

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

Ford AC, Delaney BC, Forman D, Moayyedi P



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This record should be cited as:

Ford AC, Delaney BC, 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.

This version first published online: 19 April 2006 in Issue 2, 2006.

Date of most recent substantive amendment: 01 February 2006

A B S T R A C T

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 strategy

Searches were conducted on the Cochrane Central register of Controlled Trials - CENTRAL (which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register) on The Cochrane Library (Issue 3 2002) MEDLINE (1966 to July 2002) and EMBASE (1980 to July 2002). 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 and November 2005. 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and experts in the field were contacted and asked to provide details of outstanding clinical trials and any relevant unpublished materials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 no treatment. Trials were included if they reported assessment from 2 weeks onwards.

Data collection and analysis

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

Main results

63 trials were eligible. Data extraction was not possible in 7 trials, and 56 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, 0.76) and no treatment (2 trials, 207 patients, RR = 0.37; 95% CI 0.26, 0.53). In gastric ulcer healing, no significant differences were detected between eradication therapy and UHD (14 trials, 1572 patients, RR = 1.25; 95% CI = 0.88, 1.76). In preventing duodenal ulcer recurrence no significant differences were detected between eradication therapy and maintenance therapy with UHD (4 trials, 319 patients, relative risk [RR] of ulcer recurring = 0.73; 95% CI = 0.42, 1.25), but eradication therapy was superior to no treatment (27 trials 2509 patients, RR = 0.20; 95% CI = 0.15, 0.26). In preventing gastric ulcer recurrence, eradication therapy was superior to no treatment (11 trials, 1104 patients, RR = 0.29; 95% CI 0.20, 0.42).

Authors' conclusions

A 1 to 2 weeks course of *H. pylori* eradication therapy is an effective treatment for *H. pylori* positive peptic ulcer disease.

PLAIN LANGUAGE 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

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.

BACKGROUND

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].

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.

Triple therapy regimens (acid suppressing therapy combined with two antibiotics aimed at eradicating *H. pylori*) given for 1 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.

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.

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 intervention

The tested drug had to fall within the following drug class a), the comparison regimen also had to be one of b)-i) from the list below:

a) 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 2 of the following; amoxicillin, macrolide, 5 nitroimidazole)
- iii) H2RA triple therapy (H2RA plus 2 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
- b) PPIs: lansoprazole, omeprazole, pantoprazole, rabeprazole.
- c) H2RAs: cimetidine, famotidine, nizatidine, ranitidine.
- d) Bismuth salts.
- e) Sucralfate.
- f) Regular antacid.
- g) PRN antacid.
- h) Placebo.
- i) No treatment.

Patients had to have had at least 1 week of therapy.

Types of outcome measures

Trials were included if they reported evidence of assessment from 2 weeks onwards.

The following outcomes were included in this review:

Primary

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

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

See: Cochrane Upper Gastrointestinal & Pancreatic Diseases Group methods used in reviews.

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

Trials were identified by searching the following electronic databases - The Cochrane Central register of Controlled

Trials - CENTRAL (which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register) on The Cochrane Library (Issue 3 2002) MEDLINE (1966 to July 2002) and EMBASE (1980 to July 2002). The search was updated in September 2003, November 2004 and November 2005.

The search strategy for this review has been constructed by using a combination of MESH subject headings and textwords relating to the use of eradication therapies for peptic ulcer disease in *H. pylori* positive patients.

To identify randomized controlled trials, the following search was combined with the Cochrane highly sensitive search strategy phases, one, two, and three as contained in the Reviewer's Handbook. (Clarke 2000)

MEDLINE search strategy

randomized controlled trial.pt.
 controlled clinical trial.pt.
 randomized controlled trials.sh.
 random allocation.sh.
 double blind method.sh.
 single-blind method.sh.
 or/1-6
 (animal not human).sh.
 7 not 8
 clinical trial.pt.
 exp clinical trials/
 (clin\$ adj25 trial\$).ti,ab.
 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 blind\$).mp. or
 mask\$.ti,ab. [mp=title, abstract, cas registry/ec number word,
 mesh subject heading]
 placebos.sh.
 placebo\$.ti,ab.
 random\$.ti,ab.
 research design.sh.
 or/10-17
 18 not 8
 19 not 9
 comparative study.sh.
 exp evaluation studies/
 follow up studies.sh.
 prospective studies.sh.
 (control\$ or prospectiv\$).mp. or volunteer\$.ti,ab. [mp=title,
 abstract, cas registry/ec number word, mesh subject heading]
 or/21-25
 26 not 8
 27 not (9 or 20)
 9 or 20 or 28
 exp peptic ulcer/
 exp peptic ulcer hemorrhage/
 exp peptic ulcer perforation/
 exp duodenal ulcer/

exp stomach ulcer/
 (pep\$ adj5 ulcer\$).tw.
 (stomach adj5 ulcer\$).tw.
 (duoden\$ adj5 ulcer\$).tw.
 (gastr\$ adj5 ulcer\$).tw.
 or/30-38
 exp dyspepsia/
 exp eructation/
 exp flatulence/
 exp heartburn/
 exp gastroparesis/
 exp gastric emptying/
 exp gastritis/
 dyspep\$.tw.
 (acid adj5 reflux).tw.
 belch\$.tw.
 bloat\$.tw.
 burp\$.tw.
 (early adj5 satiety).tw.
 eructation.tw.
 flatu\$.tw.
 heartburn.tw.
 indigestion.tw.
 pyro\$.tw.
 hiatus hernia.tw.
 (stomach adj5 paresis).tw.
 gastritis.tw.
 (gastric adj5 acid adj5 secretion).tw.
 (stomach adj5 acid adj5 secretion).tw.
 (gastric adj5 erosion\$).tw.
 (gastric adj5 emptying adj5 disorder\$).tw.
 (stomach adj5 emptying adj5 disorder\$).tw.
 gastroparesis.tw.
 (bleed\$ adj5 ulcer\$).tw.
 (rebleed\$ adj5 ulcer\$).tw.
 (recurrent adj5 bleed\$ adj5 ulcer\$).tw.
 (acute adj5 bleed\$ adj5 ulcer\$).tw.
 (gastrointestinal adj5 bleed\$).tw.
 (gastrointestinal adj5 rebleed\$).tw.
 (gastrointestinal adj5 hemorrhag\$).tw.
 (gastrointestinal adj5 haemorrhag\$).tw.
 (ulcer adj5 hemorrhag\$).tw.
 (ulcer adj5 haemorrhag\$).tw.
 (mucos\$ adj5 injur\$).tw.
 or/40-77
 exp anti-ulcer agents/
 exp omeprazole/
 omeprazole.tw.
 lansoprazole.tw.
 pantoprazole.tw.
 rabeprazole.tw.
 esomeprazole.tw.
 exp histamine H2 antagonists/

exp cimetidine/
 cimetidine.tw.
 exp ranitidine/
 ranitidine.tw.
 exp famotidine/
 famotidine.tw.
 exp nizatidine/
 nizatidine.tw.
 (histamine adj3 H2 adj3 antagonist\$).tw.
 (antiulcer adj5 agent\$).tw.
 (H2 adj5 receptor adj5 antagonist\$).tw.
 (proton adj3 pump adj3 inhibitor\$).tw.
 exp bismuth/
 exp antacids/
 exp alginates/
 Aluminum hydroxide/
 exp magnesium hydroxide/
 exp magnesium oxide/
 exp calcium carbonate/
 (magnesium adj5 carbonate).tw.
 exp magnesium hydroxide/
 exp magnesium oxide/
 Magnesium silicates/
 exp carbenoxolone/
 exp misoprostol/
 exp sucralfate/
 exp muscarinic antagonists/
 exp dicyclomine/
 exp pirenzepine/
 exp propantheline/
 algicon.tw.
 alginates.tw.
 (aluminum adj5 hydroxide).tw.
 (calcium adj5 carbonate).tw.
 gaviscon.tw.
 hydrotalcite.tw.
 maalox.tw.
 (magnesium adj5 hydroxide).tw.
 (magnesium adj5 oxide).tw.
 (magnesium adj5 trisilicate).tw.
 (sodium adj5 bicarbonate).tw.
 (sodium adj5 carbonate).tw.
 (mucosal adj5 protecting adj5 agent\$).tw.
 carbenoxolone.tw.
 misoprostol.tw.
 sucralfate.tw.
 antimuscarinic\$.tw.
 (muscarinic adj5 receptor adj5 antagonist\$).tw.
 dicyclomine.tw.
 pirenzepine.tw.
 propantheline.tw.
 exp macrolides/
 macrolides.tw.

exp nitroimidazoles/
nitroimidazole\$.tw.
exp tetracyclines/
tetracyclines.tw.
exp penicillins/
penicillin\$.tw.
exp bismuth/
bismuth\$.tw.
de-nol.tw.
exp clarithromycin/
clarithromycin\$.tw.
exp amoxicillin/
amoxicillin\$.tw.
amox?cillin\$.tw.
exp metronidazole/
metronidazole\$.tw.
exp tinidazole/
tinidazole\$.tw.
exp tetracycline/
tetracycline\$.tw.
exp antibiotics, tetracycline/
or/79-160
exp helicobacter pylori/
(campylobacter adj1 pylori\$).tw.
(h adj1 pylori).tw.
(pylori\$ adj250 eradicat\$).tw.
or/162-165
39 and 78
39 or 167
161 and 168
166 and 169
170 and 29

CCTR search strategy

peptic-ulcer
peptic-ulcer-hemorrhage
peptic-ulcer-perforation
duodenal-ulcer
stomach-ulcer
pep* near ulcer*
stomach near ulcer*
duoden* near ulcer*
gastr* near ulcer*
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
dyspepsia
eructation
flatulence
heartburn
gastroparesis
gastric-emptying
gastritis
dyspep*
acid near reflux*

belch*
bloat*
burp*
early near satiety
eructat*
flatu*
heartburn*
indigest*
pyro*
hiatus-hernia
stomach near paresis*
gastritis
gastr* near acid near secret*
stomach near acid near secret*
gastr* near erosion*
gastr* near emptying near disorder*
stomach near emptying near disorder*
gastropares*
bleed* near ulcer*
rebleed* near ulcer*
recurrent near bleed* near ulcer*
acute near bleed* near ulcer*
gastr* near bleed*
gastr* near rebleed*
gastr* near hemorrhag*
gastr* near haemorrhag*
ulcer near hemorrhag*
ulcer near haemorrhag*
mucos* near injur*
#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or
#20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or
#29 or #30 clib50=#31 or #32 or #33 or #34 or #35 or #36 or
#37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or
#46 or #47 or #48
proton-pump
proton near pump near inhibitor*
ppi
omeprazole
lansoprazole
pantoprazole
rabeprazole
esomeprazole
histamine-h2-antagonists
cimetidine
cimetidine
famotidine
nizatidine
ranitidine
histamine near antagon*
receptor near antagon*
anti near ulcer near agent*
antiulcer near agent
anti-ulcer-agents

bismuth	#68 or #69
antacids	#70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or
antacid*	#79 or #80 or #81 or #82 or #83 or #84 #85 or #86 #87 or #88
alginates	or #89
aluminium-hydroxide	#90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or
magnesium-oxide	#99 or #100 or #101 or #102 or #103 or #104 or #105 or #106
calcium-carbonate	#107 or #108 or #109
hydrotalcite*	#110 or #111 or #112 or #113 or #114 or #115 or #116 or #117
magnesium near carbonate	or #118 or #119 or #120 or #121 or #122 or #123 or #124 or
magnesium-silicates	#125 or #126 or #127 or #128 or #129 or #130 or #131 or #132
aluminium near hydroxide	or #133
carbenoxolone	#135 or #136 or #137
misoprostol	helicobacter-pylori
sucralfate	campylobacter-pylori
algicon	pylori near erad*
alginates	h* near pylori
calcium near carbonate	#49 or #50
gaviscon	#10 and #143
maalox	#10 or #144
magnesium near hydroxide	#145 and #138
magnesium near oxide	#139 or #140 or #141 or #142
magnesium near trisilicate	#146 and #147
sodium near bicarbonate	
mucosa* near protect* agent*	
carbenoxolone	
misoprostol	
sucralfate	
dicyclomine	
pirenzepine	
propantheline	
muscarinic-antagonists	
antimuscarinic*	
muscarinic near receptor near antagon*	
dicyclomine	
pirenzepine	
propantheline	
propantheline near bromide	
macrolides	
nitroimidazoles	
tetracyclines	
penicillins	
bismuth	
ranitidine near bismuth	
de-nol	
clarithromycin	
clarithromicin	
amoxicillin	
amoxycillin	
metronidazole	
tinidazole	
tetracycline	
134=#51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or	
#59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or	

EMBASE search strategy

exp randomized controlled trial/
randomized controlled trial.mp.
randomized controlled trial\$.tw.
exp randomization/
exp single blind method/
exp double blind method/
or/1-6
animal.hw.
human.hw.
8 not (8 and 9)
7 not 10
exp clinical trial/
clinical trial.mp.
(clin\$ adj3 (stud\$ or trial\$)).ti,ab,tw.
(clin\$ adj3 trial\$).ti,ab,tw.
((singl\$ or doubl\$ or treb\$ or tripl\$) adj3 (blind\$ or
mask\$)).ti,ab,tw.
exp placebo/
placebo\$.ti,ab,tw.
random.ti,ab,tw.
(crossover\$ or cross-over\$).ti,ab,tw.
or/12-20
21 not 10
22 not 11
exp comparative study/
exp evaluation studies/
exp prospective studies/
exp controlled study/
(control\$ or prospective\$ or volunteer\$).ti,ab,tw.

or/24-28
 29 not 10
 30 not (11 or 23)
 11 or 23 or 31
 exp peptic ulcer/
 exp peptic ulcer hemorrhage/
 exp peptic ulcer perforation/
 exp duodenal ulcer/
 exp stomach ulcer/
 (pep\$ adj5 ulcer\$).tw.
 (stomach adj5 ulcer\$).tw.
 (duoden\$ adj5 ulcer\$).tw.
 (gastr\$ adj5 ulcer\$).tw.
 or/33-41
 exp dyspepsia/
 exp eructation/
 exp flatulence/
 exp heartburn/
 exp gastroparesis/
 exp gastric emptying/
 exp gastritis/
 dyspep\$.tw.
 (acid adj5 reflux).tw.
 belch\$.tw.
 bloat\$.tw.
 burp\$.tw.
 (early adj5 satiety).tw.
 eructation.tw.
 flatu\$.tw.
 heartburn.tw.
 indigestion.tw.
 pyro\$.tw.
 hiatus hernia.tw.
 (stomach adj5 paresis).tw.
 gastritis.tw.
 (gastric adj5 acid adj5 secretion).tw.
 (stomach adj5 acid adj5 secretion).tw.
 (gastric adj5 erosion\$).tw.
 (gastric adj5 emptying adj5 disorder\$).tw.
 (stomach adj5 emptying adj5 disorder\$).tw.
 gastroparesis.tw.
 (bleed\$ adj5 ulcer\$).tw.
 (rebleed\$ adj5 ulcer\$).tw.
 (recurrent adj5 bleed\$ adj5 ulcer\$).tw.
 (acute adj5 bleed\$ adj5 ulcer\$).tw.
 (gastrointestinal adj5 bleed\$).tw.
 (gastrointestinal adj5 rebleed\$).tw.
 (gastrointestinal adj5 hemorrhag\$).tw.
 (gastrointestinal adj5 haemorrhag\$).tw.
 (ulcer adj5 hemorrhag\$).tw.
 (ulcer adj5 haemorrhag\$).tw.
 (mucos\$ adj5 injur\$).tw.
 or/43-80

exp anti-ulcer agents/
 exp omeprazole/
 omeprazole.tw.
 lansoprazole.tw.
 pantoprazole.tw.
 rabeprazole.tw.
 esomeprazole.tw.
 exp histamine H2 antagonists/
 exp cimetidine/
 cimetidine.tw.
 exp ranitidine/
 ranitidine.tw.
 exp famotidine/
 famotidine.tw.
 exp nizatidine/
 nizatidine.tw.
 (histamine adj3 H2 adj3 antagonist\$).tw.
 (antiulcer adj5 agent\$).tw.
 (H2 adj5 receptor adj5 antagonist\$).tw.
 (proton adj3 pump adj3 inhibitor\$).tw.
 exp bismuth/
 exp antacids/
 exp alginates/
 Aluminum hydroxide/
 exp magnesium hydroxide/
 exp magnesium oxide/
 exp calcium carbonate/
 (magnesium adj5 carbonate).tw.
 exp magnesium hydroxide/
 exp magnesium oxide/
 Magnesium silicates/
 exp carbenoxolone/
 exp misoprostol/
 exp sucralfate/
 exp muscarinic antagonists/
 exp dicyclomine/
 exp pirenzepine/
 exp propantheline/
 algicon.tw.
 alginates.tw.
 (alumin?um adj5 hydroxide).tw.
 (calcium adj5 carbonate).tw.
 gaviscon.tw.
 hydrotalcite.tw.
 maalox.tw.
 (magnesium adj5 hydroxide).tw.
 (magnesium adj5 oxide).tw.
 (magnesium adj5 trisilicate).tw.
 (sodium adj5 bicarbonate).tw.
 (sodium adj5 carbonate).tw.
 (mucosal adj5 protecting adj5 agent\$).tw.
 carbenoxolone.tw.
 misoprostol.tw.

sucralfate.tw.
 antimuscarinic\$.tw.
 (muscarinic adj5 receptor adj5 antagonist\$.tw.
 dicyclomine.tw.
 pirenzepine.tw.
 propantheline.tw.
 exp macrolides/
 macrolides.tw.
 exp nitroimidazoles/
 nitroimidazole\$.tw.
 exp tetracyclines/
 tetracyclines.tw.
 exp penicillins/
 penicillin\$.tw.
 exp bismuth/
 bismuth\$.tw.
 de-nol.tw.
 exp clarithromycin/
 clarithromycin\$.tw.
 exp amoxicillin/
 amoxicillin\$.tw.
 amox?cillin\$.tw.
 exp metronidazole/
 metronidazole\$.tw.
 exp tinidazole/
 tinidazole\$.tw.
 exp tetracycline/
 tetracycline\$.tw.
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 or/82-163
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 (campylobacter adj1 pylori\$.tw.
 (h adj1 pylori).tw.
 (pylori\$ adj250 eradicator\$.tw.
 or/165-168
 42 and 81
 42 or 170
 164 and 171
 172 and 169
 173 and 32

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 datasets 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:

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

METHODS OF THE REVIEW

Selection of studies

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

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

Assessment of Study Quality

Only trials which 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

(truly random or not stated/unclear)

Computer generated random numbers, coin toss, shuffles, etc are defined as truly random.

Concealment of the treatment allocation

(adequate, inadequate, unclear)

If trialists are unaware of each participant's allocation to a treatment when they are recruited, then the allocation is said to be adequately concealed. Methods such as central randomisation systems or serially numbered opaque envelopes fit this criteria. Where trials do not report the method of concealment of allocation it is deemed unclear.

Implementation of masking

(patients' masked, clinicians' masked, outcome assessors' masked)

When a placebo is used it is assumed that the participants are masked to their treatment allocation.

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.

Study quality was assessed by one reviewer and checked by a second.

Data extraction

Data was extracted by the lead reviewer and recorded onto specially developed forms. There was an unblinded check on this by a second reviewer. Data entry into RevMan 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 number reported
- quality of life
- global symptoms cured or recurred

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

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. Relative risks were combined for binary outcomes. Number needed to treat was calculated as the inverse of the risk difference from the meta-analysis. Where significant ($p < 0.1$) heterogeneity was detected possible explanations were investigated informally, and the data summarised using a random effects analysis. Reasons for heterogeneity were explored according to the following predefined criteria:

- a) Multi-centre versus single centre
- b) Country of origin
- c) Mean age of patients included in the study
- d) Method of randomisation
- e) Method of concealment of allocation
- f) Masking versus no masking
- g) Type of eradication regimen
- h) *H. pylori* eradication rate
- i) Duration of treatment
- j) Completeness of follow-up

DESCRIPTION OF STUDIES

In total, 3046 citations were identified using the search strategy outlined above. The titles and abstracts were reviewed and 89 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. A further two trials were unable to be included 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 56 articles included in the final meta-analysis contained more than one comparison and were therefore included in more than one analysis as follows:

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, Porro 1993, Porro 1996, Pounder 1997, Rauws 1990, Schwartz 1998, Shirovani 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, 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, Shirovani 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

-14 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) with a total of 1572 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
 -4 RCTs (Asaka 2001, Befrits 2004, Higuchi 2003, Malfertheiner 1999) comparing PPI triple therapy with ulcer-healing drug alone

There were 6 multi-centre trials

The smallest trial included 27 patients

The largest trial included 280 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

-1 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, Shirovani 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, Shirovani 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)

-11 RCTs (Axon 1997, Bayerdorffer 1996, Befrits 2004, Fukuda 1995b, Graham 1992, Kato 1996, Lazzaroni 1997, Malfertheiner 1999, Meining 1998, Sung 1995, Tomita 2002) with a total of 1104 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

-3 RCTs (Befrits 2004, Malfertheiner 1999, Tomita 2002) comparing PPI triple therapy with no treatment

There were 5 multi-centre trials

The smallest trial contained 59 patients

The largest trial contained 255 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)

-1 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

METHODOLOGICAL QUALITY

Two reviewers undertook an assessment of the quality of each eligible study independently. Methods of randomisation, concealment, and masking were assessed. Twelve 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) and eight (Bayerdorffer 1996, Higuchi 2003, Hosking 1992, Lam 1997, Meining 1998, Pinero 1995, Sung 1994, Sung 1995) reported the method of concealment.

RESULTS

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, Porro 1993, Porro 1996, Pounder 1997, Rauws 1990, Schwartz 1998, Shirovani 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 squared = 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) (number needed to treat (NNT) = 14; 95% CI 11 to 20).

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 squared = 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) (NNT = 2.5; 95% CI 2 to 4).

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

Fourteen 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) reported a dichotomous gastric ulcer healing outcome evaluating 1572 patients, between 1 and 3 months. Overall 22% of gastric ulcers remained unhealed in the *H. pylori* eradication group compared with 14% in the ulcer-healing drug group. There was statistically significant heterogeneity between the trial results (heterogeneity test [13 degrees of freedom] chi squared = 22.66, $p = 0.05$) 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 = 1.25; 95% CI 0.88 to 1.76) (number needed to harm (NNH) = 33; 95% CI NNT = 33 to NNH = 12.5). The Egger test suggested there was a trend for funnel plot asymmetry but this did not reach statistical significance ($p=0.055$). 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 = 1.54; 95% CI = 0.88 to 2.20. $p<0.001$), absence of blinding (logRR = 3.12; 95% CI = 1.46 to 4.78. $p<0.001$), and a greater than 10% difference in follow-up between trial arms (logRR = 3.26; 95% CI 0.87 to 5.65. $p=0.007$) increased the effect size whereas performing an intention to treat analysis (logRR = -1.61; 95% CI -0.41 to -2.81. $p=0.009$), and increasing completeness of follow-up (logRR = -8.97; 95% CI = -4.42 to -13.52. $p<0.001$) reduced the effect size.

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 squared = 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) (NNT = 8; 95% CI = 4.5 to 50).

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) (NNT = 1.5; 95% CI 1.1 to 2.3).

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 squared = 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) (NNT = 25; 95% CI NNT = 8 to NNH = 33).

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 squared = 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) (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, $p = 0.003$).

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

Eleven RCTs (Axon 1997, Bayerdorffer 1996, Befrits 2004, Fukuda 1995b, Graham 1992, Kato 1996, Lazzaroni 1997, Malfertheiner 1999, Meining 1998, Sung 1995, Tomita 2002) reported a dichotomous gastric ulcer recurrence outcome evaluating 1104 patients, between 3 months and 5 years. Overall 14% of gastric ulcers recurred in the *H. pylori* eradication group compared with 58% in the no treatment group. There was statistically significant heterogeneity between trial results (heterogeneity test [10 degrees of freedom] chi squared = 20.95, $p = 0.02$) 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 = 0.29; 95% CI 0.20 to 0.42) (NNT = 2.6; 95% CI 1.9 to 4.5). 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. 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 = 0.51; 95% CI = 0.26 to 0.76, $p < 0.001$)).

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) (NNT = 3.8; 95% CI 2.2 to 17).

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 squared = 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).

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 squared = 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).

IV. Side effect profile

a. Total number of adverse events

Forty-two 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, Shirovani 1996, Sobhani 1995, Spinzi 1994, Suarez 1999, Sung 1995, Tomita 2002, Wang 1996, Wong 1999) reported overall numbers of adverse events as a dichotomous outcome in 5614 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 [39 degrees of freedom] chi squared = 75.23, $p = 0.0004$) 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) = 2.24; 95% CI 1.72 to 2.93) (NNH = 11; 95% CI 8 to 14).

b. Diarrhoea

Twenty-nine 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, Shirovani 1996, Sobhani 1995, Sung 1995; van Zanten 1999, Wang 1996, Wong 1999) reported occurrence of diarrhoea as a dichotomous outcome in 4111 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 [28 degrees of freedom] chi squared = 18.14, $p = 0.92$). 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) = 2.87; 95% CI 2.10 to 3.92) (NNH = 20; 95% CI 14 to 25).

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, Shirovani 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 squared = 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) (NNH = 25; 95% CI 17 to 50).

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 squared = 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) (NNH = 100; 95% CI = 50 to infinity).

e. Headache

Thirteen 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) reported occurrence of headache as a dichotomous outcome in 1813 patients. Overall 4% 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 [12 degrees of freedom] chi squared = 7.21, $p = 0.84$). 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) = 1.09; 95% CI 0.67 to 1.77) (NNH = infinity; 95% CI NNT = 100 to NNH = 50).

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 squared = 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) (NNH = 25; 95% CI 20 to 50).

g. Altered taste

Twelve 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) reported occurrence of altered taste as a dichotomous outcome in 1820 patients. Overall 7% of patients in the *H. pylori* eradication group reported altered taste compared with 0.5% in the comparison regimen group. There was no statistically significant heterogeneity between trial results (heterogeneity test [11 degrees of freedom] chi squared = 5.12, $p = 0.93$). 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) = 7.77; 95% CI 3.77 to 16.01) (NNH = 12.5; 95% CI 10 to 17).

h. Stomatitis

Eight trials (Arkkila 2005, Bayerdorffer 1996, Carpintero 1997, Lazzaroni 1997, Porro 1996, Shirohani 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 [7 degrees of freedom] chi squared = 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) (NNH = 50; 95% CI 25 to infinity).

DISCUSSION

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 54% in the recurrence of duodenal ulcer, and a slightly smaller but still significant relative risk reduction of 38% 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 9% relative risk reduction in 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).

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

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 14%. 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, 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.

POTENTIAL CONFLICT OF INTEREST

Alex Ford: none declared. 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 has received fees for speaking and research funds from AstraZeneca, Wyeth Laboratories, and Abbott Laboratories.

ACKNOWLEDGEMENTS

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

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

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T A B L E S**Characteristics of included studies**

Study	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%
Allocation concealment	B – Unclear

Characteristics of included studies (Continued)

Study	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%
Allocation concealment	B – Unclear

Study	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
Notes	Eradication rates: Bi triple therapy group 78.3% PPI group 36.4%
Allocation concealment	B – Unclear

Study	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%
Allocation concealment	B – Unclear

Study	Bardhan 1997
Methods	Multi-centre RCT

Characteristics of included studies (Continued)

	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%
Allocation concealment	B – Unclear

Study 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
Allocation concealment	B – Unclear

Study 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)
Outcomes	Ulcer healing Ulcer recurrence at 1 year H. pylori eradication rates
Notes	Eradication rates: PPI dual therapy 88.9% PPI 0%
Allocation concealment	B – Unclear

Study Bayerdorffer 1996

Methods	Multi-centre RCT Single-blinded
Participants	Germany

Characteristics of included studies (Continued)

	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
Allocation concealment	A – Adequate

Study 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%
Allocation concealment	B – Unclear

Study Carpintero 1997

Methods	Single centre RCT Unblinded
Participants	Spain 122 patients with duodenal ulcer
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%
Allocation concealment	B – Unclear

Study Chen 1995

Methods	Single centre RCT Single-blinded
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Characteristics of included studies (Continued)

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
Notes	Eradication rates: Bi triple therapy 93.9% No treatment 0%
Allocation concealment	B – Unclear

Study 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%
Allocation concealment	B – Unclear

Study 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%
Allocation concealment	B – Unclear

Study Fukuda 1995a

Methods	Single centre RCT Unblinded
Participants	Japan

Characteristics of included studies (Continued)

	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
Allocation concealment	B – Unclear

Study 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
Notes	Eradication rates: PPI dual therapy 48.6% PPI 12.2% All patients received 4 weeks ranitidine 150mg od after initial therapy
Allocation concealment	B – Unclear

Study 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%
Allocation concealment	B – Unclear

Study Graham 1991

Methods	Single centre RCT Single-blinded
Participants	USA 105 patients with duodenal ulcer

Characteristics of included studies (Continued)

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
Allocation concealment	B – Unclear

Study **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
Allocation concealment	B – Unclear

Study **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 H. pylori eradication rates
Notes	Eradication rates: RBC dual therapy 40% RBC 0% Placebo 0%
Allocation concealment	B – Unclear

Study **Harford 1996**

Methods	Multi-centre RCT Double-blinded
Participants	USA 196 patients with duodenal ulcer

Characteristics of included studies (Continued)

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%
Allocation concealment	B – Unclear

Study 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
Allocation concealment	B – Unclear

Study 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%
Allocation concealment	A – Adequate

Study Hosking 1992

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

Characteristics of included studies (Continued)

Outcomes	Ulcer healing H. pylori eradication rates
Notes	Eradication rates: Bi quadruple therapy 89.7% PPI 3.9% Linked to Sung 1994
Allocation concealment	A – Adequate

Study 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
Notes	Eradication rates: PPI dual therapy 36.5% PPI 1.8%
Allocation concealment	B – Unclear

Study 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%
Allocation concealment	B – Unclear

Study 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

Characteristics of included studies (Continued)

	H. pylori eradication rates
Notes	Eradication rates: PPI triple therapy 82% PPI 0% PPI group received long-term famotidine 20mg od
Allocation concealment	B – Unclear
Study	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
Allocation concealment	B – Unclear
Study	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
Notes	Eradication rates: Clarithromycin monotherapy 70.8% Placebo 10.2% Clarithromycin patients also received amoxicillin and metronidazole
Allocation concealment	A – Adequate
Study	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

Characteristics of included studies (Continued)

	H. pylori eradication rates
Notes	Eradication rates: PPI dual therapy 62.1% PPI 6.7%
Allocation concealment	B – Unclear
Study	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%
Allocation concealment	B – Unclear
Study	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%
Allocation concealment	B – Unclear
Study	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

Characteristics of included studies (Continued)

Notes	Eradication rates: PPI triple therapy 82.4% PPI 4.2% PPI given until ulcer healing in control arm
Allocation concealment	B – Unclear
Study	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%
Allocation concealment	B – Unclear
Study	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%
Allocation concealment	A – Adequate
Study	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
Allocation concealment	B – Unclear

Characteristics of included studies (Continued)

Study	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
Allocation concealment	B – Unclear

Study	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%
Allocation concealment	B – Unclear

Study	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%
Allocation concealment	B – Unclear

Characteristics of included studies (Continued)

Study	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
Notes	Eradication rates: Bi triple therapy 63.3% PPI 10%
Allocation concealment	A – Adequate

Study	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 amoxycillin 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%
Allocation concealment	B – Unclear

Study	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
Allocation concealment	B – Unclear

Study	Pounder 1997
Methods	Multi-centre RCT Double-blinded
Participants	Multi-national

Characteristics of included studies (Continued)

	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%
Allocation concealment	B – Unclear

Study Rauws 1990

Methods	Single centre RCT Single-blinded
Participants	Netherlands 66 patients with duodenal ulcer
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 1 year 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
Allocation concealment	B – Unclear

Study 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% PPI 1.9%
Allocation concealment	B – Unclear

Study Shirovani 1996

Methods	Single centre RCT
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Characteristics of included studies (Continued)

	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%
Allocation concealment	B – Unclear

Study 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%
Allocation concealment	B – Unclear

Study Spinzi 1994

Methods	Multi-centre RCT Unblinded
Participants	Italy 53 patients with duodenal ulcer
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%
Allocation concealment	B – Unclear

Study Suarez 1999

Methods	Single centre RCT Unblinded
Participants	Cuba

Characteristics of included studies (Continued)

	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%
Allocation concealment	B – Unclear

Study 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
Allocation concealment	A – Adequate

Study 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
Allocation concealment	A – Adequate

Study Tomita 2002

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

Characteristics of included studies (Continued)

	H. pylori eradication rates
Notes	Eradication rates: PPI triple therapy 81.9% PPI / H2RA 0%
Allocation concealment	B – Unclear

Study	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%
Allocation concealment	B – Unclear

Study	Wang 1993
Methods	Single centre RCT Unblinded
Participants	Taiwan 59 patients with duodenal ulcer
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%
Allocation concealment	B – Unclear

Study	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
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
Allocation concealment	B – Unclear
Study	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
Allocation concealment	B – Unclear
Study	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%
Allocation concealment	B – Unclear

Characteristics of excluded studies

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

Characteristics of excluded studies (Continued)

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
Malferteiner 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
Xia 1995	Not truly randomised
van Zanten 2000	Not all patients had documented peptic ulcer disease

ANALYSES

Comparison 01. du acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion not healed	34	3910	Relative Risk (Fixed) 95% CI	0.66 [0.58, 0.76]

Comparison 02. du acute healing hp eradication vs. no treatment / placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion not healed	2	207	Relative Risk (Fixed) 95% CI	0.37 [0.26, 0.53]

Comparison 03. gu acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion not healed	14	1572	Relative Risk (Random) 95% CI	1.25 [0.88, 1.76]

Comparison 04. pu acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion not healed	3	287	Relative Risk (Fixed) 95% CI	0.52 [0.31, 0.85]

Comparison 05. pu acute healing hp eradication vs. no treatment / placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion not healed	1	40	Relative Risk (Fixed) 95% CI	0.15 [0.05, 0.45]

Comparison 06. du recurrence hp eradication vs. ulcer healing drug alone (after initial ulcer healing)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion recurred	4	319	Relative Risk (Fixed) 95% CI	0.73 [0.42, 1.25]

Comparison 07. du recurrence hp eradication vs. no treatment (after initial ulcer healing)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion recurred	27	2509	Relative Risk (Random) 95% CI	0.20 [0.15, 0.26]

Comparison 08. gu recurrence hp eradication vs. no treatment (after initial ulcer healing)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion recurred	11	1104	Relative Risk (Random) 95% CI	0.29 [0.20, 0.42]

Comparison 09. pu recurrence hp eradication vs. no treatment (after initial ulcer healing)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportion recurred	1	103	Relative Risk (Fixed) 95% CI	0.23 [0.09, 0.59]

Comparison 10. global symptoms persisting

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 hp eradication + ulcer healing drug vs. ulcer healing drug alone	2	180	Relative Risk (Random) 95% CI	0.86 [0.42, 1.74]
02 hp eradication vs. no treatment	2	188	Relative Risk (Random) 95% CI	1.27 [0.83, 1.93]

Comparison 11. adverse events

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Overall, proportion occurred	42	5614	Relative Risk (Random) 95% CI	2.24 [1.72, 2.93]
02 Diarrhoea, proportion occurred	29	4111	Relative Risk (Fixed) 95% CI	2.87 [2.10, 3.92]
03 Nausea/vomiting, proportion occurred	15	1533	Relative Risk (Fixed) 95% CI	3.76 [1.91, 7.37]
04 Skin rash, proportion occurred	18	2385	Relative Risk (Fixed) 95% CI	1.36 [0.78, 2.37]
05 Headache, proportion occurred	13	1813	Relative Risk (Fixed) 95% CI	1.09 [0.67, 1.77]
06 Epigastric pain, proportion occurred	11	1491	Relative Risk (Fixed) 95% CI	4.09 [1.90, 8.82]
07 Altered taste, proportion occurred	12	1820	Relative Risk (Fixed) 95% CI	7.77 [3.77, 16.01]
08 Stomatitis, proportion occurred versus not occurred	8	838	Relative Risk (Fixed) 95% CI	2.65 [0.94, 7.48]

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Humans

COVER SHEET

Title	Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients
Authors	Ford AC, Delaney BC, Forman D, Moayyedi P
Contribution of author(s)	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 PM checked data extraction and entry into RevMan PM performed meta-regression AF and PM wrote the review DF made revisions to the text of the review
Issue protocol first published	2002/4
Review first published	2003/4
Date of most recent amendment	24 February 2006
Date of most recent SUBSTANTIVE amendment	01 February 2006
What's New	Information not supplied by author

Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD003840.pub4
Cochrane Library number	CD003840
Editorial group	Cochrane Upper Gastrointestinal and Pancreatic Diseases Group
Editorial group code	HM-UPPERGI

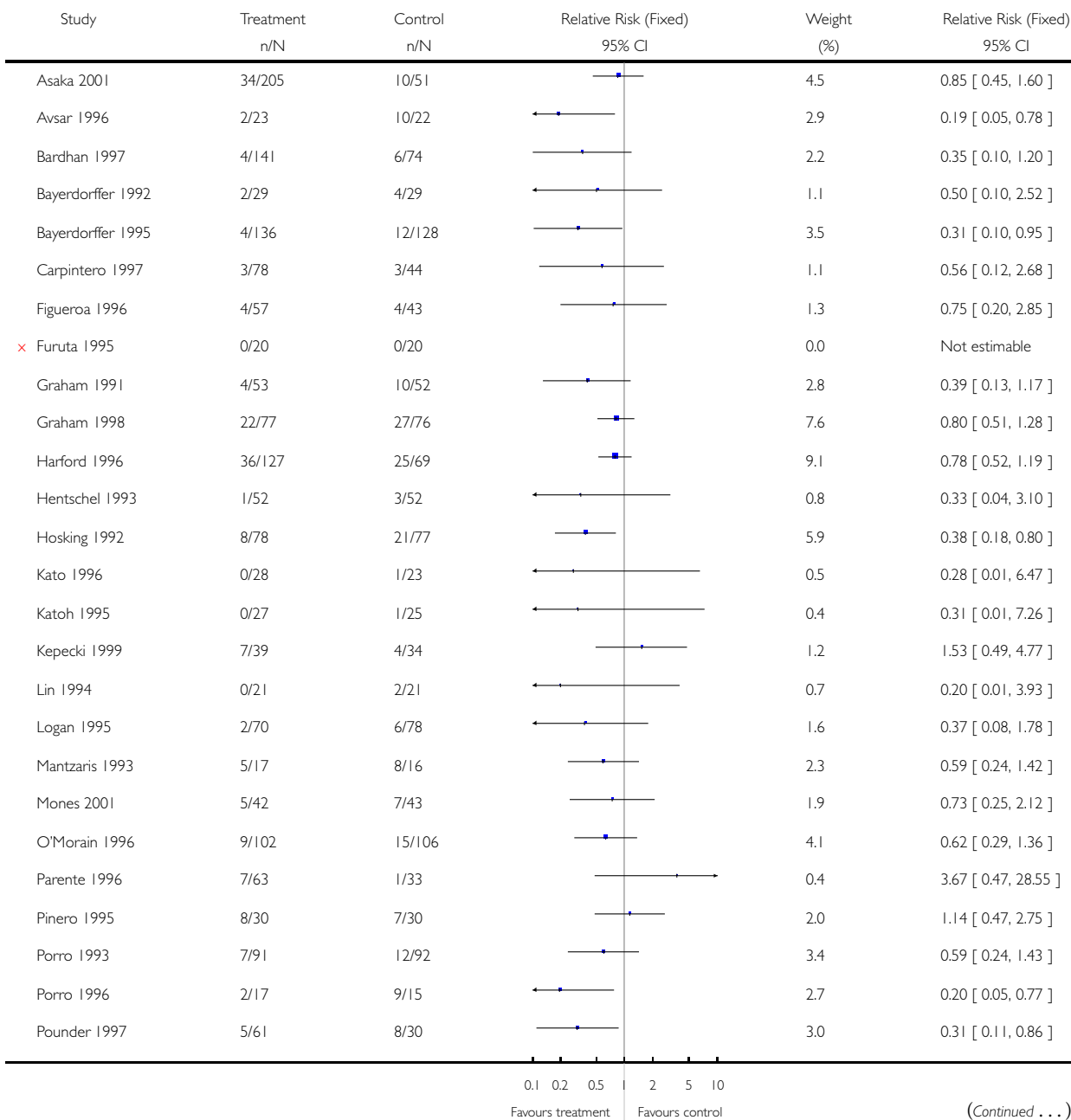
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 du acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone, Outcome 01 Proportion not healed

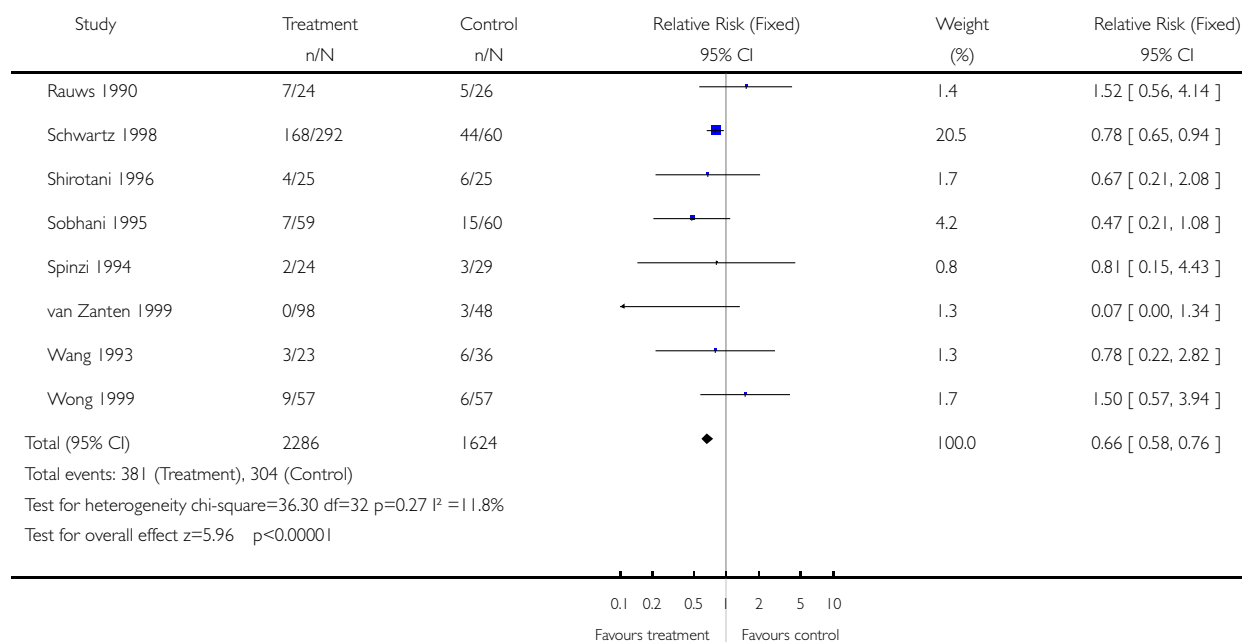
Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 01 du acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone

Outcome: 01 Proportion not healed



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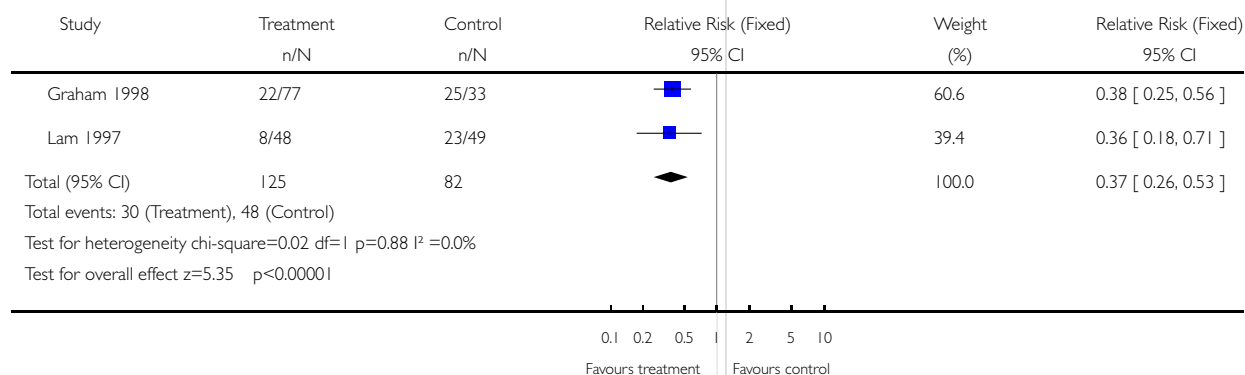


Analysis 02.01. Comparison 02 du acute healing hp eradication vs. no treatment / placebo, Outcome 01 Proportion not healed

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

Comparison: 02 du acute healing hp eradication vs. no treatment / placebo

Outcome: 01 Proportion not healed

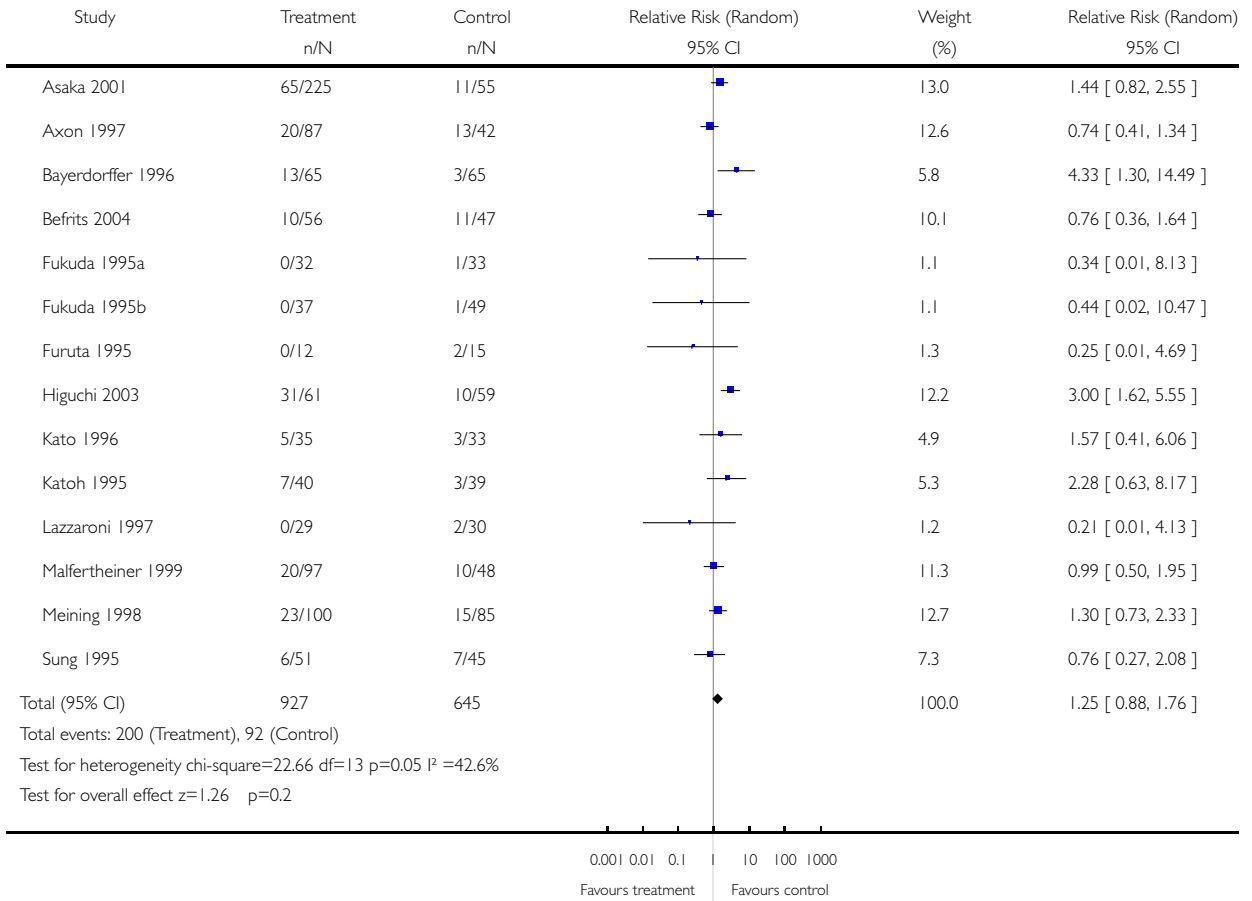


Analysis 03.01. Comparison 03 gu acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone, Outcome 01 Proportion not healed

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

Comparison: 03 gu acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone

Outcome: 01 Proportion not healed

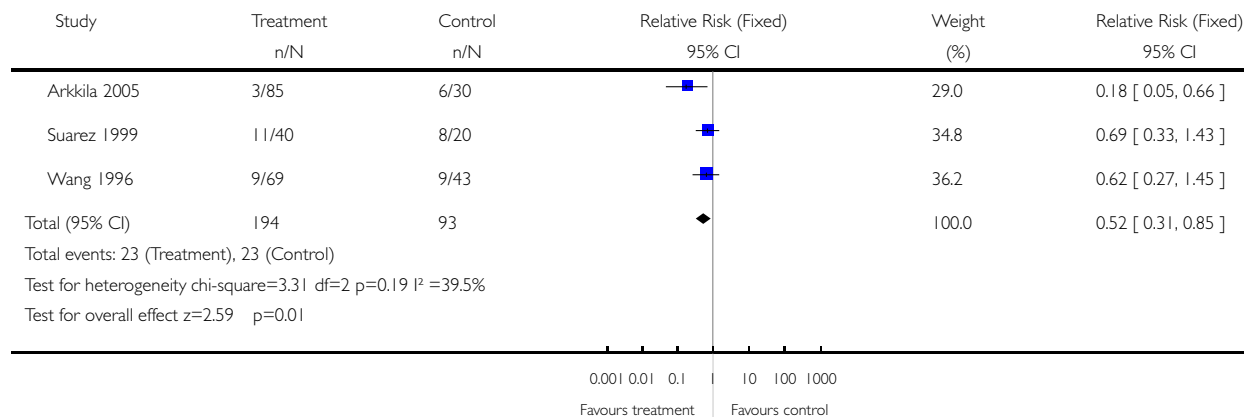


Analysis 04.01. Comparison 04 pu acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone, Outcome 01 Proportion not healed

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

Comparison: 04 pu acute healing hp eradication + ulcer healing drug vs. ulcer healing drug alone

Outcome: 01 Proportion not healed

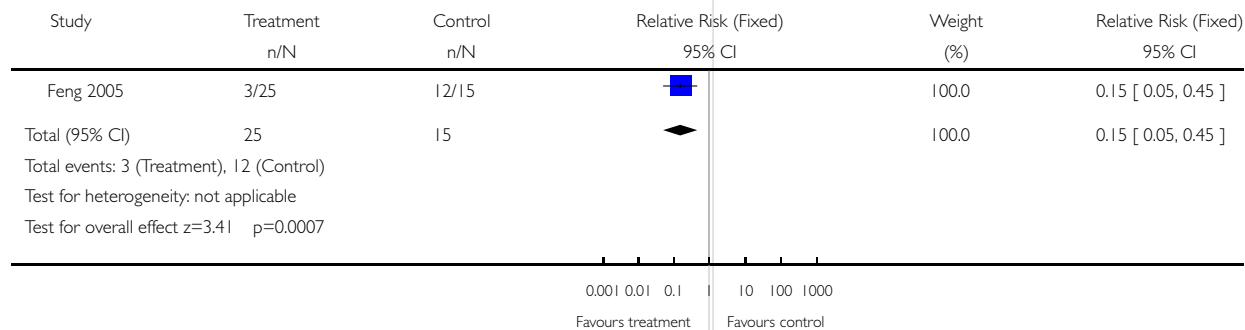


Analysis 05.01. Comparison 05 pu acute healing hp eradication vs. no treatment / placebo, Outcome 01 Proportion not healed

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

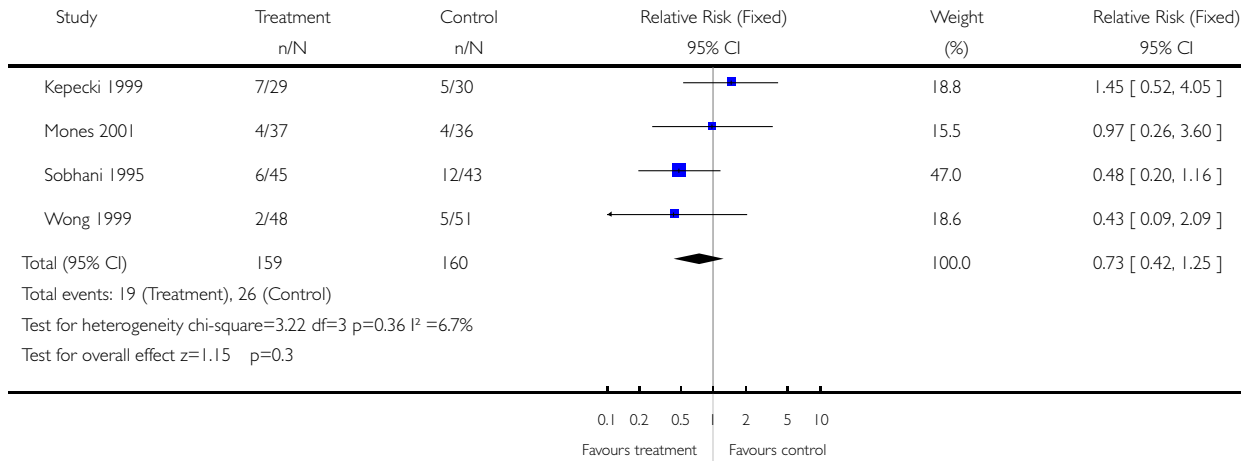
Comparison: 05 pu acute healing hp eradication vs. no treatment / placebo

Outcome: 01 Proportion not healed



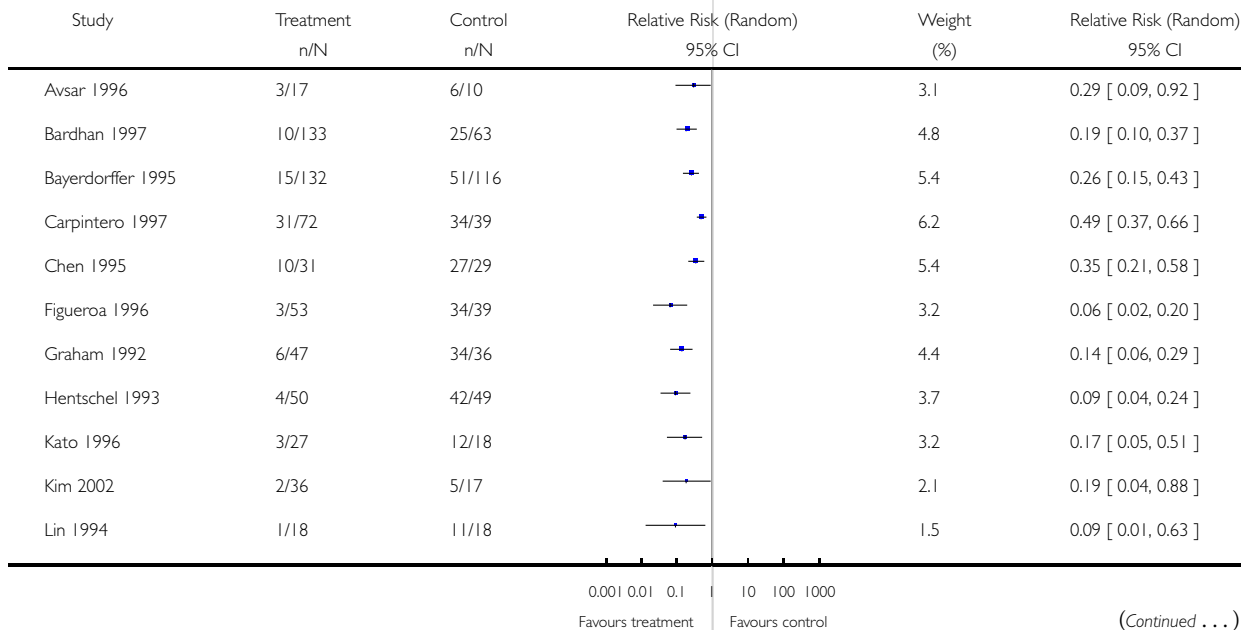
Analysis 06.01. Comparison 06 du recurrence hp eradication vs. ulcer healing drug alone (after initial ulcer healing), Outcome 01 Proportion recurred

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients
 Comparison: 06 du recurrence hp eradication vs. ulcer healing drug alone (after initial ulcer healing)
 Outcome: 01 Proportion recurred

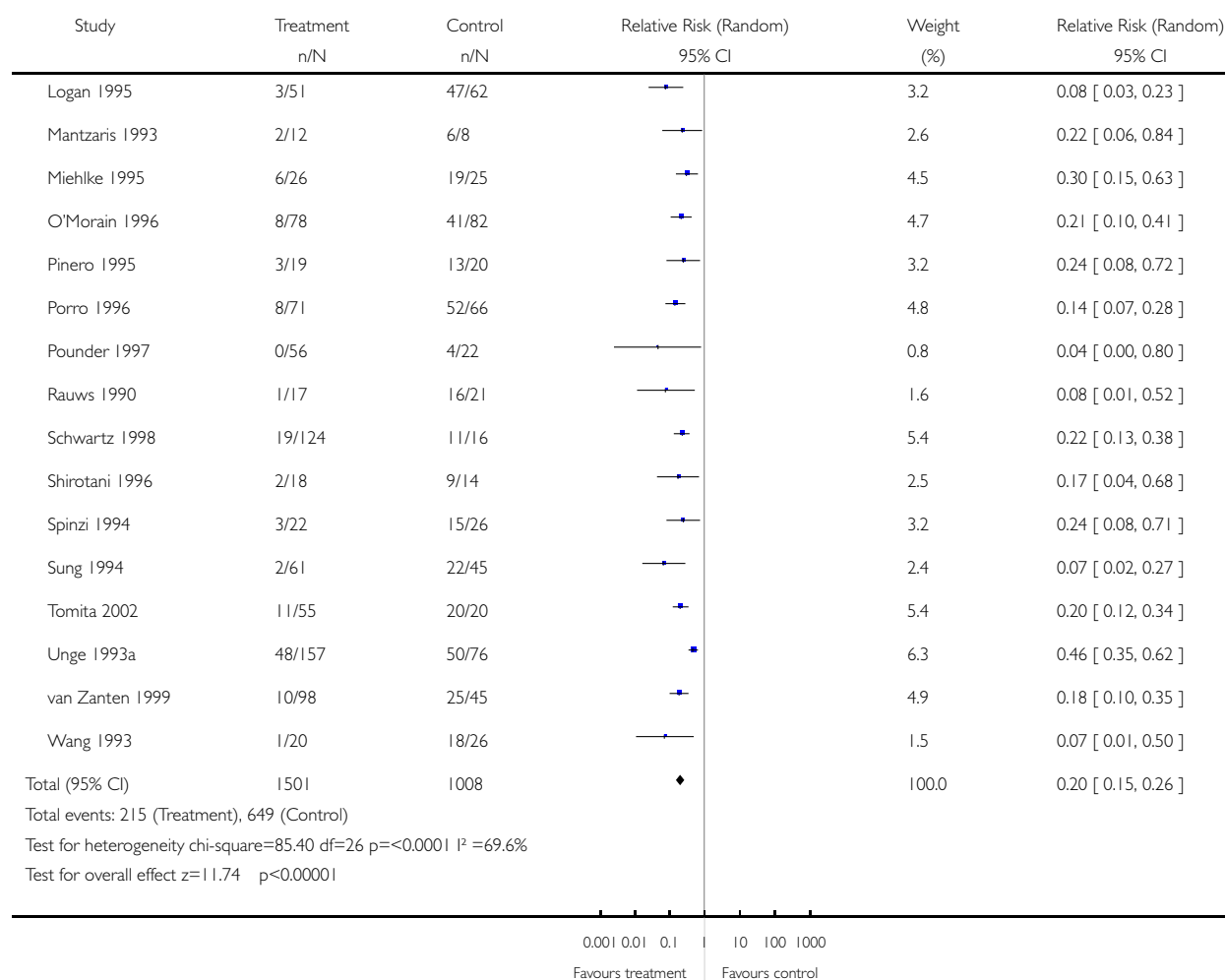


Analysis 07.01. Comparison 07 du recurrence hp eradication vs. no treatment (after initial ulcer healing), Outcome 01 Proportion recurred

Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients
 Comparison: 07 du recurrence hp eradication vs. no treatment (after initial ulcer healing)
 Outcome: 01 Proportion recurred



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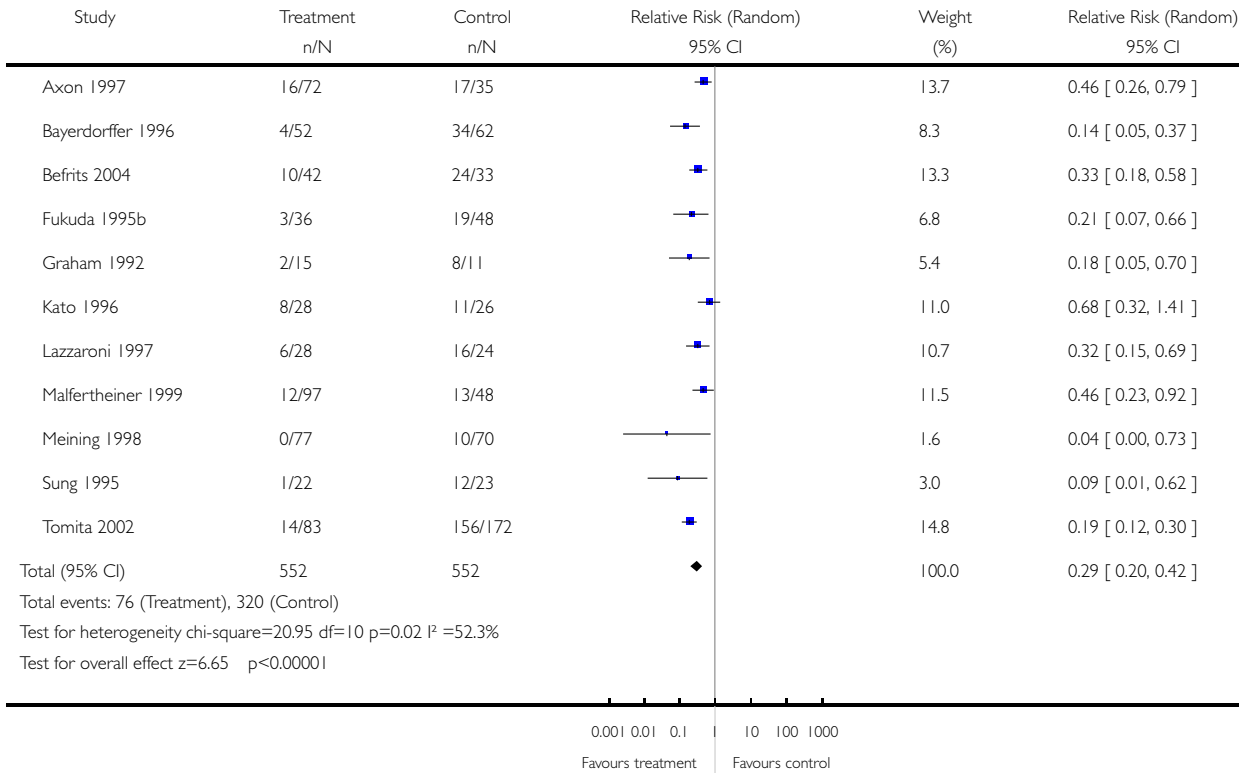


Analysis 08.01. Comparison 08 gu recurrence hp eradication vs. no treatment (after initial ulcer healing), Outcome 01 Proportion recurred

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

Comparison: 08 gu recurrence hp eradication vs. no treatment (after initial ulcer healing)

Outcome: 01 Proportion recurred

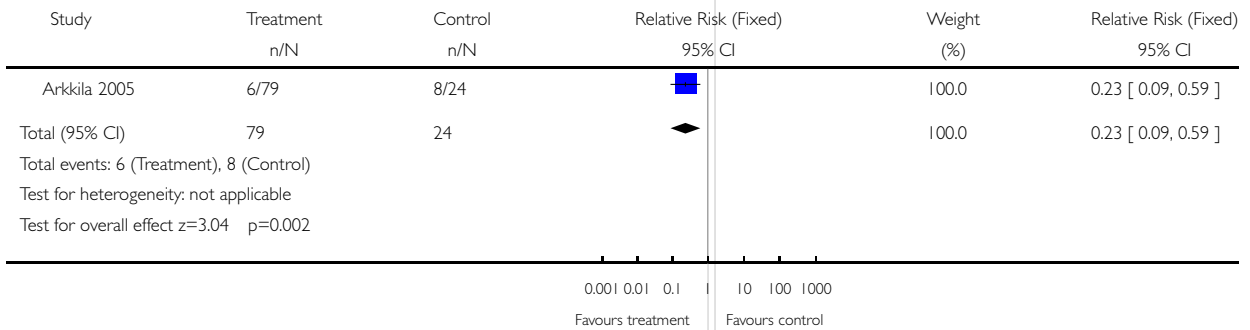


Analysis 09.01. Comparison 09 pu recurrence hp eradication vs. no treatment (after initial ulcer healing), Outcome 01 Proportion recurred

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

Comparison: 09 pu recurrence hp eradication vs. no treatment (after initial ulcer healing)

Outcome: 01 Proportion recurred

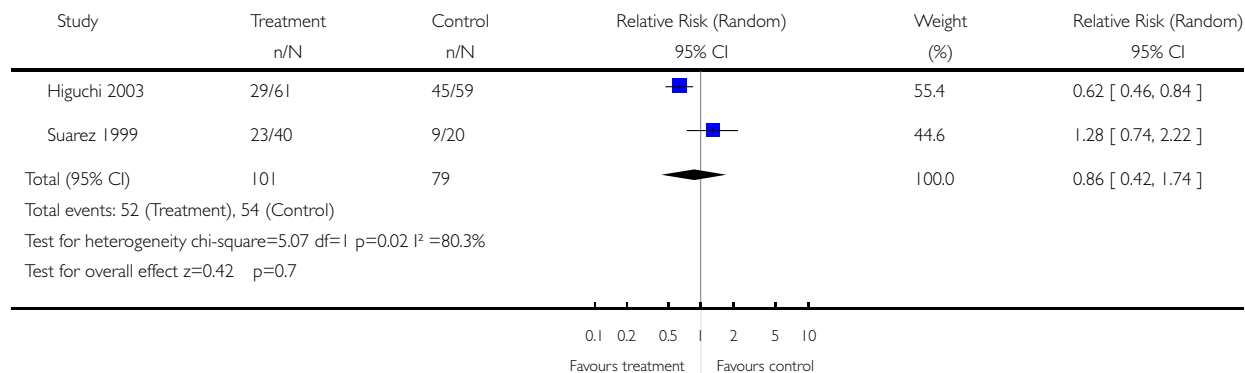


Analysis 10.01. Comparison 10 global symptoms persisting, Outcome 01 hp eradication + ulcer healing drug vs. ulcer healing drug alone

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

Comparison: 10 global symptoms persisting

Outcome: 01 hp eradication + ulcer healing drug vs. ulcer healing drug alone

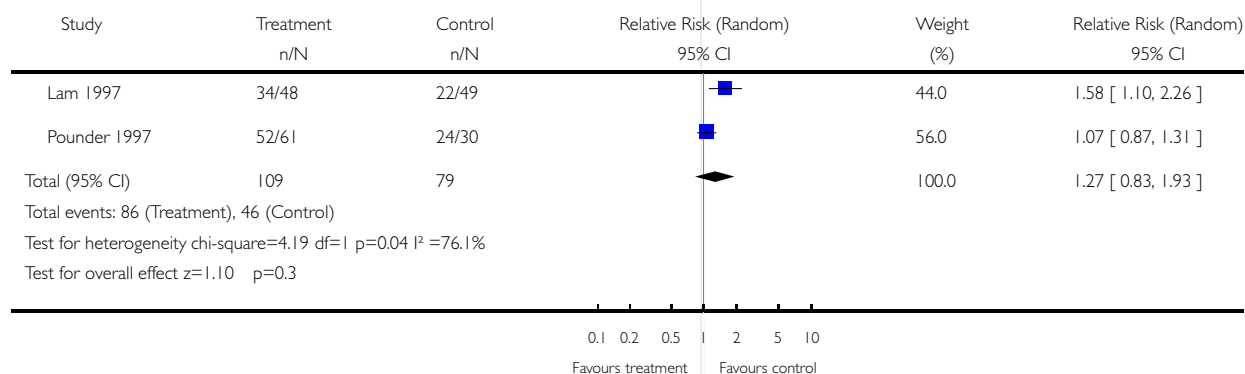


Analysis 10.02. Comparison 10 global symptoms persisting, Outcome 02 hp eradication vs. no treatment

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

Comparison: 10 global symptoms persisting

Outcome: 02 hp eradication vs. no treatment

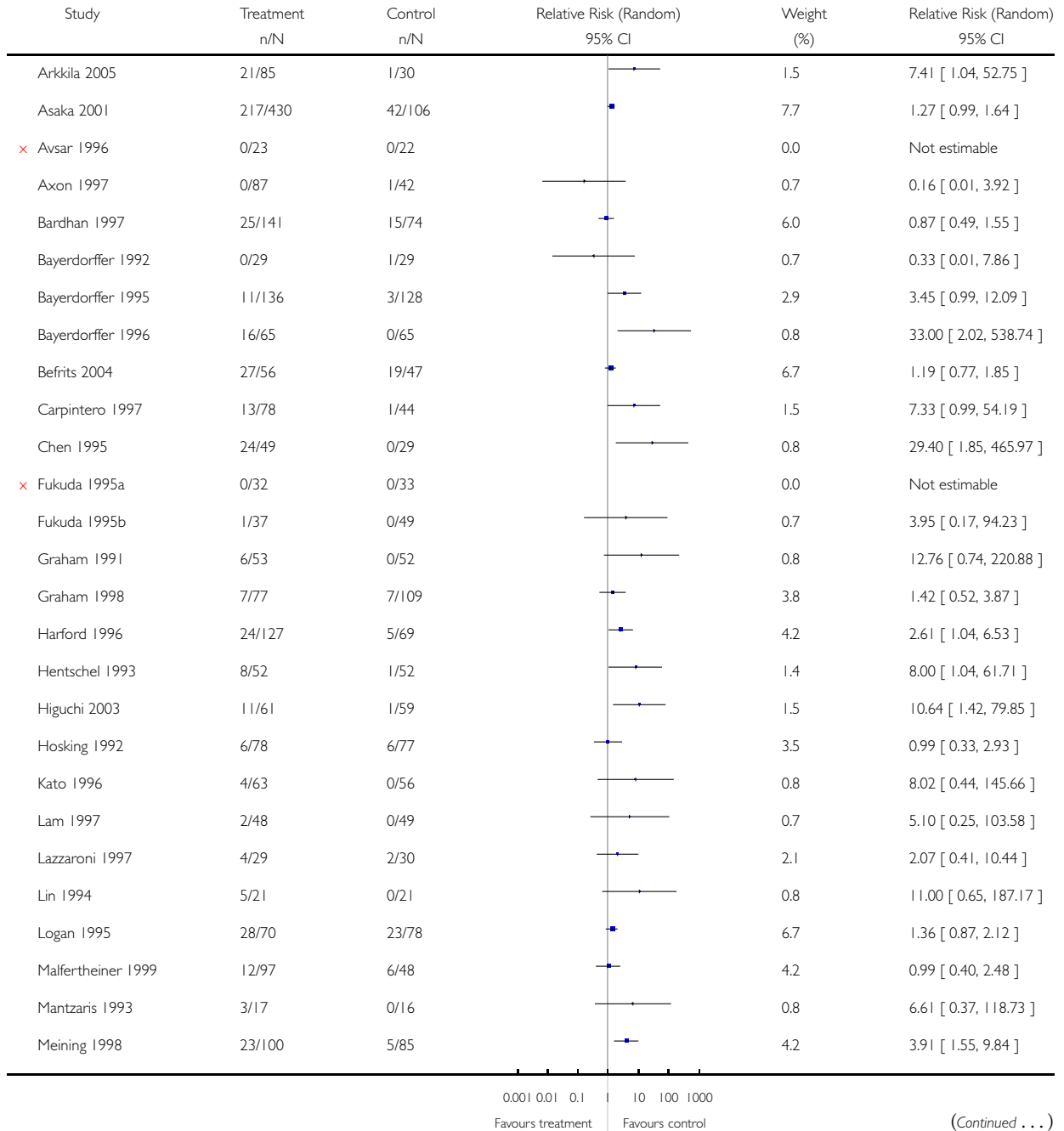


Analysis 11.01. Comparison 11 adverse events, Outcome 01 Overall, proportion occurred

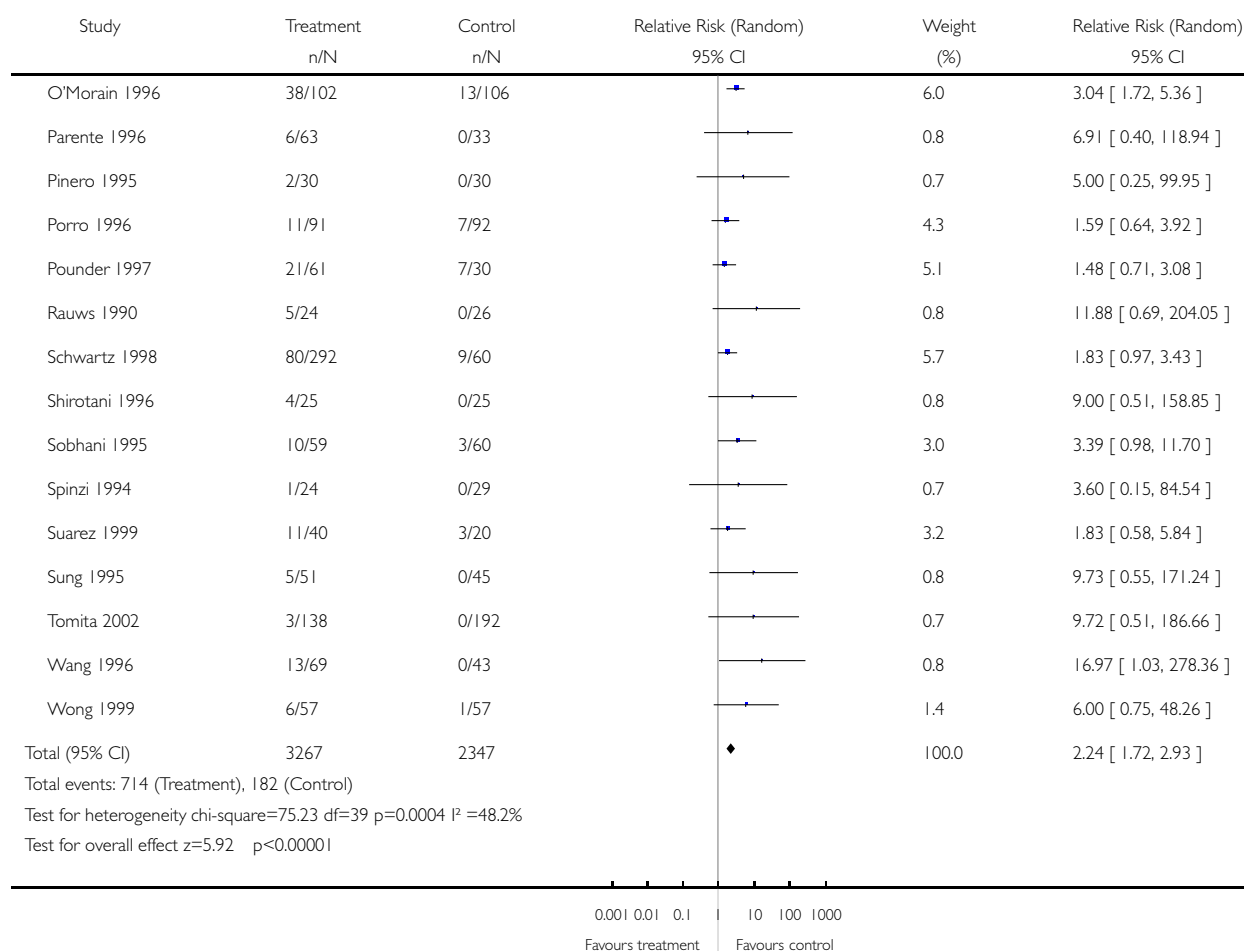
Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 11 adverse events

Outcome: 01 Overall, proportion occurred



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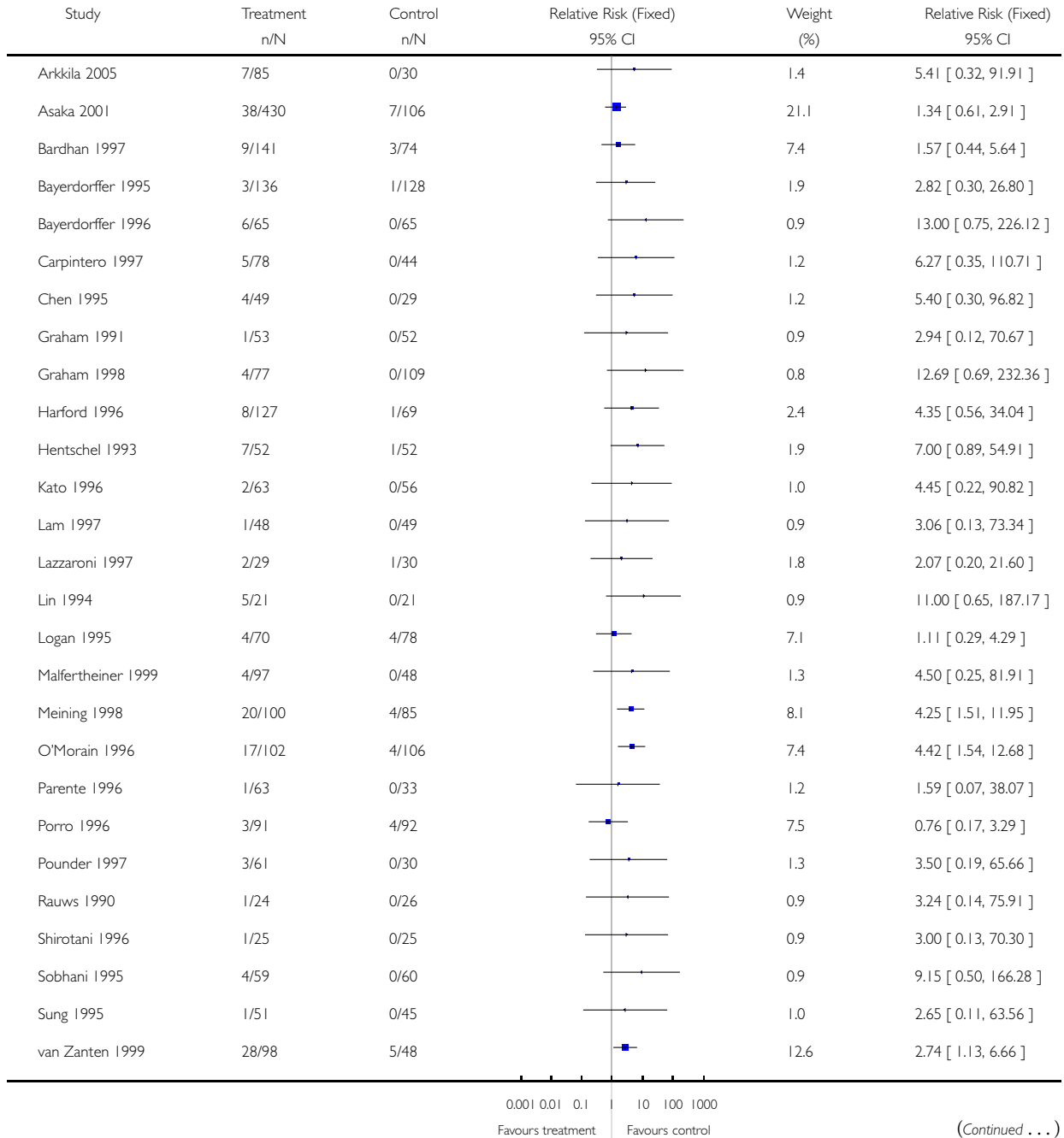


Analysis 11.02. Comparison 11 adverse events, Outcome 02 Diarrhoea, proportion occurred

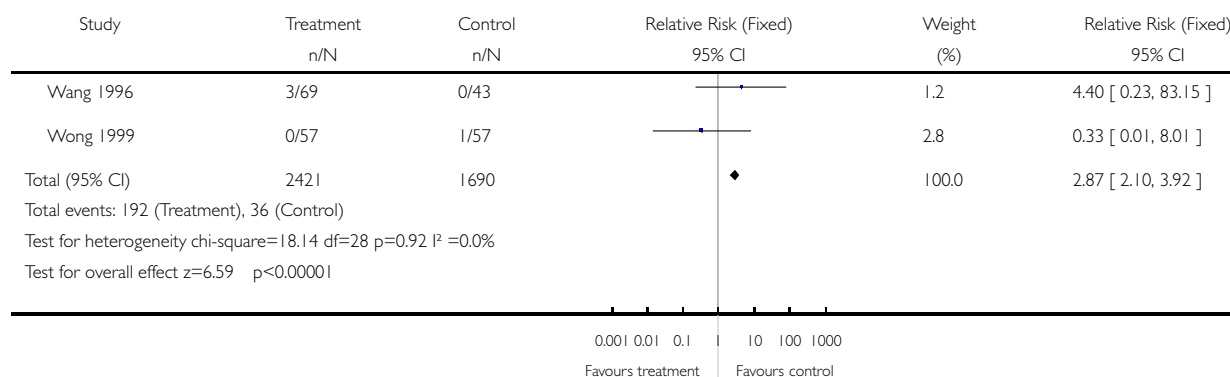
Review: Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients

Comparison: 11 adverse events

Outcome: 02 Diarrhoea, proportion occurred



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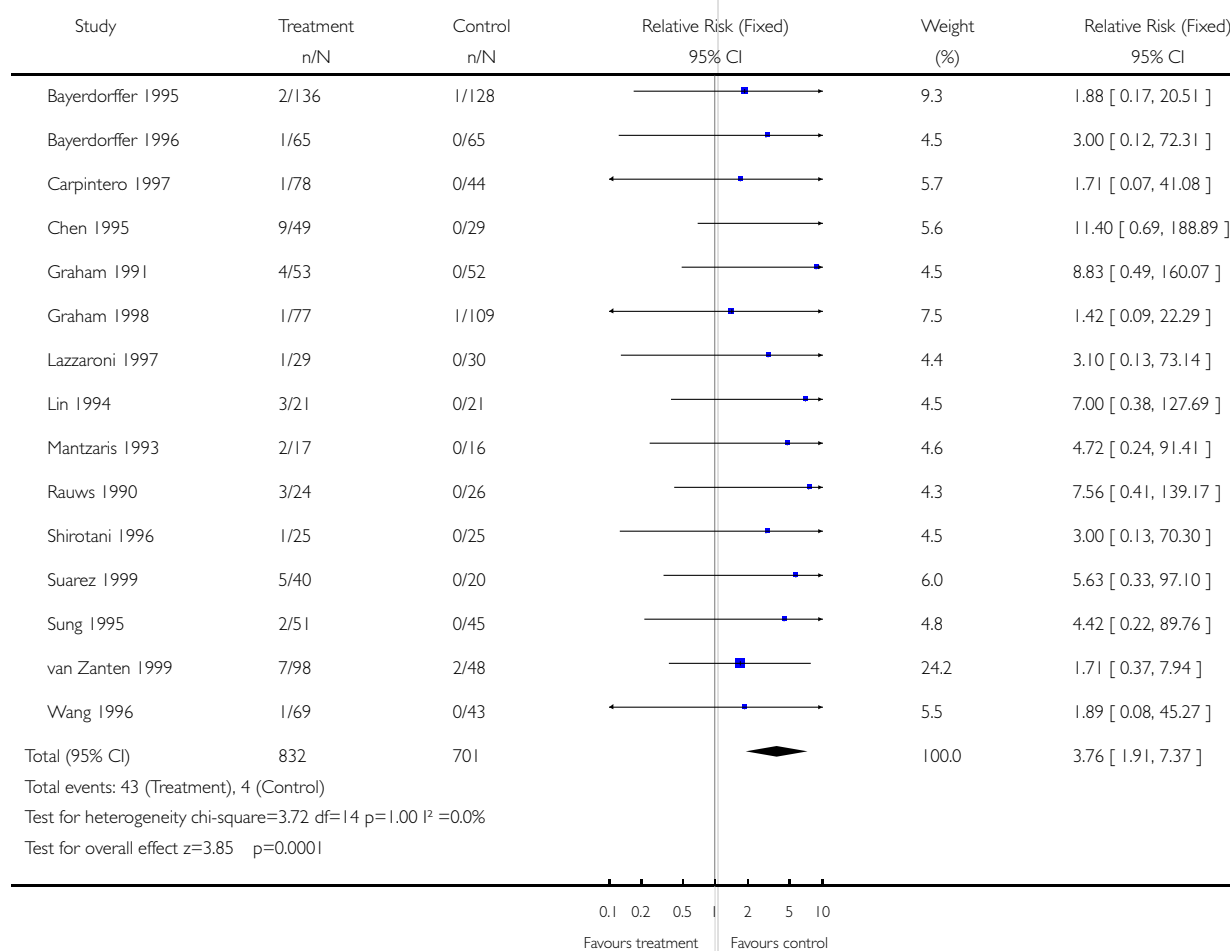


Analysis 11.03. Comparison 11 adverse events, Outcome 03 Nausea/vomiting, proportion occurred

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

Comparison: 11 adverse events

Outcome: 03 Nausea/vomiting, proportion occurred

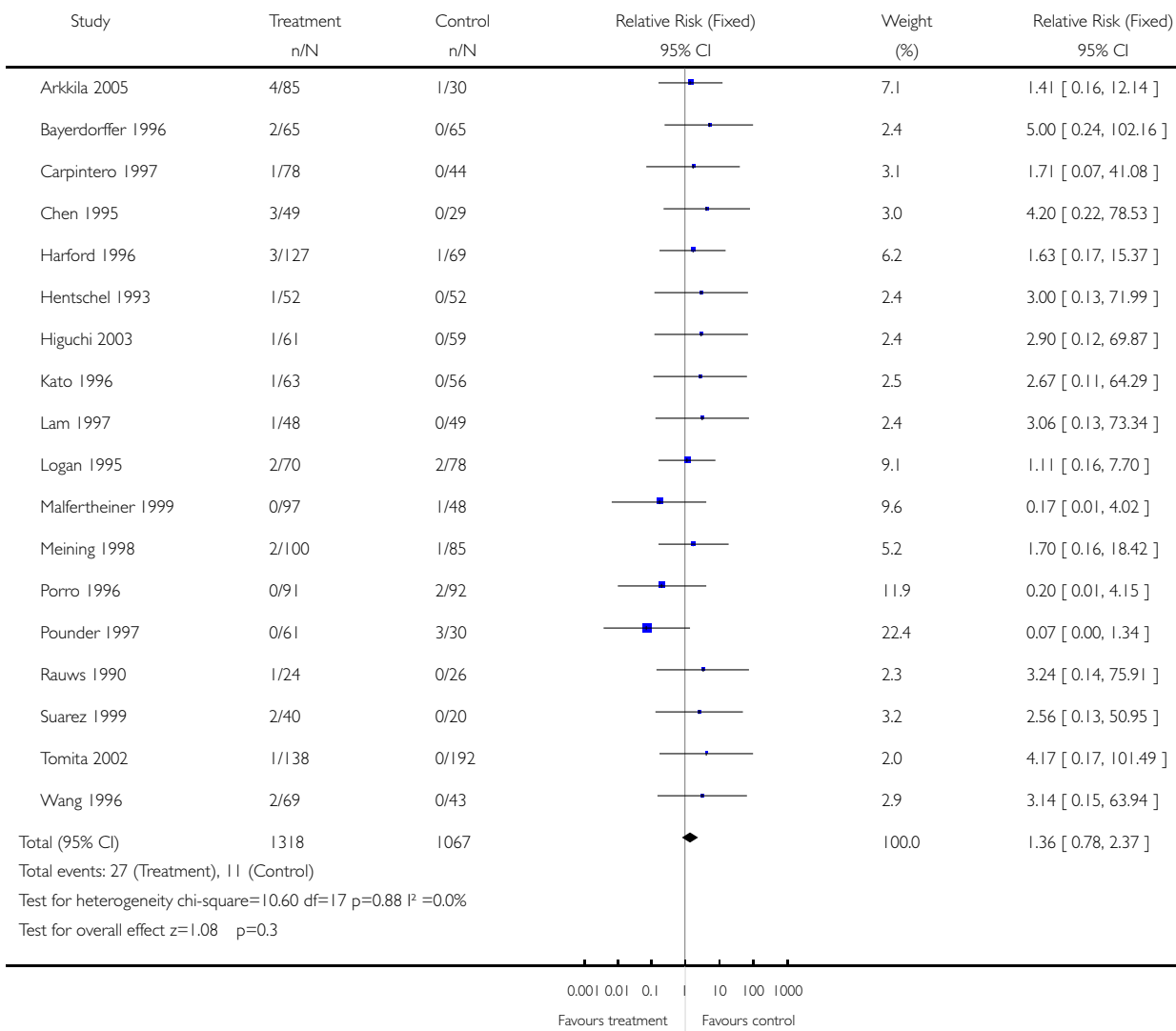


Analysis 11.04. Comparison 11 adverse events, Outcome 04 Skin rash, proportion occurred

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

Comparison: 11 adverse events

Outcome: 04 Skin rash, proportion occurred

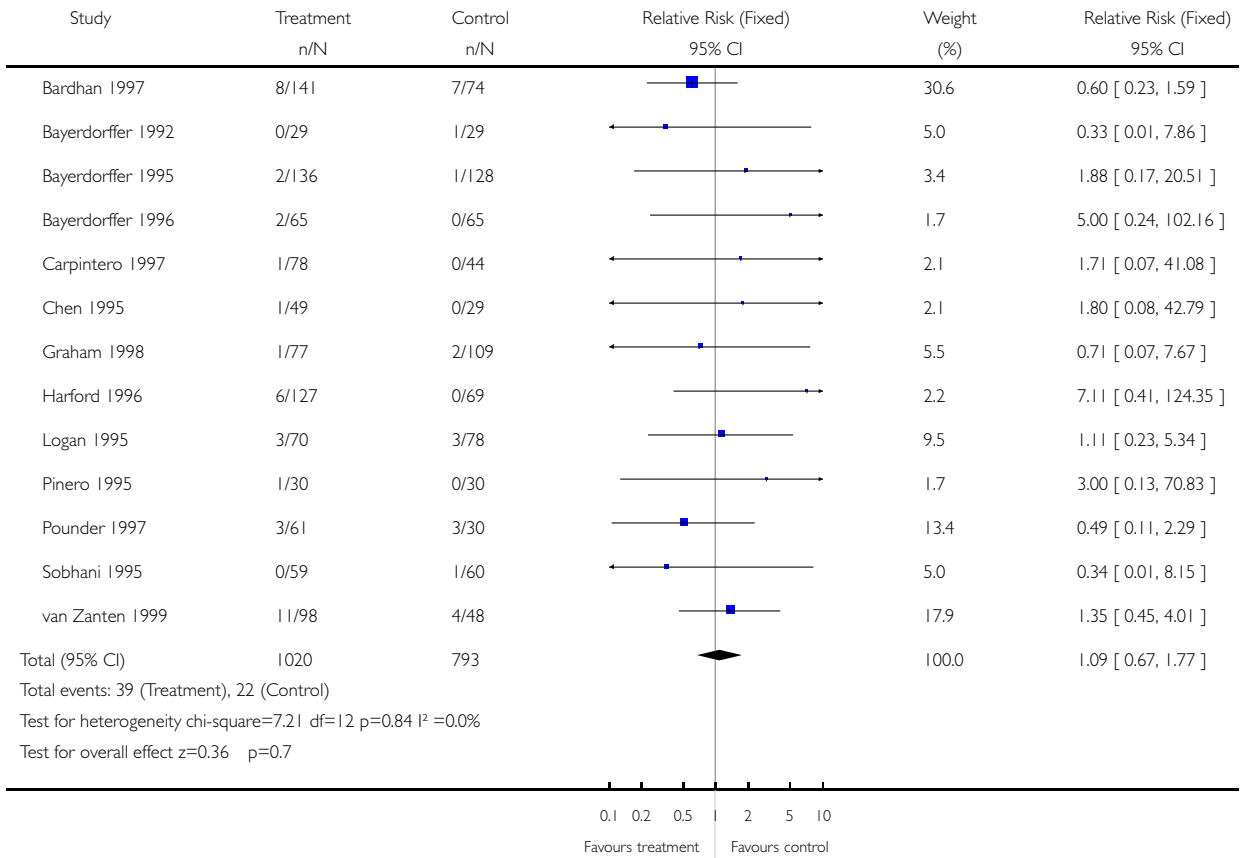


Analysis 11.05. Comparison 11 adverse events, Outcome 05 Headache, proportion occurred

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

Comparison: 11 adverse events

Outcome: 05 Headache, proportion occurred

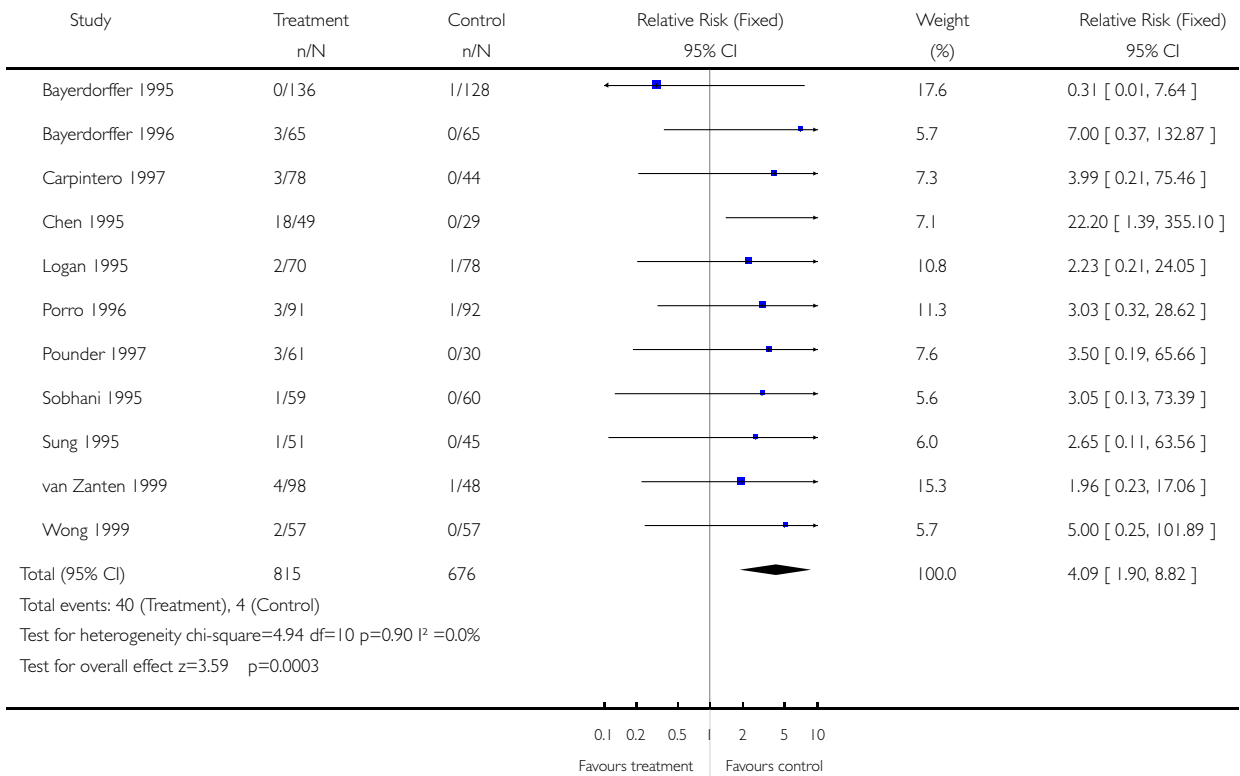


Analysis 11.06. Comparison 11 adverse events, Outcome 06 Epigastric pain, proportion occurred

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

Comparison: 11 adverse events

Outcome: 06 Epigastric pain, proportion occurred

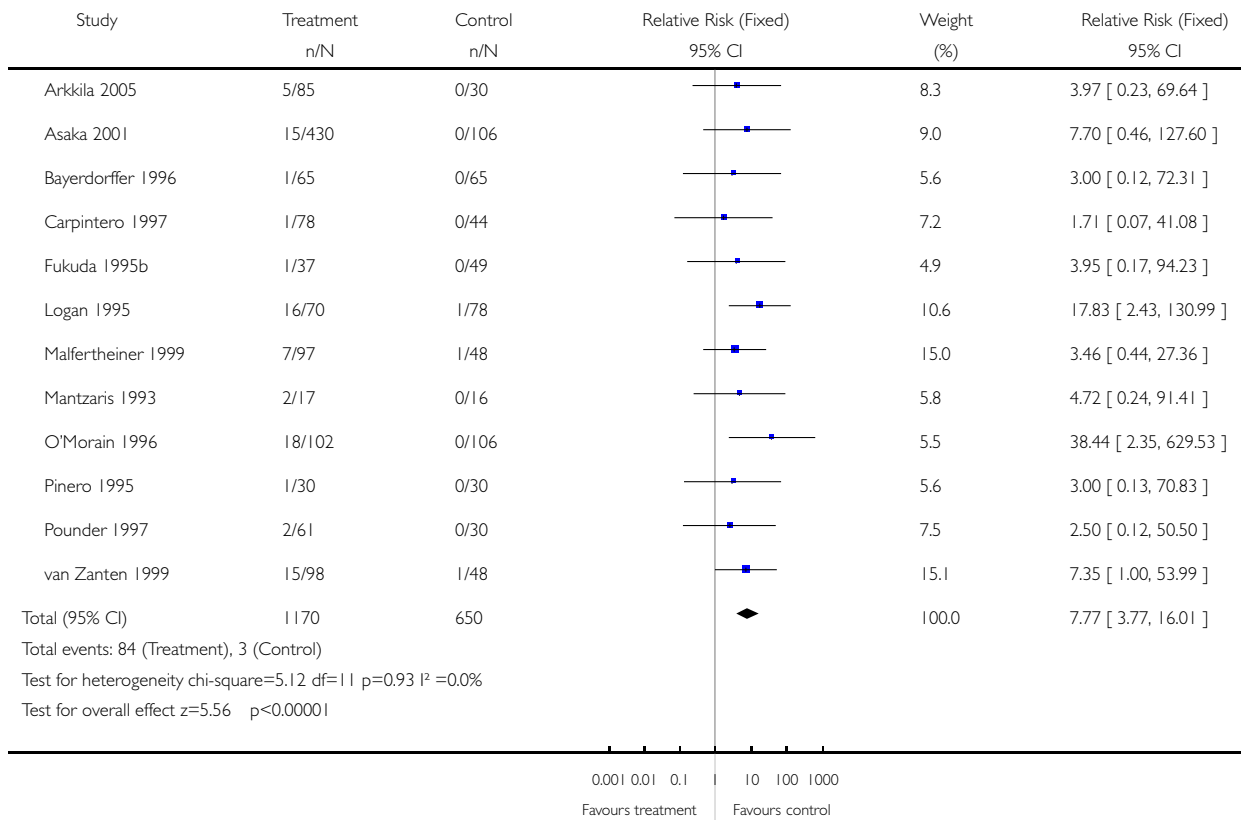


Analysis 11.07. Comparison 11 adverse events, Outcome 07 Altered taste, proportion occurred

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

Comparison: 11 adverse events

Outcome: 07 Altered taste, proportion occurred



Analysis 11.08. Comparison 11 adverse events, Outcome 08 Stomatitis, proportion occurred versus not occurred

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

Comparison: 11 adverse events

Outcome: 08 Stomatitis, proportion occurred versus not occurred

