moayyedi P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Alex C Ford[1], Brendan Delaney[2], David Forman[3], Paul Moayyedi[4]

[1]Department of Academic Medicine, St. James's University Hospital, Leeds, UK. [2]Division of Health and Social Care Research, King's College London, London, UK. [3]International Agency for Research on Cancer, Lyon, France. [4]Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, Canada

Contact address: Alex C Ford, Department of Academic Medicine, St. James's University Hospital, Beckett Street, Leeds, LS9 7TF, UK. alexf12399@yahoo.com.

Editorial group: Cochrane Upper Gastrointestinal and Pancreatic Diseases Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2011.
Review content assessed as up-to-date: 22 November 2010.

Citation: 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.

ABSTRACT

Background

Peptic ulcer disease is the cause for dyspepsia in about 10% of patients. 95% 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.

Objectives

The primary outcomes were the proportion of peptic ulcers healed initially and proportion of patients free from relapse following successful healing. Eradication therapy was compared to placebo or pharmacological therapies in *H. pylori* positive patients. Secondary aims included symptom relief and adverse effects.

Search methods

Trials were identified by searching MEDLINE (1950 to August 2010), EMBASE (1980 to 2010 week 35), and the Cochrane Central Register of Controlled Trials (Issue 2, 2010). Reference lists from trials selected by electronic searching were handsearched to identify further relevant trials. Published abstracts from conference proceedings from the United European Gastroenterology Week (published in *Gut*) and Digestive Disease Week (published in *Gastroenterology*) were handsearched. The search was updated in September 2003, November 2004, November 2005, July 2008, and August 2010. Members of the Cochrane UGPD Group, and experts in the field were contacted and asked to provide details of outstanding clinical trials and any relevant unpublished materials

Selection criteria

Randomised controlled trials of short and long-term treatment of peptic ulcer disease in *H. pylori* positive adults were analysed. Patients received at least one week of H pylori eradication compared with ulcer healing drug, placebo or not treatment. Trials were included if they reported assessment from two weeks onwards.

Data collection and analysis

Data were collected on ulcer healing, recurrence, relief of symptoms and adverse effects.

Main results

Sixty four trials were eligible. Data extraction was not possible in seven trials, and 57 trials were included. In duodenal ulcer healing, eradication therapy was superior to ulcer healing drug (UHD) (34 trials, 3910 patients, relative risk (RR) of ulcer persisting = 0.66, 95% confidence interval (CI) 0.58 to 0.76) and no treatment (two trials, 207 patients, RR 0.37, 95% CI 0.26 to 0.53). In gastric ulcer healing, no significant differences were detected between eradication therapy and UHD (15 trials, 1974 patients, RR 1.23, 95% CI 0.90 to 1.68). In preventing duodenal ulcer recurrence no significant differences were detected between eradication therapy and maintenance therapy with UHD (four trials, 319 patients, RR of ulcer recurring 0.73; 95% CI 0.42 to 1.25), but eradication therapy was superior to no treatment (27 trials 2509 patients, RR 0.20, 95% CI 0.15 to 0.26). In preventing gastric ulcer recurrence, eradication therapy was superior to no treatment (12 trials, 1476 patients, RR 0.31, 95% CI 0.22 to 0.45).

Authors' conclusions

A one to two weeks course of *H. pylori* eradication therapy is an effective treatment for *H. pylori* positive peptic ulcer disease.

PLAIN LANGUAGE SUMMARY

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

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). *Helicobacter pylori* (or *H. pylori*) causes most peptic ulcers. The review of trials found that antibiotics for *H. pylori* have a small benefit in initial healing of duodenal ulcers and a significant benefit in preventing the recurrence of both gastric and duodenal ulcers once healing has been achieved. In summary, when people with peptic ulcers have *Helicobacter pylori* infection, antibiotic treatment can help speed initial healing of some ulcers and can prevent ulcers returning

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

duodenal ulcer acute healing with H. pylori eradication + ulcer healing drug compared to ulcer healing drug alone for peptic ulcer disease in Helicobacter pylori positive patients

Patient or population: patients with peptic ulcer disease in Helicobacter pylori positive patients
Settings:
Intervention: duodenal ulcer acute healing with H. pylori eradication + ulcer healing drug
Comparison: ulcer healing drug alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ulcer healing drug alone	duodenal ulcer acute healing with H. pylori eradication + ulcer healing drug				
Proportion not healed	Medium risk population		RR 0.66 (0.58 to 0.76)	3910 (34 studies)		
	14 per 100	9 per 100 (8 to 11)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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 cost to healthcare is estimated to run into billions of pounds. 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, patients receiving successful *H. pylori* eradication had a relapse rate of approximately 5% compared with 80% of those healed on H2RAs (Penston 1996).

Initially triple therapy was instituted using bismuth salts and antibiotics, but subsequent trials replaced the bismuth with 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 ulcer separately.

How the intervention might work

In the 1970s and 80s therapy was mainly aimed at reducing acid secretion, achieved by the use of histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (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 90-95% 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.

OBJECTIVES

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

To assess the proportion of patients 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 patients 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. The first period of cross-over trials were also included.

Types of participants

All patients 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;
   i) PPI dual therapy (PPI plus either amoxicillin or clarithromycin)
   ii) PPI triple therapy (PPI plus two of the following; amoxicillin, macrolide, 5 nitroimidazole)
   iii) H2RA triple therapy (H2RA plus two of the following; amoxicillin, macrolide, 5 nitroimidazole)
   iv) Bismuth triple therapy (Bismuth salt and 5 nitroimidazole with either amoxicillin or tetracycline)
   v) Bismuth quadruple therapy (as Bismuth triple therapy, but PPI in addition)
   vi) Ranitidine Bismuth Citrate dual/triple therapy (as for PPI)

vii) Clarithromycin monotherapy

2. PPIs: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.
3. H2RAs: cimetidine, famotidine, nizatidine, ranitidine.
4. Bismuth salts.
5. Sucralfate.
6. Regular antacid.
7. PRN antacid.
8. Placebo.
9. No treatment.

Patients 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 peptic ulcer patients that remained free from relapse following successful ulcer healing.
3. Proportion of patients 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

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

Electronic searches

Trials were identified by searching MEDLINE (1950 to August 2010), EMBASE (1980 to 2010 week 35), and the Cochrane Central Register of Controlled Trials (Issue 2, 2010). 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, and August 2010. The Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE, Sensitivity maximising version, Ovid format (Higgins 2008) was combined with the following search terms to identify randomised controlled trials in MEDLINE. The MEDLINE search strategy (please see Appendix 2) was adapted for use in the other databases searched.

Searching other resources

Reference lists from trials selected by electronic searching were hand-searched to identify further relevant trials.

Abstracts

DDW and UEGW abstract books between 1994 and 2003 were hand-searched. Authors of trial reports published only as abstracts were contacted and asked to contribute full data sets or completed papers.

Correspondence

Experts in the field registered with the UGPD review group were contacted for leads on unpublished studies. In addition, the following pharmaceutical companies - Abbott-Knoll, Astra-Zeneca, Eisai, Glaxo-Smithkline, Lilly and Wyeth were contacted and asked to supply details of any outstanding clinical trials and relevant unpublished materials.

The following experts in the field were contacted:

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

Data collection and analysis

Selection of studies

The lead 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 author independently checked a sample of this selection process.

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

Data extraction and management

Data were extracted by the lead author and recorded onto specially developed forms. There was an unblinded check on this by a second author. Data entry into RevMan (RevMan 2008) was also double-checked.

The following characteristics were recorded for each trial:

- setting: primary or secondary care
- country of origin
- inclusion and exclusion criteria used
- baseline comparability between treatment groups
- treatments compared and number of patients in each arm
- drop-outs reported and their reasons
- site of ulcer
- ulcer healing rates
- ulcer recurrence rates
- complication rates
- eradication rates
- type of eradication regimen
- names, dosage, and schedule of drugs
- adverse events: the total and individual numbers reported
- quality of life
- global symptoms cured or recurred

Data were extracted as intention to treat analyses, where all drop-outs are assumed to have failed treatment.

Assessment of risk of bias in included studies

Assessment of Study Quality

Study quality was assessed by one author and checked by a second. Only trials that used the word 'random, randomly, or randomised' in their reporting were considered in this review and assessed for quality according to four characteristics:

Generation of the allocation schedule for RCT

Reported as truly random or not stated/unclear. Computer generated random numbers, coin toss, shuffles, etc are defined as truly random.

Concealment of the treatment allocation

Reported as adequate, inadequate, unclear. If investigators were unaware of each participant's allocation to a treatment when they are recruited, then the allocation was said to be adequately concealed. Methods such as central randomisation systems or serially numbered opaque envelopes fit these criteria. Where trials did not report the method of concealment of allocation it was deemed unclear.

Implementation of masking

Reported as: 'patients were masked', 'clinicians were masked', 'outcome were assessors masked'. When a placebo was used it was assumed that the participants are masked to their treatment allocation.

Measures of treatment effect

Relative risks were combined for binary outcomes. The number needed to treat was calculated 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, completeness of follow-up and intention to treat analysis were recorded, as were dropout rates by group.

Assessment of heterogeneity

Reasons for heterogeneity were explored according to the following predefined criteria:

1. Multi-centre versus single centre
2. Country of origin
3. Mean age of patients 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

Data synthesis

For binary outcomes, such as peptic ulcer healing, peptic ulcer recurrence and absence of symptoms, the impact of interventions were expressed as relative risks together with 95% confidence intervals. The data for gastric ulcer and duodenal ulcer, and for short and long-term treatment were analysed separately wherever possible. The comparison regimens were also analysed 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 possible explanations were investigated informally, and the data summarised using a random effects analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

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

- 34 RCTs (Asaka 2001; Avsar 1996; Bardhan 1997; Bayerdorffer 1992; Bayerdorffer 1995; 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; Bianchi Porro 1993; Porro 1996; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Sobhani 1995; Spinzi 1994; van Zanten 1999; Wang 1993; Wong 1999) with a total of 3910 patients which comprised:

- 9 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
- 8 RCTs (Avsar 1996; Graham 1991; Lin 1994; Mantzaris 1993; Pinero 1995; Bianchi Porro 1993; Rauws 1990; Wang 1993) comparing Bismuth triple therapy with ulcer-healing drug alone
- 5 RCTs (Asaka 2001; Kepecki 1999; Mones 2001; Porro 1996; van Zanten 1999) comparing PPI triple therapy with ulcer-healing drug alone
- 3 RCTs (Hentschel 1993; Shirotani 1996; Sobhani 1995) comparing H2RA triple therapy with ulcer-healing drug alone
- 3 RCTs (Bardhan 1997; Graham 1998; Pounder 1997) comparing Ranitidine Bismuth Citrate dual therapy with ulcer-healing drug alone
- 2 RCTs (Figueroa 1996; Hosking 1992) comparing Bismuth quadruple therapy with ulcer-healing drug alone
- 1 RCT (Parente 1996) comparing Bismuth quadruple therapy and PPI dual therapy with ulcer-healing drug alone
- 1 RCT (Carpintero 1997) comparing Bismuth triple therapy and H2RA triple therapy with ulcer-healing drug alone
- 1 RCT (Schwartz 1998) comparing PPI triple and dual therapy with ulcer-healing drug alone
- 1 RCT (Wong 1999) comparing Clarithromycin monotherapy with ulcer-healing drug alone

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

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

- 2 RCTs (Graham 1998; Lam 1997) with a total of 207 patients which comprised:
- 1 multi-centre RCT (Graham 1998) comparing Ranitidine Bismuth Citrate dual therapy with no treatment
- 1 RCT (Lam 1997) comparing Clarithromycin monotherapy with no treatment

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

- 15 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 patients which comprised:
- 8 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.
- 2 RCTs (Bayerdorffer 1996; Sung 1995) comparing Bismuth triple therapy with ulcer-healing drug alone.
- 5 RCTs (Asaka 2001; Befrits 2004; Higuchi 2003; Malfertheiner 1999; Tulassay 2008) comparing PPI triple therapy with ulcer-healing drug alone.

There were 7 multi-centre trials. The smallest trial included 27 patients. The largest trial included 402 patients.

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

No RCTs were identified.

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

- 3 RCTs (Arkkila 2005; Suarez 1999; Wang 1996) with a total of 287 patients which comprised:
- 1 RCT (Arkkila 2005) comparing Bismuth quadruple therapy, PPI triple therapy, and PPI dual therapy with ulcer-healing drug alone

- 1 RCT (Wang 1996) comparing Bismuth triple therapy and PPI dual therapy with ulcer-healing drug alone
- 1 RCT (Suarez 1999) comparing Bismuth triple therapy with ulcer-healing drug alone

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

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

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

- 4 RCTs (Kepecki 1999; Mones 2001; Sobhani 1995; Wong 1999) with a total of 319 patients which comprised:
- 2 RCTs (Kepecki 1999; Mones 2001) comparing PPI triple therapy with ulcer-healing drug alone
- 1 RCT (Sobhani 1995) comparing H2RA triple therapy with ulcer-healing drug alone
- 1 RCT (Wong 1999) comparing Clarithromycin monotherapy with ulcer-healing drug alone

There were 2 multi-centre trials: the smallest trial included 73 patients, the largest trial included 119 patients.

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

- 27 RCTs (Avsar 1996; Bardhan 1997; Bayerdorffer 1995; Carpintero 1997; Chen 1995; Figueroa 1996; Graham 1992; Hentschel 1993; Kato 1996; Kim 2002; Lin 1994; Logan 1995; Mantzaris 1993; Miehlke 1995; O'Morain 1996; Pinero 1995; Porro 1996; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Spinzi 1994; Sung 1994; Tomita 2002; Unge 1993a; van Zanten 1999; Wang 1993) with a total of 2509 patients which comprised:
- 8 RCTs (Avsar 1996; Chen 1995; Graham 1992; Lin 1994; Mantzaris 1993; Pinero 1995; Rauws 1990; Wang 1993) comparing Bismuth triple therapy with no treatment
- 7 RCTs (Bayerdorffer 1995; Kato 1996; Logan 1995; Miehlke 1995; O'Morain 1996; Spinzi 1994; Unge 1993a) comparing PPI dual therapy with no treatment
- 4 RCTs (Kim 2002; Porro 1996; Tomita 2002; van Zanten 1999) comparing PPI triple therapy with no treatment
- 2 RCTs (Hentschel 1993; Shirotani 1996) comparing H2RA triple therapy with no treatment
- 2 RCTs (Bardhan 1997; Pounder 1997) comparing Ranitidine Bismuth Citrate dual therapy with no treatment
- 2 RCTs (Figueroa 1996; Sung 1994) comparing Bismuth quadruple therapy with no treatment
- 1 RCT (Schwartz 1998) comparing PPI triple and dual therapy with no treatment
- 1 RCT (Carpintero 1997) comparing Bismuth triple therapy and H2RA triple therapy with no treatment

There were 9 multi-centre trials: the smallest trial contained 20 patients, the largest trial contained 233 patients.

9. 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

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

- 12 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 patients which comprised:
- 5 RCTs (Axon 1997; Fukuda 1995b; Kato 1996; Lazzaroni 1997; Meining 1998) comparing PPI dual therapy with no treatment
- 3 RCTs (Bayerdorffer 1996; Graham 1992; Sung 1995) comparing Bismuth triple therapy with no treatment
- 4 RCTs (Befrits 2004; Malfertheiner 1999; Tomita 2002; Tulassay 2008) comparing PPI triple therapy with no treatment

There were 6 multi-centre trials. The smallest trial contained 59 patients. The largest trial contained 372 patients.

11. 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.

12. 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 patients comparing Bismuth quadruple therapy, PPI triple therapy, and PPI dual therapy with no treatment.

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

- 4 RCTs (Higuchi 2003; Lam 1997; Pounder 1997; Suarez 1999) with a total of 368 patients which comprised:

- 1 RCT (Higuchi 2003) comparing PPI triple therapy with ulcer-healing drug alone
- 1 RCT (Lam 1997) comparing Clarithromycin monotherapy with no treatment
- 1 RCT (Pounder 1997) comparing Ranitidine Bismuth Citrate dual therapy with no treatment
- 1 RCT (Suarez 1999) comparing Bismuth triple therapy with ulcer-healing drug alone

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

No RCTs were identified.

Results of the search

In total, 3376 citations were identified using the search strategy outlined above. The titles and abstracts were reviewed and 90 papers were selected that compared a recognised *H. pylori* eradication regimen against placebo or other pharmacological therapies in *H. pylori* positive peptic ulcer disease. Twenty-six trials did not meet the eligibility criteria and were excluded (Characteristics of excluded studies). A further two trials were excluded as it was not stated if they were truly randomised and attempted correspondence with the authors was unsuccessful. Data could not be extracted from a further four trials, and one paper is awaiting translation. Some of the remaining 57 articles included in the final meta-analysis contained more than one comparison and were therefore included in more than one analysis (see 'Effects of interventions').

Included studies

Please see Characteristics of included studies.

Excluded studies

Please see Characteristics of excluded studies.

Risk of bias in included studies

Two authors undertook an assessment of the quality of each eligible study independently. Methods of randomisation, concealment, and masking were assessed. A summary of the risk of bias may be found in Figure 1 and Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

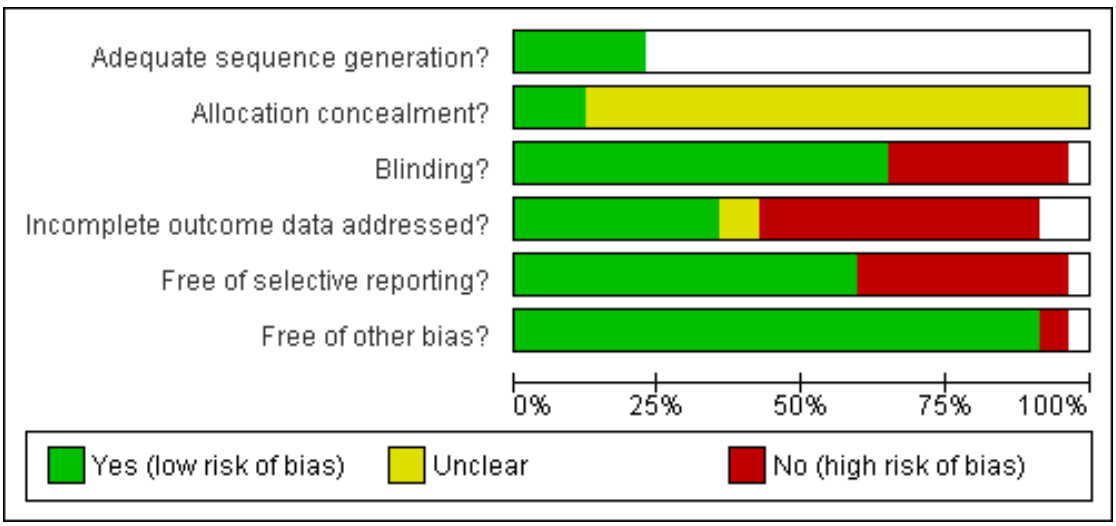
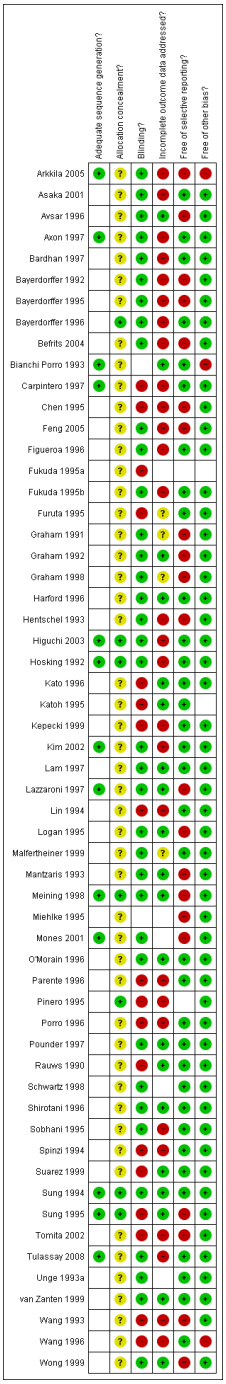


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Thirteen trials stated the method of randomisation (Arkkila 2005; Axon 1997; Carpintero 1997; Higuchi 2003; Hosking 1992; Kim 2002; Lazzaroni 1997; Meining 1998; Mones 2001; Porro 1996; Sung 1994; Sung 1995; Tulassay 2008)

Blinding

Eight trials (Bayerdorffer 1996; Higuchi 2003; Hosking 1992; Lam 1997; Meining 1998; Pinero 1995; Sung 1994; Sung 1995) reported the method of concealment.

Incomplete outcome data

Twenty-three trials (Avsar 1996; Bianchi Porro 1993; Furuta 1995; Graham 1991; Graham 1992; Graham 1998; Harford 1996; Kato 1996; Katoh 1995; Lam 1997; Lazzaroni 1997; Logan 1995; Mantzaris 1993; Meining 1998; O'Morain 1996; Pounder 1997; Rauws 1990; Shirotani 1996; Suarez 1999; Sung 1994; Sung 1995; van Zanten 1999; Wong 1999) reported patients lost to follow up.

Selective reporting

Twenty-one trials (Arkkila 2005; Avsar 1996; Bayerdorffer 1992; Bayerdorffer 1995; Befrits 2004; Chen 1995; Feng 2005; Graham 1991; Graham 1992; Graham 1998; Hentschel 1993; Lazzaroni 1997; Logan 1995; Mantzaris 1993; Meining 1998; Miehlke 1995; Mones 2001; Sung 1995; Tomita 2002; Wang 1993; Wong 1999) were not, or could not be confirmed to be, free of selective reporting.

Effects of interventions

See: **Summary of findings for the main comparison** duodenal ulcer acute healing with H. pylori eradication + ulcer healing drug compared to ulcer healing drug alone for peptic ulcer disease in Helicobacter pylori positive patients; **Summary of findings 2** duodenal ulcer acute healing with H. pylori eradication compared to no treatment / placebo for peptic ulcer disease in Helicobacter pylori positive patients; **Summary of findings 3** gastric ulcer acute healing with H. pylori eradication + ulcer healing drug compared to ulcer healing drug alone for peptic ulcer disease in Helicobacter pylori positive patients; **Summary of findings 4** duodenal ulcer recurrence with H. pylori eradication compared to no treatment (after initial ulcer healing) for peptic ulcer disease in Helicobacter pylori positive patients; **Summary of findings 5** gastric ulcer recurrence with H. pylori eradication compared to no treatment (after initial ulcer healing) for peptic ulcer disease in Helicobacter pylori positive patients

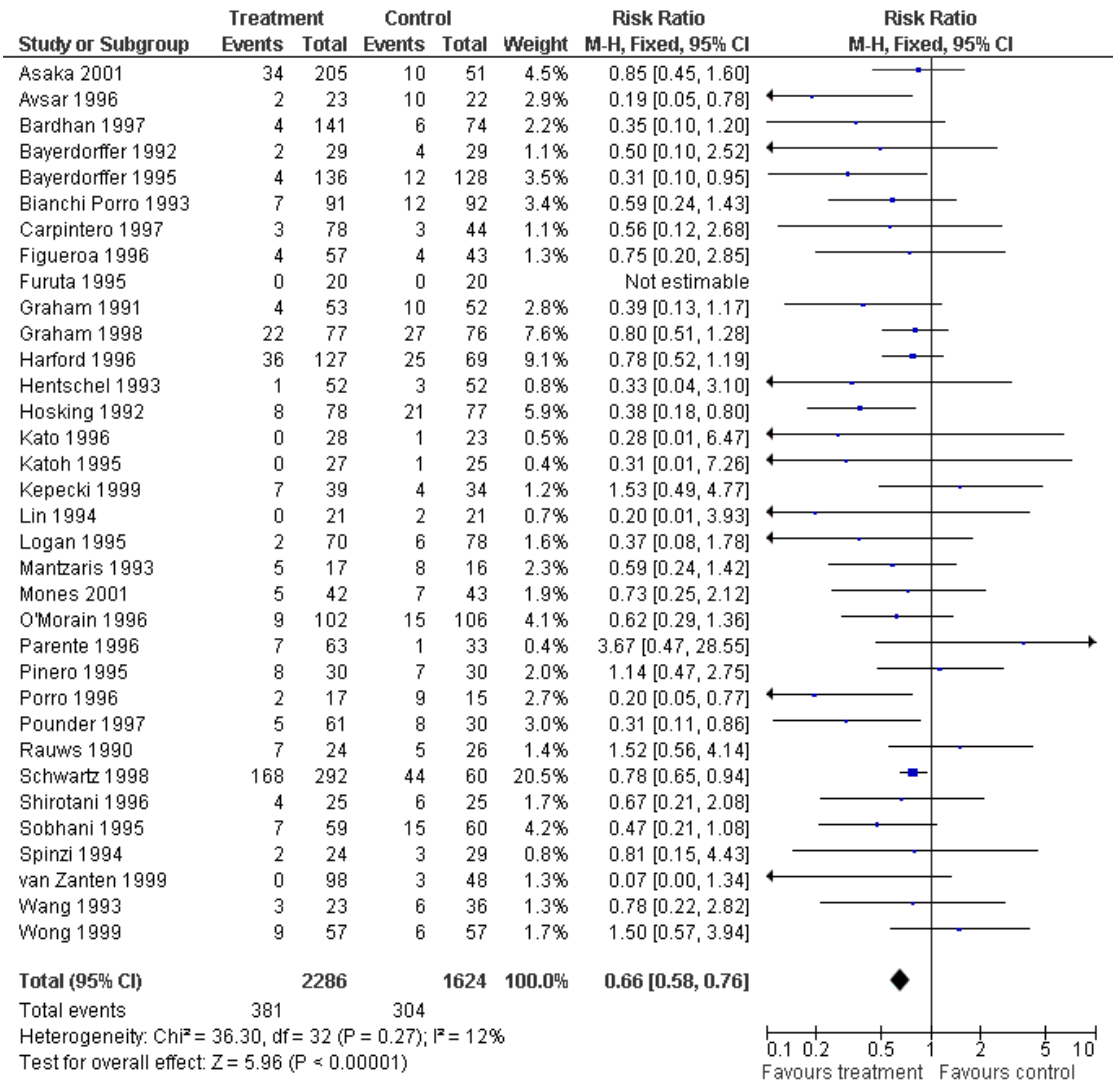
In dealing with the results obtained in this review we will, for the sake of clarity, consider them in the following order; firstly ulcer healing, secondly prevention of ulcer recurrence after initial healing, thirdly relief of symptoms of peptic ulcer, and finally side effects.

I. Ulcer healing

a. 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; 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; Bianchi Porro 1993; Porro 1996; 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 patients, between 1 and 4 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 = 36.3, 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; Figure 3) (number needed to treat (NNT) = 14; 95% CI 11 to 20).

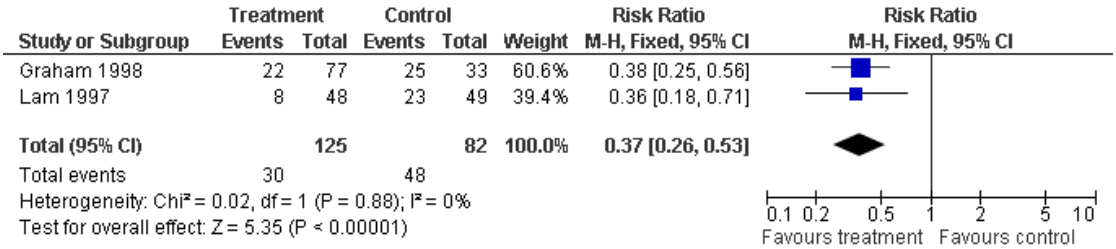
Figure 3. Forest plot of comparison: 1 duodenal ulcer acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone, outcome: 1.1 Proportion not healed.



b. 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 patients, between 2 and 3 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; Figure 4) (NNT 2.5; 95% CI 2 to 4).

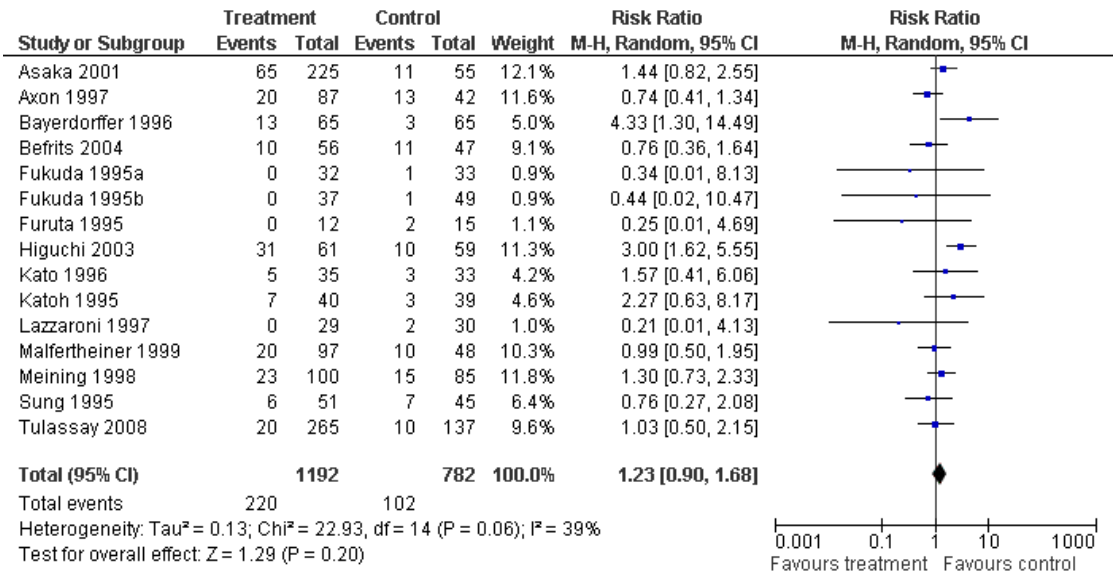
Figure 4. Forest plot of comparison: 2 duodenal ulcer acute healing hp eradication vs. no treatment / placebo, outcome: 2.1 Proportion not healed.



c. 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 patients, between 1 and 3 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; Figure 5). 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 multicentre studies (log RR 1.52; 95% CI 0.87 to 2.18. P < 0.001), absence of blinding (logRR = 3.17; 95% CI 1.53 to 4.82. P < 0.001), and a greater than 10% difference in follow-up between trial arms (logRR = 3.09; 95% CI 0.82 to 5.37. P = 0.008) increased the effect size whereas performing an intention to treat analysis (logRR = -1.55; 95% CI -0.38 to -2.72. P = 0.01), and increasing completeness of follow-up (logRR = -8.79; 95% CI -4.31 to -13.26. P < 0.001) reduced the effect size.

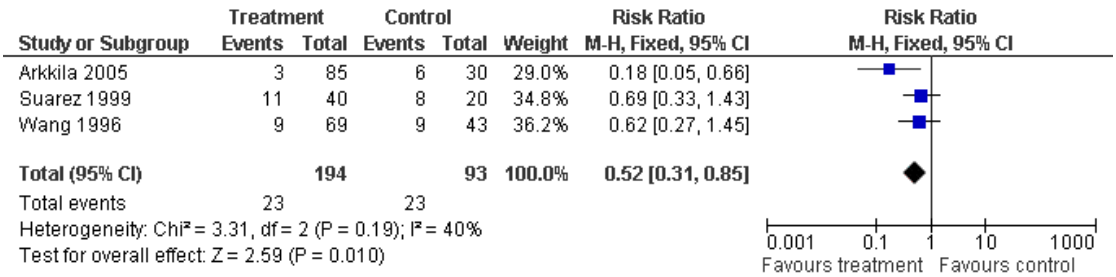
Figure 5. Forest plot of comparison: 3 gastric ulcer acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone, outcome: 3.1 Proportion not healed.



d. 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 patients, between 1 and 2 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; Figure 6) (NNT = 8; 95% CI 4.5 to 50).

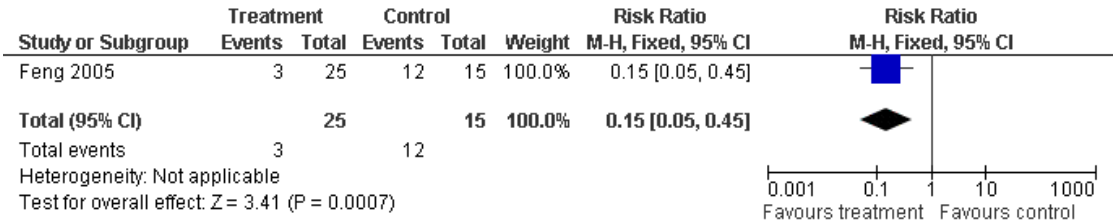
Figure 6. Forest plot of comparison: 4 peptic ulcer acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone, outcome: 4.1 Proportion not healed.



e. 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 patients, 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; Figure 7) (NNT = 1.5; 95% CI 1.1 to 2.3).

Figure 7. Forest plot of comparison: 5 peptic ulcer acute healing hp eradication vs. no treatment / placebo, outcome: 5.1 Proportion not healed.

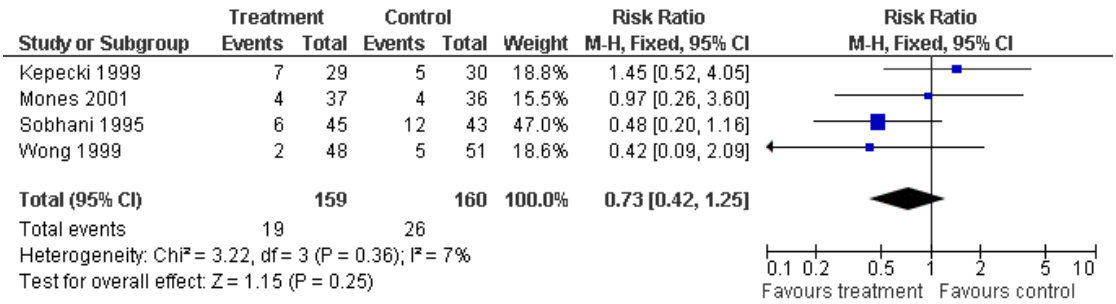


II. Preventing ulcer recurrence after initial ulcer healing

a. 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 patients, between 6 months and 2 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; Figure 8).

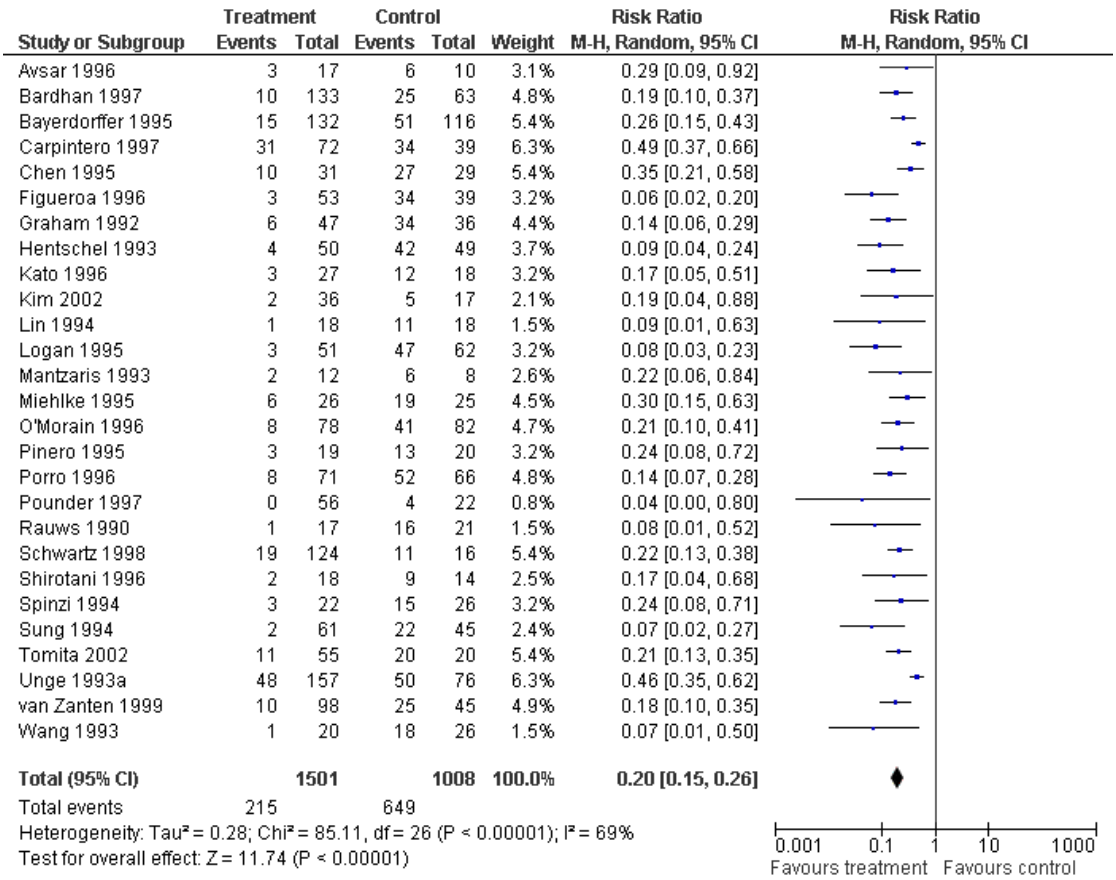
Figure 8. Forest plot of comparison: 6 duodenal ulcer recurrence hp eradication vs. ulcer healing drug alone (after initial ulcer healing), outcome: 6.1 Proportion recurred.



b. 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 1995; Carpintero 1997; Chen 1995; Figueroa 1996; Graham 1992; Hentschel 1993; Kato 1996; Kim 2002; Lin 1994; Logan 1995; Mantzaris 1993; Miehlke 1995; O'Morain 1996; Pinero 1995; Porro 1996; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Spinzi 1994; Sung 1994; Tomita 2002; Unge 1993a; van Zanten 1999; Wang 1993) reported a dichotomous duodenal ulcer recurrence outcome evaluating 2509 patients, between 2 months and 5 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 = 85.4, 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; Figure 9) (NNT = 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. 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 (logRR = -1.80; 95% CI -0.81 to -2.80. P < 0.001) and duration of eradication therapy (logRR = -0.38; 95% CI -0.27 to -0.50. P < 0.001) and increased with increasing length of follow-up (logRR = 0.006; 95% CI 0.001 to 0.010. P = 0.02) and when an intention to treat analysis was performed by the authors (logRR = 0.31; 95% CI 0.11 to 0.52. P = 0.003).

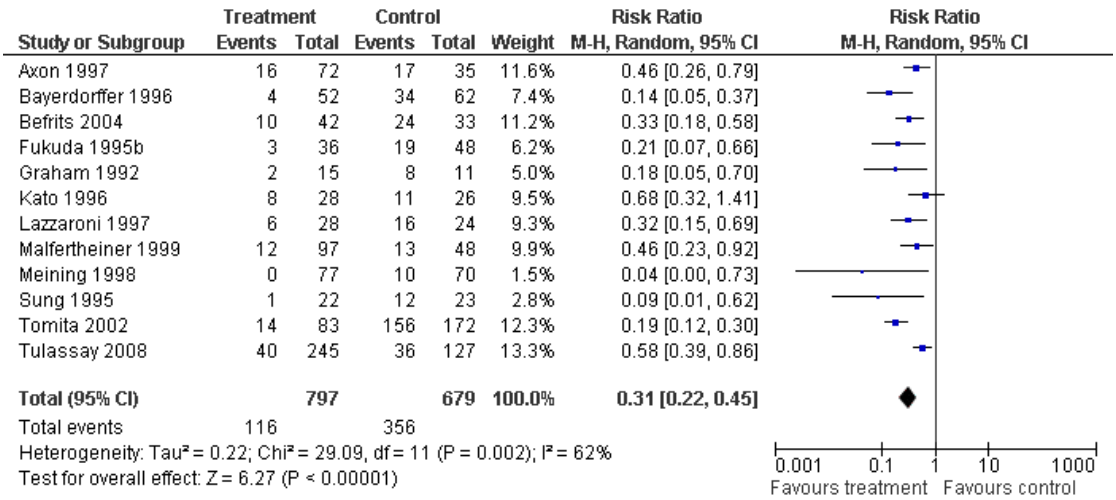
Figure 9. Forest plot of comparison: 7 duodenal ulcer recurrence hp eradication vs. no treatment (after initial ulcer healing), outcome: 7.1 Proportion recurred.



c. 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 patients, between 3 months and 5 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; Figure 10) (NNT = 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. 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 (logRR = 0.52; 95% CI 0.28 to 0.77 P < 0.001)).

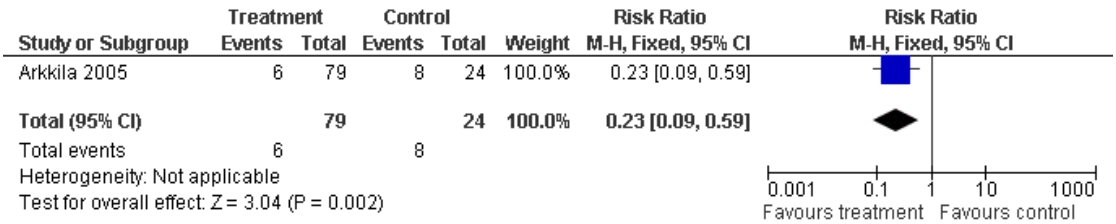
Figure 10. Forest plot of comparison: 8 gastric ulcer recurrence hp eradication vs. no treatment (after initial ulcer healing), outcome: 8.1 Proportion recurred.



d. 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 patients at 1 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; Figure 11) (NNT = 4; 95% CI 2 to 17).

Figure 11. Forest plot of comparison: 9 peptic ulcer recurrence hp eradication vs. no treatment (after initial ulcer healing), outcome: 9.1 Proportion recurred.

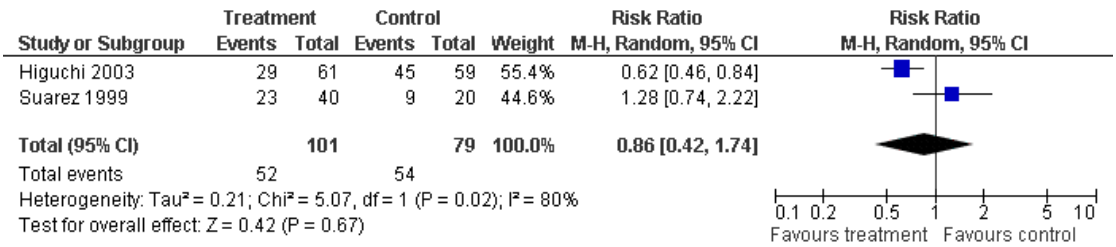


III. Relief of symptoms from peptic ulcer

a. 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 patients, between 4 and 6 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; Figure 12).

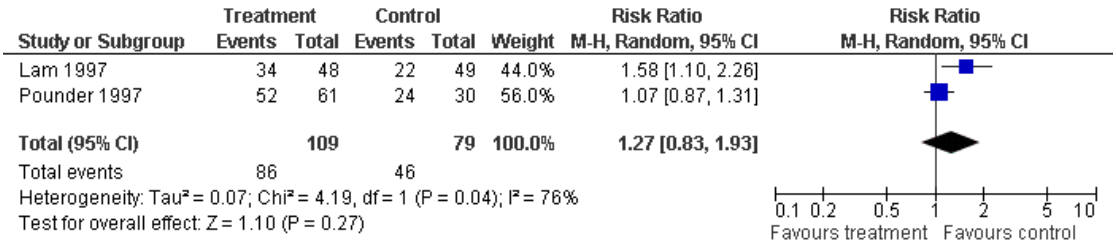
Figure 12. Forest plot of comparison: 10 global symptoms persisting, outcome: 10.1 hp eradication + ulcer healing drug vs. ulcer healing drug alone.



b. 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 patients at 4 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; Figure 13).

Figure 13. Forest plot of comparison: 10 global symptoms persisting, outcome: 10.2 hp eradication vs. no treatment.

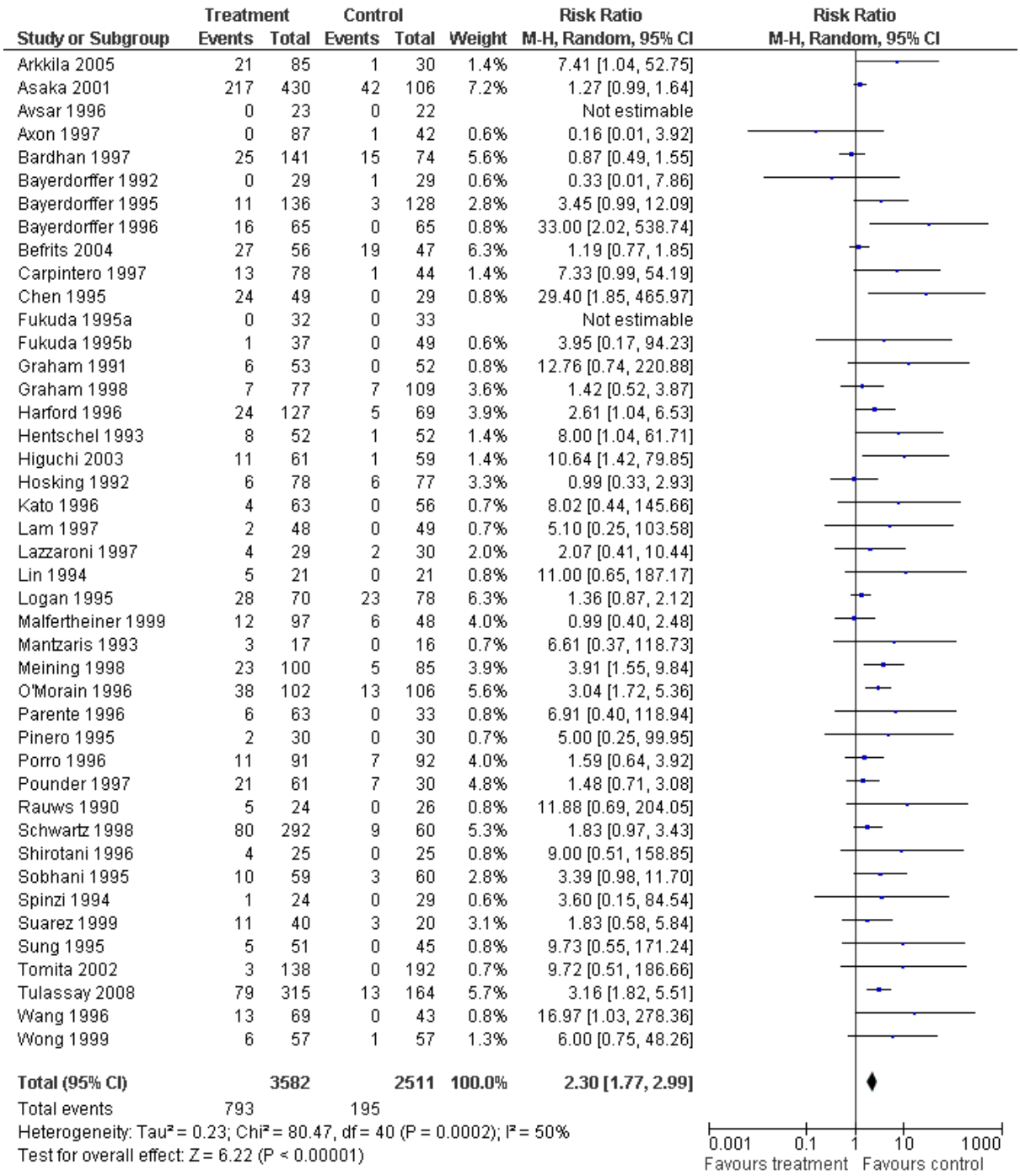


IV. Side effect profile

a. 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; 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; Porro 1996; Pounder 1997; Rauws 1990; Schwartz 1998; Shirotani 1996; Sobhani 1995; Spinzi 1994; Suarez 1999; Sung 1995; Tomita 2002; Wang 1996; Wong 1999; Tulassay 2008) reported overall numbers of adverse events as a dichotomous outcome in 6093 patients. In total 22% of patients 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; Figure 14) (NNH = 10; 95% CI 8 to 14).

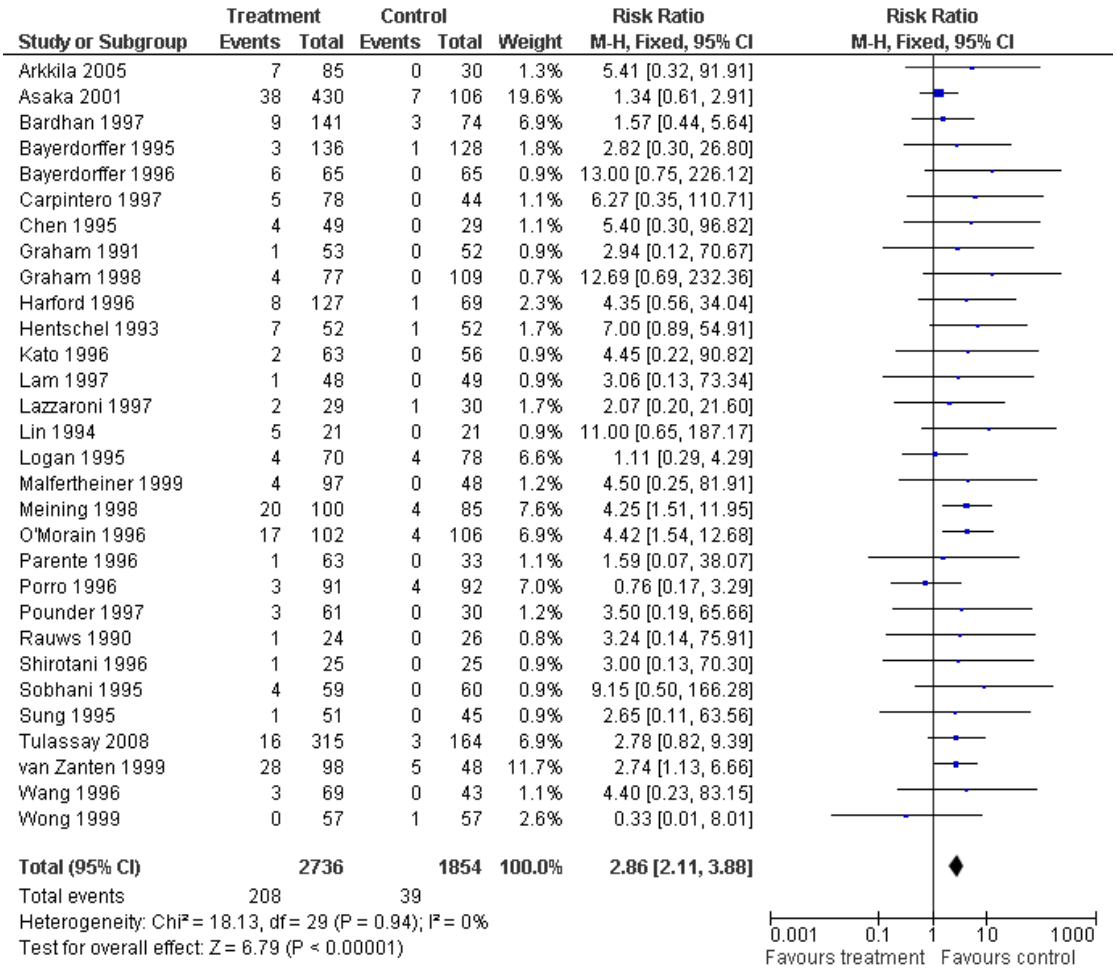
Figure 14. Forest plot of comparison: 11 adverse events, outcome: 11.1 Overall, proportion occurred.



b. Diarrhoea

Thirty trials (Arkkila 2005; Asaka 2001; Bardhan 1997; Bayerdorffer 1995; Bayerdorffer 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; Porro 1996; Pounder 1997; Rauws 1990; Shirotani 1996; Sobhani 1995; Sung 1995; van Zanten 1999; Wang 1996; Wong 1999; Tulassay 2008) reported occurrence of diarrhoea as a dichotomous outcome in 4590 patients. Overall 8% of patients 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 patients 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; Figure 15) (NNH = 24; 95% CI 17 to 37).

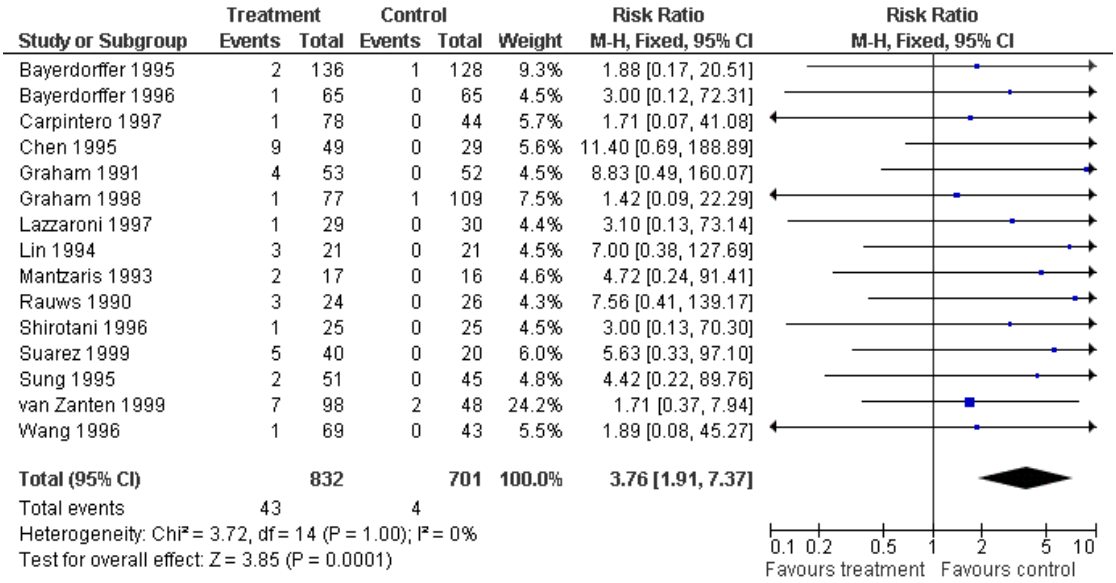
Figure 15. Forest plot of comparison: 11 adverse events, outcome: 11.2 Diarrhoea, proportion occurred.



c. 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 and/or vomiting as a dichotomous outcome in 1533 patients. Overall 5% of patients 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 patients 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; Figure 16) (NNH = 25; 95% CI 17 to 50).

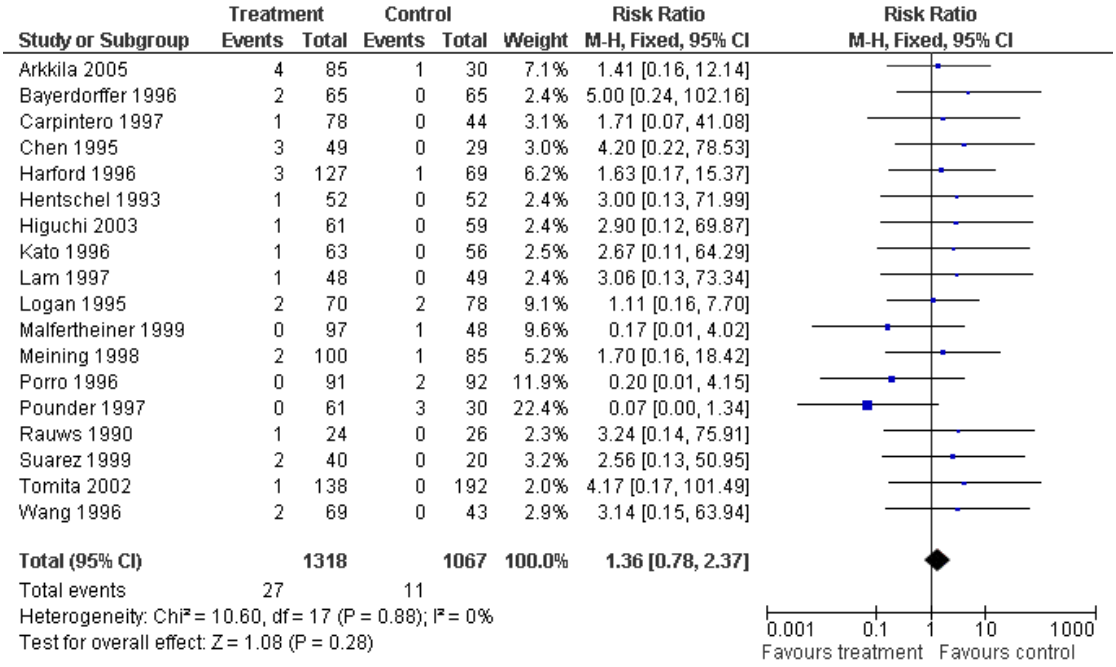
Figure 16. Forest plot of comparison: 11 adverse events, outcome: 11.3 Nausea/vomiting, proportion occurred.



d. Skin rash

Eighteen trials (Arkkila 2005; Bayerdorffer 1996; Carpintero 1997; Chen 1995; Harford 1996; Hentschel 1993; Higuchi 2003; Kato 1996; Lam 1997; Logan 1995; Malfertheiner 1999; Meining 1998; Porro 1996; Pounder 1997; Rauws 1990; Suarez 1999; Tomita 2002; Wang 1996) reported occurrence of skin rash as a dichotomous outcome in 2385 patients. Overall 2% of patients 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 patients 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; Figure 17).

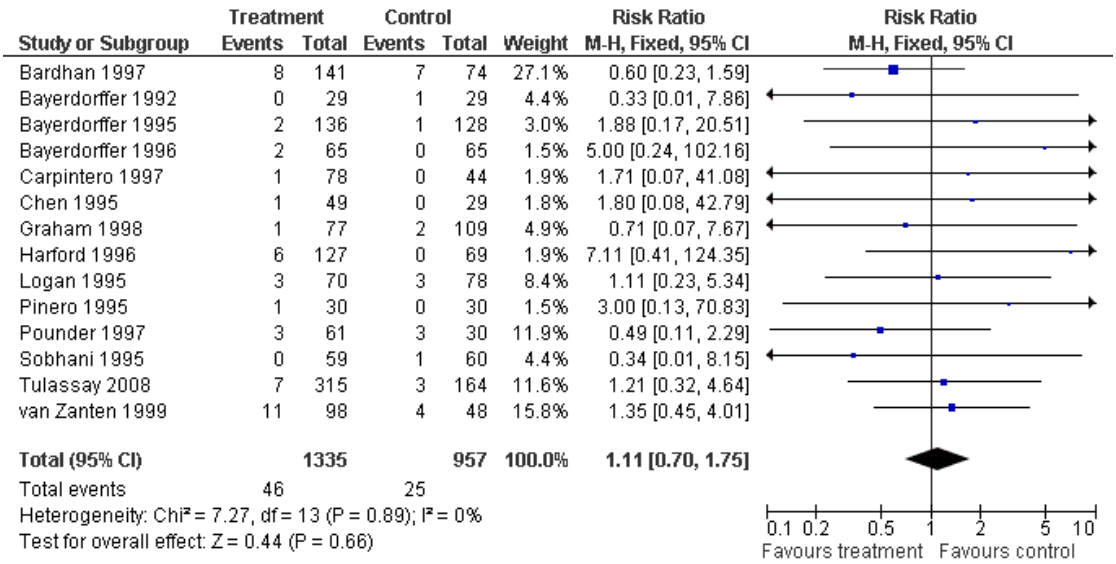
Figure 17. Forest plot of comparison: 11 adverse events, outcome: 11.4 Skin rash, proportion occurred.



e. 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; van Zanten 1999; Tulassay 2008) reported occurrence of headache as a dichotomous outcome in 2292 patients. Overall 3% of patients 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 patients 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; Figure 18).

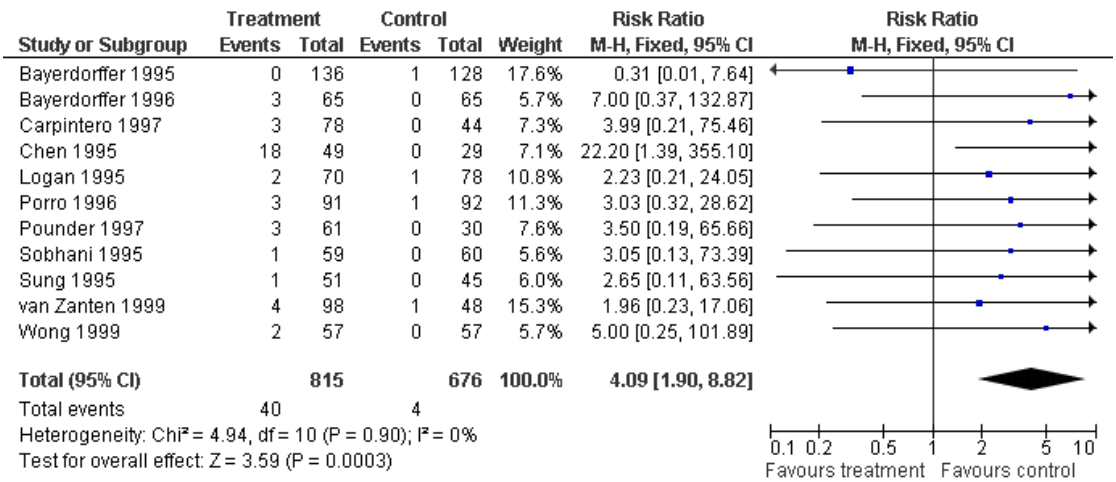
Figure 18. Forest plot of comparison: 11 adverse events, outcome: 11.5 Headache, proportion occurred.



f. Epigastric pain

Eleven trials (Bayerdorffer 1995; Bayerdorffer 1996; Carpintero 1997; Chen 1995; Logan 1995; Porro 1996; Pounder 1997; Sobhani 1995; Sung 1995; van Zanten 1999; Wong 1999) reported occurrence of epigastric pain as a dichotomous outcome in 1491 patients. Overall 5% of patients 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 patients 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; Figure 19) (NNH = 25; 95% CI 20 to 50).

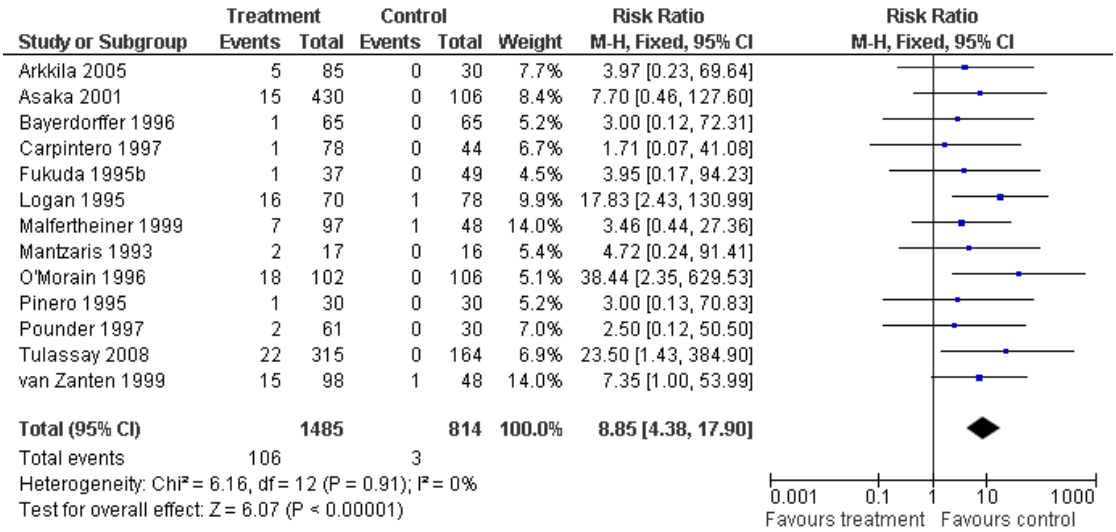
Figure 19. Forest plot of comparison: 11 adverse events, outcome: 11.6 Epigastric pain, proportion occurred.



g. 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; van Zanten 1999; Tulassay 2008) reported occurrence of altered taste as a dichotomous outcome in 2299 patients. Overall 7% of patients 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 patients 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; Figure 20) (NNH = 15; 95% CI 10 to 30).

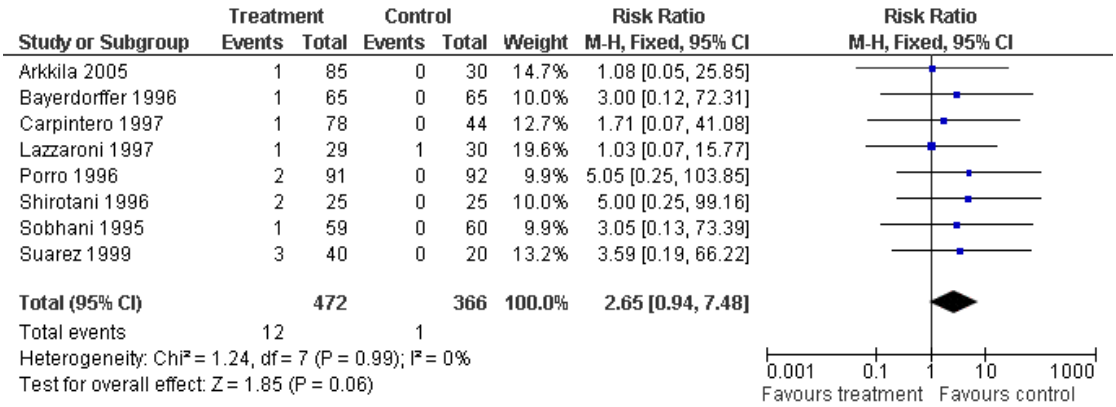
Figure 20. Forest plot of comparison: 11 adverse events, outcome: 11.7 Altered taste, proportion occurred.



h. Stomatitis

Eight trials (Arkkila 2005; Bayerdorffer 1996; Carpintero 1997; Lazzaroni 1997; Porro 1996; Shirotani 1996; Sobhani 1995; Suarez 1999) reported occurrence of stomatitis as a dichotomous outcome in 838 patients. Overall 2.5% of patients 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 patients 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; Figure 21).

Figure 21. Forest plot of comparison: 11 adverse events, outcome: 11.8 Stomatitis, proportion occurred versus not occurred.



ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

duodenal ulcer acute healing with H. pylori eradication compared to no treatment / placebo for peptic ulcer disease in Helicobacter pylori positive patients

Patient or population: patients with peptic ulcer disease in Helicobacter pylori positive patients
Settings:
Intervention: duodenal ulcer acute healing with H. pylori eradication
Comparison: no treatment / placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no treatment / placebo	duodenal ulcer acute healing with H. pylori eradication				
Proportion not healed	Medium risk population		RR 0.37 (0.26 to 0.53)	207 (2 studies)		
	61 per 100	23 per 100 (16 to 33)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

gastric ulcer acute healing with H. pylori eradication + ulcer healing drug compared to ulcer healing drug alone for peptic ulcer disease in Helicobacter pylori positive patients

Patient or population: patients with peptic ulcer disease in Helicobacter pylori positive patients
Settings:
Intervention: gastric ulcer acute healing with H. pylori eradication + ulcer healing drug
Comparison: ulcer healing drug alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ulcer healing drug alone	gastric ulcer acute healing with H. pylori eradication + ulcer healing drug				
Proportion not healed	Medium risk population		RR 1.23 (0.9 to 1.68)	1974 (15 studies)		
	13 per 100	16 per 100 (12 to 22)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

duodenal ulcer recurrence with H. pylori eradication compared to no treatment (after initial ulcer healing) for peptic ulcer disease in Helicobacter pylori positive patients

Patient or population: patients with peptic ulcer disease in Helicobacter pylori positive patients
Settings:
Intervention: duodenal ulcer recurrence with H. pylori eradication
Comparison: no treatment (after initial ulcer healing)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no treatment (after initial ulcer healing)	duodenal ulcer recurrence with H. pylori eradication				
Proportion recurred	Medium risk population		RR 0.2 (0.15 to 0.26)	2509 (27 studies)		
	67 per 100	13 per 100 (10 to 17)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

gastric ulcer recurrence with H. pylori eradication compared to no treatment (after initial ulcer healing) for peptic ulcer disease in Helicobacter pylori positive patients

Patient or population: patients with peptic ulcer disease in Helicobacter pylori positive patients
Settings:
Intervention: gastric ulcer recurrence with H. pylori eradication
Comparison: no treatment (after initial ulcer healing)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no treatment (after initial ulcer healing)	gastric ulcer recurrence with H. pylori eradication				
Proportion recurred	Medium risk population		RR 0.31 (0.22 to 0.45)	1476 (12 studies)		
	50 per 100	16 per 100 (11 to 23)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

DISCUSSION

Summary of main results

The most important finding of this review concerns the ulcer recurrence rate of both duodenal and gastric ulcer patients 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 relative risk reduction of 69% for gastric ulcer. The difference in results between duodenal and gastric ulcer probably reflect 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. Patients receiving eradication therapy report a higher incidence of side effects, with a greater than two-fold increase in the risk of adverse events in patients assigned to comparison regimen rather than *H. pylori* eradication therapy. Although these unwanted effects are only short-term they may be significant for patients (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.

Potential biases in the review process

We have explored reasons for heterogeneity in the results using meta-regression. These results need to be interpreted with caution as meta-regression 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 (Malfertheiner 2002b; Howden 1998). This approach is also advocated from a health economic perspective from models (Imperiale 1995; Briggs 1996) 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 (Moore 1994; Leodolter 2001). 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 patients 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 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 by Leodolter et al 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 and / or uncontrolled studies 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

International guidelines (Malfertheiner 2002b; Howden 1998; Lam 1998; Hunt 1999) all endorse the use of eradication therapy for *H. pylori* positive individuals with peptic ulcer disease, and the findings of this systematic review supports these recommendations. Therefore eradication therapy is clearly indicated in *H. pylori* positive peptic ulcer disease, as there are definite benefits both in terms of facilitating ulcer healing and preventing ulcer recurrence, especially for duodenal ulcer.

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.

ACKNOWLEDGEMENTS

We would like to thank Iris Gordon, Jan Lilleyman, and Karin Dearness for their help in this review.

REFERENCES

References to studies included in this review

Arkkila 2005 *{published data only}*
Arkkila PET Seppala K Kosunen TU Sipponen P Makinen J Rautelin H Farkkila M. Helicobacter pylori eradication as the sole treatment for gastric and duodenal ulcers. *European Journal of Gastroenterology and Hepatology* 2005;**17**:93–101.

Asaka 2001 *{published data only}*
Asaka M, Sugiyama T, Kato M, et al.A multicenter, double-blind study on triple therapy with lansoprazole, amoxicillin and clarithromycin for eradication of Helicobacter pylori in Japanese peptic ulcer patients. *Helicobacter* 2001;**6**(3): 254–261.

Avsar 1996 *{published data only}*
Avsar E, Kalayci C, Tozun N, et al.Refractory duodenal ulcer healing and relapse: comparison of omeprazole with Helicobacter pylori eradication. *European Journal of Gastroenterology and Hepatology* 1996;**8**:449–452.

Axon 1997 *{published data only}*
Axon AT, O'Morain CA, Bardhan KD, et al.Randomised double blind controlled study of recurrence of gastric ulcer after treatment for eradication of Helicobacter pylori infection. *British Medical Journal* 1997;**314**:565–568.

Bardhan 1997 *{published data only}*
Bardhan KD, Dallaire C, Eisold H, Duggan AE. Ranitidine bismuth citrate with clarithromycin for the treatment of duodenal ulcer. *Gut* 1997;**41**(2):181–186.

Bayerdorffer 1992 *{published data only}*
Bayerdorffer E, Mannes GA, Sommer A, et al.High dose omeprazole treatment combined with amoxicillin eradicates Helicobacter pylori. *European Journal of Gastroenterology and Hepatology* 1992;**4**:697–702.

Bayerdorffer 1995 *{published data only}*
Bayerdorffer E, Miehlke S, Mannes GA, et al.Double-blind trial of omeprazole and amoxicillin to cure Helicobacter pylori infection in patients with duodenal ulcers. *Gastroenterology* 1995;**108**:1412–1417.

Bayerdorffer 1996 *{published data only}*
Bayerdorffer E, Miehlke S, Lehn N, et al.Cure of gastric ulcer disease after cure of Helicobacter pylori infection-German Gastric Ulcer Study. *European Journal of Gastroenterology and Hepatology* 1996;**8**:343–349.

Befrits 2004 *{published data only}*
Befrits R Sjostedt S Tour R Leijonmarck C-E Hedenborg L Backman M. Long-term effects of eradication of Helicobacter pylori on relapse and histology in gastric ulcer patients: A two-year follow-up study. *Scandinavian Journal of Gastroenterology* 2004;**39**:1066–1072.

Bianchi Porro 1993 *{published data only}*
Bianchi Porro G, Parente F, Lazzaroni M. Short and long term outcome of Helicobacter pylori positive resistant duodenal ulcers treated with colloidal bismuth subcitrate plus antibiotics or sucralphate alone. *Gut* 1993;**34**: 466–469.

Carpintero 1997 *{published data only}*
Carpintero P, Blanco M, Pajares JM. Ranitidine versus colloidal bismuth subcitrate in combination with amoxicillin and metronidazole for eradicating Helicobacter pylori in patients with duodenal ulcer. *Clinical Infectious Diseases* 1997;**25**:1032–1037.

Chen 1995 *{published data only}*
Chen TS, Tsay SH, Chang FY, Lee SD. Triple therapy for the eradication of Helicobacter pylori and reduction of

duodenal ulcer relapse: comparison of 1 week and 2 week regimens and recrudescence rates over 12 months. *Journal of Gastroenterology and Hepatology* 1995;**10**:300–305.

Feng 2005 ***{published data only}***
Feng L-Y Yao X-X Jiang S-L. Effects of killing Helicobacter pylori quadruple therapy on peptic ulcer: A randomised double-blind clinical trial. *World Journal of Gastroenterology* 2005;**11**(7):1083.

Figueroa 1996 ***{published data only}***
Figueroa G, Acuna R, Troncoso M, Portell DP, Toledo MS, Albornoz V, Vigneaux J. Low H. pylori reinfection rate after triple therapy in Chilean duodenal ulcer patients. *American Journal of Gastroenterology* 1996;**91**(7):1395–1399.

Fukuda 1995a ***{published data only}***
Fukuda Y, Yamamoto I, Okui M, Tonokatsu Y, Tamura K, Shimoyama T. Combination therapy with mucosal protective agent for the eradication of Helicobacter pylori. *European Journal of Gastroenterology and Hepatology* 1995;**7 (Suppl 1)**:S45–S47.

Fukuda 1995b ***{published data only}***
Fukuda Y, Yamamoto I, Okui M, Tonokatsu Y, Shimoyama T. Combination therapies with a proton pump inhibitor for Helicobacter pylori-infected gastric ulcer patients. *Journal of Clinical Gastroenterology* 1995;**20 (Suppl 2)**:S132–S135.

Furuta 1995 ***{published data only}***
Furuta T, Futami H, Arai H, et al.Effects of lansoprazole with or without amoxicillin on ulcer healing: relation to eradication of Helicobacter pylori. *Journal of Clinical Gastroenterology* 1995;**20 (Suppl 2)**:S107–S111.

Graham 1991 ***{published data only}***
Graham DY, Lew GM, Evans DG, Evans DJJ, Klein PD. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. A randomized controlled trial. *Annals of Internal Medicine* 1991;**115**(4):266–269.

Graham 1992 ***{published data only}***
Graham DY, Lew GM, Klein PD, et al.Effect of treatment of Helicobacter pylori infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. *Annals of Internal Medicine* 1992;**116**(9):705–708.

Graham 1998 ***{published data only}***
Graham DY, Breiter JR, Ciociola AA, Sykes DL, McSorley DJ. An alternative non-macrolide, non-imidazole treatment regimen for curing Helicobacter pylori and duodenal ulcers: ranitidine bismuth citrate plus amoxicillin. The RBC H. pylori Study Group. *Helicobacter* 1998;**3**(2):125–131.

Harford 1996 ***{published data only}***
Harford W, Lanza F, Arora A, et al.Double-blind, multicenter evaluation of lansoprazole and amoxicillin dual therapy for the cure of Helicobacter pylori infection. *Helicobacter* 1996;**1**(4):243–250.

Hentschel 1993 ***{published data only}***
Hentschel E, Brandstatter G, Dragosics B, et al.Effect of ranitidine and amoxicillin plus metronidazole on the eradication of Helicobacter pylori and the recurrence of duodenal ulcer. *New England Journal of Medicine* 1993;**328** (5):308–312.

Higuchi 2003 ***{published data only}***
Higuchi K, Fujiwara Y, Tominaga K, et al.Is eradication sufficient to heal gastric ulcers in patients infected with Helicobacter pylori? A randomized, controlled prospective study. *Alimentary Pharmacology and Therapeutics* 2003;**17**: 111–117.

Hosking 1992 ***{published data only}***
Hosking SW, Ling TK, Yung MY, et al.Randomised controlled trial of short term treatment to eradicate Helicobacter pylori in patients with duodenal ulcer. *British Medical Journal* 1992;**305**:502–504.

Kato 1996 ***{published data only}***
Kato M, Asaka M, Kudo M, et al.Effects of lansoprazole plus amoxycillin on the cure of Helicobacter pylori infection in Japanese peptic ulcer patients. *Alimentary Pharmacology and Therapeutics* 1996;**10**:821–827.

Katoh 1995 ***{published data only}***
Katoh M, Asaka M, Kudoh M, Kagaya H, Katagiri M, Takeda H. Clinical efficacy of lansoprazole in eradication of Helicobacter pylori. *Journal of Clinical Gastroenterology* 1995;**20 (Suppl 2)**:S112–S114.

Kepecki 1999 ***{published data only}***
Kepekci Y, Kadayifci A. Does the eradication of Helicobacter pylori cure duodenal ulcer disease in communities with a high prevalence rate? Comparison with long-term acid suppression. *International Journal of Clinical Practice* 1999; **53**(7):505–508.

Kim 2002 ***{published data only}***
Kim JS, Kim SG, Choi IJ, et al.Effect of Helicobacter pylori eradication on duodenal ulcer scar in patients with no clinical history of duodenal ulcer. *Alimentary Pharmacology and Therapeutics* 2002;**16**:275–280.

Lam 1997 ***{published data only}***
Lam S-K, Ching C-K, Lai K-C, et al.Does treatment of Helicobacter pylori with antibiotics alone heal duodenal ulcer? A randomised double blind placebo controlled study. *Gut* 1997;**41**:43–48.

Lazzaroni 1997 ***{published data only}***
Lazzaroni M, Perego M, Bargiggia S, et al.Helicobacter pylori eradication in the healing and recurrence of benign gastric ulcer: a two-year, double-blind, placebo controlled study. *Italian Journal of Gastroenterology and Hepatology* 1997;**29**:220–227.

Lin 1994 ***{published data only}***
Lin JT, Wang JT, Wu MS, Lee WY, Yang JC, Wang TH. Prospective, randomized study of H2-blocker and triple therapy for duodenal ulcer treatment and the eradication of Helicobacter pylori. *Journal of the Formosan Medical Association* 1994;**93**(5):368–373.

Logan 1995 ***{published data only}***
Logan RP, Bardhan KD, Celestin LR, et al.Eradication of Helicobacter pylori and prevention of recurrence of duodenal ulcer: a randomized, double-blind, multi-

centre trial of omeprazole with or without clarithromycin. *Alimentary Pharmacology and Therapeutics* 1995;**9**:417–423.

Malfertheiner 1999 ***{published data only}***
Malfertheiner P, Bayerdorffer E, Diete U, et al.The GUMACH study: the effect of 1-week omeprazole triple therapy on Helicobacter pylori infection in patients with gastric ulcer. *Alimentary Pharmacology and Therapeutics* 1999;**13**:703–712.

Mantzaris 1993 ***{published data only}***
Mantzaris GJ, Hatzis A, Tamvakologos G, Petraki K, Spiliades C, Triadaphyllou G. Prospective, randomized, investigator-blind trial of Helicobacter pylori infection treatment in patients with refractory duodenal ulcers. Healing and long-term relapse rates. *Digestive Diseases and Sciences* 1993;**38**(6):1132–1136.

Meining 1998 ***{published data only}***
Meining A, Hochter W, Weingart J, et al.Double-blind trial of omeprazole and amoxicillin in the cure of Helicobacter pylori infection in gastric ulcer patients. The Ulcer Study Group, Germany. *Scandinavian Journal of Gastroenterology* 1998;**33**:49–54.

Miehlke 1995 ***{published data only}***
Miehlke S, Bayerdorffer E, Lehn N, et al.Two-year follow-up of duodenal ulcer patients treated with omeprazole and amoxicillin. *Digestion* 1995;**56**:187–193.

Mones 2001 ***{published data only}***
Mones J, Rodrigo L, Sancho F, et al.Helicobacter pylori eradication versus one-year maintenance therapy: effect on relapse and gastritis outcome. *Revista Espanola de Enfermedades Digestivas* 2001;**93**(6):381–389.

O'Morain 1996 ***{published data only}***
O'Morain C, Dettmer A, Rambow A, von Fritsch E, Fraser AG. Double-blind, multicenter, placebo-controlled evaluation of clarithromycin and omeprazole for Helicobacter pylori-associated duodenal ulcer. *Helicobacter* 1996;**1**(3):130–137.

Parente 1996 ***{published data only}***
Parente F, Maconi G, Bargiggia S, Colombo E, Bianchi PG. Comparison of two lansoprazole-antibiotic combinations (amoxycillin or classical triple therapy) for treatment of H. pylori infection in duodenal ulcer patients. *Alimentary Pharmacology and Therapeutics* 1996;**10**:211–213.

Pinero 1995 ***{published data only}***
Pinero R, Pacheco M, Urrestarazu M, Serrano N, Olavarria R, Poleo JR. Helicobacter pylori eradication heals the duodenal ulcer. Randomized, simple, and controlled study with omeprazole. *Revista de la Sociedad Venezolana de Gastroenterologia* 1995;**49**(2):111–115.

Porro 1996 ***{published data only}***
Bianchi Porro G, Lazzaroni M, Bargiggia S, et al.Omeprazole coupled with two antibiotics for Helicobacter pylori eradication and prevention of ulcer recurrence. *American Journal of Gastroenterology* 1996;**91**(4):695–700.

Pounder 1997 ***{published data only}***
Pounder RE, Wyeth JW, Duggan AE, et al.Ranitidine bismuth citrate with clarithromycin for the eradication of Helicobacter pylori and for ulcer healing. *Helicobacter* 1997;**2**(3):132–139.

Rauws 1990 ***{published data only}***
Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of Helicobacter pylori. *The Lancet* 1990; **335**:1233–1235.

Schwartz 1998 ***{published data only}***
Schwartz H, Krause R, Sahba B, et al.Triple versus dual therapy for eradicating Helicobacter pylori and preventing ulcer recurrence: a randomized, double-blind, multicenter study of lansoprazole, clarithromycin, and/or amoxicillin in different dosing regimens. *American Journal of Gastroenterology* 1998;**93**(4):584–590.

Shirotani 1996 ***{published data only}***
Shirotani T, Okada M, Murayama H, et al.Effect of the eradication of Helicobacter pylori on duodenal ulcer healing and ulcer relapse: Randomized controlled study in Japan. *Journal of Gastroenterology* 1996;**31**:175–181.

Sobhani 1995 ***{published data only}***
Sobhani I, Chastang C, de Korwin J-D, et al.Antibiotic versus maintenance therapy in the prevention of duodenal ulcer recurrence: Results of a multicentric double-blind randomized trial. *Gastroenterol Clin Biol* 1995;**19**:252–258.

Spinzi 1994 ***{published data only}***
Spinzi GC, Sangiovanni A, Imperiali G, et al.Prevention of duodenal ulcer relapse with amoxycillin and omeprazole. *European Journal of Gastroenterology and Hepatology* 1994;**6**: 599–602.

Suarez 1999 ***{published data only}***
Suarez MS, Gonzalez CJ, Velasco IC, Sabatier CA, Castillo HJ. Three treatment schemes with colloidal bismuth subcitrate (Q-ULCER) in peptic ulcer with Helicobacter pylori. *Archives of Medical Research* 1999;**30**:55–59.

Sung 1994 ***{published data only}***
Sung JJ, Chung SC, Ling TKW, et al.One-year follow-up of duodenal ulcers after 1-week triple therapy for Helicobacter pylori. *American Journal of Gastroenterology* 1994;**89**(2): 199–202.

Sung 1995 ***{published data only}***
Sung JJ, Chung SC, Ling TK, et al.Antibacterial treatment of gastric ulcers associated with Helicobacter pylori. *New England Journal of Medicine* 1995;**332**:139–42.

Tomita 2002 ***{published data only}***
Tomita T, Fukuda Y, Tamura J, et al.Successful eradication of Helicobacter pylori prevents relapse of peptic ulcer disease. *Alimentary Pharmacology and Therapeutics* 2002;**16** (Suppl 2):204–209.

Tulassay 2008 ***{published data only}***
Tulassay Z, Stolte M, Sjolund M, Engstrand L, Butruk E, Malfertheiner P, Dite P, Tchernev K, Wong BCY, Gottlow M, Eklund S, Wrangstadh M, Nagy P. Effect of esomeprazole triple therapy on eradication rates of

Helicobacter pylori, gastric ulcer healing and prevention of relapse in gastric ulcer patients.. *European Journal of Gastroenterology and Hepatology* 2008;**20**:526–536.

Unge 1993a ***{published data only}***
Unge P, Gad A, Eriksson K, et al.Amoxicillin added to omeprazole prevents relapse in the treatment of duodenal ulcer patients. *European Journal of Gastroenterology and Hepatology* 1993;**5**:325–331.

van Zanten 1999 ***{published data only}***
van Zanten SJOV, Bradette M, Farley A, et al.The DU-MACH study: eradication of Helicobacter pylori and ulcer healing in patients with acute duodenal ulcer using omeprazole based triple therapy. *Alimentary Pharmacology and Therapeutics* 1999;**13**:289–295.

Wang 1993 ***{published and unpublished data}***
Wang WM, Chen CY, Jan CM, et al.Eradication of Helicobacter pylori infection and the recurrence of duodenal ulcers. *Journal of the Formosan Medical Association* 1993;**92** (8):721–724.

Wang 1996 ***{published data only}***
Wang K, Lin HJ, Chua RT, et al.Omeprazole plus amoxicillin versus triple therapy eradicates Helicobacter pylori in the Chinese with peptic ulcer disease. *Chinese Medical Journal* 1996;**57**:184–190.

Wong 1999 ***{published data only}***
Wong BC, Lam SK, Lai KC, et al.Triple therapy for Helicobacter pylori eradication is more effective than long-term maintenance antisecretory treatment in the prevention of recurrence of duodenal ulcer: a prospective long-term follow-up study. *Alimentary Pharmacology and Therapeutics* 1999;**13**:303–309.

References to studies excluded from this review

Al-Assi 1995 ***{published data only}***
Al-Assi MT, Cole RA, Karttunen TJ, et al.Treatment of Helicobacter pylori infection with omeprazole-amoxicillin combination therapy versus ranitidine/sodium bicarbonate-amoxicillin. *American Journal of Gastroenterology* 1995;**90** (9):1411–1414.

Bayerdorffer 1993 ***{published data only}***
Bayerdorffer E, Mannes GA, Sommer A, et al.Long-term follow-up after eradication of Helicobacter pylori with a combination of omeprazole and amoxycillin. *Scandinavian Journal of Gastroenterology* 1993;**28 Suppl 196**:19–25.

Bytzer 2000 ***{published data only}***
Bytzer P, Aalykke C, Rune S, et al.Eradication of Helicobacter pylori compared with long-term acid suppression in duodenal ulcer disease. A randomized trial with 2-year follow-up. The Danish Ulcer Study Group. *Scandinavian Journal of Gastroenterology* 2000;**35**: 1023–1032.

Dogan 1997 ***{published data only}***
Dogan UB, Tuncer C, Dursun A, et al.A randomized prospective trial comparing results of different therapeutic regimens in the treatment of duodenal ulcer and Helicobacter pylori infection. *Turkish Journal of Gastroenterology* 1997;**8**:342–345.

Gisbert 2000 ***{published data only}***
Gisbert JP, Blanco M, Pajares JM. Effect of Helicobacter pylori eradication on histological lesions of gastric mucosa. An 18-month follow-up study. *Revista Clinica Espanola* 2000;**200**(9):480–484.

Hosking 1994 ***{published data only}***
Hosking SW, Ling TKW, Chung SCS, et al.Duodenal ulcer healing by eradication of Helicobacter pylori without anti-acid treatment: randomised controlled trial. *The Lancet* 1994;**343**:508–510.

Kohli 1995 ***{published data only}***
Kohli Y, Kato T, Azuma T, Ito S, Hirai M. Lansoprazole treatment of Helicobacter pylori-positive peptic ulcers. *Journal of Clinical Gastroenterology* 1995;**20 (Suppl 1)**: S48–S51.

Labenz 1993 ***{published data only}***
Labenz J, Gyenes E, Ruhl G, et al.Omeprazole plus amoxicillin: efficacy of various treatment regimens to eradicate Helicobacter pylori. *American Journal of Gastroenterology* 1993;**88**(4):491–495.

Laine 2000 ***{published data only}***
Laine L, Fennerty MB, Osato M, et al.Esomeprazole-based Helicobacter pylori eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *American Journal of Gastroenterology* 2000;**95**(12):3393–3398.

Lind 1996 ***{published data only}***
Lind T, Veldhuyzen VZ, Unge P, et al.Eradication of Helicobacter pylori using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I Study. *Helicobacter* 1996;**1**(3):138–144.

Malfertheiner 2002a ***{published data only}***
Malfertheiner P, Dent J, Zeijlon L, et al.Impact of Helicobacter pylori eradication on heartburn in patients with gastric or duodenal ulcer disease-results from a randomized trial programme. *Alimentary Pharmacology and Therapeutics* 2002;**16**:1431–1442.

Nakata 1995 ***{published data only}***
Nakata H, Itoh H, Nishioka S. Efficacy of lansoprazole and amoxicillin in eradicating Helicobacter pylori: evaluation using 13C-UBT and Monoclonal H. pylori antibody testing. *Journal of Clinical Gastroenterology* 1995;**20 (Suppl 2)**:S118–S120.

O'Riordan 1990 ***{published data only}***
O'Riordan T, Mathai E, Tobin E, et al.Adjuvant antibiotic therapy in duodenal ulcers treated with colloidal bismuth subcitrate. *Gut* 1990;**31**:999–1002.

Parente 1998 ***{published data only}***
Parente F, Bargiggia S, Bollani S, Colombo E, Porro GB. Continuous maintenance with low-dose lansoprazole versus Helicobacter pylori eradication in the prevention of duodenal ulcer recurrence. *Hepato-Gastroenterology* 1998; **45**:990–993.

Peterson 1996 *{published data only}*
Peterson WL, Ciociola AA, Sykes DL, McSorley DJ, Webb DD. Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating H. pylori and reducing ulcer recurrence. RBC H. pylori Study Group. *Alimentary Pharmacology and Therapeutics* 1996;**10**: 251–261.

Prach 1998 *{published data only}*
Prach AT, Malek M, Tavakoli M, Hopwood D, Senior BW, Murray FE. H2-antagonist maintenance therapy versus Helicobacter pylori eradication in patients with chronic duodenal ulcer disease: a prospective study. *Alimentary Pharmacology and Therapeutics* 1998;**12**:873–880.

Rune 1993 *{published data only}*
Rune SJ, Justesen T, Moller Hansen J, et al.Prevention of duodenal ulcer recurrence with penicillin. *Scandinavian Journal of Gastroenterology* 1993;**28**:438–442.

Shimoyama 1995 *{published data only}*
Shimoyama T, Munakata A, Mizuki I, et al.Eradication of Helicobacter pylori with lansoprazole and clarithromycin in gastric ulcer patients. *Journal of Clinical Gastroenterology* 1995;**20 (Suppl 2)**:S125–S127.

Sonnenberg 1998 *{published data only}*
Sonnenberg A, Schwartz JS, Cutler AF, Vakil N, Bloom BS. Cost savings in duodenal ulcer therapy through Helicobacter pylori eradication compared with conventional therapies: results of a randomized, double-blind, multicenter trial. Gastrointestinal Utilization Trial Study Group. *Archives of Internal Medicine* 1998;**158**:852–860.

Sonnenberg 1999 *{published data only}*
Sonnenberg A, Pauly MP, Levenson SD, Schwartz JS. Antibiotic therapy of Helicobacter pylori infection reduces healthcare expenditures related to duodenal ulcer. *American Journal of Managed Care* 1999;**5**:53–59.

Sugiyama 1995 *{published data only}*
Sugiyama T, Hisano K, Ochiai T, et al.Lansoprazole versus lansoprazole plus amoxicillin treatment for eradication of Helicobacter pylori in patients with gastric ulcer. *Journal of Clinical Gastroenterology* 1995;**20 (Suppl 2)**:S104–S106.

Tavakoli 1999 *{published data only}*
Tavakoli M, Prach AT, Malek M, Hopwood D, Senior BW, Murray FE. Decision analysis of histamine H2-receptor antagonist maintenance therapy versus Helicobacter pylori eradication therapy: a randomised controlled trial in patients with continuing pain after duodenal ulcer. *Pharmacoeconomics* 1999;**16**(4):355–365.

Tham 1996 *{published data only}*
Tham TC, Collins JS, Molloy C, Sloan JM, Bamford KB, Watson RG. Randomised controlled trial of ranitidine versus omeprazole in combination with antibiotics for eradication of Helicobacter pylori. *Ulster Medical Journal* 1996;**65**(2):131–136.

Unge 1993b *{published data only}*
Unge P, Ekstrom P. Effects of combination therapy with omeprazole and an antibiotic on Helicobacter pylori and duodenal ulcer disease. *Scandinavian Journal of Gastroenterology* 1993;**28 Suppl 196**:17–18.

van Zanten 2000 *{published data only}*
van Zanten SV, Farley A, Marcon N, et al.Bismuth-based triple therapy with bismuth subcitrate, metronidazole and tetracycline in the eradication of Helicobacter pylori: A randomized, placebo controlled, double-blind study. *Canadian Journal of Gastroneterology* 2000;**14**(7):599–602.

Xia 1995 *{published data only}*
Xia HX, Gilvarry J, Beattie S, et al.Recrudescence of Helicobacter pylori infection in patients with healed duodenal ulcer after treatment with different regimens. *American Journal of Gastroenterology* 1995;**90**(8): 1221–1225.

Additional references

Briggs 1996
Briggs A, H, Sculpher MJ, Logan RP, et al.Cost-effectiveness of screening for and eradication of Helicobacter pylori in management of dyspeptic patients under 45 years of age. *BMJ* 1996;**312**:1321–1325.

Dobrilla 1993
Dobrilla G, Zancanella L, Amplatz S. The need for long-term treatment of peptic ulcer. *Alimentary Pharmacology and Therapeutics.* 1993;**7 (Suppl 2)**:3–15.

Feldman 1995
Feldman M. Suppression of acid secretion in peptic ulcer disease. *Journal of Clinical Gastroenterology* 1995;**20 (Suppl 1)**:s1–6.

Higgins 2008
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1*. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org., updated September 2008.

Howden 1998
Howden C, Hunt RH. Guidelines for the management of Helicobacter pylori. *American Journal of Gastroenterology* 1998;**93**:2330–2338.

Hunt 1997
Hunt RH. Peptic ulcer disease: defining the treatment strategies in the era of Helicobacter pylori. *American Journal of Gastroenterology* 1997;**92(Suppl 4)**:36s–40s.

Hunt 1999
Hunt RH, Fallone CA, Thomson ABR. Canadian Helicobacter pylori Consensus Conference update: infections in adults. *Canadian Journal of Gastroenterology* 1999;**13**:213–217.

Imperiale 1995
Imperiale TF, Speroff T, Cebul RD, et al.A cost analysis of alternative treatments for duodenal ulcer. *Annals of Internal Medicine* 1995;**123**:665–672.

Lam 1998
Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of Helicobacter

pylori infection. *Journal of Gastroenterology and Hepatology* 1998;**13**:1–12.

Lau 1998
Lau J, Ioannidis JPA, Schmidt CH. Summing up evidence: one answer is not always enough. *Lancet* 1998;**351**:123–7.

Leodolter 2001
Leodolter A, Kulig M, Brasch H, et al.A meta-analysis comparing eradication, healing and relapse rates in patients with Helicobacter pylori-associated gastric or duodenal ulcer. *Alimentary Pharmacology and Therapeutics* 2001;**15**: 1949–1958.

Malfertheiner 2002b
Malfertheiner P, Megraud F, O'Morain C, et al.Current concepts in the management of Helicobacter pylori infection - the Maastricht 2-2000 Consensus Report. *Alimentary Pharmacology and Therapeutics* 2002;**16**:167–180.

Moayyedi 2000
Moayyedi P, Feltbower R, Crocombe W, et al.The effectiveness of omeprazole, clarithromycin and tinidazole in eradicating Helicobacter pylori in a community screen and treat programme. *Alimentary Pharmacology and Therapeutics* 2000;**14**:719–728.

Moher 1999
Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A. Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses. *Health Technology Assessment* 1999;**3**(12):i–iv.

Moore 1994
Moore RA. Helicobacter pylori and peptic ulcer. A systematic review of effectiveness and an overview of the economic benefits of implementing what is known to be effective. http://www.jr2.ox.ac.uk/bandolier 1994.

Penston 1993
Penston JG. A decade of experience with long-term continuous treatment of peptic ulcers with H2-receptor antagonists. *Alimentary Pharmacology and Therapeutics.* 1993;**7 (Suppl 2)**:27–33.

Penston 1996
Penston JG. Clinical aspects of Helicobacter pylori eradication therapy in peptic ulcer disease. *Alimentary Pharmacology and Therapeutics* 1996;**10(4)**:469–86.

Peterson 1990
Peterson WL. Pathogenesis and therapy of peptic ulcer disease. *Journal of Clinical Gastroenterology* 1990;**12 (Suppl 2)**:s1–6.

RevMan 2008
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Tytgat 1998
Tytgat GN. Treatment of peptic ulcer. *Digestion* 1998;**59 (5)**:446–52.

References to other published versions of this review

Ford 2003
Ford A, Delaney B, Moayyedi P. A systematic review of Helicobacter pylori eradication therapy in duodenal and gastric ulcer healing and maintenance. Gut. 2003; Vol. 52 (suppl I):A17.

* *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 patients with peptic ulcer
Interventions	Bi quadruple therapy (2 weeks colloidal bismuth subcitrate 120mg qds, lansoprazole 30mg bd, tetracycline 500mg qds, and metronidazole 400mg qds) PPI triple therapy (2 weeks lansoprazole 30mg bd, amoxicillin 500mg qds, and clarithromycin 500mg tds) PPI dual therapy (lansoprazole 30mg bd and amoxicillin 500mg qds) versus PPI (lansoprazole 30mg bd for 2 weeks, then 30mg 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Treatment groups were determined by a list of random numbers generated by computer
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Endoscopists were blinded for the treatment.
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	No	Collected serology for H. pylori status but did not record these data
Free of other bias?	No	Patients in placebo arm had H. pylori eradication at 8 weeks so 12 month follow not randomised

Asaka 2001

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Avsar 1996

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

Avsar 1996 (*Continued*)

Notes	Eradication rates: Bi triple therapy group 78.3% PPI group 36.4%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"Endoscopies were performed by one of the authors, who was blinded to the clinical data, bacteriological findings and treatment regimen"
Incomplete outcome data addressed? All outcomes	Yes	20/45 (44%) lost to follow up
Free of selective reporting?	No	Symptom data collected but not reported in sufficient detail
Free of other bias?	Yes	

Axon 1997

Methods	Multi-centre RCT Double-blinded
Participants	UK and Eire 129 patients with gastric ulcer
Interventions	PPI dual therapy (8 weeks omeprazole 40mg od and 2 weeks amoxicillin 750mg bd) versus PPI (8 weeks omeprazole 40mg 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"randomisation... From a computer generated randomisation list"

Axon 1997 (*Continued*)

Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double blind, double dummy design"
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Bardhan 1997

Methods	Multi-centre RCT Double-blinded
Participants	Multi-national 232 patients with duodenal ulcer
Interventions	RBC dual therapy (2 weeks RBC 400mg/800mg bd and clarithromycin 250mg qds, then 2 weeks RBC 400mg bd) versus RBC (4 weeks RBC 400mg 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double blind,double dummy"
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Bayerdorffer 1992

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"investigator blinded clinical trial"
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	No	endoscopy performed if symptoms recurred but this data not given
Free of other bias?	Yes	

Bayerdorffer 1995

Methods	Multi-centre RCT Double-blinded
Participants	Germany 264 patients with duodenal ulcer
Interventions	PPI dual therapy (2 weeks omeprazole 40mg tds and amoxicillin 750mg tds, then 4 weeks omeprazole 20mg od) versus PPI (2 weeks omeprazole 40mg tds then 4 weeks omeprazole 20mg od)

Bayerdorffer 1995 (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double blind" "placebo treatment"
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	No	Highlighted differences in pretreatment with omeprazole but it is hard to believe that this was the only subgroup analysed
Free of other bias?	Yes	

Bayerdorffer 1996

Methods	Multi-centre RCT Single-blinded
Participants	Germany 130 patients with gastric ulcer
Interventions	Bi triple therapy (8 weeks bismuth subsalicylate 600mg tds, 10 days amoxicillin 500mg bd and tinidazole 1g bd) versus PPI (8 weeks omeprazole 20mg 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

Bayerdorffer 1996 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	"Randomisation was carried out by a central study secretariat"
Blinding? All outcomes	Yes	"investigator blinded"
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Befrits 2004

Methods	Multi-centre RCT Double-blinded
Participants	Sweden 103 patients with gastric ulcer
Interventions	PPI triple therapy (1 week omeprazole 20mg bd, metronidazole 400mg bd, clarithromycin 250mg bd) versus PPI (1 week omeprazole 20mg bd then 3 weeks 20mg 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double blind?.using placebo of the same size and appearance as conventional metronidazole and clarithromycin tablets"
Incomplete outcome data addressed? All outcomes	No	

Befrits 2004 (*Continued*)

Free of selective reporting?	No	Symptom data collected but not reported in sufficient detail
Free of other bias?	Yes	

Bianchi Porro 1993

Methods	Single centre RCT Double-blinded
Participants	Italy 183 patients with duodenal ulcer
Interventions	PPI triple therapy (4 weeks omeprazole 20mg od, 2 weeks metronidazole 250mg qds and amoxicillin 1g tds) versus PPI (4 weeks omeprazole 20mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year H. pylori eradication rates
Notes	Eradication rates: PPI triple therapy 78% PPI 1.1%

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"allocated, according to a randomised list"
Allocation concealment?	Unclear	B - Unclear
Incomplete outcome data addressed? All outcomes	Yes	Reported according to H. pylori status for 12 month data rather than randomised groups
Free of selective reporting?	Yes	
Free of other bias?	No	Reported data according to H. pylori status rather than ITT

Carpintero 1997

Methods	Single centre RCT Unblinded
Participants	Spain 122 patients with duodenal ulcer

Carpintero 1997 (*Continued*)

Interventions	Bi triple therapy (6 weeks colloidal bismuth subcitrate 120mg qds, 12 days amoxicillin 500mg tds and metronidazole 500mg bd) or H2RA triple therapy (6 weeks ranitidine 300mg qds, 12 days amoxicillin 500mg tds and metronidazole 500mg bd) versus H2RA (6 weeks ranitidine 300mg 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"treatment assignments were determined by a list of random numbers generated by computer"
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	data only on group A 39/44, Group B 38/40 and group C 34/38 at 12 months
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Chen 1995

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

Chen 1995 (*Continued*)

Notes	Eradication rates: Bi triple therapy 93.9% No treatment 0%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	No	Dyspepsia symptoms obtained but not reported
Free of other bias?	Yes	

Feng 2005

Methods	Single centre RCT Double-blinded
Participants	China 75 patients with peptic ulcer
Interventions	PPI triple therapy (10 days lansoprazole 30mg qds, clarithromycin 250mg bd, amoxicillin 500mg bd) versus 'killing' quadruple therapy (10 days lansoprazole 30mg qds, clarithromycin 250mg bd, amoxicillin 500mg bd and 4 weeks H. pylori 'killing' capsule 6 bd) versus placebo
Outcomes	Ulcer healing at 4 weeks Ulcer recurrence at 5 years H. pylori eradication rates
Notes	Eradication rates: PPI triple therapy 94% PPI 0%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Feng 2005 (*Continued*)

Blinding? All outcomes	Yes	"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 addressed? All outcomes	No	data from 5 patients not reported on at one year
Free of selective reporting?	No	Dyspepsia symptoms data obtained but not reported (only that upper abdominal pain was significantly less ($P < 0.05$) in group B)
Free of other bias?	Yes	

Figueroa 1996

Methods	Single centre RCT Unblinded
Participants	Chile 113 patients with duodenal ulcer
Interventions	Bi quadruple therapy (4 weeks omeprazole 20mg qds, bismuth subsalicylate 524mg qds, amoxicillin 500mg tds and metronidazole 250mg tds) versus PPI (4 weeks omeprazole 20mg 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"single blind"
Incomplete outcome data addressed? All outcomes	No	

Figueroa 1996 (*Continued*)

Free of selective reporting?	Yes	
Free of other bias?	Yes	

Fukuda 1995a

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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	

Fukuda 1995b

Methods	Single centre RCT Single-blinded
Participants	Japan 86 patients with gastric ulcer
Interventions	PPI dual therapy (8 weeks lansoprazole 30mg qds and 2 weeks clarithromycin 200mg tds/amoxicillin 500mg tds) versus PPI (8 weeks omeprazole 20mg qds or lansoprazole 30mg qds)
Outcomes	Ulcer healing Ulcer recurrence at 40 weeks H. pylori eradication rates

Fukuda 1995b (*Continued*)

Notes	Eradication rates: PPI dual therapy 48.6% PPI 12.2% All patients received 4 weeks ranitidine 150mg od after initial therapy

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"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 addressed? All outcomes	No	Data from 2 patients missing
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Furuta 1995

Methods	Single centre RCT Unblinded
Participants	Japan 67 patients with gastric or duodenal ulcer
Interventions	PPI dual therapy (6 weeks lansoprazole 30mg qds and 2 weeks amoxicillin 1-2g qds) versus PPI (6 weeks lansoprazole 30mg qds)
Outcomes	Ulcer healing H. pylori eradication rates
Notes	Eradication rates: PPI dual therapy 62.5% PPI 0%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	

Furuta 1995 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Numbers not given at end of follow up just percentages
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Graham 1991

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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"results were not shared with the endoscopist"
Incomplete outcome data addressed? All outcomes	Unclear	percentages rather than numbers given for follow up data (6 loss to follow up in the eradication group)
Free of selective reporting?	No	Symptom data collected but not reported
Free of other bias?	Yes	

Graham 1992

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"the endoscopist was blinded to the treatment status of the patient"
Incomplete outcome data addressed? All outcomes	Yes	83/112 (74%) with ulcer healing agreed to enter follow up part of study
Free of selective reporting?	No	Symptom data collected but not reported
Free of other bias?	Yes	

Graham 1998

Methods	Multi-centre RCT Double-blinded
Participants	USA and Puerto Rico 153 patients with duodenal ulcer
Interventions	RBC dual therapy (4 weeks RBC 400mg bd, 2 weeks amoxicillin 500mg qds) versus Bi (4 weeks RBC 400mg bd) and placebo
Outcomes	Ulcer healing Ulcer recurrence at 6 months

Graham 1998 (*Continued*)

	H. pylori eradication rates	
Notes	Eradication rates: RBC dual therapy 40% RBC 0% Placebo 0%	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double blind" placebo
Incomplete outcome data addressed? All outcomes	Unclear	24 week data reported as percentage not absolute numbers
Free of selective reporting?	No	24 week data according to H. pylori status not randomised groups
Free of other bias?	Yes	

Harford 1996

Methods	Multi-centre RCT Double-blinded	
Participants	USA 196 patients with duodenal ulcer	
Interventions	PPI dual therapy (2 weeks lansoprazole 30mg bd/tds and amoxicillin 1g tds) versus PPI (2 weeks lansoprazole 30mg tds)	
Outcomes	Ulcer healing H. pylori eradication rates	
Notes	Eradication rates: PPI dual therapy 55.1% PPI 0%	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Harford 1996 (*Continued*)

Blinding? All outcomes	Yes	"matching placebos were supplied to maintain the double-blind nature of the study"
Incomplete outcome data addressed? All outcomes	Yes	Ulcer data missing on 50/262 (19%) subjects
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Hentschel 1993

Methods	Two centre RCT Double-blinded
Participants	Austria 104 patients with duodenal ulcer
Interventions	H2RA triple therapy (6 weeks ranitidine 300mg od, 12 days amoxicillin 750mg tds and metronidazole 500mg tds) versus H2RA (6 weeks ranitidine 300mg od)
Outcomes	Ulcer healing Ulcer recurrence at 1 year H. pylori eradication rates
Notes	Eradication rates: H2RA triple therapy 88.5% H2RA 1.9% If ulcer not healed at 6 weeks ranitidine continued for a further 4 weeks

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"identical appearing placebos"
Incomplete outcome data addressed? All outcomes	No	1/104 dropped out (from eradication group)
Free of selective reporting?	No	Histology taken but not reported
Free of other bias?	Yes	

Higuchi 2003

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

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"a table of random numbers was used to generate the randomisation sequence"
Allocation concealment?	Yes	A - Adequate "using sealed opaque envelopes numbered sequentially and containing the assignment"
Blinding? All outcomes	Yes	"Patients and their physicians were aware of the treatment assignment, but endoscopists and pathologists were not"
Incomplete outcome data addressed? All outcomes	No	109/120 (91%) completed trial
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Hosking 1992

Methods	Single centre RCT Single-blinded
Participants	Hong Kong 155 patients with duodenal ulcer

Hosking 1992 (*Continued*)

Interventions	Bi quadruple therapy (4 weeks omeprazole 40mg qds, 1 week colloidal bismuth subcitrate 120mg qds, tetracycline 500mg qds and metronidazole 400mg qds) versus PPI (4 weeks omeprazole 40mg qds)
Outcomes	Ulcer healing H. pylori eradication rates
Notes	Eradication rates: Bi quadruple therapy 89.7% PPI 3.9% Linked to Sung 1994

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"randomised by instructions"
Allocation concealment?	Yes	A - Adequate "randomised ? in consecutively numbered sealed opaque envelopes"
Blinding? All outcomes	Yes	"staff performing the endoscopic and bacteriologic assessments were unaware of the drugs the patient had been taking"
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Kato 1996

Methods	Single centre RCT Unblinded
Participants	Japan 119 patients with gastric or duodenal ulcer
Interventions	PPI dual therapy {6 weeks (DU)/8 weeks (GU) lansoprazole 30mg od and 2 weeks amoxicillin 500mg qds} versus PPI {6 weeks (DU)/8 weeks (GU) lansoprazole 30mg od}
Outcomes	Ulcer healing Ulcer recurrence at 1 year H. pylori eradication rates

Kato 1996 (*Continued*)

Notes	Eradication rates: PPI dual therapy 36.5% PPI 1.8%	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	99/119 (83%) completed 1 year follow up
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Katoh 1995

Methods	Single centre RCT Unblinded	
Participants	Japan 133 patients with gastric or duodenal ulcer	
Interventions	PPI dual therapy {6 weeks (DU)/8 weeks (GU) lansoprazole 30mg od and 2 weeks amoxicillin 500mg 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% PPI 9.4%	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	

Katoh 1995 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Kepecki 1999

Methods	Single centre RCT Unblinded
Participants	Turkey 73 patients with duodenal ulcer
Interventions	PPI triple therapy (1 week omeprazole 20mg bd, amoxicillin 1g bd and metronidazole 500mg tds, then 3 weeks omeprazole 20mg od) versus PPI (1 week omeprazole 20mg bd then 3 weeks 20mg 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 20mg od

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Kim 2002

Methods	Single centre RCT Single-blinded
Participants	South Korea 53 patients with duodenal ulcer
Interventions	PPI triple therapy (1 week omeprazole 20mg bd, amoxicillin 1g bd and clarithromycin 500mg 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% Patients not eradicated with triple therapy received Bi quadruple therapy

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"randomised?.using a computer generated list"
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"two experienced endoscopists, who were blind to the clinical data"
Incomplete outcome data addressed? All outcomes	No	"no patient was lost to follow up"
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Lam 1997

Methods	Single centre RCT Double-blinded
Participants	Hong Kong 97 patients with duodenal ulcer
Interventions	Clarithromycin monotherapy (2 weeks clarithromycin 250mg qds) versus placebo
Outcomes	Ulcer healing Global symptoms cured H. pylori eradication rates

Lam 1997 (*Continued*)

Notes	Eradication rates: Clarithromycin monotherapy 70.8% Placebo 10.2% Clarithromycin patients also received amoxicillin and metronidazole

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"placebo capsules were identical in appearance and taste"
Incomplete outcome data addressed? All outcomes	Yes	81/97 (83%) completed the trial
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Lazzaroni 1997

Methods	Single centre RCT Double-blinded
Participants	Italy 59 patients with gastric ulcer
Interventions	PPI dual therapy (4 weeks omeprazole 20mg bd and 2 weeks amoxicillin 1g tds) versus PPI (4 weeks omeprazole 20mg bd)
Outcomes	Ulcer healing Ulcer recurrence at 1 year H. pylori eradication rates
Notes	Eradication rates: PPI dual therapy 62.1% PPI 6.7%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"allocated according to a computer generated randomisation list"
Allocation concealment?	Unclear	B - Unclear

Lazzaroni 1997 (*Continued*)

Blinding? All outcomes	Yes	"double blind" placebo
Incomplete outcome data addressed? All outcomes	Yes	15/59 (25%) lost to follow up
Free of selective reporting?	No	Symptom data collected but not reported in sufficient detail
Free of other bias?	Yes	

Lin 1994

Methods	Single centre RCT Unblinded
Participants	Taiwan 42 patients with duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds, 1 week metronidazole 250mg qds and amoxicillin 500mg qds) versus H2RA (4 weeks famotidine 20mg 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	3/42 (7%) lost to follow up at 12 months
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Logan 1995

Methods	Multi-centre RCT Double-blinded
Participants	UK 148 patients with duodenal ulcer
Interventions	PPI dual therapy (4 weeks omeprazole 40mg od and 2 weeks clarithromycin 500mg tds) versus PPI (4 weeks omeprazole 40mg 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"identically appearing placebo"
Incomplete outcome data addressed? All outcomes	Yes	"17 clarithromycin treated patients lost to follow up"
Free of selective reporting?	No	Symptom data not reported at one year
Free of other bias?	Yes	

Malfertheiner 1999

Methods	Multi-centre RCT Double-blinded
Participants	Germany, Hungary and Poland 145 patients with gastric ulcer
Interventions	PPI triple therapy (1 week omeprazole 20mg bd, amoxicillin 1g bd and clarithromycin 500mg bd or 1 week omeprazole 20mg bd, metronidazole 400mg bd and clarithromycin 250mg bd) versus PPI (1 week omeprazole 20mg bd)
Outcomes	Ulcer healing Ulcer recurrence at 6 months H. pylori eradication rates

Malfertheiner 1999 (*Continued*)

Notes	Eradication rates: PPI triple therapy 82.4% PPI 4.2% PPI given until ulcer healing in control arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"identical tablets/capsules containing active drug or placebo"
Incomplete outcome data addressed? All outcomes	Unclear	Number lost to follow up at 6 months not stated
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Mantzaris 1993

Methods	Single centre RCT Single-blinded
Participants	Greece 33 patients with duodenal ulcer
Interventions	Bi triple therapy (8 weeks colloidal bismuth subcitrate 120mg qds, 2 weeks tetracycline 500mg qds and metronidazole 500mg tds) versus Bi (8 weeks colloidal bismuth subcitrate 120mg 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Mantzaris 1993 (*Continued*)

Blinding? All outcomes	Yes	"Endoscopies were all performed by the same physician who was unaware of the patient's treatment category"
Incomplete outcome data addressed? All outcomes	Yes	3/12 in H. pylori eradication arm withdrew because of side effects
Free of selective reporting?	No	Symptom data collected but not reported in sufficient detail
Free of other bias?	Yes	

Meining 1998

Methods	Multi-centre RCT Double-blinded
Participants	Germany 185 patients with gastric ulcer
Interventions	PPI dual therapy (2 weeks omeprazole 40mg bd and amoxicillin 750mg tds then 2 weeks omeprazole 20mg od) versus PPI (2 weeks omeprazole 40mg bd then 2 weeks omeprazole 20mg 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"Each centre had its own randomisation list"
Allocation concealment?	Yes	A - Adequate "Randomisation was carried out by a central study secretariat"
Blinding? All outcomes	Yes	"amoxicillin-placebo" "double-blind trial"
Incomplete outcome data addressed? All outcomes	Yes	23/185 (12%) missed follow up
Free of selective reporting?	No	Symptom data collected but not reported

Meining 1998 (*Continued*)

Free of other bias?	Yes	

Miehlke 1995

Methods	Multi-centre RCT Single-blinded
Participants	As Bayerdorffer 1992
Interventions	As Bayerdorffer 1992
Outcomes	Ulcer recurrence at 2 years
Notes	Linked to Bayerdorffer 1992

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Free of selective reporting?	No	Symptom data collected but not reported
Free of other bias?	Yes	

Mones 2001

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

Risk of bias

Mones 2001 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"using a computerized randomisation program"
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double blind" "antibiotic matching placebo"
Free of selective reporting?	No	Dyspepsia symptoms obtained but not reported
Free of other bias?	Yes	

O'Morain 1996

Methods	Multi-centre RCT Double-blinded
Participants	Eire, Germany and New Zealand 208 patients with duodenal ulcer
Interventions	PPI dual therapy (2 weeks omeprazole 40mg od and clarithromycin 500mg tds, then 2 weeks omeprazole 20mg od) versus PPI (2 weeks omeprazole 40mg od then 2 weeks 20mg 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double-blind" "identically appearing placebo"
Incomplete outcome data addressed? All outcomes	Yes	33/208 (16%) did not have follow up endoscopy
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Parente 1996

Methods	Single centre RCT Unblinded
Participants	Italy 96 patients with duodenal ulcer
Interventions	PPI dual therapy (4 weeks lansoprazole 30mg bd and 2 weeks amoxicillin 1g tds) and Bi quadruple therapy (4 weeks lansoprazole 30mg od, 2 weeks bismuth 240mg bd, amoxicillin 1g tds and tinidazole 500mg bd) versus PPI (4 weeks lansoprazole 30mg 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Pinero 1995

Methods	Single centre RCT Unblinded
Participants	Venezuela 60 patients with duodenal ulcer
Interventions	Bi triple therapy (2 weeks colloidal bismuth subcitrate 120mg qds, amoxicillin 500mg tds and metronidazole 500mg tds) versus PPI (4 weeks omeprazole 20mg 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	
Free of other bias?	Yes	

Porro 1996

Methods	Single centre RCT Unblinded
Participants	Italy 32 patients with duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds, 1 week amoxicillin 1g tds and tinidazole 500mg bd) versus sucralfate (4 weeks 1g qds)
Outcomes	Ulcer healing H. pylori eradication rates
Notes	If no ulcer healing patients crossed over to other therapy, therefore unable to extract eradication rates

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	

Porro 1996 (*Continued*)

Free of other bias?	Yes	

Pounder 1997

Methods	Multi-centre RCT Double-blinded
Participants	Multi-national 91 patients with duodenal ulcer
Interventions	RBC dual therapy (2 weeks RBC 400mg/800mg bd and clarithromycin 250mg qds, then 2 weeks RBC 400mg bd) versus RBC (4 weeks 400mg 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"blinded study' "placebo capsules"
Incomplete outcome data addressed? All outcomes	Yes	10/95 (11%) lost to follow up
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Rauws 1990

Methods	Single centre RCT Single-blinded
Participants	Netherlands 66 patients with duodenal ulcer

Rauws 1990 (*Continued*)

Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds and amoxicillin 375mg tds, 10 days metronidazole 500mg tds) versus Bi (4 weeks colloidal bismuth subcitrate 120mg qds)
Outcomes	Ulcer healing Ulcer recurrence at 1year H. pylori eradication rates
Notes	Eradication rates: Bi triple therapy 62.5% Bi 7.7% All patients received a further 4 weeks ranitidine 150mg od

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	"open study"
Incomplete outcome data addressed? All outcomes	Yes	5/24 on triple therapy withdrew due to side effects 11 others lost to follow up
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Schwartz 1998

Methods	Multi-centre RCT Double-blinded
Participants	USA 352 patients with duodenal ulcer
Interventions	PPI dual therapy (2 weeks lansoprazole 30mg bd and clarithromycin 500mg bd/tds or 2 weeks lansoprazole 30mg bd/tds and amoxicillin 1g tds) and triple therapy (2 weeks lansoprazole 30mg bd, amoxicillin 1g bd and clarithromycin 500mg bd) versus PPI (2 weeks lansoprazole 30mg 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%

Schwartz 1998 (*Continued*)

	PPI 1.9%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"all study medication was matched with placebo to maintain the double-blind nature of the study"
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Shirotani 1996

Methods	Single centre RCT Single-blinded
Participants	Japan 50 patients with duodenal ulcer
Interventions	H2RA triple therapy (6 weeks cimetidine 400mg bd, 2 weeks amoxicillin 300mg tds and metronidazole 250mg tds) versus H2RA (6 weeks cimetidine 400mg 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"endoscopic examinations were ultimately judged by an experienced endoscopist who was also not informed of the treatment"
Incomplete outcome data addressed? All outcomes	Yes	8/50 (16%) were lost to follow up
Free of selective reporting?	Yes	

Shirotani 1996 (*Continued*)

Free of other bias?	Yes	

Sobhani 1995

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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double blind, double dummy"
Incomplete outcome data addressed? All outcomes	No	9/97 (9%) of healed ulcer patients were lost to follow up over 6 months
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Spinzi 1994

Methods	Multi-centre RCT Unblinded
Participants	Italy 53 patients with duodenal ulcer

Spinzi 1994 (*Continued*)

Interventions	PPI dual therapy (4 weeks omeprazole 20mg od, 2 weeks amoxicillin 1g bd) versus PPI (4 weeks omeprazole 20mg 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	3/53 (6%) dropped out
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Suarez 1999

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

Risk of bias

Suarez 1999 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	7/60 (12%) drop outs
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Sung 1994

Methods	Single centre RCT Single-blinded
Participants	As Hosking
Interventions	As Hosking
Outcomes	Ulcer recurrence at 1 year
Notes	Linked to Hosking 1992

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"treatment assignments were determined with a list of random numbers generated by computer"
Allocation concealment?	Yes	A - Adequate "randomly assigned to one of two treatment groups with the use of sealed envelopes"
Blinding? All outcomes	Yes	Endoscopist were blinded to the treatment given
Incomplete outcome data addressed? All outcomes	Yes	20/126 (16%) loss to follow up
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Sung 1995

Methods	Single centre RCT Unblinded
Participants	Hong Kong 96 patients with gastric ulcer
Interventions	Bi triple therapy (1 week colloidal bismuth subcitrate 120mg qds, tetracycline 500mg qds and metronidazole 400mg qds) versus PPI (4 weeks omeprazole 20mg 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 patients received antacids and PPI patients received further PPI

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	treatment assignments were determined with a list of random numbers generated by computer
Allocation concealment?	Yes	A - Adequate "randomly assigned to one of two treatment groups with the use of sealed envelopes"
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	85/100 (85%) completed the trial
Free of selective reporting?	No	Symptom data collected but not reported in sufficient detail
Free of other bias?	Yes	

Tomita 2002

Methods	Single centre RCT Unblinded
Participants	Japan 445 patients with gastric or duodenal ulcer

Tomita 2002 (*Continued*)

Interventions	PPI triple therapy {6 weeks (DU) / 8 weeks (GU) lansoprazole 30mg od or omeprazole 20mg od, 2 weeks amoxicillin 1.5g od and clarithromycin 400mg od} versus PPI {6 weeks (DU) / 8 weeks (GU) lansoprazole 30mg od or omeprazole 20mg od} or H2RA {6 weeks (DU) / 8 weeks (GU) famotidine 40mg od or cimetidine 800mg od}
Outcomes	Ulcer recurrence at 5 years H. pylori eradication rates
Notes	Eradication rates: PPI triple therapy 81.9% PPI / H2RA 0%

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	32/445 (7%) loss to follow up
Free of selective reporting?	No	Symptom data collected but not reported
Free of other bias?	Yes	

Tulassay 2008

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

Tulassay 2008 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"randomised ?.according to a computer-generated list"
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"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 addressed? All outcomes	No	14/480 (3%) no primary end point data
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Unge 1993a

Methods	Multi-centre RCT Double-blinded
Participants	Sweden 233 patients with duodenal ulcer
Interventions	PPI dual therapy (4 weeks omeprazole 40mg od and 2 weeks amoxicillin 750mg bd) versus PPI (4 weeks omeprazole 40mg 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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"double blind and used a single placebo technique"
Free of selective reporting?	Yes	

Unge 1993a (*Continued*)

Free of other bias?	Yes	

van Zanten 1999

Methods	Multi-centre RCT Double-blinded
Participants	Canada 146 patients with duodenal ulcer
Interventions	PPI triple therapy (1 week omeprazole 20mg bd, amoxicillin 1g bd and clarithromycin 500mg bd or 1 week omeprazole 20mg bd, metronidazole 400mg bd and clarithromycin 250mg bd then 3 weeks omeprazole 20mg od) versus PPI (4 weeks omeprazole 20mg 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	17/146 (12%) loss to follow up (n = 9) or not included in ulcer relapse analysis (n = 8)
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Wang 1993

Methods	Single centre RCT Unblinded
Participants	Taiwan 59 patients with duodenal ulcer

Wang 1993 (*Continued*)

Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 120mg qds, 2 weeks tetracycline 500mg qds and metronidazole 250mg qds) versus H2RA (4 weeks ranitidine 150mg bd) and Bi (4 weeks colloidal bismuth subcitrate 120mg 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	No	H2RA given until ulcers healed but these data are not given
Free of other bias?	Yes	

Wang 1996

Methods	Single centre RCT Unblinded
Participants	Taiwan 112 patients with gastric and duodenal ulcer
Interventions	Bi triple therapy (4 weeks colloidal bismuth subcitrate 300mg qds, 1 week amoxicillin 750mg bd and metronidazole 500mg tds) and PPI dual therapy (4 weeks omeprazole 20mg bd/qds and 10 days amoxicillin 750mg bd) versus PPI (4 weeks omeprazole 20mg qds) and H2RA (4 weeks nizatidine/ranitidine 150mg 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 patients received 4 weeks H2RA after initial therapy

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Free of other bias?	No	Reported according to H. pylori status and not randomised groups

Wong 1999

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

Risk of bias

Wong 1999 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	"the endoscopists were blinded to the treatment type and any clinical information related to the patients"
Incomplete outcome data addressed? All outcomes	Yes	15/114 (13%) drop outs
Free of selective reporting?	No	Symptom data collected but not reported
Free of other bias?	Yes	

bd: twice per day
od: once per day
qds: four times per day
tds: three times per day

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

Study	Reason for exclusion
Al-Assi 1995	No ulcer healing or recurrence data
Bayerdorffer 1993	Same study as Bayerdorffer 1992 and Miehlke with recurrence data at 18 months
Bytzer 2000	Not all patients H. pylori positive, and no way of extracting data for just the H. pylori positive patients
Dogan 1997	Control arm of the trial were all H. pylori negative
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

(*Continued*)

Malfertheiner 2002a	No ulcer healing or recurrence data
Nakata 1995	Not truly randomised
O'Riordan 1990	Not truly randomised
Parente 1998	Not truly randomised
Peterson 1996	Not all patients H. pylori positive, and no way of extracting data for just the H. pylori positive patients
Prach 1998	Not all patients 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 patients with peptic ulcer disease
Unge 1993b	Same study as Unge 1993a
van Zanten 2000	Not all patients had documented peptic ulcer disease
Xia 1995	Not truly randomised

DATA AND ANALYSES

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

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]

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

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]

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

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]

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

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]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion not healed	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.05, 0.45]

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

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]

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

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]

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

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]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion recurred	1	103	Risk Ratio (M-H, Fixed, 95% CI)	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 hp 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 hp eradication vs. no treatment	2	188	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.83, 1.93]

Comparison 11. adverse events

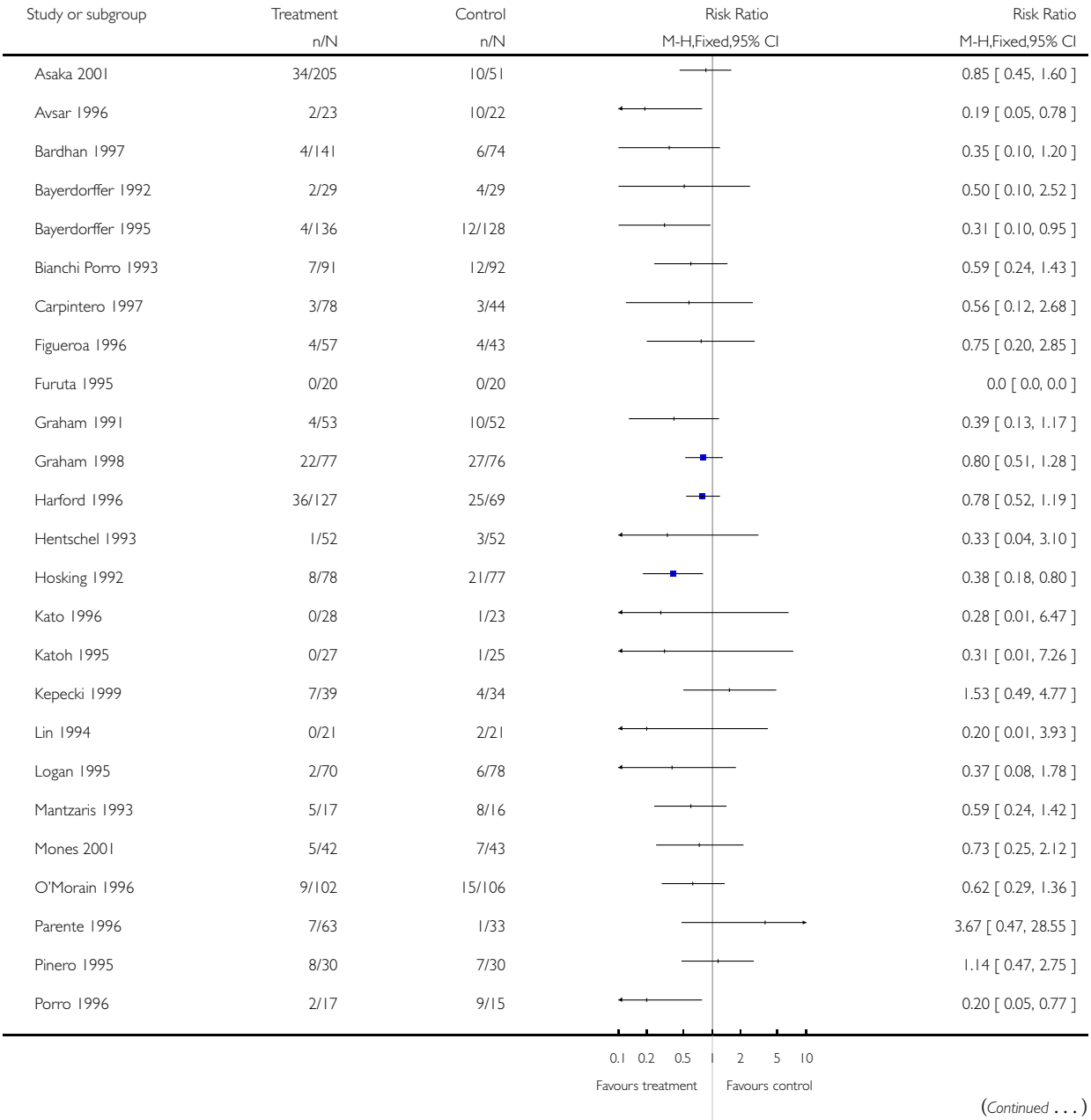
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall, proportion occurred	43	6093	Risk Ratio (M-H, Random, 95% CI)	2.30 [1.77, 2.99]
2 Diarrhoea, proportion occurred	30	4590	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [2.11, 3.88]
3 Nausea/vomiting, proportion 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 1.1. Comparison 1 duodenal ulcer acute healing with *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone, Outcome 1 Proportion not healed.

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

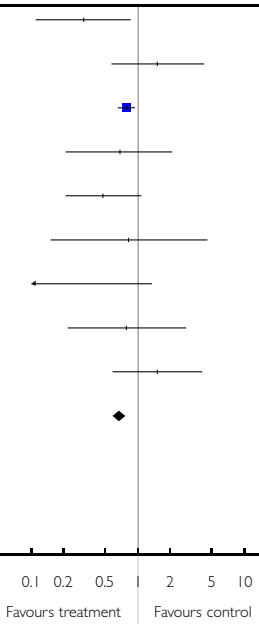
Outcome: 1 Proportion not healed



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Pounder 1997	5/61	8/30		0.31 [0.11, 0.86]
Rauws 1990	7/24	5/26		1.52 [0.56, 4.14]
Schwartz 1998	168/292	44/60		0.78 [0.65, 0.94]
Shirotani 1996	4/25	6/25		0.67 [0.21, 2.08]
Sobhani 1995	7/59	15/60		0.47 [0.21, 1.08]
Spinzi 1994	2/24	3/29		0.81 [0.15, 4.43]
van Zanten 1999	0/98	3/48		0.07 [0.00, 1.34]
Wang 1993	3/23	6/36		0.78 [0.22, 2.82]
Wong 1999	9/57	6/57		1.50 [0.57, 3.94]
Total (95% CI)	**2286**	**1624**		**0.66 [0.58, 0.76]**
Total events: 381 (Treatment), 304 (Control)				
Heterogeneity: Chi^2 = 36.30, df = 32 (P = 0.27); I^2 =12%				
Test for overall effect: Z = 5.96 (P < 0.00001)				



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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

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		60.6 %	0.38 [0.25, 0.56]
Lam 1997	8/48	23/49		39.4 %	0.36 [0.18, 0.71]
Total (95% CI)	**125**	**82**		**100.0 %**	**0.37 [0.26, 0.53]**
Total events: 30 (Treatment), 48 (Control)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 5.35 (P < 0.00001)					

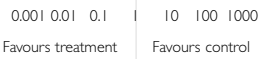
Analysis 3.1. Comparison 3 gastric ulcer acute healing with *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone, Outcome 1 Proportion not healed.

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

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		12.1 %	1.44 [0.82, 2.55]
Axon 1997	20/87	13/42		11.6 %	0.74 [0.41, 1.34]
Bayerdorffer 1996	13/65	3/65		5.0 %	4.33 [1.30, 14.49]
Befrits 2004	10/56	11/47		9.1 %	0.76 [0.36, 1.64]
Fukuda 1995a	0/32	1/33		0.9 %	0.34 [0.01, 8.13]
Fukuda 1995b	0/37	1/49		0.9 %	0.44 [0.02, 10.47]
Furuta 1995	0/12	2/15		1.1 %	0.25 [0.01, 4.69]
Higuchi 2003	31/61	10/59		11.3 %	3.00 [1.62, 5.55]
Kato 1996	5/35	3/33		4.2 %	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		1.0 %	0.21 [0.01, 4.13]
Malfertheiner 1999	20/97	10/48		10.3 %	0.99 [0.50, 1.95]
Meining 1998	23/100	15/85		11.8 %	1.30 [0.73, 2.33]
Sung 1995	6/51	7/45		6.4 %	0.76 [0.27, 2.08]
Tulassay 2008	20/265	10/137		9.6 %	1.03 [0.50, 2.15]
Total (95% CI)	**1192**	**782**		**100.0 %**	**1.23 [0.90, 1.68]**
Total events: 220 (Treatment), 102 (Control)					
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 22.93$, df = 14 (P = 0.06); $I^2 = 39\%$					
Test for overall effect: Z = 1.29 (P = 0.20)					



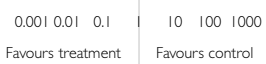
Analysis 4.1. Comparison 4 peptic ulcer acute healing with *H. pylori* eradication + ulcer healing drug vs. ulcer healing drug alone, Outcome 1 Proportion not healed.

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

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		29.0 %	0.18 [0.05, 0.66]
Suarez 1999	11/40	8/20		34.8 %	0.69 [0.33, 1.43]
Wang 1996	9/69	9/43		36.2 %	0.62 [0.27, 1.45]
Total (95% CI)	**194**	**93**		**100.0 %**	**0.52 [0.31, 0.85]**
Total events: 23 (Treatment), 23 (Control)					
Heterogeneity: Chi^2 = 3.31, df = 2 (P = 0.19); I^2 =40%					
Test for overall effect: Z = 2.59 (P = 0.0095)					



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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

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
Feng 2005	3/25	12/15		100.0 %	0.15 [0.05, 0.45]
Total (95% CI)	**25**	**15**		**100.0 %**	**0.15 [0.05, 0.45]**
Total events: 3 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.41 (P = 0.00066)					

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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

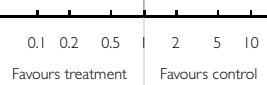
Outcome: 1 Proportion recurred

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		18.8 %	1.45 [0.52, 4.05]
Mones 2001	4/37	4/36		15.5 %	0.97 [0.26, 3.60]
Sobhani 1995	6/45	12/43		47.0 %	0.48 [0.20, 1.16]
Wong 1999	2/48	5/51		18.6 %	0.43 [0.09, 2.09]
Total (95% CI)	**159**	**160**		**100.0 %**	**0.73 [0.42, 1.25]**

Total events: 19 (Treatment), 26 (Control)

Heterogeneity: $Chi^2 = 3.22$, df = 3 (P = 0.36); $I^2 = 7\%$

Test for overall effect: Z = 1.15 (P = 0.25)



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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

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		3.1 %	0.29 [0.09, 0.92]
Bardhan 1997	10/133	25/63		4.8 %	0.19 [0.10, 0.37]
Bayerdorffer 1995	15/132	51/116		5.4 %	0.26 [0.15, 0.43]
Carpintero 1997	31/72	34/39		6.3 %	0.49 [0.37, 0.66]
Chen 1995	10/31	27/29		5.4 %	0.35 [0.21, 0.58]
Figueroa 1996	3/53	34/39		3.2 %	0.06 [0.02, 0.20]
Graham 1992	6/47	34/36		4.4 %	0.14 [0.06, 0.29]
Hentschel 1993	4/50	42/49		3.7 %	0.09 [0.04, 0.24]
Kato 1996	3/27	12/18		3.2 %	0.17 [0.05, 0.51]
Kim 2002	2/36	5/17		2.1 %	0.19 [0.04, 0.88]
Lin 1994	1/18	11/18		1.5 %	0.09 [0.01, 0.63]
Logan 1995	3/51	47/62		3.2 %	0.08 [0.03, 0.23]
Mantzaris 1993	2/12	6/8		2.6 %	0.22 [0.06, 0.84]
Miehlke 1995	6/26	19/25		4.5 %	0.30 [0.15, 0.63]
O'Morain 1996	8/78	41/82		4.7 %	0.21 [0.10, 0.41]
Pinero 1995	3/19	13/20		3.2 %	0.24 [0.08, 0.72]
Porro 1996	8/71	52/66		4.8 %	0.14 [0.07, 0.28]
Pounder 1997	0/56	4/22		0.8 %	0.04 [0.00, 0.80]
Rauws 1990	1/17	16/21		1.5 %	0.08 [0.01, 0.52]
Schwartz 1998	19/124	11/16		5.4 %	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]
Sung 1994	2/61	22/45		2.4 %	0.07 [0.02, 0.27]
Tomita 2002	11/55	20/20		5.4 %	0.21 [0.13, 0.35]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Unge 1993a	48/157	50/76		6.3 %	0.46 [0.35, 0.62]
van Zanten 1999	10/98	25/45		4.9 %	0.18 [0.10, 0.35]
Wang 1993	1/20	18/26		1.5 %	0.07 [0.01, 0.50]
Total (95% CI)	**1501**	**1008**		**100.0 %**	**0.20 [0.15, 0.26]**

Total events: 215 (Treatment), 649 (Control)

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 85.11$, df = 26 (P<0.00001); $I^2 = 69\%$

Test for overall effect: Z = 11.74 (P < 0.00001)

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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

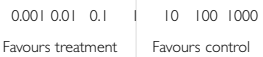
Outcome: 1 Proportion recurred

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		11.6 %	0.46 [0.26, 0.79]
Bayerdorffer 1996	4/52	34/62		7.4 %	0.14 [0.05, 0.37]
Befrits 2004	10/42	24/33		11.2 %	0.33 [0.18, 0.58]
Fukuda 1995b	3/36	19/48		6.2 %	0.21 [0.07, 0.66]
Graham 1992	2/15	8/11		5.0 %	0.18 [0.05, 0.70]
Kato 1996	8/28	11/26		9.5 %	0.68 [0.32, 1.41]
Lazzaroni 1997	6/28	16/24		9.3 %	0.32 [0.15, 0.69]
Malfertheiner 1999	12/97	13/48		9.9 %	0.46 [0.23, 0.92]
Meining 1998	0/77	10/70		1.5 %	0.04 [0.00, 0.73]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Sung 1995	1/22	12/23		2.8 %	0.09 [0.01, 0.62]
Tomita 2002	14/83	156/172		12.3 %	0.19 [0.12, 0.30]
Tulassay 2008	40/245	36/127		13.3 %	0.58 [0.39, 0.86]
Total (95% CI)	**797**	**679**		**100.0 %**	**0.31 [0.22, 0.45]**
Total events: 116 (Treatment), 356 (Control)					
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 29.09$, df = 11 (P = 0.002); $I^2 = 62\%$					
Test for overall effect: Z = 6.27 (P < 0.00001)					



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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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

Outcome: 1 Proportion recurred

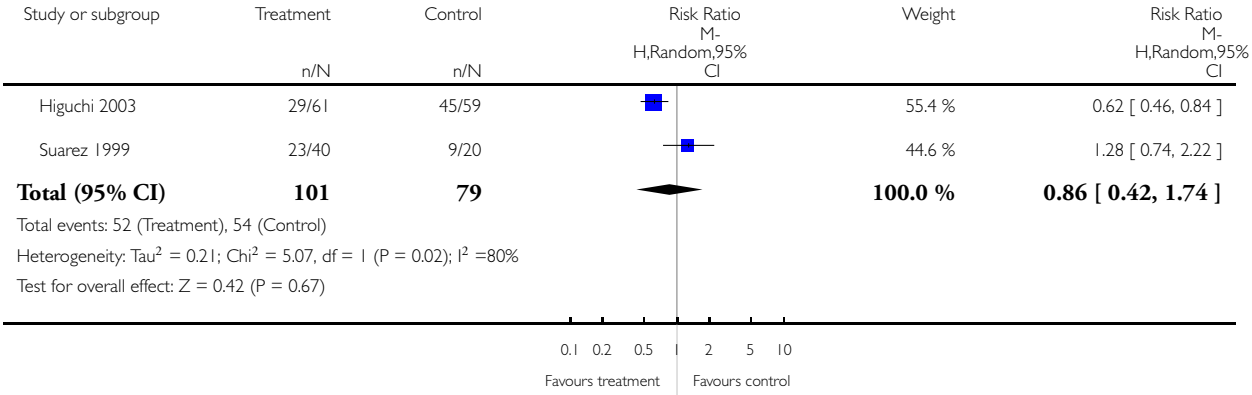
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Arkkila 2005	6/79	8/24		100.0 %	0.23 [0.09, 0.59]
Total (95% CI)	**79**	**24**		**100.0 %**	**0.23 [0.09, 0.59]**
Total events: 6 (Treatment), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.04 (P = 0.0024)					

Analysis 10.1. Comparison 10 global symptoms persisting, Outcome 1 hp eradication + ulcer healing drug vs. ulcer healing drug alone.

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 10 global symptoms persisting

Outcome: 1 hp eradication + ulcer healing drug vs. ulcer healing drug alone

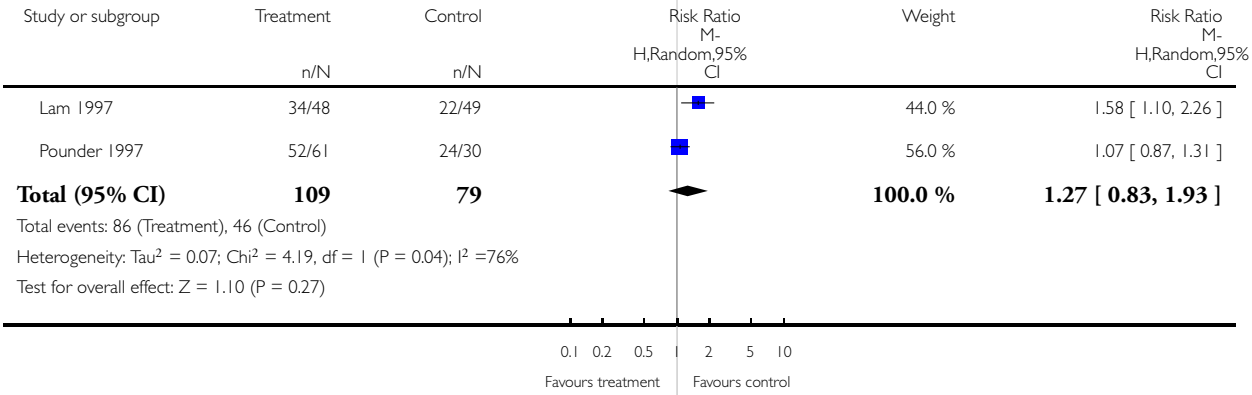


Analysis 10.2. Comparison 10 global symptoms persisting, Outcome 2 hp eradication vs. no treatment.

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 10 global symptoms persisting

Outcome: 2 hp eradication vs. no treatment



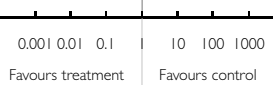
Analysis 11.1. Comparison 11 adverse events, Outcome 1 Overall, proportion occurred.

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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	Risk Ratio M-H,Random,95% CI
Arkkila 2005	21/85	1/30		7.41 [1.04, 52.75]
Asaka 2001	217/430	42/106		1.27 [0.99, 1.64]
Avsar 1996	0/23	0/22		0.0 [0.0, 0.0]
Axon 1997	0/87	1/42		0.16 [0.01, 3.92]
Bardhan 1997	25/141	15/74		0.87 [0.49, 1.55]
Bayerdorffer 1992	0/29	1/29		0.33 [0.01, 7.86]
Bayerdorffer 1995	11/136	3/128		3.45 [0.99, 12.09]
Bayerdorffer 1996	16/65	0/65		33.00 [2.02, 538.74]
Befrits 2004	27/56	19/47		1.19 [0.77, 1.85]
Carpintero 1997	13/78	1/44		7.33 [0.99, 54.19]
Chen 1995	24/49	0/29		29.40 [1.85, 465.97]
Fukuda 1995a	0/32	0/33		0.0 [0.0, 0.0]
Fukuda 1995b	1/37	0/49		3.95 [0.17, 94.23]
Graham 1991	6/53	0/52		12.76 [0.74, 220.88]
Graham 1998	7/77	7/109		1.42 [0.52, 3.87]
Harford 1996	24/127	5/69		2.61 [1.04, 6.53]
Hentschel 1993	8/52	1/52		8.00 [1.04, 61.71]
Higuchi 2003	11/61	1/59		10.64 [1.42, 79.85]
Hosking 1992	6/78	6/77		0.99 [0.33, 2.93]
Kato 1996	4/63	0/56		8.02 [0.44, 145.66]
Lam 1997	2/48	0/49		5.10 [0.25, 103.58]
Lazzaroni 1997	4/29	2/30		2.07 [0.41, 10.44]
Lin 1994	5/21	0/21		11.00 [0.65, 187.17]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Logan 1995	28/70	23/78		1.36 [0.87, 2.12]
Malfertheiner 1999	12/97	6/48		0.99 [0.40, 2.48]
Mantzaris 1993	3/17	0/16		6.61 [0.37, 118.73]
Meining 1998	23/100	5/85		3.91 [1.55, 9.84]
O'Morain 1996	38/102	13/106		3.04 [1.72, 5.36]
Parente 1996	6/63	0/33		6.91 [0.40, 118.94]
Pinero 1995	2/30	0/30		5.00 [0.25, 99.95]
Porro 1996	11/91	7/92		1.59 [0.64, 3.92]
Pounder 1997	21/61	7/30		1.48 [0.71, 3.08]
Rauws 1990	5/24	0/26		11.88 [0.69, 204.05]
Schwartz 1998	80/292	9/60		1.83 [0.97, 3.43]
Shirotani 1996	4/25	0/25		9.00 [0.51, 158.85]
Sobhani 1995	10/59	3/60		3.39 [0.98, 11.70]
Spinzi 1994	1/24	0/29		3.60 [0.15, 84.54]
Suarez 1999	11/40	3/20		1.83 [0.58, 5.84]
Sung 1995	5/51	0/45		9.73 [0.55, 171.24]
Tomita 2002	3/138	0/192		9.72 [0.51, 186.66]
Tulassay 2008	79/315	13/164		3.16 [1.82, 5.51]
Wang 1996	13/69	0/43		16.97 [1.03, 278.36]
Wong 1999	6/57	1/57		6.00 [0.75, 48.26]
Total (95% CI)	**3582**	**2511**	◆	**2.30 [1.77, 2.99]**

Total events: 793 (Treatment), 195 (Control)

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 80.47$, df = 40 (P = 0.00016); $I^2 = 50\%$

Test for overall effect: Z = 6.22 (P < 0.00001)

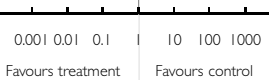
Analysis 11.2. Comparison 11 adverse events, Outcome 2 Diarrhoea, proportion occurred.

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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		1.3 %	5.41 [0.32, 91.91]
Asaka 2001	38/430	7/106		19.6 %	1.34 [0.61, 2.91]
Bardhan 1997	9/141	3/74		6.9 %	1.57 [0.44, 5.64]
Bayerdorffer 1995	3/136	1/128		1.8 %	2.82 [0.30, 26.80]
Bayerdorffer 1996	6/65	0/65		0.9 %	13.00 [0.75, 226.12]
Carpintero 1997	5/78	0/44		1.1 %	6.27 [0.35, 110.71]
Chen 1995	4/49	0/29		1.1 %	5.40 [0.30, 96.82]
Graham 1991	1/53	0/52		0.9 %	2.94 [0.12, 70.67]
Graham 1998	4/77	0/109		0.7 %	12.69 [0.69, 232.36]
Harford 1996	8/127	1/69		2.3 %	4.35 [0.56, 34.04]
Hentschel 1993	7/52	1/52		1.7 %	7.00 [0.89, 54.91]
Kato 1996	2/63	0/56		0.9 %	4.45 [0.22, 90.82]
Lam 1997	1/48	0/49		0.9 %	3.06 [0.13, 73.34]
Lazzaroni 1997	2/29	1/30		1.7 %	2.07 [0.20, 21.60]
Lin 1994	5/21	0/21		0.9 %	11.00 [0.65, 187.17]
Logan 1995	4/70	4/78		6.6 %	1.11 [0.29, 4.29]
Malfertheiner 1999	4/97	0/48		1.2 %	4.50 [0.25, 81.91]
Meining 1998	20/100	4/85		7.6 %	4.25 [1.51, 11.95]
O'Morain 1996	17/102	4/106		6.9 %	4.42 [1.54, 12.68]
Parente 1996	1/63	0/33		1.1 %	1.59 [0.07, 38.07]
Porro 1996	3/91	4/92		7.0 %	0.76 [0.17, 3.29]
Pounder 1997	3/61	0/30		1.2 %	3.50 [0.19, 65.66]
Rauws 1990	1/24	0/26		0.8 %	3.24 [0.14, 75.91]
Shirotani 1996	1/25	0/25		0.9 %	3.00 [0.13, 70.30]
Sobhani 1995	4/59	0/60		0.9 %	9.15 [0.50, 166.28]
Sung 1995	1/51	0/45		0.9 %	2.65 [0.11, 63.56]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tulassay 2008	16/315	3/164		6.9 %	2.78 [0.82, 9.39]
van Zanten 1999	28/98	5/48		11.7 %	2.74 [1.13, 6.66]
Wang 1996	3/69	0/43		1.1 %	4.40 [0.23, 83.15]
Wong 1999	0/57	1/57		2.6 %	0.33 [0.01, 8.01]
Total (95% CI)	**2736**	**1854**		**100.0 %**	**2.86 [2.11, 3.88]**

Total events: 208 (Treatment), 39 (Control)

Heterogeneity: Chi^2 = 18.13, df = 29 (P = 0.94); I^2 =0.0%

Test for overall effect: Z = 6.79 (P < 0.00001)

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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

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		9.3 %	1.88 [0.17, 20.51]
Bayerdorffer 1996	1/65	0/65		4.5 %	3.00 [0.12, 72.31]
Carpintero 1997	1/78	0/44		5.7 %	1.71 [0.07, 41.08]
Chen 1995	9/49	0/29		5.6 %	11.40 [0.69, 188.89]
Graham 1991	4/53	0/52		4.5 %	8.83 [0.49, 160.07]
Graham 1998	1/77	1/109		7.5 %	1.42 [0.09, 22.29]
Lazzaroni 1997	1/29	0/30		4.4 %	3.10 [0.13, 73.14]
Lin 1994	3/21	0/21		4.5 %	7.00 [0.38, 127.69]
Mantzaris 1993	2/17	0/16		4.6 %	4.72 [0.24, 91.41]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rauws 1990	3/24	0/26		4.3 %	7.56 [0.41, 139.17]
Shirotani 1996	1/25	0/25		4.5 %	3.00 [0.13, 70.30]
Suarez 1999	5/40	0/20		6.0 %	5.63 [0.33, 97.10]
Sung 1995	2/51	0/45		4.8 %	4.42 [0.22, 89.76]
van Zanten 1999	7/98	2/48		24.2 %	1.71 [0.37, 7.94]
Wang 1996	1/69	0/43		5.5 %	1.89 [0.08, 45.27]
Total (95% CI)	**832**	**701**		**100.0 %**	**3.76 [1.91, 7.37]**

Total events: 43 (Treatment), 4 (Control)

Heterogeneity: Chi^2 = 3.72, df = 14 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 3.85 (P = 0.00012)

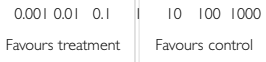
Analysis 11.4. Comparison 11 adverse events, Outcome 4 Skin rash, proportion occurred.

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 11 adverse events

Outcome: 4 Skin rash, 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	4/85	1/30		7.1 %	1.41 [0.16, 12.14]
Bayerdorffer 1996	2/65	0/65		2.4 %	5.00 [0.24, 102.16]
Carpintero 1997	1/78	0/44		3.1 %	1.71 [0.07, 41.08]
Chen 1995	3/49	0/29		3.0 %	4.20 [0.22, 78.53]
Harford 1996	3/127	1/69		6.2 %	1.63 [0.17, 15.37]
Hentschel 1993	1/52	0/52		2.4 %	3.00 [0.13, 71.99]
Higuchi 2003	1/61	0/59		2.4 %	2.90 [0.12, 69.87]



(*Continued* . . .)

(. . . *Continued*)

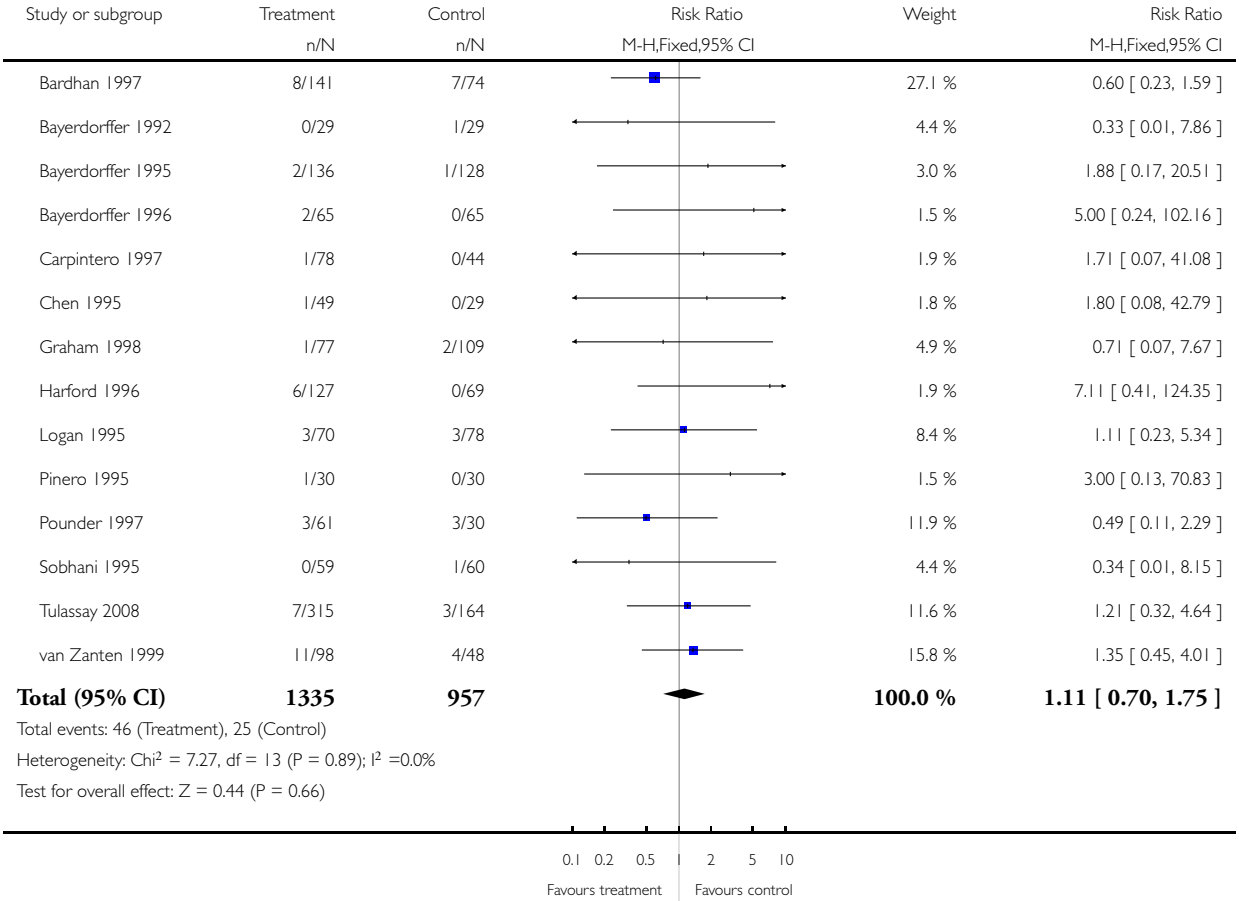
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kato 1996	1/63	0/56		2.5 %	2.67 [0.11, 64.29]
Lam 1997	1/48	0/49		2.4 %	3.06 [0.13, 73.34]
Logan 1995	2/70	2/78		9.1 %	1.11 [0.16, 7.70]
Malfertheiner 1999	0/97	1/48		9.6 %	0.17 [0.01, 4.02]
Meining 1998	2/100	1/85		5.2 %	1.70 [0.16, 18.42]
Porro 1996	0/91	2/92		11.9 %	0.20 [0.01, 4.15]
Pounder 1997	0/61	3/30		22.4 %	0.07 [0.00, 1.34]
Rauws 1990	1/24	0/26		2.3 %	3.24 [0.14, 75.91]
Suarez 1999	2/40	0/20		3.2 %	2.56 [0.13, 50.95]
Tomita 2002	1/138	0/192		2.0 %	4.17 [0.17, 101.49]
Wang 1996	2/69	0/43		2.9 %	3.14 [0.15, 63.94]
Total (95% CI)	**1318**	**1067**		**100.0 %**	**1.36 [0.78, 2.37]**
Total events: 27 (Treatment), 11 (Control)					
Heterogeneity: Chi^2 = 10.60, df = 17 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 1.08 (P = 0.28)					

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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 11 adverse events

Outcome: 5 Headache, proportion occurred



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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 11 adverse events

Outcome: 6 Epigastric pain, 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	0/136	1/128		17.6 %	0.31 [0.01, 7.64]
Bayerdorffer 1996	3/65	0/65		5.7 %	7.00 [0.37, 132.87]
Carpintero 1997	3/78	0/44		7.3 %	3.99 [0.21, 75.46]
Chen 1995	18/49	0/29		7.1 %	22.20 [1.39, 355.10]
Logan 1995	2/70	1/78		10.8 %	2.23 [0.21, 24.05]
Porro 1996	3/91	1/92		11.3 %	3.03 [0.32, 28.62]
Pounder 1997	3/61	0/30		7.6 %	3.50 [0.19, 65.66]
Sobhani 1995	1/59	0/60		5.6 %	3.05 [0.13, 73.39]
Sung 1995	1/51	0/45		6.0 %	2.65 [0.11, 63.56]
van Zanten 1999	4/98	1/48		15.3 %	1.96 [0.23, 17.06]
Wong 1999	2/57	0/57		5.7 %	5.00 [0.25, 101.89]
Total (95% CI)	**815**	**676**		**100.0 %**	**4.09 [1.90, 8.82]**

Total events: 40 (Treatment), 4 (Control)

Heterogeneity: $Chi^2 = 4.94$, df = 10 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 3.59 (P = 0.00033)

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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 11 adverse events

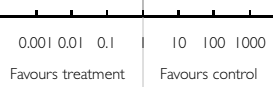
Outcome: 7 Altered taste, proportion occurred

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	5/85	0/30		7.7 %	3.97 [0.23, 69.64]
Asaka 2001	15/430	0/106		8.4 %	7.70 [0.46, 127.60]
Bayerdorffer 1996	1/65	0/65		5.2 %	3.00 [0.12, 72.31]
Carpintero 1997	1/78	0/44		6.7 %	1.71 [0.07, 41.08]
Fukuda 1995b	1/37	0/49		4.5 %	3.95 [0.17, 94.23]
Logan 1995	16/70	1/78		9.9 %	17.83 [2.43, 130.99]
Malfertheiner 1999	7/97	1/48		14.0 %	3.46 [0.44, 27.36]
Mantzaris 1993	2/17	0/16		5.4 %	4.72 [0.24, 91.41]
O'Morain 1996	18/102	0/106		5.1 %	38.44 [2.35, 629.53]
Pinero 1995	1/30	0/30		5.2 %	3.00 [0.13, 70.83]
Pounder 1997	2/61	0/30		7.0 %	2.50 [0.12, 50.50]
Tulassay 2008	22/315	0/164		6.9 %	23.50 [1.43, 384.90]
van Zanten 1999	15/98	1/48		14.0 %	7.35 [1.00, 53.99]
Total (95% CI)	**1485**	**814**		**100.0 %**	**8.85 [4.38, 17.90]**

Total events: 106 (Treatment), 3 (Control)

Heterogeneity: $Chi^2 = 6.16$, df = 12 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 6.07 (P < 0.00001)



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

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 11 adverse events

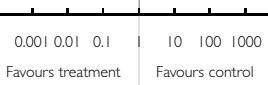
Outcome: 8 Stomatitis, proportion occurred versus not occurred

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	1/85	0/30		14.7 %	1.08 [0.05, 25.85]
Bayerdorffer 1996	1/65	0/65		10.0 %	3.00 [0.12, 72.31]
Carpintero 1997	1/78	0/44		12.7 %	1.71 [0.07, 41.08]
Lazzaroni 1997	1/29	1/30		19.6 %	1.03 [0.07, 15.77]
Porro 1996	2/91	0/92		9.9 %	5.05 [0.25, 103.85]
Shirotani 1996	2/25	0/25		10.0 %	5.00 [0.25, 99.16]
Sobhani 1995	1/59	0/60		9.9 %	3.05 [0.13, 73.39]
Suarez 1999	3/40	0/20		13.2 %	3.59 [0.19, 66.22]
Total (95% CI)	**472**	**366**		**100.0 %**	**2.65 [0.94, 7.48]**

Total events: 12 (Treatment), 1 (Control)

Heterogeneity: Chi^2 = 1.24, df = 7 (P = 0.99); I^2 =0.0%

Test for overall effect: Z = 1.85 (P = 0.065)



APPENDICES

Appendix 1. CENTRAL search strategy

1. exp peptic ulcer/
2. exp peptic ulcer hemorrhage/
3. exp peptic ulcer perforation/
4. exp duodenal ulcer/
5. exp stomach ulcer/
6. (pep$ adj5 ulcer$).tw.
7. (stomach adj5 ulcer$).tw.
8. (duoden$ adj5 ulcer$).tw.
9. (gastr$ adj5 ulcer$).tw.
10. or/1-9
11. exp dyspepsia/
12. exp eructation/

13. exp flatulence/
14. exp heartburn/
15. exp gastroparesis/
16. exp gastric emptying/
17. exp gastritis/
18. dyspep$.tw.
19. (acid adj5 reflux).tw.
20. belch$.tw.
21. bloat$.tw.
22. burp$.tw.
23. (early adj5 satiety).tw.
24. eructation.tw.
25. flatu$.tw.
26. heartburn.tw.
27. indigestion.tw.
28. pyro$.tw.
29. hiatus hernia.tw.
30. (stomach adj5 paresis).tw.
31. gastritis.tw.
32. (gastric adj5 acid adj5 secretion).tw.
33. (stomach adj5 acid adj5 secretion).tw.
34. (gastric adj5 erosion$).tw.
35. (gastric adj5 emptying adj5 disorder$).tw.
36. (stomach adj5 emptying adj5 disorder$).tw.
37. gastroparesis.tw.
38. (bleed$ adj5 ulcer$).tw.
39. (rebleed$ adj5 ulcer$).tw.
40. (recurrent adj5 bleed$ adj5 ulcer$).tw.
41. (acute adj5 bleed$ adj5 ulcer$).tw.
42. (gastrointestinal adj5 bleed$).tw.
43. (gastrointestinal adj5 rebleed$).tw.
44. (gastrointestinal adj5 hemorrhag$).tw.
45. (gastrointestinal adj5 haemorrhag$).tw.
46. (ulcer adj5 hemorrhag$).tw.
47. (ulcer adj5 haemorrhag$).tw.
48. (mucos$ adj5 injur$).tw.
49. or/11-48
50. exp anti-ulcer agents/
51. exp omeprazole/
52. omeprazole.tw.
53. lansoprazole.tw.
54. pantoprazole.tw.
55. rabeprazole.tw.
56. esomeprazole.tw.
57. exp histamine H2 antagonists/
58. exp cimetidine/
59. cimetidine.tw.
60. exp ranitidine/
61. ranitidine.tw.
62. exp famotidine/
63. famotidine.tw.
64. exp nizatidine/
65. nizatidine.tw.

66. (histamine adj3 H2 adj3 antagonist$).tw.
67. (antiulcer adj5 agent$).tw.
68. (H2 adj5 receptor adj5 antagonist$).tw.
69. (proton adj3 pump adj3 inhibitor$).tw.
70. exp bismuth/
71. exp antacids/
72. exp alginates/
73. Aluminum hydroxide/
74. exp magnesium hydroxide/
75. exp magnesium oxide/
76. exp calcium carbonate/
77. (magnesium adj5 carbonate).tw.
78. exp magnesium hydroxide/
79. exp magnesium oxide/
80. Magnesium silicates/
81. exp carbenoxolone/
82. exp misoprostol/
83. exp sucralfate/
84. exp muscarinic antagonists/
85. exp dicyclomine/
86. exp pirenzepine/
87. exp propantheline/
88. algicon.tw.
89. alginates.tw.
90. (alumin?um adj5 hydroxide).tw.
91. (calcium adj5 carbonate).tw.
92. gaviscon.tw.
93. hydrotalcite.tw.
94. maalox.tw.
95. (magnesium adj5 hydroxide).tw.
96. (magnesium adj5 oxide).tw.
97. (magnesium adj5 trisilicate).tw.
98. (sodium adj5 bicarbonate).tw.
99. (sodium adj5 carbonate).tw.
100. (mucosal adj5 protecting adj5 agent$).tw.
101. carbenoxolone.tw.
102. misoprostol.tw.
103. sucralfate.tw.
104. antimuscarinic$.tw.
105. (muscarinic adj5 receptor adj5 antagonist$).tw.
106. dicyclomine.tw.
107. pirenzepine.tw.
108. propantheline.tw.
109. exp macrolides/
110. macrolides.tw.
111. exp nitroimidazoles/
112. nitroimidazole$.tw.
113. exp tetracyclines/
114. tetracyclines.tw.
115. exp penicillins/
116. penicillin$.tw.
117. exp bismuth/
118. bismuth$.tw.

119. de-nol.tw.
120. exp clarithromycin/
121. clarithromycin$.tw.
122. exp amoxicillin/
123. amoxycillin$.tw.
124. amox?cillin$.tw.
125. exp metronidazole/
126. metronidazole$.tw.
127. exp tinidazole/
128. tinidazole$.tw.
129. exp tetracyclines/
130. tetracycline$.tw.
131. anti-bacterial agents/
132. or/50-131
133. exp helicobacter pylori/
134. (campylobacter adj1 pylori$).tw.
135. (h adj1 pylori).tw.
136. (pylori$ adj250 eradicat$).tw.
137. or/133-136
138. 10 and 49
139. 10 or 138
140. 132 and 139
141. 137 and 140
142. limit 141 to yr="2008 -Current"

Appendix 2. MEDLINE search strategy

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 ed=20080701-20100822

Appendix 3. EMBASE search strategy

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 em=200831-201035

WHAT'S NEW

Last assessed as up-to-date: 22 November 2010.

Date	Event	Description
1 September 2010	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 2008)

PM checked data extraction and entry into RevMan (RevMan 2008)

PM performed meta-regression

AF and PM wrote the review

DF made revisions to the text of the review

DECLARATIONS OF INTEREST

Alex Ford: none.

Brendan Delaney: has received speaker's fees from Astra Zeneca and AxCan Pharma, holds grants from the MRC and NHS R&D programme and is supported by an NHS R&D Primary Care Career Scientist Award (No. CSA99/008).

David Forman: has received speakers/consulting fees from AstraZeneca, Wyeth, and Takeda.

Paul Moayyedi: chair at McMaster University partly funded by an unrestricted donation by AstraZeneca, and has received consultants and speakers bureau fees from AstraZeneca, AxCan Pharma, Nycomed, and Johnson and Johnson.

INDEX TERMS

Medical Subject Headings (MeSH)

*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]

MeSH check words

Adult; Humans