Helicobacter pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer (Review)

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[Intervention Review]

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ABSTRACT

Background

Peptic ulcer is the main cause for upper gastrointestinal haemorrhage, and *Helicobacter pylori* (*H.pylor*i) infection is the main etiologic factor for peptic ulcer disease. Maintenance antisecretory therapy is the standard long-term treatment for patients with bleeding ulcers to prevent recurrent bleeding. The efficacy of *H. pylori* eradication for the prevention of rebleeding from peptic ulcer is unknown.

Objectives

To compare the efficacy of *H. pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer.

Search methods

We searched the Cochrane Controlled Trials Register (the Cochrane Library issue 4, 2003), MEDLINE (January 1966 to January 2004), EMBASE (January 1988 to January 2004), CINAHL (January 1982 to January 2004), and reference lists of articles. We also conducted a manual search from several congresses. The search strategy was re-run in January 2005 and October 2008, but no new trials were found.

Selection criteria

Controlled clinical trials comparing the efficacy of *H. pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer.

Data collection and analysis

Data extraction and quality assessment of studies was done by two reviewers. Study authors were contacted for additional information.

Main results

Seven studies with a total of 578 patients were included in the first comparison: mean percentage of rebleeding in *H. pylori* eradication therapy group was 2.9%, and in the non-eradication therapy group without subsequent long-term maintenance antisecretory therapy it was 20% (OR 0.17, 95% CI 0.10 to 0.32; there was no statistical evidence of heterogeneity; NNT was 7, 95% CI 5 to 11). Three studies with a total of 470 patients were included in the second comparison: mean percentage of rebleeding in *H. pylori* eradication therapy group was 1.6%, and in non-eradication therapy group with long-term maintenance antisecretory therapy it was 5.6% (OR 0.24, 95% CI 0.09 to 0.67; heterogeneity was not demonstrated; NNT was 20, 95% CI 12 to 100). Subgroup analyses were carried out to examine the effect of NSAIDS and of excluding H.pylori eradication failures from the analyses.

Authors' conclusions

Treatment of *H. pylori* infection is more effective than antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) in preventing recurrent bleeding from peptic ulcer. All patients with peptic ulcer bleeding should be tested for *H. pylori* infection, and eradication therapy should be prescribed to *H. pylori*-positive patients.

PLAIN LANGUAGE SUMMARY

Antibiotics vs. acid suppression therapy (with or without long-term maintenance acid suppression therapy) for the prevention of recurrent bleeding from peptic ulcer

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. Bleeding in the gut can be life-threatening. Several treatments aim to heal the ulcer and prevent future bleeding. These include acid-suppressing drugs and antibiotics to treat *Helicobacter pylori*, a bacterium that causes most peptic ulcers. The review found that, for people who have had a bleeding peptic ulcer caused by *Helicobacter pylori*, treatment with antibiotics more effectively prevents gastrointestinal re-bleeding than acid-suppressing drugs. Antibiotics when *Helicobacter pylori* infection is present are also cheaper and more convenient than long-term acid-suppressing drugs.

BACKGROUND

Description of the condition

Upper gastrointestinal haemorrhage is a major cause of morbidity, mortality and medical care costs, with peptic ulcer being the most frequent source of bleeding (Laine 1994). It has been estimated that approximately 2-3% of duodenal ulcer patients who are not receiving antisecretory therapy are likely to develop haemorrhage during each year of follow-up study, giving a cumulative risk of haemorrhage after 5 years of approximately 10-14% (Mignon 1994). Furthermore, patients whose ulcers have bled once have an increased risk of further rebleeding, compared with those with uncomplicated ulcer disease. Thus, among patients who present with a bleeding ulcer, approximately one-third will develop recurrent bleeding in the following 1-2 years, and 40-50% within the subsequent 10 years, if left untreated after ulcer healing (Petersen 1995; Laine 1996). Furthermore, patients with bleeding ulcers account for an overall mortality rate that has remained around 5 to 10% for the past 50 years, despite improved medical and surgical treatments, the development of diagnostic and therapeutic endoscopy, and the availability of intensive care units (Gilbert 1990; Penston 1992; Laine 1994).

Description of the intervention

Maintenance antisecretory therapy has been the standard long-term treatment for patients with bleeding ulcers to prevent recurrent bleeding, despite the fact that only two randomised studies have specifically examined such options in patients with peptic ulcer haemorrhage (Murray 1988; Jensen 1994). The first study

found no significant difference in the rate of recurrent bleeding between ranitidine maintenance therapy and placebo, but the number of bleeding episodes was so small that a treatment benefit could not be demonstrated (Murray 1988); the second study reported significantly fewer episodes of haemorrhage among patients taking ranitidine maintenance antisecretory regimen when compared with placebo (Jensen 1994).

Helicobacter pylori (*H. pylori*) infection is the main etiologic factor for peptic ulcer disease. However, although the role of this microorganism on non-complicated peptic ulcer has been definitively established (Kuipers 1995), the precise relationship between *H. pylori* and complicated ulcer disease has hardly been studied (Gisbert 2003). *H. pylori* eradication has been demonstrated to dramatically reduce the rate of ulcer recurrence (Hopkins 1996). Therefore, it would seem logical to assume that *H. pylori* cure would also represent an effective strategy to prevent recurrence of ulcer bleeding. In 1994, the National Institutes of Health (NIH) Consensus Conference panel stated that, although preliminary studies indicate that cure of *H. pylori* infection prevents recurrent ulcer bleeding at rates equal to those of maintenance antisecretory therapy, until these studies can be confirmed, maintenance antisecretory "may be prudent" in such patients even after *H. pylori* eradication, in view of high risks associated with rebleeding (NIH 1994). Two years later, in 1996, the NIH Consensus Conference did not go any further, stating that "several trials indicate that *H. pylori* eradication also reduces the recurrence of ulcer complications, but the magnitude of this reduction remains to be firmly established" (Soll 1996).

Why it is important to do this review

Although several authors have reported administration of *H. pylori* eradication treatment to patients with a history of peptic ulcer haemorrhage with the intention to prevent recurrence of bleeding, only a few studies have included a control group treated with "traditional" antisecretory non-eradicating therapy (followed or not by long-term maintenance antisecretory therapy). Furthermore, the number of patients included in these "eradication" studies has been small and, as the incidence of rebleeding episodes is relatively low (especially when antisecretory maintenance treatment is prescribed and follow-up limited), efficacy differences between groups may not be demonstrated due to a problem of statistical power of individual studies. Consequently, as the true efficacy of *H. pylori* eradication for the prevention of recurrent bleeding from peptic ulcer is unknown, it remains unclear whether maintenance antisecretory therapy must be continued or stopped in patients with a history of peptic ulcer haemorrhage and prior *H. pylori* eradication.

Finally, in addition to efficacy reasons, other relevant arguments may advocate the use of eradication therapy instead of maintenance antisecretory treatment. Firstly, the cost of antibiotic therapy is lower than long-term management by antisecretory drugs, mainly because the financial outlay for medication in the former approach is not cumulative as with the later. Secondly, one disadvantage of maintenance antisecretory therapy is the requirement for long-term compliance, which may not be sustained but wane, especially when symptoms are absent. And thirdly, it seems obvious that 7-10 days of antibiotic therapy is more convenient for the patients than many years of daily continuous antisecretory treatment.

With these antecedents, we aimed to perform a systematic review and a meta-analysis to compare the efficacy of *H. pylori* eradication therapy vs. antisecretory non-eradication therapy (followed or not by long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer.

OBJECTIVES

To compare the efficacy of *H. pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled clinical trials were eligible for inclusion in the review.

Types of participants

- Patients with a previous episode of peptic ulcer bleeding.
- Patients were included if bleeding was severe enough to warrant hospitalisation, haematemesis or melena was evident, or a drop in haemoglobin level of more than 2 g/dL occurred.
- The presence of an ulcer had to be documented endoscopically and no other potential bleeding source had to be found during initial evaluation.
- Studies designed to follow patients up for less than 6 months were excluded.
- Studies with all patients taking NSAIDs were excluded. *H. pylori* infection and NSAIDs seem to be mainly independent risk factors for peptic ulcer bleeding (Hawkey 2001). If all patients were taking NSAIDs prior to the bleeding episode, then the efficacy of *H. pylori* eradication for the prevention of recurrent bleeding in these patients would be masked, as most complications would be attributable to NSAIDs and therefore not prevented by eradicating the organism.

Types of interventions

H. pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy).

Types of outcome measures

- Recurrence of bleeding during follow-up (after prescribing eradication or antisecretory treatment) of more than 6 months.
- Rebleeding during follow-up was assessed with the same criteria used for initial evaluation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Controlled Trials Register (the Cochrane Library issue 4, 2003), MEDLINE (January 1966 to January 2004), EMBASE (January 1988 to January 2004), CINAHL (January 1982 to January 2004), and reference lists of articles. We also conducted a manual search from several congresses. The search strategy was re-run in January 2005, but no new trials were found. Searches in all databases were updated and re-run in October 2008. We did not confine our search to English language publications.

The Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE, Sensitivity maximising version, Ovid format (Higgins 2008), was combined with the search terms in Appendix 1 to identify randomised controlled trials in MEDLINE. The MEDLINE search strategy was adapted for use in the other databases searched.

Searching other resources

Reference lists from the trials selected by electronic searching were handsearched to identify further relevant trials. Review articles examining the role of *H. pylori* infection on gastroduodenal haemorrhage were also searched to identify articles which met the inclusion criteria.

We also conducted a manual search of abstracts from 1995 to 2003 from the International Workshop on Gastroduodenal Pathology and *Helicobacter pylori* (EHPSG) published in Gut, the American Digestive Disease Week (DDW) published in Gastroenterology and the United European Gastroenterology Week (UEGW) published in Gut.

We included abstracts from congresses on the grounds that many negative studies are never published as a full paper, and the inclusion of abstracts thus prevents, or at least reduces, publication bias. Authors of trial reports published only as abstracts were contacted and asked to contribute full datasets or completed papers.

Abstracts of the articles selected in each of these multiple searches were reviewed and those meeting the inclusion criteria were recorded.

Data collection and analysis

Selection of studies

The Trials Search Co-ordinator for the Cochrane UGPD Group scanned the results of the electronic searches and removed all the obviously irrelevant references. These results were then independently assessed by two reviewers to ascertain if they were eligible for inclusion in the review. For the 2008 update, the authors reviewed the results of the updated searches and selected reports of studies for further scrutiny. The selection criteria were applied independently by two reviewers according to the pre-stated eligibility criteria, and where disagreements occurred they were resolved by consensus.

Only studies that clearly stated information about the number of treated patients and the number of patients with recurrent bleeding in each therapeutic group (*H. pylori* eradication group and non-eradication group) were included. The success of eradication therapy had to be based on the negative results of two tests or one test repeated twice during follow-up in order to make sure that *H. pylori* has been eliminated. *H. pylori* eradication success or failure had to be confirmed at least 4 weeks after antibiotic treatment has been completed.

Data extraction and management

The following variables were extracted in a predefined data extraction form (see 'Characteristics of included studies'): author, year of publication, type of publication (complete article or abstract), type of participants (duodenal or gastric ulcer, or both), NSAID use previous to the inclusion in the study (yes/no; if yes, percentage of patients taking NSAIDs), intervention (*H. pylori* eradication treatment or antisecretory treatment; including drugs, dose, schedule and duration), maintenance antisecretory therapy (yes/no; if yes, drug, dose and schedule of administration), follow-up (months), quality score (see Jadad score in previous section, including items of randomisation, double blinding, and description of withdrawal/dropouts; concealment of allocation of the sequence of randomisation was also separately assessed), and rebleeding rate (raw numbers and percentages in each therapeutic group). Publications identified as duplicates were excluded; when more than one version of the same trial was retrieved, only the most recent data were considered. Extraction of studies was done independently by two reviewers. Discrepancies in the interpretation were resolved by consensus.

Assessment of risk of bias in included studies

The quality of the studies was assessed using the score proposed by Jadad et al (Jadad 1996) based on 3 items:

1. Randomisation;
2. Double blinding; and
3. Description of withdrawals and dropouts.

The items are presented as questions to elicit yes or no answers. Points awarded for items 1 and 2 depended on the quality of the description of the methods to generate the sequence of randomisation and/or on the quality of the description of the method of double blinding. If the trial had been described as randomised and/or double blind, but there was no description of the methods used to generate the sequence of randomisation or the double blinding conditions, one point was awarded in each case. If the method of generating the sequence of randomisation and/or blinding had been described, one additional point was given to each item if the method was appropriate. A method to generate randomisation sequences was regarded as adequate if it allowed each study participant to have the same chance of receiving each intervention, and if the investigators could not predict which intervention was next. Double blinding was considered appropriate if it was stated or implied that neither the person doing the assessment nor the study participant could identify the intervention being assessed. Conversely, if the method of generating the sequence of randomisation and/or blinding was described but not appropriate, the relevant item was given zero points. The third item, withdrawals and dropouts, was awarded as zero points for a negative answer and one point for a positive. For a positive answer, the number of withdrawals and dropouts and the reasons had to be stated in each of the comparison groups. If there were no withdrawals, it should have been stated in the report.

Quality assessment of studies was done independently by two reviewers. Discrepancies in the interpretation were resolved by consensus.

Measures of treatment effect

Meta-analysis was performed combining the Odds Ratios (OR) of the individual studies in a global OR, using both a random effect model (DerSimonian and Laird) and a fixed effect model (Peto method). Significance and 95% confidence intervals (95% CI) were provided for the combined OR. All calculations were performed with the Cochrane Collaboration's RevMan 4.2.

"Absolute risk reduction" (ARR; or "risk difference"), "relative risk reduction" (RRR), and "numbers needed to treat" (NNT) to prevent one episode of rebleeding were also calculated for the pooled data.

Data synthesis

The main outcome considered in this study was "percentage of patients having recurrence of bleeding" due to peptic ulcer.

Dropouts were considered as not having recurrent bleeding, as it is the most frequent outcome (see Background). In addition, it seems to be exceptional that patients having recurrent bleeding are lost for follow-up, as it is logical to assume that these patients will be finally included in the analysis

Sensitivity analysis

Subanalyses were planned a priori depending on: Quality of the studies (based on quality score proposed by Jadad, see appropriate section), type of ulcer disease (duodenal/gastric), and duration of follow-up. Furthermore, subanalyses excluding those studies where rebleeding could be potentially explained by NSAID use were planned. Finally, assessment of potential role for *H. pylori* eradication failure, or recurrence of *H. pylori* infection, in patients with rebleeding were also planned.

RESULTS

Description of studies

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

Included studies

Seven studies finally fulfilled the inclusion criteria and contained data for the first planned comparison: *H. pylori* eradication therapy vs. non-eradication therapy with antisecretors without subsequent long-term maintenance antisecretory therapy (Arkkila 2003; Bataga 1997; Graham 1993; Jaspersen 1995a; Lai 2000; Rokkas 1995; Vcev 1996). Detailed characteristics of the studies are shown in the table 'Characteristics of included studies'. Three-hundred and seventy five patients were included in the eradication therapy group, while 203 were included in the group receiving non-eradication therapy. Details of eradication and antisecretory treatment of included studies are summarized in Table 1. Three studies prescribed, as eradication regimen, a bismuth-based triple therapy, three other studies prescribed omeprazole-based dual therapy (omeprazole plus amoxicillin), and in one study both eradication regimens were used. These eradication regimens were administered for 10 to 14 days.

With respect to the second planned comparison (*H. pylori* eradication therapy vs. non-eradication therapy with antisecretors followed by long-term maintenance antisecretory therapy), three studies fulfilled the inclusion criteria (Riemann 1997; Santander 1996; Sung 1997), detailed characteristics of them also being shown in the table 'Characteristics of included studies'. Two-hundred and fifty seven patients were included in the eradication therapy group, while 213 received long-term maintenance antisecretory therapy. Details of eradication and antisecretory treatment of

included studies are summarized in Table 1. One study prescribed, as eradication regimen, a bismuth-based triple therapy, a second study prescribed omeprazole-based dual therapy (omeprazole plus amoxicillin), and in a third study both regimens were used. These eradication regimens were administered for 7 to 12 days. Antisecretory maintenance therapy with ranitidine 150 mg od was administered in two studies, while in a third study ranitidine 150 mg od or omeprazole 20 mg od was used as maintenance regimen.
No new included studies were found when the searches were run again in 2005 and 2008.

Excluded studies

Excluded studies and respective causes of exclusion are summarized in the table 'Characteristics of excluded studies'. As shown in the table, causes of exclusion were: rebleeding not evaluated, less than six-month follow-up, no control group (all patients received *H. pylori* eradication therapy), no previous upper gastrointestinal bleeding, all patients received NSAIDs, no *H. pylori* eradication group, or control group included only *H. pylori*-negative patients or patients with unknown *H. pylori* status.

Risk of bias in included studies

Assessment of study quality

From the seven studies included in the first comparison (eradication therapy vs. non-eradication therapy without subsequent maintenance antisecretory therapy), two studies had a Jadad's quality score of 1, two more studies had a score of 2, and the three remaining studies had a score of 3 (see table of 'Characteristics of included studies') (a score > or = 3 has been reported to indicate high quality; Jadad 1996). All studies were randomised, but none of them were double-blinded. Allocation concealment was adequate in only two studies. One study was only in abstract form (and not in complete article form) (Vcev 1996).
From the three studies included in the second comparison (*H. pylori* eradication therapy vs. non-eradication therapy with long-term maintenance antisecretory therapy), two studies had a Jadad's quality score of 2, and the remaining study had a score of 1 (see table of 'Characteristics of included studies'). This last study was controlled but not randomised, although it was stated that "prospective allocation into the *H. pylori* treatment regimen or the maintenance regimen was performed". None of the studies were double-blinded. Allocation concealment was adequate in only one study. All the studies were in complete article form.

Effects of interventions

Comparison 1 - Eradication versus non eradication therapy (without long term maintenance antisecretory therapy)

Seven studies with a total of 578 participants were included in the first comparison: mean percentage of rebleeding in *H. pylori* eradication therapy group was 2.9% (95% CI 0.10 to 0.32), and in the non-eradication therapy group without subsequent long-term maintenance antisecretory therapy it was 20% (95% CI 14 to 25%). The OR for this comparison was 0.17 (95% CI 0.10 to 0.32; P<0.00001) using a fixed effect model, and 0.20 (95% CI 0.10 to 0.41; P<0.00001) with a random effect model. Respective values for the RR were 0.22 (95% CI 0.12 to 0.40; P<0.00001) and 0.26 (95% CI 0.14 to 0.48; P<0.0001). There was no statistically significant heterogeneity (test for heterogeneity chi-square = 6.14, P=0.41). ARR or "risk difference" between the two groups was -0.15 (95% CI -0.21 to -0.09; P<0.00001) with the fixed and (RD -0.17; 95% CI -0.26 to -0.08; P<0.0002 Analysis 1.1) with the random effect models. The NNT with eradication therapy to prevent one episode of rebleeding, compared with non-eradication therapy, was 7 (95% CI 5 to 11) with the fixed effect model.

NSAID use

One of the participants who had recurrence of haemorrhage in the study by Lai et al (Lai 2000) took NSAIDs at the time of rebleeding. Thus, subanalysis of the data excluding this patient resulted in rebleeding rate of 10/374 (2.7%, 95% CI 1.5 to 5%) in the group receiving *H. pylori* eradication therapy, OR of 0.16 (95% CI 0.09 to 0.30; P<0.00001; Analysis 1.2), RR of 0.20 (95% CI 0.11 to 0.38; P<0.00001), ARR of -0.15 (95% CI -0.21 to -0.10; P<0.00001), and NNT of 7 (95% CI 5 to 10) (fixed effect model).

H. pylori eradication failure

In the study by Lai et al (Lai 2000), four out of the six participants with a rebleeding episode in the eradication treatment group had failed to eradicate *H. pylori* infection. In the study by Vcev et al (Vcev 1996), all the three participants with recurrence of bleeding had failed to eradicate *H. pylori* infection with antibiotic therapy. Therefore, when these seven participants were excluded from the analysis, rebleeding occurred in 4/371 participants (1.1%, 95% CI 0.4 to 2.7%) in *H. pylori* eradication therapy group, OR was 0.10 (95% CI 0.05 to 0.19; P<0.00001), RR 0.10 (95% CI 0.05 to 0.24; P<0.00001), ARR -0.17 (95% CI -0.23 to -0.12;P<0.00001; Analysis 1.3), and NNT 6 (95% CI 3 to 7) (fixed effect model).

Recurrent bleeding considering high quality studies

Of the studies included in Comparison 1, when only the three high quality studies (having a Jadad's quality score of 3) were included (see table of 'Characteristics of included studies'), the Peto OR

was 0.27; 95% CI 0.12 to 0.61, P= 0.002; Analysis 1.4), RR 0.33 (95% CI 0.15 to 0.70; P=0.004), ARR -0.10 (95% CI -0.17 to -0.03; P=0.004), and NNT 10 (95% CI 6 to 33) (fixed effect model).

Comparison 2 - Eradication therapy versus long term maintenance anti-secretory therapy.

Three studies with a total of 470 participants were included. Mean percentage of rebleeding in *H. pylori* eradication therapy group was 1.6% (95% CI 0.6 to 3.9%), and in non-eradication therapy group with long-term maintenance antisecretory therapy it was 5.6% (95% CI 2.5 to 8.7%). The OR for this comparison was 0.24 (Peto OR 0.24; 95% CI 0.09 to 0.67; P=0.007; Analysis 2.1) using a fixed effect model, and 0.26 (95% CI 0.08 to 0.80; P= 0.02) with a random effect model. Respective values for RR were 0.27 (95% CI 0.09 to 0.77; P=0.01) and 0.28 (95% CI 0.10 to 0.82; P=0.02). There was no statistically significant heterogeneity (test for heterogeneity chi-square = 0.89, P=0.64). ARR or "risk difference" between the two groups was -0.05 (95% CI -0.08 to -0.01; P=0.02) with the fixed effect model, and -0.04 (95% CI -0.09 to -0.01; P=0.10) with the random effect model. The NNT with eradication therapy to prevent one episode of rebleeding, compared with long-term maintenance antisecretory therapy, was 20 (95% CI 12 to 100) with the fixed effect model.

NSAID use

There were two participants suffering from recurrence of haemorrhage in the study by Riemann et al (Riemann 1997), who had taken NSAIDs at the time of rebleeding (and they were *H. pylori*-negative). Subanalysis of the data excluding these two participants in the group receiving *H. pylori* eradication therapy were: rebleeding rate of 2/255 (0.78%, 95% CI 0.22 to 2.8%), RR of 0.16 (95% CI 0.04 to 0.58; P=0.005), OR of 0.14 (95% CI 0.05 to 0.43; P=0.0006; Analysis 2.2), ARR of -0.05 (95% CI -0.09 to -0.02; P=0.003), and NNT of 20 (95% CI 11 to 50) (fixed effect model).

Recurrent bleeding considering high quality studies

When trying to perform separate comparisons depending on the quality of studies in Comparison 2, all studies were classified as low quality (one of which was non-randomised (Santander 1996)), and therefore the influence of this variable could not be adequately assessed.

Additional planned subanalyses

Type of ulcer disease

In the first comparison, Eradication versus non eradication therapy (without long term maintenance antisecretory therapy), all but two studies included participants with only duodenal ulcers (see table of "Characteristics of included studies"), thus precluding adequate subanalysis of the results depending on the ulcer location (duodenal or gastric). Furthermore, in the second comparison, the three studies included participants with both duodenal and gastric ulcer, precluding again planned subanalysis.

Duration of follow-up

From the 10 studies included in the meta-analysis, all but two had a similar follow-up of 12 months (see table of "Characteristics of included studies"). Therefore, the influence of this variable on the outcome of the review (e.g. rate of rebleeding) could not be adequately assessed.

Recurrence of *H. pylori* infection

In the first comparison, one of the participants who had recurrence of haemorrhage in the study by Lai et al (Lai 2000) had recurrence of *H. pylori* infection at the time of rebleeding, while in the second comparison, *H. pylori* recurrence occurred in the two participants having recurrence of haemorrhage in the study by Santander et al (Santander 1996).

Rebleeding in participants with *H. pylori* eradication success

Rebleeding in participants in whom *H. pylori* eradication was achieved (and did not receive maintenance antisecretory therapy) in studies included in the meta-analysis and in other uncontrolled studies from the literature are summarized in Table 2. Overall, from 1370 participants in whom *H. pylori* infection had been eradicated, mean rate of rebleeding (weighted mean) was 1.24% (95% CI 0.8 to 2%). However, as the follow-up time markedly varied among studies, this factor needs to be taken into account. Thus, follow-up periods in each study, measured in patient-years, and respective yearly bleeding (in patient-years^{-1}), are also included in Table 2. A total of 2179 patient-years of follow-up was calculated from all studies. A total of 17 rebleedings were observed among participants with *H. pylori* eradication success, yielding a yearly recurrence of 0.78% (95% CI 0.5 to 1.2) patient-years^{-1}.

DISCUSSION

Summary of main results

The main result of the present meta-analysis is that rebleeding is less frequent after *H. pylori* eradication therapy than after non-

eradication antisecretory therapy, both with or without subsequent long-term maintenance antisecretory therapy, with ORs of about 0.17-0.25. This advantage is expressed by a NNT with eradication therapy to prevent one episode of rebleeding of only 7 when compared with ulcer healing treatment alone, and of 20 when compared with long-term maintenance antisecretory therapy (mainly because the risk of rebleeding with maintenance antisecretory therapy was relatively low), in agreement with results of previous report (Sharma 2001).

The decision of whether maintenance antisecretory therapy must be continued or stopped in patients with a history of peptic ulcer haemorrhage and prior *H. pylori* eradication will depend on the true efficacy of *H. pylori* eradication for the prevention of recurrent bleeding. Thus, mean rebleeding rate in patients in whom *H. pylori* eradication was achieved (and did not receive maintenance antisecretory therapy) in studies included in the meta-analysis and in other uncontrolled studies from the literature (see Table 2) was of only 1.24%. However, as the follow-up time markedly varied among studies (many of them being higher than 12 months), the risk of rebleeding is better expressed as "yearly" recurrence of bleeding, which was of only 0.78% patient-years^{-1}.

In brief, probability of having recurrence of haemorrhage after *H. pylori* eradication is less than 1% per year, which arguments against the necessity or prescribing maintenance antisecretory therapy in these cases. Two recent randomised studies (Lai 1998; Pellicano 2001) have directly compared, after anti-*H. pylori* therapy had been prescribed and eradication confirmed, long-term maintenance antisecretory therapy vs. no treatment, reporting no differences in rebleeding rates, during a mean follow-up period of up to 47 months. Furthermore, the protective effect of *H. pylori* eradication seems to be maintained at least in the medium-term follow-up, as rebleeding rates of 0% have been reported even after 24 months (Amendola 1999; Loperfido 2001; Macri 1998; Pellicano 2001). This observation seems to agree with the relatively low incidence of reinfection reported after *H. pylori* eradication, at least in developed countries, as discussed later.

Therefore, the results of our systematic review support the recommendation that it is unnecessary to continue antisecretory maintenance therapy in patients with a history of peptic ulcer bleeding and prior *H. pylori* eradication (Laine 1995; McColl 1995; Laine 1996). It must be emphasized, therefore, that in patients with previous peptic ulcer bleeding the success of *H. pylori* eradication should always be confirmed (McColl 1995; Howden 1998; van Leerdam 2002). In case of initial eradication failures, re-treatment should be prescribed. In clinical practice, several studies have demonstrated that *H. pylori* eradication can finally be achieved in almost all patients if several rescue therapies are consecutively given (Gisbert 2002). The rare patients with a hypersecretory state or true idiopathic ulcers with coincident *H. pylori* infection may have recurrent bleeding despite *H. pylori* eradication (Laine 1995). However, this should be a very uncommon occurrence and, probably, does not justify the routine use of maintenance antisecretory therapy after *H. pylori* eradication (Laine 1995; Laine 1996).

Nevertheless, as it has been shown by the present meta-analysis, the prescription of *H. pylori* eradication therapy does not always prevent recurrence of bleeding, and several explanations could be suggested. Firstly, as antibiotic regimens are not 100% effective to treat *H. pylori* infection, eradication failures may explain, obviously, some of the rebleedings. For example, in the study by Lai et al (Lai 2000), 4 out of the 6 patients with a rebleeding episode in the eradication treatment group had failed to eradicate *H. pylori* infection; and in the study by Vcev et al (Vcev 1996), all the three patients with recurrence of bleeding had failed to eradicate *H. pylori* infection with antibiotic therapy. Therefore, when these seven patients were excluded from the analysis, the rebleeding rate in the eradication therapy group was of only 1.1%.

Secondly, as recurrence of *H. pylori* infection seems to be an important cause of subsequent ulcer recurrence (and consequent rebleeding) (Gisbert 1998), the study of incidence of the organism's recurrence represents an important issue, as high reinfection rate offsets the expected beneficial effects of *H. pylori* eradication. In the comparison, one of the patients who had recurrence of haemorrhage in the study by Lai et al (Lai 2000) had recurrence of *H. pylori* infection at the time of rebleeding, while in the second comparison *H. pylori* recurrence occurred in the two patients having recurrence of haemorrhage in the study by Santander et al (Santander 1996). Other studies have also reported rebleeding only in patients with reinfection (Jaspersen 1995b). Fortunately, recurrence of *H. pylori* infection seems to be a relatively infrequent event in developed countries (Cutler 1993; Forbes 1994; Elta 1994; Bell 1996; Xia 1997; Gisbert 1998) and, therefore, initial *H. pylori* eradication is likely to confer long-term protection from rebleeding. Nevertheless, in countries where the rate of reinfection is higher, rebleeding may be a relevant problem even in patients with initial successful eradication.

Thirdly, NSAID intake probably explains a major percentage of rebleedings occurring despite *H. pylori* eradication. The use of these drugs at the time of rebleeding seemed to explain some of the episodes in the studies included in this meta-analysis (Lai 2000; Riemann 1997), and also in other studies (Huellin 1998). Although excluding from the analysis those patients with NSAID use will give us more strict data about the true role of *H. pylori* eradication in the prevention of recurrent bleeding, in clinical practice a relevant group of patients will probably take these drugs. Because clinical research, unlike basic science research, has clinical practicality as its foundation and not pure knowledge, we must probably accept the real results (including patients taking NSAIDs) as predictive of outcome for the population in question (Barthel 1997).

Several advantages are associated with *H. pylori* eradication therapy, when compared with long-term maintenance antisecretory therapy in patients with previous peptic ulcer bleeding. Firstly, as previously shown, the first strategy is more effective than the second. It must be emphasized that the prevention of rebleeding

with antisecretory maintenance therapy is, in any case, incomplete, since about 5-10% of the patients who receive this regimen have recurrent bleeding (Jensen 1994; Laine 1996; Jaspersen 1995c). Furthermore, some data exist suggesting that continued administration of H2 receptor antagonist leads to pharmacological tolerance, with a decrease in its effect in controlling gastric acid secretion (Lachman 2000). Secondly, one disadvantage of maintenance antisecretory therapy is the requirement for long-term compliance; patient compliance with antisecretors may not be sustained but wane, especially when symptoms are absent. Thirdly, it is obvious that 7-10 days of antibiotic therapy is more convenient for the patients than many years of continuous antisecretory treatment; therefore, even if these two forms of therapy would be equivalent (in terms of efficacy), it makes much more sense to choose the treatment that requires only a few days of therapy rather than the one that requires daily medication forever.

Finally, maintenance therapy is expensive. The cost of antibiotic therapy is lower than long-term management by antisecretory drugs, mainly because the financial outlay for medication in the former approach is not cumulative as with the later (Jonsson 1996; Sonnenberg 1999). The present meta-analysis clearly shows that the strategy of testing for *H. pylori* and treating if positive in patients with previous upper gastrointestinal haemorrhage secondary to peptic ulcer is considerably more effective than PPI maintenance therapy or no treatment. In addition, cost-effectiveness analysis underlines that this strategy is also the most favourable from a financial point of view even when wide variations of the current scenario are considered. Sharma et al (Sharma 2001) compared treatment of *H. pylori* infection with other approaches to prevent recurrent ulcer haemorrhage to determine the least costly strategy. Decision model-based cost minimization analysis demonstrated that treatment of *H. pylori* infection was the least costly strategy unless the incidence of complicated recurrences after treatment was over 6%, or the cost of confirming eradication was over $741. Other authors have compared several strategies for the prevention of recurrent ulcer-related haemorrhage, from a cost-effectiveness perspective (Ofman 2002). Decision analysis was used to compare the cost-per-recurrent haemorrhage prevented for 11 strategies over 1 year. The test/retest eradication strategy with maintenance PPI therapy for *H. pylori*-negative patients was most effective (prevention of recurrence in 96%). The test/retest eradication strategy with maintenance H2 receptor antagonist therapy for *H. pylori*-negative patients was least costly ($1070). The test/retest strategies were dominant with average cost-effectiveness ratios of 1118-1310 $/recurrent haemorrhage prevented with maintenance antisecretory therapy. These studies shows that the strategies based on the diagnosis and treatment of *H. pylori* are cost-effective for the prevention of recurrent ulcer-related haemorrhage because they result in fewer recurrent haemorrhages and fewer patients requiring antisecretory therapy. In summary, these studies emphasize that the relative "small" advantage in preventing rebleeding results in a substantial health-care cost saving.

Although, based on aforementioned arguments, it seems logical to test all patients with peptic ulcer bleeding for *H. pylori* infection, and to prescribe eradication therapy to *H. pylori*-positive patients, in clinical practice this strategy seems to have limited divulgation. Thus, it is disappointing that relatively few patients admitted to hospital with peptic ulcer haemorrhage appear to be tested for the infection or to be treated when present. In this respect, a recent study on a high number of such patients admitted to US hospitals found that only 56% were tested for *H. pylori* infection or appropriately treated for it (Hood 1999). These discouraging results regarding the implementation of *H. pylori* testing and treating have been confirmed in a review of case notes and endoscopy records of patients presenting to Auckland Hospital (Garrigan 1999). Finally, in another study aimed to investigate current management of ulcer haemorrhage in the Netherlands, it was found that *H. pylori* eradication was confirmed by only 64% of the physicians (van Leerdam 2002). In summary, it seems evident that management of patients with previous peptic ulcer haemorrhage is only partly in accordance with evidence-based medicine.

Overall completeness and applicability of evidence

The present meta-analysis suffers from several possible limitations. Firstly, some limitation of the studies included need to be recognized: they were relatively small, none of them were double-blinded (the overall quality of the studies was low), and the follow-up period was limited to only one year in most cases. In this respect, it remains to be demonstrated that the beneficial effects of *H. pylori* eradication are maintained in the future, mainly because, as previously mentioned, *H. pylori* reinfection could be a problem in the long-term management. Secondly, the studies included in the meta-analysis were not homogeneous regarding *H. pylori* eradication regimen (and therefore regarding efficacy to successfully eradicate the organism); however, it seems that the prophylactic effect of *H. pylori* eradication on recurrence of haemorrhage depends mainly, or perhaps exclusively, on the capacity to eradicate the infection, which is supported by the encouraging results obtained with many different antibiotic regimens. Thirdly, antisecretory maintenance therapy also differed among different studies; thus, while some authors prescribed H2 receptor antagonist, others used PPI. Nevertheless, the findings of the meta-analysis were not statistically heterogeneous, thus suggesting that the combination of the study results is reasonable.

Quality of the evidence

Quality scales and Cochrane reviews

The Cochrane Handbook explicitly discourages the use of quality scales in Cochrane systematic reviews (Higgins 2008; section 8.3.3 and section 8.10.1)

However the present review evaluates the quality using the Jadad scale for historical reasons (quality assessment was performed in the previously published version of the review). None of the studies included in the meta-analysis were double-blinded and the overall quality of the studies included was low. Only three studies showed acceptable quality (score > 3) based on Jadad scale while the remaining scored lower.

AUTHORS' CONCLUSIONS

Implications for practice

Treatment of *H. pylori* infection is more effective than antisecretory non-eradicating therapy (with or without long-term maintenance antisecretory therapy) in preventing recurrent bleeding from peptic ulcer. When *H. pylori* eradication therapy is compared with ulcer healing treatment alone (without subsequent long-term maintenance antisecretory therapy), the magnitude of the beneficial effect of the first strategy is remarkable (NNT of only about 7, and even 6 if *H. pylori* eradication success is confirmed). However, when the comparison is performed against long-term maintenance antisecretory therapy, the "clinical impact" on the recurrence of bleeding is smaller (NNT of 20), mainly because the risk of rebleeding with maintenance therapy is relatively low. Nevertheless, in addition to efficacy, other relevant advantages of *H. pylori* eradication treatment, such as better compliance, better convenience, and lower cost, advised also for the use of antibiotic therapy. Finally, it seems unnecessary to continue antisecretory maintenance therapy in patients with a history of peptic ulcer bleeding and prior *H. pylori* eradication. Consequently, all patients with peptic ulcer bleeding should be tested for *H. pylori* infection, and eradication therapy should be prescribed to *H. pylori*-positive patients.

Implications for research

The findings of this review are relatively robust and unlikely to change with the result of further short- or medium-term follow-up trials. Although further short term trials of greater sample size would be useful, the main area of uncertainly is the assessment of the long-term beneficial results of *H. pylori* eradication and the role of the factors which could explain recurrence of bleeding despite *H. pylori* eradication success (especially NSAID use and *H. pylori* reinfection).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arkkila 2003

Methods	Randomized Not double-blinded
Participants	Duodenal and gastric ulcer Some patients used NSAIDs (19%) or ASA (35%)
Interventions	OBAM/OA vs. O No maintenance antisecretory therapy
Outcomes	Rebleeding Follow-up 12 months in all patients
Notes	Q=3 Eradication rates: 92% in eradication groups, and 4% in antisecretory group

Risk of bias

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

Bataga 1997

Methods	Randomized Not double-blinded
Participants	Duodenal ulcer NSAID use unknown
Interventions	BAM (with or without endoscopic haemostasis) vs. H2-antagonist No maintenance antisecretory therapy
Outcomes	Rebleeding Follow-up 12 months in all patients
Notes	Q=1 Eradication rates not provided in any group Abstract form only (no complete article)

Risk of bias

Bataga 1997 (*Continued*)

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

Graham 1993

Methods	Randomized Not double-blinded
Participants	Duodenal and gastric ulcer Some patients (28%) used NSAIDs
Interventions	BMT vs. ranitidine No maintenance antisecretory therapy
Outcomes	Rebleeding Mean follow-up 12 months in eradication group, and 9 months in antisecretory group
Notes	Q=2 Eradication rates: 81% in eradication group, and 0% in antisecretory group

Risk of bias

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

Jaspersen 1995a

Methods	Randomized Not double-blinded
Participants	Duodenal ulcer. No patient used NSAIDs
Interventions	OA vs. O No maintenance antisecretory therapy
Outcomes	Rebleeding Follow-up 12 months in all patients

Jaspersen 1995a (*Continued*)

Notes	Q=2 Eradication rates: 83% in eradication group, and 5% in antisecretory group

Risk of bias

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

Lai 2000

Methods	Randomized Not double-blinded
Participants	Duodenal ulcer No patient used NSAIDs
Interventions	BAM vs. B No maintenance antisecretory therapy
Outcomes	Rebleeding Mean follow-up 53 months
Notes	Q=3 Eradication rates: 85% in eradication group, and 2% in antisecretory group

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Consecutive patients were randomized and the treatment was determined by a list of random numbers generated by computer"
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	

Riemann 1997

Methods	Randomized Not double-blinded
Participants	Duodenal and gastric ulcer No patient used NSAIDs
Interventions	OA vs. ranitidine (as maintenance antisecretory therapy)
Outcomes	Rebleeding Mean follow-up 19 months
Notes	Q=2 Eradication rates: 89% in eradication group, and not provided in antisecretory group

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	

Rokkas 1995

Methods	Randomized Not double-blinded
Participants	Duodenal ulcer Some patients (6%) used NSAIDs
Interventions	OA vs. O No maintenance antisecretory therapy
Outcomes	Rebleeding Follow-up 12 months in all patients
Notes	Q=3 Eradication rates: 81% in eradication group, and 13% in antisecretory group

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Random allocation of patients was achieved by opening scaled envelopes according to a computer-generated program of random numbers"

Rokkas 1995 (*Continued*)

Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	

Santander 1996

Methods	Not randomised Not double-blinded
Participants	Duodenal and gastric ulcer No patient used NSAIDs
Interventions	OA/OC/BAM vs. ranitidine/O (as maintenance antisecretory therapy)
Outcomes	Rebleeding Follow-up 12 months in all patients
Notes	Q=1 Eradication rates: 100% in eradication group (retreatment was prescribed in failures), and not provided in antisecretory group

Risk of bias

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

Sung 1997

Methods	Randomized Not double-blinded
Participants	Duodenal and gastric ulcer No patient used NSAIDs
Interventions	BAM vs. ranitidine (as maintenance antisecretory therapy)
Outcomes	Rebleeding Median follow-up 12 months

Sung 1997 (*Continued*)

Notes	Q=2 Eradication rates: 98% in eradication group, and 6% in antisecretory group

Risk of bias

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

Vcev 1996

Methods	Randomized Not double-blinded
Participants	Duodenal ulcer NSAID use unknown
Interventions	OA vs. O No maintenance antisecretory therapy
Outcomes	Rebleeding Follow-up 12 months in all patients
Notes	Q=1 Eradication rates: 72% in eradication group, and 0% in antisecretory group

Risk of bias

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

Intervention (treatment): B: bismuth; A: amoxicillin; M: metronidazole; O: omeprazole; C: clarithromycin; T: tetracycline; details of eradication and antisecretory treatment are provided in additional table (01).
NSAIDs: non-steroidal anti-inflammatory drugs (taken by the patient previous to the inclusion in the study).
ASA: acetylsalicylic acid (taken by the patient previous to the inclusion in the study).
Q: quality score (Jadad scale, from 0 to 5 points, see appropriate section).

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

Study	Reason for exclusion
Adamek 1994	Rebleeding not evaluated
Altorjay 2000	Rebleeding not evaluated Less than six-month follow-up
Amendola 1999	No control group (all patients received *H. pylori* eradication therapy)
Arkkila 2001	Insufficient data (no response from the authors)
Capurso 2001	No previous upper gastrointestinal bleeding No control group (all patients received *H. pylori* eradication therapy)
Chan 1997	All patients received NSAIDs
Chan 1998	Rebleeding not evaluated
Chan 2001	All patients received NSAIDs
Chan 2002a	All patients received NSAIDs
Chan 2002b	All patients received NSAIDs No previous upper gastrointestinal bleeding in one group
Chen 1996	No control group (all patients received *H. pylori* eradication therapy) Less than six-month follow-up
Chen 1998	No control group (all patients received *H. pylori* eradication therapy) Less than six-months follow-up
Di Mario 1997	No control group (all patients received *H. pylori* eradication therapy)
Fakhreih 1995	No control group (all patients received *H. pylori* eradication therapy)
Gisbert 1995	No control group (all patients -one- received *H. pylori* eradication therapy)
Gisbert 1999	No control group (all patients received *H. pylori* eradication therapy)
Hsieh 2001	Rebleeding not evaluated
Huellin 1998	No control group (all patients received *H. pylori* eradication therapy)
Jaspersen 1994a	No control group (all patients received *H. pylori* eradication therapy)

(*Continued*)

Jaspersen 1994b	No control group (all patients received *H. pylori* eradication therapy) Less than six-month follow-up
Jaspersen 1995b	No control group (all patients received *H. pylori* eradication therapy)
Krizman 1997	No control group (all patients received *H. pylori* eradication therapy)
Kung 1997	No control group (all patients received *H. pylori* eradication therapy) Less than six-month follow-up
Labenz 1994	No control group (all patients received *H. pylori* eradication therapy)
Lai 1998	No control group (all patients received *H. pylori* eradication therapy)
Lai 2000b	Rebleeding not evaluated.
Lee 1998	Rebleeding not evaluated
Lee 1999	No control group (all patients received *H. pylori* eradication therapy)
Lin 1999	No *H. pylori* eradication group
Loperfido 2001	No control group (all patients received *H. pylori* eradication therapy)
Macri 1998	No control group (all patients received *H. pylori* eradication therapy)
Martino 1998	No control group (all patients received *H. pylori* eradication therapy) No previous upper gastrointestinal bleeding
Pamos 1998	Control group included only *H. pylori*-negative patients or patients with unknown *H. pylori* status
Pauly 1997	No control group (all *H. pylori*-positive patients received eradication therapy)
Pazzi 1996	No control group (all patients received *H. pylori* eradication therapy)
Pazzi 1999	No control group (all patients received *H. pylori* eradication therapy)
Pellicano 2001	No control group (all patients received *H. pylori* eradication therapy)
Pica 1996	No control group (all patients received *H. pylori* eradication therapy)
Romero 2000	Rebleeding not evaluated
Ruiz Gomez 2002	Rebleeding not evaluated
Seppälä 1995	Insufficient data (no response from the authors)

(*Continued)*

Sheu 1996	Rebleeding not evaluated
Sheu 1999	Rebleeding not evaluated
Sheu 2002	No control group (all patients received *H. pylori* eradication therapy) Less than six-month follow-up
Siu 1999	No control group (all patients received *H. pylori* eradication therapy)
Sonnenberg 1999	No previous upper gastrointestinal bleeding
van der Voort 2001	Stress ulcer bleeding No previous upper gastrointestinal bleeding
Vergara 2000	No control group (all patients received *H. pylori* eradication therapy)

NSAIDs: non-steroidal anti-inflammatory drugs

DATA AND ANALYSES

Comparison 1. Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent bleeding	7	578	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.10, 0.32]
2 Recurrent bleeding excluding NSAID users	7	577	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.09, 0.30]
3 Recurrent bleeding excluding H. pylori eradication failures	7	574	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.10 [0.05, 0.19]
4 Recurrent bleeding considering high quality studies	3	374	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.12, 0.61]

Comparison 2. Eradication therapy vs. long-term maintenance antisecretory therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent bleeding	3	470	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.24 [0.09, 0.67]
2 Recurrent bleeding excluding NSAID users	3	468	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.05, 0.43]

Analysis 1.1. Comparison 1 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy), Outcome 1 Recurrent bleeding.

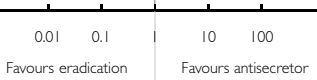
Review: Helicobacter pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer

Comparison: 1 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy)

Outcome: 1 Recurrent bleeding

Study or subgroup	Eradication tx. n/N	No eradication tx. n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Arkkila 2003	2/176	3/47		7.7 %	0.09 [0.01, 0.81]
Bataga 1997	0/27	3/20		6.6 %	0.09 [0.01, 0.89]
Graham 1993	0/17	4/14		8.4 %	0.09 [0.01, 0.68]
Jaspersen 1995a	0/29	6/22		12.5 %	0.08 [0.01, 0.42]
Lai 2000	6/60	12/60		36.3 %	0.46 [0.17, 1.25]
Rokkas 1995	0/16	5/15		10.2 %	0.09 [0.01, 0.61]
Vcev 1996	3/50	7/25		18.4 %	0.15 [0.04, 0.62]
Total (95% CI)	**375**	**203**		**100.0 %**	**0.17 [0.10, 0.32]**

Total events: 11 (Eradication tx.), 40 (No eradication tx.)
Heterogeneity: Chi?? = 6.14, df = 6 (P = 0.41); I?? =2%
Test for overall effect: Z = 5.68 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy), Outcome 2 Recurrent bleeding excluding NSAID users.

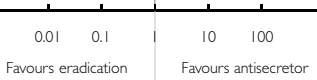
Review: Helicobacter pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer

Comparison: 1 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy)

Outcome: 2 Recurrent bleeding excluding NSAID users

Study or subgroup	Eradication tx. n/N	No eradication tx. n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Arkkila 2003	2/176	3/47		7.8 %	0.09 [0.01, 0.81]
Bataga 1997	0/27	3/20		6.7 %	0.09 [0.01, 0.89]
Graham 1993	0/17	4/14		8.5 %	0.09 [0.01, 0.68]
Jaspersen 1995a	0/29	6/22		12.7 %	0.08 [0.01, 0.42]
Lai 2000	5/59	12/60		35.2 %	0.39 [0.14, 1.09]
Rokkas 1995	0/16	5/15		10.4 %	0.09 [0.01, 0.61]
Vcev 1996	3/50	7/25		18.7 %	0.15 [0.04, 0.62]
Total (95% CI)	**374**	**203**		**100.0 %**	**0.16 [0.09, 0.30]**

Total events: 10 (Eradication tx.), 40 (No eradication tx.)
Heterogeneity: Chi?? = 4.90, df = 6 (P = 0.56); I?? =0.0%
Test for overall effect: Z = 5.86 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy), Outcome 3 Recurrent bleeding excluding H. pylori eradication failures.

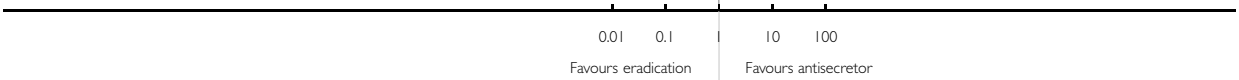
Review: Helicobacter pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer

Comparison: 1 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy)

Outcome: 3 Recurrent bleeding excluding H. pylori eradication failures

Study or subgroup	Eradication tx. n/N	No eradication tx. n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Arkkila 2003	2/176	3/47		8.7 %	0.09 [0.01, 0.81]
Bataga 1997	0/27	3/20		7.5 %	0.09 [0.01, 0.89]
Graham 1993	0/17	4/14		9.5 %	0.09 [0.01, 0.68]
Jaspersen 1995a	0/29	6/22		14.2 %	0.08 [0.01, 0.42]
Lai 2000	2/56	12/60		33.2 %	0.22 [0.07, 0.66]
Rokkas 1995	0/16	5/15		11.6 %	0.09 [0.01, 0.61]
Vcev 1996	0/50	7/25		15.3 %	0.04 [0.01, 0.20]
Total (95% CI)	**371**	**203**		**100.0 %**	**0.10 [0.05, 0.19]**

Total events: 4 (Eradication tx.), 40 (No eradication tx.)
Heterogeneity: Chi?? = 3.30, df = 6 (P = 0.77); I?? =0.0%
Test for overall effect: Z = 6.96 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy), Outcome 4 Recurrent bleeding considering high quality studies.

Review: Helicobacter pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer

Comparison: 1 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy)

Outcome: 4 Recurrent bleeding considering high quality studies

Study or subgroup	Eradication tx. n/N	No eradication tx. n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Arkkila 2003	2/176	3/47		14.2 %	0.09 [0.01, 0.81]
Lai 2000	6/60	12/60		67.0 %	0.46 [0.17, 1.25]
Rokkas 1995	0/16	5/15		18.8 %	0.09 [0.01, 0.61]
Total (95% CI)	**252**	**122**		**100.0 %**	**0.27 [0.12, 0.61]**

Total events: 8 (Eradication tx.), 20 (No eradication tx.)
Heterogeneity: Chi?? = 3.28, df = 2 (P = 0.19); I?? =39%
Test for overall effect: Z = 3.14 (P = 0.0017)
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Eradication therapy vs. long-term maintenance antisecretory therapy, Outcome 1 Recurrent bleeding.

Review: Helicobacter pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer

Comparison: 2 Eradication therapy vs. long-term maintenance antisecretory therapy

Outcome: 1 Recurrent bleeding

Study or subgroup	Eradication tx. n/N	Maintenance antisec. n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Riemann 1997	2/47	4/48		39.1 %	0.51 [0.10, 2.62]
Santander 1996	2/84	5/41		40.4 %	0.16 [0.03, 0.80]
Sung 1997	0/126	3/124		20.5 %	0.13 [0.01, 1.27]
Total (95% CI)	**257**	**213**		**100.0 %**	**0.24 [0.09, 0.67]**

Total events: 4 (Eradication tx.), 12 (Maintenance antisec.)

Heterogeneity: Chi?? = 1.31, df = 2 (P = 0.52); I?? =0.0%

Test for overall effect: Z = 2.72 (P = 0.0065)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Eradication therapy vs. long-term maintenance antisecretory therapy, Outcome 2 Recurrent bleeding excluding NSAID users.

Review: Helicobacter pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer

Comparison: 2 Eradication therapy vs. long-term maintenance antisecretory therapy

Outcome: 2 Recurrent bleeding excluding NSAID users

Study or subgroup	Eradication tx. n/N	Maintenance antisec. n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Riemann 1997	0/45	4/48		30.4 %	0.13 [0.02, 0.99]
Santander 1996	2/84	5/41		46.2 %	0.16 [0.03, 0.80]
Sung 1997	0/126	3/124		23.4 %	0.13 [0.01, 1.27]
Total (95% CI)	**255**	**213**		**100.0 %**	**0.14 [0.05, 0.43]**

Total events: 2 (Eradication tx.), 12 (Maintenance antisec.)
Heterogeneity: Chi?? = 0.02, df = 2 (P = 0.99); I?? =0.0%
Test for overall effect: Z = 3.45 (P = 0.00056)
Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Details of eradication and antisecretory treatment of included studies

Study ID	Eradication treatment	Antisecretory treatment
Arkkila 2003	Bismuth subcitrate, 120 q.i.d., for 14 days, amoxicillin, 500 mg q.i.d., metronidazole, 400 mg t.i.d., and omeprazole, 40 mg o.d., for 28 days; amoxicillin, 500 mg q.i.d., for 14 days, and omeprazole, 40 mg o.d., for 28 days	Omeprazole, 40 mg o.d., for 28 days plus placebo q.i.d. , for 14 days
Bataga 1997	H2-antagonist (dose not stated) for 7 days, followed by bismuth subcitrate, 240 mg b.i.d., metronidazole, 500 mg t.i.d., and amoxicillin 500 mg t.i.d., for 10 days (with and without endoscopic haemostasis with pure ethanol)	H2-antagonist (dose not stated) and antiacids for 7 days
Graham 1993	Bismuth subsalicylate 5-8 tablets daily, metronidazole, 250 mg t.i.d., and tetracycline, 500 mg q.i.d., for 14 days, and ranitidine, 300 mg o.d., until ulcer healing	Ranitidine, 300 mg o.d., until ulcer healing
Jaspersen 1995a	Omeprazole, 40 mg o.d. and amoxicillin, 1 g b.i.d., for 14 days	Omeprazole, 40 mg o.d., for 14 days

Table 1. Details of eradication and antisecretory treatment of included studies (*Continued*)

Lai 2000	Metronidazole, 300 mg q.i.d., and amoxicillin, 500 mg q.i.d., for 14 days, and tripotassium dicitrato bismuthate, 120 mg q.i.d., until ulcer healing	Tripotassium dicitrato bismuthate, 120 mg q.i.d., until ulcer healing
Riemann 1997	Omeprazole, 60 mg b.i.d, and amoxicillin, 750 mg t.i.d., for 10 days, followed by omeprazole, 20 mg o.d., for 30 days	Ranitidine, 300 mg o.d., for 6 weeks, followed by antisecretory maintenance therapy with ranitidine, 150 mg o.d
Rokkas 1995	Omeprazole, 20 mg o.d. for 30 days, followed by omeprazole, 20 mg t.i.d., and amoxicillin, 500 mg q.i.d., for 14 days	Omeprazole, 20 mg o.d., for 30 days, followed by omeprazole, 20 mg t.i.d., for 14 days
Santander 1996	Omeprazole, 20 mg b.i.d., and clarithromycin, 500 mg t.i.d., for 12 days; or omeprazole, 20 mg b.i.d., and amoxicillin, 500 mg t.i.d., for 10 days; or bismuth subsalicylate, 240 mg b.i.d., for 30 days, metronidazole, 500 mg t.i.d., for 10 days, and amoxicillin, 500 mg t.i.d., for 10 days	Antisecretory maintenance therapy with ranitidine, 150 mg o.d., or omeprazole, 20 mg o.d
Sung 1997	Bismuth subsalicylate, 120 mg q.i.d., metronidazole, 400 mg q.i.d., tetracycline, 500 mg q.i.d., and ranitidine, 300 mg o.d., for 7 days	Ranitidine, 300 mg o.d., for 6 weeks, followed by antisecretory maintenance therapy with ranitidine, 150 mg o.d
Vcev 1996	Omeprazole, 20 or 40 mg o.d, and amoxicillin, 500 mg q.i.d. or 1 g b.i.d., for 14 days, followed by omeprazole, 20 mg o.d., for 14 days	Omeprazole, 20 mg o.d., for 30 days
Footnotes:	o.d.: once per day; b.i.d.: two times per day; t.i.d.: three times per day; q.i.d.: four times per day	

Table 2. Rebleeding in H. pylori eradicated patients and no maintenance antisecretory treatment

Author & year	N. of patients	Mean follow-up (mo.)	Rebleeding (%)	Notes	Follow-up (p-y)	Yearly rebleeding (%
Arkkila 2003	176	12	2 (1.1%)	The two patients had Dieulafoy's ulcer	176	1.1
Bataga 1997	-	12	0 (0%)			
Graham 1993	13	12	0 (0%)		13	0
Jaspersen 1995a	24	12	0 (0%)		24	0

Table 2. Rebleeding in H. pylori eradicated patients and no maintenance antisecretory treatment (*Continued*)

Lai 2000	41	53	2 (4.9%)	One of these patients took NSAIDs at the time of rebleeding; another patient had recurrence of *H. pylori* infection at the time of rebleeding	177	3.4
Riemann 1997	42	19	2 (4.8%)	The two patients took NSAIDs at the time of rebleeding (and were *H. pylori*-negative)	66	3
Rokkas 1995	13	12	0 (0%)		13	0
Santander 1996	84	12	2 (2.4%)	The two patients had recurrence of *H. pylori* infection at the time of rebleeding	84	2.4
Sung 1997	108	12	0 (0%)		108	0
Vcev 1996	36	12	0 (0%)		36	0
Studies not included in the meta-analysis						
Amendola 1999	42	24	0 (0%)		84	0
Di Mario 1997	40	21	0 (0%)		70	0
Fakhreih 1995	61	12	3 (4.9%)		61	4.9
Gisbert 1999	111	12	0 (0%)		111	0
Huellin 1998	80	18	1 (1.2%)	This patient took NSAIDs at the time of rebleeding	120	0.8

Table 2. Rebleeding in H. pylori eradicated patients and no maintenance antisecretory treatment (*Continued*)

Jaspersen 1995b	29	12	1 (3.4%)	This patient had recurrence of *H. pylori* infection at the time of rebleeding	29	3.4
Krizman 1997	33	17	0 (0%)		47	0
Labenz 1994	42	17	0 (0%)		59	0
Lai 1998	29	11	0 (0%)		27	0
Lee 1999	92	15	0 (0%)		115	0
Loperfido 2001	38	24	0 (0%)		76	0
Macri 1998	21	48	0 (0%)		84	0
Pamos 1998	31	18	0 (0%)		46	0
Pazzi 1999	39	47	4 (10.3%)		153	2.6
Pellicano 2001	46	47	0 (0%)		180	0
Pica 1996	6	12	0 (0%)		6	0
Vergara 2000	93	27	0 (0%)		209	0
Total	1370		17 (1.24%)		2179	0.78
Footnotes:	p-y: patient-years	NSAIDs: non-steroidal anti-inflammatory drugs				

APPENDICES

Appendix 1. MEDLINE Search strategy

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. humans.sh.
11. 9 and 10
12. exp peptic ulcer hemorrhage/
13. exp peptic ulcer perforation/
14. (bleed$ adj5 ulcer$).tw.
15. (rebleed$ adj5 ulcer$).tw.
16. (recurrent adj5 bleed$ adj5 ulcer$).tw.
17. (acute adj5 bleed$ adj5 ulcer$).tw.
18. exp gastrointestinal hemorrhage/
19. (gastrointestinal adj5 bleed$).tw.
20. (gastrointestinal adj5 rebleed$).tw.
21. (gastrointestinal adj5 hemorrhag$).tw.
22. (gastrointestinal adj5 haemorrhag$).tw.
23. (ulcer adj5 hemorrhag$).tw.
24. (ulcer adj5 haemorrhag$).tw.
25. (ulcer adj5 perforat$).tw.
26. exp helicobacter pylori/
27. pylori$.tw.
28. or/12-25
29. or/26-27
30. 11 and 28 and 29
31. limit 30 to yr="2005 - 2008"

WHAT'S NEW

Last assessed as up-to-date: 22 June 2009.

Date	Event	Description
21 September 2010	Amended	Contact details updated.
23 July 2009	Review declared as stable	Searches, tables and figures last updated June 2009. Review declared stable by authors and no future updates planned

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 4, 2003

Date	Event	Description
23 June 2009	New search has been performed	Updated
30 October 2008	Amended	Converted to new review format.
17 January 2005	New search has been performed	Minor update, new studies sought but none found
8 February 2004	New search has been performed	New studies found and included or excluded

CONTRIBUTIONS OF AUTHORS

JP Gisbert developed the protocol, performed the main search strategy, assessed eligibility, extracted the data, performed the statistical analyses (meta-analysis), and wrote the manuscript.

S Khorrami, X Calvet and E Gené were involved in the search strategy, checked eligibility and data extraction.

F Carballo and E Dominguez-Muñoz were involved in developing the protocol and provided senior support in overseeing the project.

DECLARATIONS OF INTEREST

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INDEX TERMS

Medical Subject Headings (MeSH)

*Helicobacter pylori; Anti-Ulcer Agents [*therapeutic use]; Helicobacter Infections [*drug therapy]; Peptic Ulcer [*drug therapy; microbiology]; Peptic Ulcer Hemorrhage [*prevention & control]; Recurrence [prevention & control]

MeSH check words

Humans