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Eradication Therapy in *Helicobacter pylori* Positive Peptic Ulcer Disease: Systematic Review and Economic Analysis

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BACKGROUND AND AIM: We conducted a systematic review and economic analysis to ascertain the efficacy of eradication therapy in the treatment of *H. pylori* positive peptic ulcer disease.

METHODS: Comprehensive search of electronic databases, bibliographies of retrieved articles, contact with pharmaceutical companies, and experts in the field to identify published and unpublished literature from 1966 to the present. The data were incorporated into a Monte Carlo simulation Markov model that incorporated all the uncertainty in the estimates to evaluate cost-effectiveness.

RESULTS: Fifty-two trials were included in the final metaanalysis. In duodenal ulcer healing, *H. pylori* eradication therapy was superior to ulcer healing drug (relative risk (RR) of ulcer persisting = 0.66; 95% confidence interval (CI) = 0.58 to 0.76) and no treatment (RR = 0.37; 95% CI 0.26 to 0.53). In gastric ulcer healing, *H. pylori* eradication therapy was not statistically superior to ulcer healing drug (RR = 1.32; 95% CI = 0.92 to 1.90). In preventing duodenal ulcer recurrence, *H. pylori* eradication therapy was not statistically superior to maintenance therapy with ulcer healing drug (RR of ulcer recurring = 0.73; 95% CI = 0.42 to 1.25), but was superior to no treatment (RR = 0.19; 95% CI = 0.15 to 0.26). In preventing gastric ulcer recurrence, *H. pylori* eradication was superior to no treatment (RR = 0.31; 95% CI 0.19 to 0.48). The Markov model suggested *H. pylori* eradication is cost-effective for duodenal ulcer over 1 year and gastric ulcer over 2 years with over 95% confidence despite the uncertainty in the data.

CONCLUSIONS: *H. pylori* eradication therapy reduces the recurrence of peptic ulcer disease and is cost-effective.

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INTRODUCTION

The discovery of *Helicobacter pylori* and its causal role in peptic ulcer disease is one of the major medical advances of the 20th century. It has caused a paradigm shift in our treatment of peptic ulcer disease. Narrative reviews have suggested that the yearly relapse rate of 80% for duodenal ulcer and 60% for gastric ulcer can be reduced to less than 5% after successful *H. pylori* eradication. This is more effective than antisecretory drugs alone (1) and numerous health economic models suggest *H. pylori* eradication is the most cost-effective option for peptic ulcer disease (2). These data have resulted in most international guidelines advocating the use of *H. pylori* eradication therapy in peptic ulcer disease (3). It is surprising, therefore, that there has been a paucity of systematic review data to assess the effectiveness of this therapy both in terms of ulcer healing and recurrence, and symptom relief. Furthermore, there has been no systematic assessment of the incidence of adverse events from eradication therapy for peptic ulcer disease.

Systematic collection of randomized controlled trial data on the impact of *H. pylori* eradication in duodenal and gastric ulcer are required so that these can be incorporated in a health economic model. There will still be uncertainty in the costs and effects of alternative strategies of managing peptic ulcer disease. These have traditionally been evaluated by sensitivity analyses but this approach assumes that all values in the range assessed are equally possible, which is not statistically correct. Sensitivity analyses can only assess the uncertainty in a few variables at a time whereas an approach that incorporates all the uncertainty in the model is preferable. Techniques have been developed which fulfill these criteria (4) but these have not been applied to the assessment of peptic ulcer disease management.

We have, therefore, conducted a systematic literature review of the efficacy of eradication therapy in *H. pylori* positive peptic ulcer disease with support from the Upper Gastrointestinal and Pancreatic Diseases Review Group of the Cochrane Collaboration. We have also constructed a health economic model using the data from the review to establish

the most cost-effective strategy for managing peptic ulcer disease to inform future guidelines.

MATERIALS AND METHODS

Systematic Review

SEARCH STRATEGY. Trials were identified from the Cochrane Controlled Trials Register, Medline, Embase, and CINAHL (search strategy available on request) electronic databases until December 2002. No language restrictions were applied. A recursive search of the retrieved articles' bibliographies was performed, and abstract books and conference proceedings between 1994 and 2002 were handsearched. Pharmaceutical companies were contacted and asked to supply details of any outstanding clinical trials and relevant unpublished materials, and experts in the field were contacted for information on unpublished studies.

ELIGIBILITY AND DATA EXTRACTION. Randomized controlled trials evaluating adults with peptic ulcer disease diagnosed at endoscopy or at barium meal that fulfilled predefined eligibility criteria (box) were included. A second reviewer, blinded to the initial assessment also evaluated all full articles for eligibility. Where disagreements arose, a third reviewer adjudicated and a consensus view was taken.

Data were recorded onto specially developed standard forms and was extracted as intention to treat analysis by the lead reviewer. There was an unblinded check on this by a second reviewer. The setting, country of origin, site of ulcer, type of eradication regimen and dose of drugs, ulcer healing and recurrence rates, adverse events, and eradication rates were recorded. In addition, the methodological quality of trials was assessed by adequacy of allocation of concealment (scored as "adequate," "uncertain," or "clearly inadequate").

OUTCOME ASSESSMENT. The principal outcomes studied were the proportion of peptic ulcers healed, the proportion of peptic ulcer patients remaining free from relapse, the proportion of patients achieving complete relief of symptoms and improvement in quality of life, and the incidence of adverse effects associated with the different treatments.

DATA ANALYSIS. All data were recorded as dichotomous outcomes (healed/not healed or symptom presents/absent) and the impacts of different interventions were expressed as a relative risk (RR) with a 95% confidence interval (CI). The number needed to treat (NNT) and its 95% confidence interval was calculated as the reciprocal of the risk difference from the metaanalysis. The data for gastric and duodenal ulcer healing and recurrence were analyzed separately wherever trial reporting allowed this. Comparison regimens were also analyzed separately. Where significant heterogeneity between trial results was detected a random effects model was used, and meta-regression was performed to explore the reasons for the heterogeneity. All analyses were performed using the metan and metareg commands in Stata version 8.0 (Stata Corporation, Texas, USA).

The review was undertaken according to a protocol published in the Cochrane library and will be regularly updated as a Cochrane review as more information becomes available (5). Regimens that do not achieve optimum eradication rates were included in the review to ensure all data on the effect of *H. pylori* eradication were evaluated. Currently, PPI triple therapy and bismuth salt quadruple therapy are the recommended strategies. We conducted a *post hoc* subgroup analysis evaluating only these therapies in preventing DU relapse compared with no treatment. The result of this subgroup analysis was compared with the main analysis that included all regimens to evaluate the efficacy of optimum therapy.

Health Economic Model

Estimates from the systematic review were incorporated into a Markov model (Data Professional release 9, TreeAge, Williamstown, MA, USA) to establish the cost effectiveness of *H. pylori* eradication therapy in duodenal and gastric ulcer disease.

STRATEGIES COMPARED IN THE MODEL. The model compared four strategies in both duodenal (DU) and gastric ulcer (GU) patients. A theoretical "do nothing" strategy where patients were seen but offered no treatment despite remaining symptomatic, an intermittent one month course of proton pump inhibitor (PPI) therapy if the ulcer relapsed to a maximum of two courses, maintenance PPI therapy with a doubling of the dose for 1 month if the ulcer relapsed, or a 1-month course of PPI therapy and *H. pylori* eradication with a further month of PPI therapy if the ulcer relapsed. The "do nothing" strategy does not reflect clinical practice but was evaluated so that the relative risks from the metaanalysis of randomized trials could be correctly included in the model. All strategies were evaluated over 1 year, as this was the time frame over which reliable data were available. As *H. pylori* eradication is expected to have long-term benefits the data were extrapolated over further years if necessary.

COSTS AND OUTCOMES IDENTIFIED IN THE MODEL. The model evaluated the impact of *H. pylori* eradication from a U.S. third party payer perspective incorporating the costs of medication and visits to the gastroenterologist as given in published sources (Tables 1 and 2). The effectiveness of therapy was measured as the number of months of minimal or no dyspeptic symptoms during the year. Healing rates with PPI therapy and relapse rates with maintenance therapy or no treatment for both DU and GU were obtained from the systematic review. The relative risk of these events after *H. pylori* eradication in DU and GU patients was also obtained from the review, as were adverse events with both therapies. We assumed that all patients would be reviewed by a gastroenterologist after 1 month and if patients remained symptomatic despite treatment they would see a gastroenterologist up to a maximum of three times per year. We assumed that

Table 1. The Value of Variables that Have Uncertainty Included in the Models Evaluating Different Strategies of Managing *H. pylori* Positive Gastric and Duodenal Ulcer Patients

Variable	Value	Uncertainty	Distribution
Healing rate of DU with H_2RA	85%*	95% CI = 81 to 88%*	Beta
Healing rate of GU with H_2RA	89%*	95% CI = 84 to 93%*	Beta
Annual relapse rate of DU on no treatment	64%*	95% CI = 57 to 70%*	Beta
Annual relapse rate of GU on no treatment	57%*	95% CI = 34 to 57%*	Beta
Relative risk of DU persisting after *H. pylori* eradication + H_2RA	0.66*	95% CI = 0.58 to 0.76*	Log normal
Relative risk of DU relapse after *H. pylori* eradication	0.20*	95% CI = 0.15 to 0.26*	Log normal
Relative risk of GU relapse after *H. pylori* eradication	0.28*	95% CI = 0.18 to 0.43*	Log normal
Relative risk of DU and GU relapse with maintenance H_2RA *versus H. pylori* eradication	1.37*	95% CI = 0.8 to 2.37*	Log normal
Relative risk of adverse event with *H. pylori* eradication	2.28*	95% CI = 1.72 to 3.02*	Log normal
Cost per patient of managing (69) adverse event	$115	SD = $115**	Gamma
Proportion symptomatic despite peptic ulcer healing (70–76)	33%†	95% CI = 25% to 43%	Beta

*Data from present systematic review.
**Conservative estimate based on mean value given in reference (69).
†From a review of observational studies (68–73).

33% patients with healed ulcers would remain symptomatic and 50% of these would respond to maintenance PPI therapy. Patients on maintenance PPI therapy would have a general office visit every 6 months. The remaining patients would only be symptomatic with an ulcer recurrence and all recurrences were symptomatic. Duodenal ulcer patients did not receive any more endoscopies but gastric ulcer patients all had an endoscopy after 1 month to check healing and had up to three endoscopies if the ulcer did not heal or recurred. Costs and benefits were not discounted as the strategies were compared over a 1-year time frame.

DATA ANALYSIS. The main areas of uncertainty in the model are outlined in Table 1. The dispersion of the data is given by the 95% confidence intervals or standard deviation and a distribution is assigned to each of these variables. A beta distribution was assigned to proportions, a lognormal distribution to relative risks, and a gamma distribution to cost data (Table 1). Certain variables such as costs of drugs are not uncertain for an individual patient but do vary among health maintenance organizations. These variables were tested across a plausible range in traditional sensitivity analyses (Table 2). A probabilistic analysis was then conducted using Monte Carlo simulation of 1,000 and the results were expressed as cost-effectiveness acceptability curves (Data Professional version 9). These plot the probability of a given strategy being cost-effective according to the maximum willingness to pay to have an extra 1 month free from dyspepsia with the do-nothing strategy as baseline.

RESULTS

Systematic Review

Figure 1 summarizes the results of the initial search strategy and the trials that were excluded with relevant reasons. Of the 52 trials included in the final metaanalysis some reported more than one outcome and were included in more than one analysis as detailed (6–57). The characteristics of included trials are given in Table 2. Two trials did not report gastric and duodenal ulcer separately and are, therefore, not included in some of the results reported below (50, 56).

METHODOLOGICAL QUALITY OF INCLUDED STUDIES. According to the system for grading reporting of generation of randomization schedule and method of concealment, only eleven studies reported a truly random allocation and eight an adequate concealment of allocation.

H. PYLORI ERADICATION THERAPY PLUS ULCER-HEALING (UHD) DRUG *VERSUS* UHD ALONE IN DUODENAL ULCER HEALING. Thirty-four trials (6, 7, 9–11, 13, 15, 18, 19, 21–23, 25–28, 32, 33, 35, 38–49, 54–55, 57) reported duodenal ulcer healing rates in a total of 3,910 patients (see Fig. 2). There was an overall healing rate of 83% in the *H. pylori* eradication therapy group, compared to 81% in the UHD group. There was no significant heterogeneity between trial results. The RR of the ulcer persisting after *H. pylori* eradication was 0.66 (95% CI = 0.58 to 0.76), and the NNT was 14 (95% CI = 11 to 20).

Table 2. The Value of Variables with no Uncertainty Assigned Included in the Models Evaluating Different Strategies of Managing *H. pylori* Positive Gastric and Duodenal Ulcer Patients

Variable	Value	Range for Sensitivity Analysis
Cost of 10 day course of *H. pylori* eradication therapy (69)	$220	$20–600
Cost of one month PPI therapy (77) (generic omeprazole 20 mg od)	$22.49	$18–90
Cost of gastroenterology office visit (69)	$232	$50–250
Cost of general medicine office visit (69)	$99	$10–150
Cost of endoscopy (69)	$500	$100–1,000
Healing rate of GU and DU with no treatment (21)	25%	None
Proportion of patients with adverse events on H_2RA*	8%	None

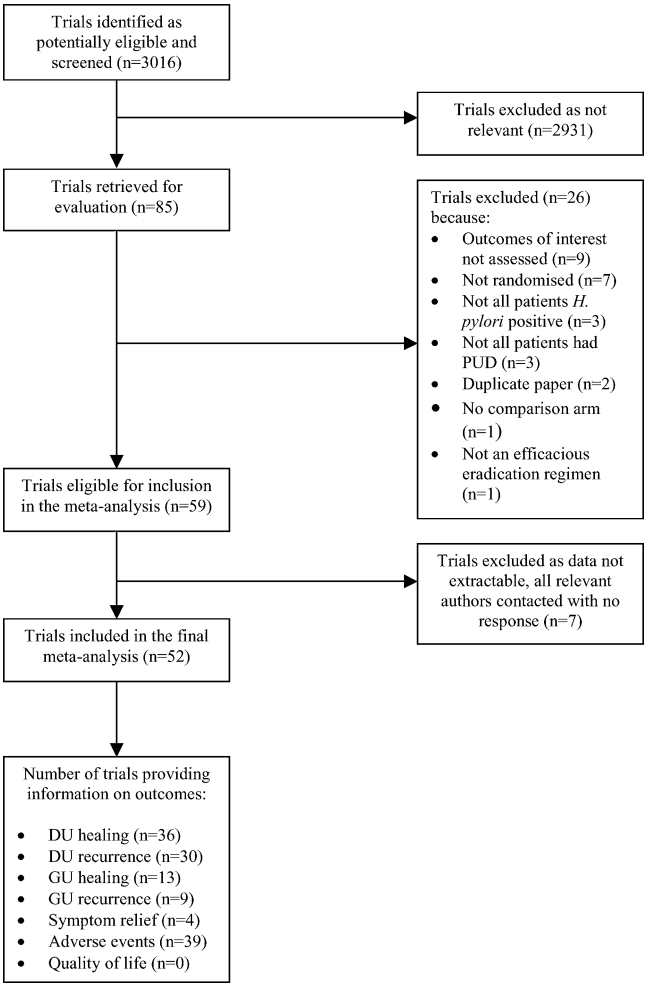

Figure 1. Flow diagram of assessment of identified studies.

H. PYLORI ERADICATION THERAPY *VERSUS* NO TREATMENT IN DUODENAL ULCER HEALING. Two trials (21, 30) reported duodenal ulcer healing rates in a total of 207 patients. The overall healing rate was 76% with eradication therapy compared to 41.5% with no treatment. There was no significant heterogeneity between trial results, and the RR of the ulcer persisting after *H. pylori* eradication was 0.37 (95% CI interval = 0.26 to 0.53). The NNT was 2.5 (95% CI = 2 to 4).

H. PYLORI ERADICATION THERAPY PLUS UHD *VERSUS* UHD ALONE IN GASTRIC ULCER HEALING. Thirteen trials (6, 8, 12, 16–18, 24, 26, 27, 31, 34, 36, 52) reported gastric ulcer healing in 1,469 patients (Fig. 3). The overall healing rate was 78% with eradication compared to 86.5% with UHD alone. There was statistically significant heterogeneity between the trial results (heterogeneity test [12 degrees of freedom] $\chi^2 = 20.78$, $p = 0.054$) and a random effects model was used. The RR of ulcer persisting after eradication therapy was 1.32 (95% CI = 0.92 to 1.90). The Egger test suggested there was a trend for funnel plot asymmetry but this did not reach statistical significance ($p = 0.07$). Meta-regression suggested that multicenter studies (log RR = 1.16; 95% CI = 0.56 to 1.75. $p < 0.001$) and absence of blinding (logRR = 2.17; 95% CI = 0.82 to 3.52. $p = 0.002$) increased the effect size whereas increasing completeness of follow-up (logRR = −2.49; 95% CI = −0.03 to −4.95. $p = 0.048$) reduced the effect size.

H. PYLORI ERADICATION THERAPY *VERSUS* MAINTENANCE THERAPY WITH UHD IN PREVENTING DUODENAL ULCER RECURRENCE (FOLLOWING INITIAL ULCER HEALING). Four trials (28, 38, 48, 57) reported duodenal ulcer recurrence in 319 patients. The overall recurrence rate was 12% in the group who received *H. pylori* eradication *versus* 16% in those receiving long-term UHD. There was no significant heterogeneity between trial results, and the RR of ulcer recurring after eradication therapy was 0.73 (95% CI = 0.42 to 1.25).

H. PYLORI ERADICATION *VERSUS* NO TREATMENT IN PREVENTING DUODENAL ULCER RECURRENCE (FOLLOWING INITIAL ULCER HEALING). Twenty-six trials (7, 9, 11,13–15, 20, 23, 26, 29, 32, 33, 35, 37, 39, 41, 43–47, 49, 51, 53, 54, 55) reported on 2,434 patients (Fig. 4). The range of *H. pylori* eradication rates achieved was 42–100% with an average of 72%. In those who received eradication therapy the recurrence rate was 14% compared to 64% in those who received no treatment. There was statistically significant heterogeneity between trial results (heterogeneity test (25 degrees of freedom) χ^2 squared = 84.98, $p < 0.00001$) and a random effects model was used. The RR of ulcer recurrence after eradication therapy was 0.19 (95% CI = 0.15 to 0.26), and the NNT was 2 (95% CI = 1.7 to 2.3).

Egger test revealed funnel plot asymmetry ($p = 0.042$) with a preponderance of trials with few events showing large effects when sample size was used as a measure of study size, suggesting publication bias. Metaregression revealed that the relative risk of recurrence reduced with increasing eradication rate (logRR = −1.80; 95% CI = −0.81 to −2.79. $p < 0.001$) and duration of eradication therapy (logRR = −0.39; 95% CI = −0.27 to −0.51. $p < 0.001$) and increased with increasing length of follow-up (logRR = 0.006; 95% CI = 0.001 to 0.011. $p = 0.02$) and when an intention to treat analysis was performed by the authors (logRR = 0.32; 95% CI = 0.11 to 0.54. $p = 0.003$).

There were five trials (15, 29, 43, 51, 54) that used PPI triple therapy or bismuth salt quadruple therapy evaluating 531 patients. The range of eradication rates achieved was 78–90% with an average of 83%. The recurrence rate was 8% in the eradication therapy group compared to 65% in the control group. The RR for recurrence of a DU after eradication therapy was 0.14 (95% CI = 0.09 to 0.20) in this subgroup.

H. PYLORI ERADICATION THERAPY *VERSUS* NO TREATMENT IN PREVENTING GASTRIC ULCER RECURRENCE (FOLLOWING INITIAL ULCER HEALING). Nine trials (8, 12, 17, 20, 26, 31, 34, 36, 52) were

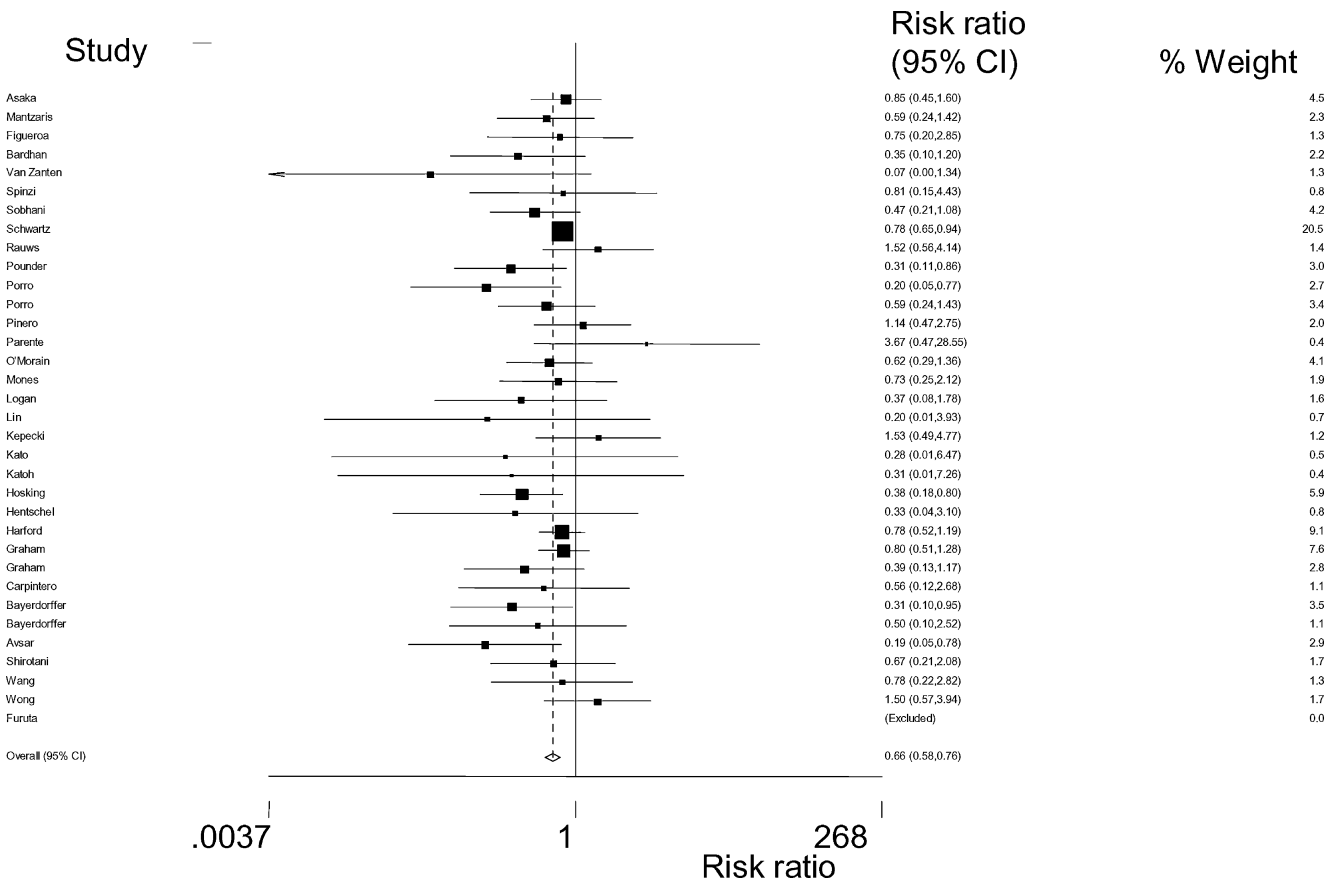

Figure 2. *H. pylori* eradication therapy plus ulcer-healing drug *versus* ulcer-healing drug alone in the healing of duodenal ulcer.

identified containing 774 patients (Fig. 5). The overall recurrence rate was 12% in the eradication group *versus* 40% in the no-treatment group. Again there was significant heterogeneity between trial results heterogeneity test (8 degrees of freedom) χ^2 squared = 15.61, $p = 0.048$) and a random effects model was used. The RR of gastric ulcer recurrence after eradication therapy was 0.31 (95% CI = 0.19 to 0.48), and the NNT was 3 (95% CI = 2.3 to 5). There was no

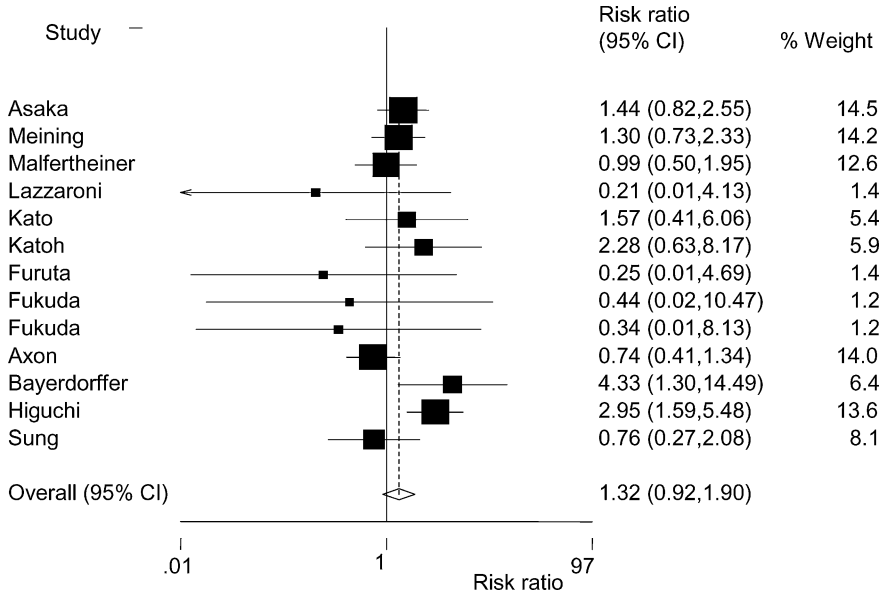

Figure 3. *H. pylori* eradication therapy plus ulcer-healing drug *versus* ulcer-healing drug alone in the healing of gastric ulcer.

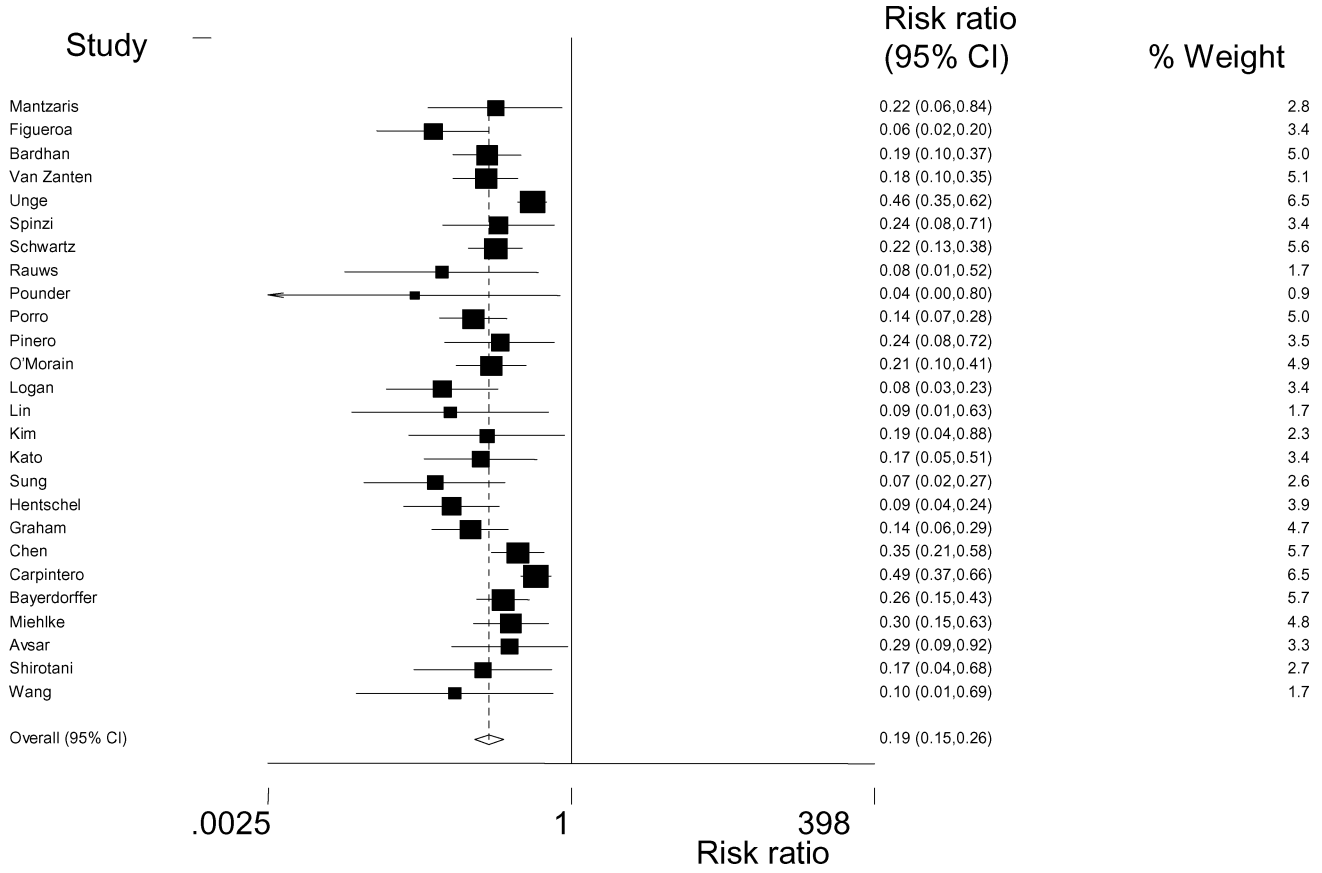

Figure 4. *H. pylori* eradication therapy *versus* no treatment in preventing the recurrence of duodenal ulcer (after initial ulcer had been healed).

evidence of publication bias and meta-regression suggested 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 = 0.25 to 0.77. $p < 0.001$)).

H. PYLORI ERADICATION THERAPY *VERSUS* COMPARISON REGIMEN IN THE RELIEF OF SYMPTOMS OF PEPTIC ULCER. Only four trials (24, 30, 44, 50) reported on relief of symptoms in a total of 368 patients, and

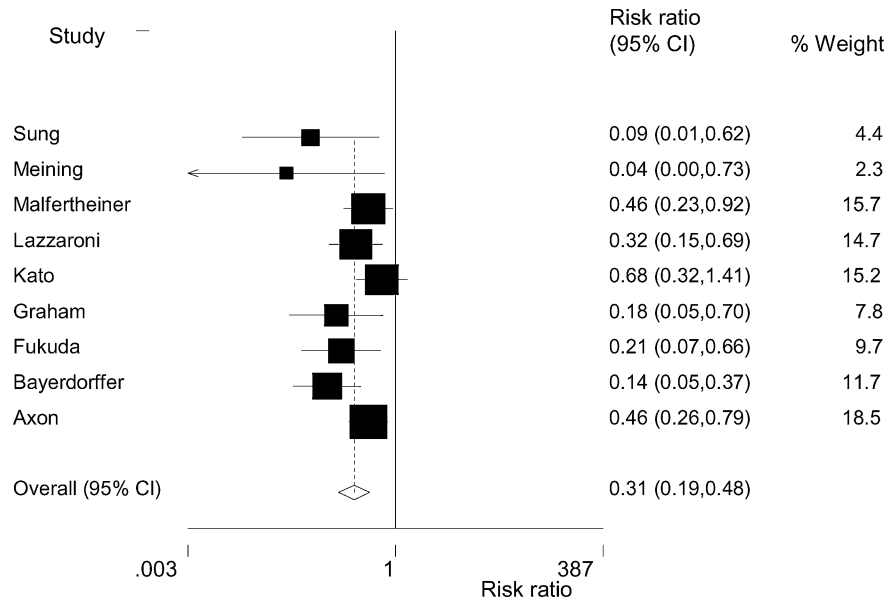

Figure 5. *H. pylori* eradication therapy *versus* no treatment in preventing the recurrence of gastric ulcer (after initial ulcer had been healed).

Table 3. Characteristics of Included Studies

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Asaka 2001	Multicenter RCT	Japan	PPI triple therapy {5 wk (DU)/ 7 wk (GU) lansoprazole 30 mg bd, 1 week amoxicillin 750 mg bd, and clarithromycin 200 mg/400 mg bd} *versus* PPI {5 wk (DU)/7 wk (GU) lansoprazole 30 mg bd}	Ulcer healing	Eradication rates:	B
	Double-blinded	536 patients with gastric or duodenal ulcer		*H. pylori* eradication rates	PPI triple therapy group 76.9%	
					PPI group 1.89%	
Avsar 1996	Single center RCT	Turkey	Bi triple therapy (4 wk colloidal bismuth subcitrate 120 mg qds, 2 wk tetracycline 250 mg qds, and metronidazole 250 mg tds) *versus* PPI (8 wk omeprazole 40 mg od)	Ulcer healing	Eradication rates:	B
	Single-blinded	45 patients with duodenal ulcer		Ulcer recurrence at 1 yr	Bi triple therapy group 78.3%	
				H. pylori eradication rates	PPI group 36.4%	
Axon 1997	Multicenter RCT	UK and Eire	PPI dual therapy (8 wk omeprazole 40 mg od, and 2 wk amoxycillin 750 mg bd) *versus* PPI (8 wk omeprazole 40 mg od)	Ulcer healing	Eradication rates:	B
	Double-blinded	129 patients with gastric ulcer		Ulcer recurrence at 1 yr	PPI dual therapy group 48.3%	
				H. pylori eradication rates	PPI group 4.8%	
Bardhan 1997	Multicenter RCT	Multinational	RBC dual therapy (2 wk RBC 400 mg/800 mg bd, and clarithromycin 250 mg qds, then 2 wk RBC 400 mg bd) *versus* RBC (4 wk RBC 400 mg bd)	Ulcer healing	Eradication rates:	B
	Double-blinded	232 patients with duodenal ulcer		Ulcer recurrence at 28 wk	RBC dual therapy 76.6%	
				H. pylori eradication rates	RBC 1.4%	
Bayerdorffer 1992	Multicenter RCT	Germany	PPI dual therapy (10 days omeprazole 40 mg bd, and amoxycillin 1 g bd, then 4 1/2 wk omeprazole 20 mg od) *versus* PPI (10 days omeprazole 40 mg bd, then 4 1/2 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	B
	Single-blinded	58 patients with duodenal ulcer		*H. pylori* eradication rates	PPI dual therapy 75.9%	
					PPI 0% linked to Miehlke	

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Bayerdorffer 1995	Multicenter RCT	Germany	PPI dual therapy (2 wk omeprazole 40 mg tds, and amoxycillin 750 mg tds, then 4 wk omeprazole 20 mg od) *versus* PPI (2 wk omeprazole 40 mg tds, then 4 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	B
	Double-blinded	264 patients with duodenal ulcer		Ulcer recurrence at 1 yr	PPI dual therapy 88.9%	
				H. pylori eradication rates	PPI 0%	
Bayerdorffer 1996	Multicenter RCT	Germany	Bi triple therapy (8 wk bismuth subsalicylate 600 mg tds, 10 days amoxicillin 500 mg bd, and tinidazole 1 g bd) *versus* PPI (8 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	A
	Single-blinded	130 patients with gastric ulcer		Ulcer recurrence at 18 months	Bi triple therapy 66.1%	
				H. pylori eradication rates	PPI 7.7%	
					If ulcer not healed at 8 wk Bi/PPI continued for a further 4 wk	
Carpintero 1997	Single center RCT	Spain	Bi triple therapy (6 wk colloidal bismuth subcitrate 120 mg qds, 12 days amoxicillin 500 mg tds, and metronidazole 500 mg bd) or H_2RA triple therapy (6 wk ranitidine 300 mg qds, 12 days amoxicillin 500 mg tds, and metronidazole 500 mg bd) *versus* H_2RA (6 wk ranitidine 300 mg qds)	Ulcer healing	Eradication rates:	B
	Unblinded	122 patients with duodenal ulcer		Ulcer recurrence at 18 months	Bi triple therapy 86.8%	
				H. pylori eradication rates	H_2RA triple therapy 25%	
					H_2RA 0%	
Chen 1995	Single center RCT	Taiwan	Bi triple therapy (1 or 2 wk colloidal bismuth subcitrate 120 mg qds, amoxycillin 500 mg tds, and metronidazole 500 mg tds) *versus* no treatment	Ulcer recurrence at 1 yr	Eradication rates:	B
	Single-blinded	62 patients with duodenal ulcer		*H. pylori* eradication rates	Bi triple therapy 93.9%	
					No treatment 0%	
Figueroa 1996	Single center RCT	Chile	Bi quadruple therapy (4 wk omeprazole 20 mg qds, bismuth subsalicylate 524 mg qds, amoxicillin 500 mg tds, and metronidazole 250 mg tds) *versus* PPI (4 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	B

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
	Unblinded	113 patients with duodenal ulcer		Ulcer recurrence at 1 yr	Bi quadruple therapy 82.5%	
				H. pylori eradication rates	PPI 0%	
Fukuda 1995a	Single center RCT	Japan	PPI dual therapy (8 wk lansoprazole 30 mg od, and 2 wk clarithromycin 200 mg tds) *versus* PPI (8 wk omeprazole 20 mg od or lansoprazole 30 mg od)	Ulcer healing	Eradication rates:	B
	Unblinded	65 patients with gastric ulcer		*H. pylori* eradication rates	PPI dual therapy 62.5% PPI 24.2% All patients received 4 wk ranitidine 150 mg od after initial therapy	
Fukuda 1995b	Single center RCT	Japan	PPI dual therapy (8 wk lansoprazole 30 mg qds, and 2 wk clarithromycin 200 mg tds/amoxicillin 500 mg tds) *versus* PPI (8 wk omeprazole 20 mg qds or lansoprazole 30 mg qds)	Ulcer healing	Eradication rates:	B
	Single-blinded	86 patients with gastric ulcer		Ulcer recurrence at 40 wk *H. pylori* eradication rates	PPI dual therapy 48.6% PPI 12.2% All patients received 4 wk ranitidine 150 mg od after initial therapy	
Furuta 1995	Single center RCT	Japan	PPI dual therapy (6 wk lansoprazole 30 mg qds, and 2 wk amoxicillin 1–2 g qds) *versus* PPI (6 wk lansoprazole 30 mg qds)	Ulcer healing	Eradication rates:	B
	Unblinded	67 patients with gastric or duodenal ulcer		*H. pylori* eradication rates	PPI dual therapy 62.5% PPI 0%	
Graham 1991	Single center RCT	USA	Bi triple therapy (2 wk bismuth subsalicylate 300 mg qds/ 150 mg tds + 300 mg nocte, tetracycline 500 mg qds, and metronidazole 250 mg tds) *versus* H_2RA (16 wk ranitidine 300 mg od)	Ulcer healing	Eradication rates:	B
	Single-blinded	105 patients with duodenal ulcer		*H. pylori* eradication rates	Bi triple therapy 82.7% H_2RA 0% All patients received 16 wk H_2RA	

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Graham 1992	Single center RCT	USA	Bi triple therapy (2 wk bismuth subsalicylate 300 mg qds/150 mg tds + 300 mg nocte, tetracycline 500 mg qds, and metronidazole 250 mg tds) *versus* H_2RA (16 wk ranitidine 300 mg od)	Ulcer recurrence at 1 yr	Eradication rates:	B
	Single-blinded	109 patients with gastric or duodenal ulcer		*H. pylori* eradication rates	Bi triple therapy 88.7%	
					H_2RA 0%	
					All patients received 16 wk H_2RA	
Graham 1998	Multicenter RCT	USA and Puerto Rico	RBC dual therapy (4 wk RBC 400 mg bd, 2 wk amoxicillin 500 mg qds) *versus* Bi (4 wk RBC 400 mg bd) and placebo	Ulcer healing	Eradication rates:	B
	Double-blinded	153 patients with duodenal ulcer		Ulcer recurrence at 6 months	RBC dual therapy 40%	
				H. pylori eradication rates	RBC 0%	
					Placebo 0%	
Harford 1996	Multicenter RCT	USA	PPI dual therapy (2 wk lansoprazole 30 mg bd/tds, and amoxicillin 1 g tds) *versus* PPI (2 wk lansoprazole 30 mg tds)	Ulcer healing	Eradication rates:	B
	Double-blinded	196 patients with duodenal ulcer		*H. pylori* eradication rates	PPI dual therapy 55.1%	
					PPI 0%	
Hentschel 1993	Two center RCT	Austria	H_2RA triple therapy (6 wk ranitidine 300 mg od, 12 days amoxicillin 750 mg tds, and metronidazole 500 mg tds) *versus* H_2RA (6 wk ranitidine 300 mg od)	Ulcer healing	Eradication rates:	B
	Double-blinded	104 patients with duodenal ulcer		Ulcer recurrence at 1 yr	H_2RA triple therapy 88.5%	
				H. pylori eradication rates	H_2RA 1.9%	
					If ulcer not healed at 6 wk ranitidine continued for a further 4 wk	
Higuchi 2003	Two center RCT	Japan	PPI triple therapy (1 week lansoprazole 30 mg od or rabeprazole 20 mg od, plus amoxicillin 1.5 g od, and clarithromycin 800 mg od) *versus* PPI (lansoprazole 30 mg od or rabeprazole 20 mg od)	Ulcer healing	Eradication rates:	A

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
	Single-blinded	120 patients with gastric ulcer		Global symptoms cured	PPI triple therapy 83.6%	
				H. pylori eradication rates	PPI 0%	
Hosking 1992	Single center RCT	Hong Kong	Bi quadruple therapy (4 wk omeprazole 40 mg qds, 1 week colloidal bismuth subcitrate 120 mg qds, tetracycline 500 mg qds, and metronidazole 400 mg qds) *versus* PPI (4 wk omeprazole 40 mg qds)	Ulcer healing	Eradication rates:	A
	Single-blinded	155 patients with duodenal ulcer		*H. pylori* eradication rates	Bi quadruple therapy 89.7%	
					PPI 3.9%	
					Linked to Sung 1994	
Kato 1996	Single center RCT	Japan	PPI dual therapy {6 wk (DU)/8 wk (GU) lansoprazole 30 mg od, and 2 wk amoxycillin 500 mg qds} *versus* PPI {6 wk (DU)/8 wk (GU) lansoprazole 30 mg od}	Ulcer healing	Eradication rates:	B
	Unblinded	119 patients with gastric or duodenal ulcer		Ulcer recurrence at 1 yr	PPI dual therapy 36.5%	
				H. pylori eradication rates	PPI 1.8%	
Katoh 1995	Single center RCT	Japan	PPI dual therapy {6 wk (DU)/8 wk (GU) lansoprazole 30 mg od, and 2 wk amoxycillin 500 mg qds} *versus* PPI {6 wk (DU)/8 wk (GU) lansoprazole 30 mg od}	Ulcer healing	Eradication rates:	B
	Unblinded	133 patients with gastric or duodenal ulcer		*H. pylori* eradication rates	PPI dual therapy 38.8%	
					PPI 9.4%	
Kepecki 1999	Single center RCT	Turkey	PPI triple therapy (1 week omeprazole 20 mg bd, amoxycillin 1 g bd, and metronidazole 500 mg tds, then 3 wk omeprazole 20 mg od) *versus* PPI (1 week omeprazole 20 mg bd, then 3 wk 20 mg od)	Ulcer healing	Eradication rates:	B
	Unblinded	73 patients with duodenal ulcer		Ulcer recurrence at 2 yr	PPI triple therapy 82%	
				H. pylori eradication rates	PPI 0%	
					PPI group received long-term famotidine 20 mg od	

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Kim 2002	Single center RCT	South Korea	PPI triple therapy (1 week omeprazole 20 mg bd, amoxicillin 1 g bd, and clarithromycin 500 mg bd) *versus* no treatment	Ulcer recurrence at 30 months	Eradication rates:	B
	Single-blinded	53 patients with duodenal ulcer		*H. pylori* eradication rates	PPI triple therapy 83.3% No treatment 0% Patients not eradicated with triple therapy received Bi quadruple therapy	
Lam 1997	Single center RCT	Hong Kong	Clarithromycin monotherapy (2 wk clarithromycin 250 mg qds) *versus* placebo	Ulcer healing	Eradication rates:	A
	Double-blinded	97 patients with duodenal ulcer		Global symptoms cured *H. pylori* eradication rates	Clarithromycin monotherapy 70.8% Placebo 10.2% Clarithromycin patients also received amoxicillin and metronidazole	
Lazzaroni 1997	Single center RCT	Italy	PPI dual therapy (4 wk omeprazole 20 mg bd, and 2 wk amoxicillin 1 g tds) *versus* PPI (4 wk omeprazole 20 mg bd)	Ulcer healing	Eradication rates:	B
	Double-blinded	59 patients with gastric ulcer		Ulcer recurrence at 1 yr *H. pylori* eradication rates	PPI dual therapy 62.1% PPI 6.7%	
Lin 1994	Single center RCT	Taiwan	Bi triple therapy (4 wk colloidal bismuth subcitrate 120 mg qds, 1 week metronidazole 250 mg qds, and amoxicillin 500 mg qds) *versus* H_2RA (4 wk famotidine 20 mg bd)	Ulcer healing	Eradication rates:	B
	Unblinded	42 patients with duodenal ulcer		Ulcer recurrence at 1 yr *H. pylori* eradication rates	Bi triple therapy 100% H_2RA 4.8%	
Logan 1995	Multicenter RCT	UK	PPI dual therapy (4 wk omeprazole 40 mg od, and 2 wk clarithromycin 500 mg tds) *versus* PPI (4 wk omeprazole 40 mg od)	Ulcer healing	Eradication rates:	B
	Double-blinded	148 patients with duodenal ulcer		Ulcer recurrence at 1 yr *H. pylori* eradication rates	PPI dual therapy 81.4% PPI 1.3%	

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Malfertheiner 1999	Multicenter RCT	Germany, Hungary, and Poland	PPI triple therapy (1 week omeprazole 20 mg bd, amoxycillin 1 g bd, and clarithromycin 500 mg bd or 1 week omeprazole 20 mg bd, metronidazole 400 mg bd, and clarithromycin 250 mg bd) *versus* PPI (1 week omeprazole 20 mg bd)	Ulcer healing	Eradication rates:	B
	Double-blinded	145 patients with gastric ulcer		Ulcer recurrence at 6 months	PPI triple therapy 82.4%	
				H. pylori eradication rates	PPI 4.2%	
					PPI given until ulcer healing in control arm	
Mantzaris 1993	Single center RCT	Greece	Bi triple therapy (8 wk colloidal bismuth subcitrate 120 mg qds, 2 wk tetracycline 500 mg qds, and metronidazole 500 mg tds) *versus* Bi (8 wk colloidal bismuth subcitrate 120 mg qds)	Ulcer healing	Eradication rates:	B
	Single-blinded	33 patients with duodenal ulcer		Ulcer recurrence at 18 months	Bi triple therapy 58.8%	
				H. pylori eradication rates	Bi 6.3%	
Meining 1998	Multicenter RCT	Germany	PPI dual therapy (2 wk omeprazole 40 mg bd, and amoxicillin 750 mg tds, then 2 wk omeprazole 20 mg od) *versus* PPI (2 wk omeprazole 40 mg bd, then 2 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	A
	Double-blinded	185 patients with gastric ulcer		Ulcer recurrence at 3 months	PPI dual therapy 61%	
				H. pylori eradication rates	PPI 5.9%	
Miehlke 1995	Multicenter RCT	Germany	PPI dual therapy (10 days omeprazole 40 mg bd, and amoxycillin 1 g bd, then 4 1/2 wk omeprazole 20 mg od) *versus* PPI (10 days omeprazole 40 mg bd, then 4 1/2 wk omeprazole 20 mg od)	Ulcer recurrence at 2 yr	Linked to Bayerdorffer 1992	B
	Single-blinded	58 patients with duodenal ulcer				
Mones 2001	Multi-center RCT	Spain	PPI triple therapy (1 week omeprazole 20 mg bd, amoxicillin 1 g bd, and clarithromycin 500 mg bd, then 3 wk omeprazole 20 mg od) *versus* PPI (1 week omeprazole 20 mg bd, then 3 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	B

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
	Double-blinded	85 patients with duodenal ulcer		Ulcer recurrence at 1 yr	PPI triple therapy 76.2%	
				H. pylori eradication rates	PPI 0%	
					PPI patients given 1 yr of ranitidine 150 mg od	
O'Morain 1996	Multicenter RCT	Eire, Germany and New Zealand	PPI dual therapy (2 wk omeprazole 40 mg od, and clarithromycin 500 mg tds, then 2 wk omeprazole 20 mg od) *versus* PPI (2 wk omeprazole 40 mg od, then 2 wk 20 mg od)	Ulcer healing	Eradication rates:	B
	Double-blinded	208 patients with duodenal ulcer		Ulcer recurrence at 6 months	PPI dual therapy 62.7%	
				H. pylori eradication rates	PPI 0.9%	
Parente 1996	Single center RCT	Italy	PPI dual therapy (4 wk lansoprazole 30 mg bd, and 2 wk amoxicillin 1 g tds) and Bi quadruple therapy (4 wk lansoprazole 30 mg od, 2 wk bismuth 240 mg bd, amoxicillin 1 g tds, and tinidazole 500 mg bd) *versus* PPI (4 wk lansoprazole 30 mg od)	Ulcer healing	Eradication rates:	B
	Unblinded	96 patients with duodenal ulcer		*H. pylori* eradication rates	PPI dual therapy 51.6%	
					Bi quadruple therapy 81.3%	
					PPI 3%	
Pinero 1995	Single center RCT	Venezuela	Bi triple therapy (2 wk colloidal bismuth subcitrate 120 mg qds, amoxicillin 500 mg tds, and metronidazole 500 mg tds) *versus* PPI (4 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	A
	Unblinded	60 patients with duodenal ulcer		Ulcer recurrence at 3 months	Bi triple therapy 63.3%	
				H. pylori eradication rates	PPI 10%	
Porro 1993	Single center RCT	Italy	PPI triple therapy (4 wk omeprazole 20 mg od, 2 wk metronidazole 250 mg qds, and amoxycillin 1 g tds) *versus* PPI (4 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	B
	Double-blinded	183 patients with duodenal ulcer		Ulcer recurrence at 1 yr	PPI triple therapy 78%	

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
				H. pylori eradication rates	PPI 1.1%	
Porro 1996	Single center RCT	Italy	Bi triple therapy (4 wk colloidal bismuth subcitrate 120 mg qds, 1 week amoxicillin 1 g tds, and tinidazole 500 mg bd) *versus* sucralfate (4 wk 1 g qds)	Ulcer healing	If no ulcer healing patients crossed over to other therapy, therefore unable to extract eradication rates	B
	Unblinded	32 patients with duodenal ulcer		*H. pylori* eradication rates		
Pounder 1997	Multicenter RCT	Multinational	RBC dual therapy (2 wk RBC 400 mg/800 mg bd, and clarithromycin 250 mg qds, then 2 wk RBC 400 mg bd) *versus* RBC (4 wk 400 mg bd)	Ulcer healing	Eradication rates:	B
	Double-blinded	91 patients with duodenal ulcer		Ulcer recurrence at 2 months	RBC dual therapy 57.4%	
				Global symptoms cured	RBC 0%	
				H. pylori eradication rates		
Rauws 1990	Single center RCT	Netherlands	Bi triple therapy (4 wk colloidal bismuth subcitrate 120 mg qds, and amoxicillin 375 mg tds, 10 days metronidazole 500 mg tds) *versus* Bi (4 wk colloidal bismuth subcitrate 120 mg qds)	Ulcer healing	Eradication rates:	B
	Single-blinded	66 patients with duodenal ulcer		Ulcer recurrence at 1 yr	Bi triple therapy 62.5%	
				H. pylori eradication rates	Bi 7.7%	
					All patients received a further 4 wk ranitidine 150 mg od	
Schwartz 1998	Multicenter RCT	USA	PPI dual therapy (2 wk lansoprazole 30 mg bd, and clarithromycin 500 mg bd/tds, or 2 wk lansoprazole 30 mg bd/tds, and amoxicillin 1 g tds) and triple therapy (2 wk lansoprazole 30 mg bd, amoxicillin 1 g bd, and clarithromycin 500 mg bd) *versus* PPI (2 wk lansoprazole 30 mg tds)	Ulcer healing	Eradication rates:	B
	Double-blinded	352 patients with duodenal ulcer		Ulcer recurrence at 6 months	PPI dual therapy 65.5%	

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
				H. pylori eradication rates	PPI triple therapy 93.6% PPI 1.9%	
Shirotani 1996	Single center RCT	Japan	H_2RA triple therapy (6 wk cimetidine 400 mg bd, 2 wk amoxicillin 300 mg tds, and metronidazole 250 mg tds) *versus* H_2RA (6 wk cimetidine 400 mg bd)	Ulcer healing	Eradication rates:	B
	Single-blinded	50 patients with duodenal ulcer		Ulcer recurrence at 6 months	H_2RA triple therapy 56%	
				H. pylori eradication rates	H_2RA 0%	
Sobhani 1995	Multicenter RCT	France	H_2RA triple therapy (6 wk famotidine 40 mg od, 1 week amoxicillin 500 mg qds, and tinidazole 500 mg tds) *versus* H_2RA (6 wk famotidine 40 mg od, then 20 wk 20 mg od)	Ulcer healing	Eradication rates:	B
	Double-blinded	119 patients with duodenal ulcer		Ulcer recurrence at 6 months	H_2RA triple therapy 42.4%	
				H. pylori eradication rates	H_2RA 1.7%	
Spinzi 1994	Multicenter RCT	Italy	PPI dual therapy (4 wk omeprazole 20 mg od, 2 wk amoxicillin 1 g bd) *versus* PPI (4 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	B
	Unblinded	53 patients with duodenal ulcer		Ulcer recurrence at 6 months	PPI dual therapy 41.7%	
				H. pylori eradication rates	PPI 6.9%	
Suarez 1999	Single center RCT	Cuba	Bi triple therapy (6 wk colloidal bismuth subcitrate 240 mg bd, 10 days metronidazole 500 mg tds, and tetracycline 500 mg tds/amoxicillin 750 mg bd) *versus* Bi (6 wk colloidal bismuth subcitrate 240 mg bd)	Ulcer healing	Eradication rates:	B
	Unblinded	60 patients with gastric and duodenal ulcer		Global symptoms cured	Bi triple therapy 22.5%	
				H. pylori eradication rates	Bi 0%	
Sung 1994	Single center RCT	Hong Kong	Bi quadruple therapy (4 wk omeprazole 40 mg qds, 1 week colloidal bismuth subcitrate 120 mg qds, tetracycline 500 mg qds, and metronidazole 400 mg qds) *versus* PPI (4 wk omeprazole 40 mg qds)	Ulcer recurrence at 1 yr	Linked to Hosking 1992	A
	Single-blinded	155 patients with duodenal ulcer				

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Sung 1995	Single center RCT	Hong Kong	Bi triple therapy (1 week colloidal bismuth subcitrate 120 mg qds, tetracycline 500 mg qds, and metronidazole 400 mg qds) *versus* PPI (4 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	A
	Unblinded	96 patients with gastric ulcer		Ulcer recurrence at 1 yr *H. pylori* eradication rates	Bi triple therapy 80.4% PPI 11.1% If no healing at 4 wk triple therapy patients received antacids and PPI patients received further PPI	
Unge 1993	Multicenter RCT	Sweden	PPI dual therapy (4 wk omeprazole 40 mg od, and 2 wk amoxicillin 750 mg bd) *versus* PPI (4 wk omeprazole 40 mg od)	Ulcer recurrence at 6 months	Eradication rates:	B
	Double-blinded	233 patients with duodenal ulcer		*H. pylori* eradication rates	PPI dual therapy 53.5% PPI 3.9%	
van Zanten 1999	Multicenter RCT	Canada	PPI triple therapy (1 week omeprazole 20 mg bd, amoxycillin 1 g bd, and clarithromycin 500 mg bd or 1 week omeprazole 20 mg bd, metronidazole 400 mg bd, and clarithromycin 250 mg bd, then 3 wk omeprazole 20 mg od) *versus* PPI (4 wk omeprazole 20 mg od)	Ulcer healing	Eradication rates:	B
	Double-blinded	146 patients with duodenal ulcer		Ulcer recurrence at 6 months *H. pylori* eradication	PPI 0%	
Wang 1993	Single center RCT	Taiwan	Bi triple therapy (4 wk colloidal bismuth subcitrate 120 mg qds, 2 wk tetracycline 500 mg qds, and metronidazole 250 mg qds) *versus* H_2RA (4 wk ranitidine 150 mg bd) and Bi (4 wk colloidal bismuth subcitrate 120 mg qds)	Ulcer healing	Eradication rates:	B
	Unblinded	59 patients with duodenal ulcer		Ulcer recurrence at 6 months *H. pylori* eradication rates	Bi triple therapy 82.6% H_2RA 0% Bi 0%	

(continued)

Table 3. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Wang 1996	Single center RCT	Taiwan	Bi triple therapy (4 wk colloidal bismuth subcitrate 300 mg qds, 1 week amoxicillin 750 mg bd, and metronidazole 500 mg tds) and PPI dual therapy (4 wk omeprazole 20 mg bd/qds, and 10 days amoxicillin 750 mg bd) *versus* PPI (4 wk omeprazole 20 mg qds) and H_2RA (4 wk nizatidine/ranitidine 150 mg bd)	Ulcer healing	Eradication rates:	B
	Unblinded	112 patients with gastric and duodenal ulcer		*H. pylori* eradication rates	Bi triple therapy 68% PPI dual therapy 50% PPI 4.5% H_2RA 0% All patients received 4 wk H_2RA after initial therapy	
Wong 1999	Single center RCT	Hong Kong	Clarithromycin monotherapy (2 wk 250 mg qds) *versus* PPI (1 yr omeprazole 20 mg od)	Ulcer healing	Eradication rates:	B
	Single-blinded	114 patients with duodenal ulcer		Ulcer recurrence at 1 yr *H. pylori* eradication rates	Clarithromycin monotherapy 66.7% PPI 7% Clarithromycin patients also received 4 wk sucralfate 1 g qds and 2 wk metronidazole 300 mg qds	

all data were at 4–6 wk. A total of 34% patients receiving eradication therapy reported symptom resolution and 37% in the comparison regimen group. There was significant heterogeneity between trial results (heterogeneity test (1 degree of freedom) $\chi^2 = 5.07$, $p = 0.02$) and a random effects model was used. The RR of symptoms persisting after eradication therapy was 1.05 (95% CI = 0.72 to 1.55).

ADVERSE EVENTS. Thirty-nine trials (6–14, 16, 17, 19, 21–26, 30–36, 39–41, 43–50, 52, 56, 57) reported on overall adverse event rates in 5,066 patients. Adverse events occurred in 22% of those receiving *H. pylori* eradication and only 8% of those in the comparison regimen group. The RR of adverse events following eradication therapy was 2.28 (95% CI = 1.72 to 3.02). The Number Needed to Harm (NNH) was 11 (95% CI = 8 to 14). Commonest adverse events reported were diarrhea, nausea, and vomiting.

Economic Analysis

H. PYLORI ERADICATION FOR DUODENAL ULCER DISEASE. In the base case analysis intermittent PPI dominated no treatment, as it was less expensive and more effective (Table 4). Similarly *H. pylori* eradication dominated maintenance PPI therapy (Table 4). When the two nondominated strategies were compared, *H. pylori* eradication on average cost an extra $131 and resulted in an extra 1.5 months free from dyspepsia compared with intermittent PPI therapy, giving an incremental cost effectiveness ratio of $87/month free from dyspepsia. This is below the threshold of $182/month free from upper GI symptoms suggested patients would be willing to pay in a recent study (58). The base case does not, however, take into account the uncertainty in the data. When this was evaluated the model suggests that there is greater than 95% certainty that *H. pylori* eradication is the most cost-effective strategy provided there is a willingness to pay of at

Table 4. Baseline Results of Decision Analysis Models Evaluating Different Strategies of Managing *H. pylori* Positive Gastric and Duodenal Ulcer Patients

Strategy	Disease	Cost ($)	Months free from dyspepsia	Incremental cost-effectiveness
Do nothing	DU	$580	1.9	Dominated by intermittent PPI
Intermittent PPI	DU	$514	7.2	Baseline
Maintenance PPI	DU	$683	7.9	Dominated by *H. pylori* eradication
H. pylori eradication	DU	$645	8.7	$87/month free from dyspepsia
Do nothing	GU	$3031	2.0	Dominated by *H. pylori* eradication
Intermittent PPI	GU	$1545	8.3	Dominated by *H. pylori* eradication
Maintenance PPI	GU	$1459	8.5	Dominated by *H. pylori* eradication
H. pylori eradication	GU	$1369	8.6	Average = $159/month free from dyspepsia

least $112/month free from dyspepsia (Fig. 6). At no willingness to pay value was there any likelihood that maintenance PPI therapy was a cost-effective option. This was robust to all sensitivity analyses except for the cost of *H. pylori* eradication. If there is a willingness to pay of $182/month free from dyspepsia then intermittent PPI therapy was likely to be more cost-effective if eradication therapy cost more than $393.

H. PYLORI ERADICATION FOR GASTRIC ULCER DISEASE. In the base case analysis again all strategies were dominated by *H. pylori* eradication. This cost an average of $1,402 and resulted in 10.6 months free from dyspepsia giving a cost effectiveness ratio of $129/month free from dyspepsia, which is again below the threshold patients are willing to pay for symptom control (58). The uncertainty in the data, however, meant that at the threshold of $182/month free of dyspepsia we can only be 94% certain that *H. pylori* eradication is the most cost-effective strategy. *H. pylori* eradication would be expected to have a longer-term effect on gastric ulcer recurrence (59), however, and so we evaluated a 2-year follow-up. Cost-effectiveness acceptability curves suggested that there is greater than 95% certainty that *H. pylori* eradication is the most cost-effective strategy in gastric ulcer patients whatever the willingness to pay/month free from dyspepsia. This result was robust to all sensitivity analysis over 2 years provided results of randomized controlled trials can be extrapolated to this period.

DISCUSSION

This is the most comprehensive systematic review of the efficacy of *H. pylori* eradication in peptic ulcer disease. Two previous systematic reviews have been reported, but both had limitations. The first considered gastric and duodenal ulcer as a single disease entity rather than individually, and as it was

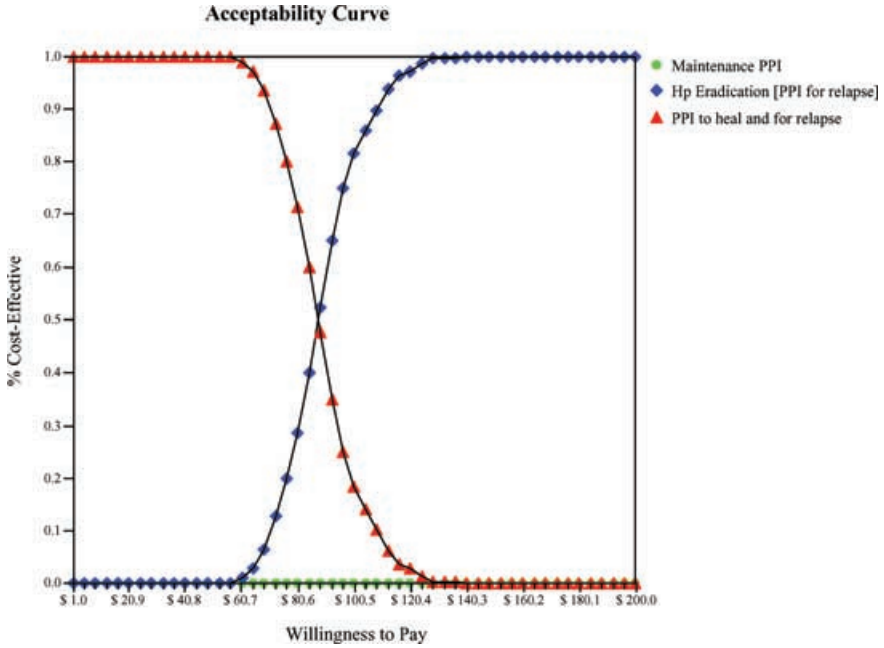

Figure 6. Cost-effectiveness acceptability curve of intermittent PPI, maintenance PPI, and *H. pylori* eradication *versus* no treatment in *H. pylori* positive duodenal ulcer disease over a one-year time frame. The colored line gives the probability that the relevant strategy is cost-effective for a given willingness to pay per month free from dyspepsia.

published in 1994 there has been considerable information reported in the intervening years (60). The second contained nonrandomized and uncontrolled studies in the analysis, and only included trials of proton pump inhibitor-based eradication regimens (61).

The reduction in duodenal and gastric ulcer recurrence with eradication therapy compared to no treatment reported in this review is less than the effect suggested by earlier reviews. We evaluated all *H. pylori* eradication therapies including clarithromycin monotherapy and PPI dual therapies. These usually give suboptimal *H. pylori* eradication rates and this may explain the reduced effect of anit-*H. pylori* therapy on peptic ulcer recurrence. This is unlikely to be the main explanation of our findings, however, as the subgroup analysis just evaluating PPI triple therapy and bismuth salt quadruple therapy only showed a modest reduction in duodenal ulcer recurrence. Furthermore, the mean eradication rate achieved in trials that evaluated DU recurrence was 72% and this is similar to the eradication rates achieved in primary care (62). The main explanation for our findings is likely to be the rigorous use of intention to treat data, and, therefore, gives a more realistic estimate of what is achievable.

This is also the first systematic review to provide a summary estimate of the side effects of *H. pylori* eradication therapy in peptic ulcer disease patients. These occurred over twice as frequently in those given *H. pylori* eradication with the commonest adverse events being diarrhea, nausea, and vomiting. The majority of these are short-term while the benefits are long lasting. Nevertheless the patient should be informed of the risks as well as benefits of treatment. Our data also suggest that *H. pylori* eradication with acid suppression improves healing of duodenal ulcers compared with acid suppression alone. The majority of randomized controlled trials did report a statistically significant effect in favor of *H. pylori* eradication because the trials had insufficient size to demonstrate this modest effect. Our data also show a trend toward a lower healing rate for gastric ulcers in patients allocated to *H. pylori* eradication. This may relate to acid suppressive therapy being more effective in the presence of *H. pylori* but as the result was not statistically significant, more data are needed before definite conclusions can be reached.

As with other health economic models (2, 63–65) our analysis suggests *H. pylori* eradication is the most cost-effective strategy for infected duodenal ulcer patients. Previous models have suggested that *H. pylori* eradication is cost-saving in duodenal ulcer patients (2, 63–65) whilst our results are more conservative. This is due to the use of a probabilistic analysis that incorporates the uncertainty in the model and the use of systematic review data, which gives more conservative efficacy estimates than previous reports. A previous randomized controlled trial (66) also suggested that *H. pylori* eradication may cost less than intermittent H_2RA therapy but this study used a higher monthly cost of ranitidine ($90) whereas this therapy is much cheaper now. The model also suggests that *H. pylori* eradication may take two years before we can be confident that it is cost-effective in positive gastric ulcer patients. This is consistent with *H. pylori* eradication having less of an impact in reducing gastric ulcer recurrence and a lower overall relapse of the disease. The overall effect in favor of eradication therapy is still impressive, however, and adds further weight to international guidelines recommending its use in peptic ulcer disease.

Randomized controlled trials consistently suggested that *H. pylori* eradication reduced the relapse rate of peptic ulcer disease but the magnitude of this effect was variable. 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 (67). 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 (68). The reduction of effect size with intention to treat analysis in the long-term duodenal ulcer recurrence trials is also consistent with this literature (680 and the increase in effect size with increasing eradication rate is biologically plausible. The latter finding could be clinically useful as it provides information on the likely impact of future improvements in *H. pylori* eradication therapy. Metaregression suggests that if there is a 10% increase in eradication rate there will be an absolute reduction in duodenal ulcer relapse rate of 2% (95% CI = 1% to 3%) (relative risk falls from 0.19 to 0.15 (95% CI = 0.14 to 0.18)). This is close to the change in relative risk that is seen when only PPI triple or bismuth salt quadruple therapies are evaluated in a subgroup analysis.

Finally, we have highlighted a lack of data regarding the relief of symptoms from peptic ulcer disease following eradication therapy. There were only four RCTs evaluating symptoms in the healing of peptic ulcers and we did not identify any trial that evaluated symptom relief in the long-term. This is the most relevant outcome for patients and should be addressed in future trials.

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REFERENCES

1. Penston JG. Clinical aspects of *Helicobacter pylori* eradication therapy in peptic ulcer disease. Aliment Pharm Ther 1996;10:469–86.
2. Imperiale TF, Speroff T, Cebul RD, et al. A cost analysis of alternative treatments for duodenal ulcer. Ann Int Med 1995;123:665–72.
3. Talley NJ, Silverstein MD, Agreus L, et al. AGA technical review: Evaluation of dyspepsia. Gastroenterology 1998;114:582–95.
4. O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: An introduction to statistical issues and methods. Statistical Methods in Medical Research 2002;11:455–68.
5. Ford AC, Delaney BC, Forman D, et al. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. (Protocol for a Cochrane Review). Cochrane Database Syst Rev 2003.
6. Asaka M, Sugiyama T, Kato M, et al. A multicenter, double-blind study on triple therapy with lansoprazole, amoxicillin and clarithromycin for eradication of *Helicobacter pylori* in Japanese peptic ulcer patients. Helicobacter 2001;6:254–61.
7. Avsar E, Kalayci C, Tozun N, et al. Refractory duodenal ulcer healing and relapse: Comparison of omeprazole with *Helicobacter pylori* eradication. Eur J Gastroenterol Hepatol 1996;8:449–52.
8. Axon AT, O'Morain CA, Bardhan KD, et al. Randomized double-blind controlled study of recurrence of gastric ulcer after treatment for eradication of *Helicobacter pylori* infection. Br Med J 1997;314:565–8.
9. Bardhan KD, Dallaire C, Eisold H, et al. Ranitidine bismuth citrate with clarithromycin for the treatment of duodenal ulcer. Gut 1997;41:181–6.
10. Bayerdorffer E, Mannes GA, Sommer A, et al. High dose omeprazole treatment combined with amoxicillin eradicates *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1992;4:697–702.
11. Bayerdorffer E, Miehlke S, Mannes GA, et al. Double-blind trial of omeprazole and amoxicillin to cure *Helicobacter pylori* infection in patients with duodenal ulcers. Gastroenterology 1995;108:1412–7.
12. Bayerdorffer E, Miehlke S, Lehn N, et al. Cure of gastric ulcer disease after cure of *Helicobacter pylori* infection-German Gastric Ulcer Study. Eur J Gastroenterol Hepatol 1996;8:343–9.
13. Carpintero P, Blanco M, Pajares JM. Ranitidine versus colloidal bismuth subcitrate in combination with amoxicillin and metronidazole for eradicating *Helicobacter pylori* in patients with duodenal ulcer. Clin Infect Dis 1997;25:1032–7.
14. Chen TS, Tsay SH, Chang FY, et al. Triple therapy for the eradication of *Helicobacter pylori* and reduction of duodenal ulcer relapse: Comparison of 1 week and 2 week regimens and recrudescence rates over 12 months. J Gastroenterol Hepatol 1995;10:300–5.
15. Figueroa G, Acuna R, Troncoso M, et al. Low *H. pylori* reinfection rate after triple therapy in Chilean duodenal ulcer patients. Am J Gastroenterol 1996;91:1395–9.
16. Fukuda Y, Yamamoto I, Okui M, et al. Combination therapy with mucosal protective agent for the eradication of *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1995;7(Suppl 1):S45–S47.
17. Fukuda Y, Yamamoto I, Okui M, et al. Combination therapies with a proton pump inhibitor for *Helicobacter pylori*-infected gastric ulcer patients. J Clin Gastroenterol 1995;20(Suppl 2):S132–S135.
18. Furuta T, Futami H, Arai H, et al. Effects of lansoprazole with or without amoxicillin on ulcer healing: Relation to eradication of *Helicobacter pylori*. J Clin Gastroenterol 1995;20(Suppl 2):S107–S111.
19. Graham DY, Lew GM, Evans DG, et al. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. A randomized controlled trial. Ann Intern Med 1991;115:266–9.
20. Graham DY, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. Ann Intern Med 1992;116:705–8.
21. Graham DY, Breiter JR, Ciociola AA, et al. and the RBC *H. pylori* Study Group. An alternative non-macrolide, non-imidazole treatment regimen for curing *Helicobacter pylori* and duodenal ulcers: Ranitidine bismuth citrate plus amoxicillin. Helicobacter 1998;3:125–131.
22. Harford W, Lanza F, Arora A, et al. Double-blind, multicenter evaluation of lansoprazole and amoxicillin dual therapy for the cure of *Helicobacter pylori* infection. Helicobacter 1996;1:243–50.
23. Hentschel E, Brandstatter G, Dragosics B, et al. Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. N Engl J Med 1993;328:308–12.
24. Higuchi K, Fujiwara Y, Tominaga K, et al. Is eradication sufficient to heal gastric ulcers in patients infected with *Helicobacter pylori*? A randomized, controlled prospective study. Aliment Pharm Ther 2003;17:111–7.
25. Hosking SW, Ling TK, Yung MY, et al. Randomized controlled trial of short-term treatment to eradicate *Helicobacter pylori* in patients with duodenal ulcer. Br Med J 1992;305:502–4.
26. Kato M, Asaka M, Kudo M, et al. Effects of lansoprazole plus amoxycillin on the cure of *Helicobacter pylori* infection in Japanese peptic ulcer patients. Aliment Pharm Ther 1996;10:821–7.
27. Katoh M, Asaka M, Kudoh M, et al. Clinical efficacy of lansoprazole in eradication of *Helicobacter pylori*. J Clin Gastroenterol 1995;20(Suppl 2):S112–S114.
28. Kepekci Y, Kadayifci A. Does the eradication of *Helicobacter pylori* cure duodenal ulcer disease in communities with a high prevalence rate? Comparison with long-term acid suppression. Int J Clin Pract 1999;53:505–8.
29. Kim JS, Kim SG, Choi IJ, et al. Effect of *Helicobacter pylori* eradication on duodenal ulcer scar in patients with no clinical history of duodenal ulcer. Aliment Pharm Ther 2002;16:275–80.
30. Lam S-K, Ching C-K, Lai K-C, et al. Does treatment of *Helicobacter pylori* with antibiotics alone heal duodenal ulcer? A randomized double blind placebo controlled study. Gut 1997;41:43–8.
31. Lazzaroni M, Perego M, Bargiggia S, et al. *Helicobacter pylori* eradication in the healing and recurrence of benign gastric ulcer: A two-year, double-blind, placebo controlled study. Ital J Gastroenterol Hepatol 1997;29:220–7.
32. Lin JT, Wang JT, Wu MS, et al. Prospective, randomized study of H2-blocker and triple therapy for duodenal ulcer treatment and the eradication of *Helicobacter pylori*. J Formos Med Assoc 1994;93:368–73.
33. Logan RP, Bardhan KD, Celestin LR, et al. Eradication of *Helicobacter pylori* and prevention of recurrence of duodenal ulcer: A randomized, double-blind, multi-centre trial of omeprazole with or without clarithromycin. Aliment Pharm Ther 1995;9:417–23.

34. Malfertheiner P, Bayerdorffer E, Diete U, et al. The GUMACH study: The effect of 1-week omeprazole triple therapy on *Helicobacter pylori* infection in patients with gastric ulcer. Aliment Pharm Ther 1999;13:703–12.
35. Mantzaris GJ, Hatzis A, Tamvakologos G, et al. Prospective, randomized, investigator-blind trial of *Helicobacter pylori* infection treatment in patients with refractory duodenal ulcers. Healing and long-term relapse rates. Dig Dis Sci 1993;38:1132–6.
36. Meining A, Hochter W, Weingart J, et al. and the Ulcer Study Group, Germany. Double-blind trial of omeprazole and amoxicillin in the cure of *Helicobacter pylori* infection in gastric ulcer patients. Scand J Gastroenterol 1998;33:49–54.
37. Miehlke S, Bayerdorffer E, Lehn N, et al. Two-year follow-up of duodenal ulcer patients treated with omeprazole and amoxicillin. Digestion 1995;56:187–93.
38. Mones J, Rodrigo L, Sancho F, et al. *Helicobacter pylori* eradication versus one-year maintenance therapy: Effect on relapse and gastritis outcome. Rev Esp Enferm Dig 2001;93:381–9.
39. O'Morain C, Dettmer A, Rambow A, et al. Double-blind, multicenter, placebo-controlled evaluation of clarithromycin and omeprazole for *Helicobacter pylori*-associated duodenal ulcer. Helicobacter 1996;1:130–7.
40. Parente F, Maconi G, Bargiggia S, et al. Comparison of two lansoprazole-antibiotic combinations (amoxycillin or classical triple therapy) for treatment of *H. pylori* infection in duodenal ulcer patients. Aliment Pharm Ther 1996;10:211–3.
41. Pinero R, Pacheco M, Urrestarazu M, et al. *Helicobacter pylori* eradication heals the duodenal ulcer. Randomized, simple, and controlled study with omeprazole. Rev Socied Venez Gastroenterol 1995;49:111–5.
42. Porro GB, Parente F, Lazzaroni M. Short and long-term outcome of *Helicobacter pylori* positive resistant duodenal ulcers treated with colloidal bismuth subcitrate plus antibiotics or sucralphate alone. Gut 1993;34:466–9.
43. Porro GB, Lazzaroni M, Bargiggia S, et al. Omeprazole coupled with two antibiotics for *Helicobacter pylori* eradication and prevention of ulcer recurrence. Am J Gastroenterol 1996;91:695–700.
44. Pounder RE, Wyeth JW, Duggan AE, et al. Ranitidine bismuth citrate with clarithromycin for the eradication of *Helicobacter pylori* and for ulcer healing. Helicobacter 1997;2:132–9.
45. Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. Lancet 1990;335:1233–5.
46. Schwartz H, Krause R, Sahba B, et al. Triple versus dual therapy for eradicating *Helicobacter pylori* and preventing ulcer recurrence: A randomized, double-blind, multicenter study of lansoprazole, clarithromycin, and/or amoxicillin in different dosing regimens. Am J Gastroenterol 1998;93:584–90.
47. Shirotani T, Okada M, Murayama H, et al. Effect of the eradication of *Helicobacter pylori* on duodenal ulcer healing and ulcer relapse: Randomized controlled study in Japan. J Gastroenterol 1996;31:175–81.
48. Sobhani I, Chastang C, de Korwin J-D, et al. Antibiotic versus maintenance therapy in the prevention of duodenal ulcer recurrence: Results of a multicentric double-blind randomized trial. Gastroenterol Clin Biol 1995;19:252–8.
49. Spinzi GC, Sangiovanni A, Imperiali G, et al. Prevention of duodenal ulcer relapse with amoxycillin and omeprazole. Eur J Gastroenterol Hepatol 1994;6:599–602.
50. Suarez MS, Cansino JG, Ilizalde CV, et al. Three treatment schemes with colloidal bismuth subcitrate (Q-ULCER) in peptic ulcer with *Helicobacter pylori*. Arch Med Res 1999;30:55–9.
51. Sung JJ, Chung SC, Ling TKW, et al. One-year follow-up of duodenal ulcers after 1-week triple therapy for *Helicobacter pylori*. Am J Gastroenterol 1994;89:199–202.
52. Sung JJ, Chung SC, Ling TK, et al. Antibacterial treatment of gastric ulcers associated with *Helicobacter pylori*. N Engl J Med 1995;332:139–42.
53. Unge P, Gad A, Eriksson K, et al. Amoxicillin added to omeprazole prevents relapse in the treatment of duodenal ulcer patients. Eur J Gastroenterol Hepatol 1993;5:325–31.
54. Van Zanten SJOV, Bradette M, Farley A, et al. The DUMACH study: Eradication of *Helicobacter pylori* and ulcer healing in patients with acute duodenal ulcer using omeprazole based triple therapy. Aliment Pharm Ther 1999;13:289–95.
55. Wang WM, Chen CY, Jan CM, et al. Eradication of *Helicobacter pylori* infection and the recurrence of duodenal ulcers. J Formos Med Assoc 1993;92:721–4.
56. Wang K, Lin HJ, Chua RT, et al. Omeprazole plus amoxicillin versus triple therapy eradicates *Helicobacter pylori* in the Chinese with peptic ulcer disease. Chin Med J 1996;57:184–90.
57. Wong BCY, Lam SK, Lai KC, et al. Triple therapy for *Helicobacter pylori* eradication is more effective than long-term maintenance antisecretory treatment in the prevention of recurrence of duodenal ulcer: A prospective long-term follow-up study. Aliment Pharm Ther 1999;13:303–9.
58. Kleinman L, McIntosh E, Ryan M, et al. Willingness to pay for complete symptom relief of gastroesophageal reflux disease. Arch Intern Med 2002;162:1361–6.
59. Van der Hulst RW, Rauws EA, Koycu B, et al. Prevention of ulcer recurrence after eradication of *Helicobacter pylori*: A prospective long-term follow-up study. Gastroenterology 1997;113:1082–6.
60. Moore RA. Helicobacter pylori and peptic ulcer. A systematic review of effectiveness and an overview of the economic benefits of implementing what is known to be effective. http://www.jr2.ox.ac.uk/bandolier 1994.
61. Leodolter A, Kulig M, Brasch H, et al. A meta-analysis comparing eradication, healing and relapse rates in patients with Helicobacter pylori-associated gastric or duodenal ulcer. Aliment Pharm Ther 2001;15:1949–58.
62. Moayyedi P, Feltbower R, Crocombe W, et al. The effectiveness of omeprazole, clarithromycin and tinidazole in eradicating *Helicobacter pylori* in a community screen and treat program. Aliment Pharmacol Ther 2000;14:719–28.
63. O'Brien B, Goeree R, Mohamed AH, et al. Cost-effectiveness of *Helicobacter pylori* eradication for the long-term management of duodenal ulcer in Canada. Arch Intern Med 1995;155:1958–64.
64. Briggs AH, Sculpher MJ, Logan RP, et al. Cost-effectiveness of screening for and eradication of *Helicobacter pylori* in management of dyspeptic patients under 45 years of age. Br Med J 1996;312:1321–5.
65. Fendrick AM, McCort JT, Chernew ME, et al. Immediate eradication of *Helicobacter pylori* in patients with previously documented peptic ulcer disease: Clinical and economic effects. Am J Gastroenterol 1997;92:2017–24.
66. Sonnenberg A, Schwartz JS, Cutler AF, et al. Cost savings in duodenal ulcer therapy through *Helicobacter pylori* eradication compared with conventional therapies. Arch Intern Med 1998;158:852–60.

67. Lau J, Ioannidis JPA, Schmidt CH. Summing up evidence: One answer is not always enough. Lancet 1998;351:123–7.
68. Moher D, Cook DJ, Jadad AR, et al. Assessing the quality of reports of randomized trials: Implications for the conduct of meta-analyses. Health Technology Assessment 1999;3:1–106.
69. Spiegel BM, Vakil NM, Ofman JJ. Dyspepsia management in primary care: A decision analysis of competing strategies. Gastroenterology 2002;122:1270–85.
70. Manes G, Mosca S, De Nucci C. High prevalence of reflux symptoms in duodenal ulcer patients who develop gastro-oesophageal reflux disease after curing Helicobacter pylori infection. Dig Liver Dis 2001;33:665–70.
71. Vincze A, Karadi O, Hunyady B, et al. One year follow-up of patients after successful helicobacter pylori eradication therapy. J Physiol 2001;95:457–60.
72. McColl KE, Dickson A, El-Nujumi A, et al. Symptomatic benefit 1–3 years after H. pylori eradication in ulcer patients: Impact of gastroesophageal reflux disease. Am J Gastroenterol 2000;95:101–5.
73. Vakil N, Hahn B, McSorley D. Recurrent symptoms and gastro-oesophageal reflux disease in patients with duodenal ulcer treated for Helicobacter pylori infection. Aliment Pharmacol Ther 2000;14:45–51.
74. Chen TS, Chang FY, Lee SD, et al. Recurrence of H. pylori infection and dyspeptic symptoms after successful eradication in patients cured of duodenal ulcer disease. Hepato-Gastroenterology 1999;46:252–6.
75. McColl KE, el-Nujumi A, Murray LS, et al. Assessment of symptomatic response as predictor of Helicobacter pylori status following eradication therapy in patients with ulcer. Gut 1998;42:618–22.
76. Phull PS, Halliday D, Price AB, et al. Absence of dyspeptic symptoms as a test of Helicobacter pylori eradication. Br Med J 1996;312:349–50.
77. http://www.drugstore.com/products—listed price of one months generic omperazole 20 mg od.

Eligibility criteria for inclusion in systematic review

- *H. pylori* positive on serology, CLO test, urease breath test, biopsy for histology and/or culture, or a combination of these tests
- Efficacious eradication therapy*
- Suitable comparative intervention±
- Proportion of ulcers healed/recurred on repeat endoscopy/barium meal

We define efficacious eradication therapy as one of the following:

- Proton pump inhibitor (PPI) dual therapy (PPI plus either amoxycillin or clarithromycin)
- PPI/H_2 receptor antagonist (H_2RA) triple therapy (PPI/H_2RA plus two of the following; amoxycillin, macrolide, 5 nitroimidazole)
- Bismuth triple therapy (Bismuth salt and 5 nitroimidazole with either amoxycillin or tetracycline)
- Bismuth quadruple therapy (as Bismuth triple therapy, but PPI in addition)
- Ranitidine Bismuth Citrate dual/triple therapy (as for PPI)
- Clarithromycin monotherapy

We define a suitable comparative intervention as:

- Antisecretory therapy (PPI or H_2RA)
- Bismuth salts
- Sucralfate
- Regular/as required antacid
- Placebo
- No treatment