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Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
Figure 1.	6
Figure 2.	7
Figure 3.	8
Figure 4.	9
Figure 5.	10
RESULTS	10
DISCUSSION	18
AUTHORS' CONCLUSIONS	21
ACKNOWLEDGEMENTS	21
REFERENCES	22
CHARACTERISTICS OF STUDIES	26
DATA AND ANALYSES	34
Analysis 1.1. Comparison 1 Main analysis, Outcome 1 Mortality - 30 days or at point closest to 30 days.	35
Analysis 1.2. Comparison 1 Main analysis, Outcome 2 Rebleeding within 30 days.	35
Analysis 1.3. Comparison 1 Main analysis, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.	35
Analysis 1.4. Comparison 1 Main analysis, Outcome 4 Patients requiring blood transfusion (post hoc analysis).	36
Analysis 1.5. Comparison 1 Main analysis, Outcome 5 Proportion of patients with stigmata of recent haemorrhage.	36
Analysis 1.6. Comparison 1 Main analysis, Outcome 6 Proportion of patients with blood in stomach (post hoc analysis).	36
Analysis 1.7. Comparison 1 Main analysis, Outcome 7 Proportion of patients with active bleeding.	37
Analysis 1.8. Comparison 1 Main analysis, Outcome 8 Endoscopic haemostatic therapy at index endoscopy.	37
Analysis 2.1. Comparison 2 Analysis according to degree of allocation concealment, Outcome 1 Mortality.	38
Analysis 2.2. Comparison 2 Analysis according to degree of allocation concealment, Outcome 2 Rebleeding within 30 days. ...	38
Analysis 2.3. Comparison 2 Analysis according to degree of allocation concealment, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.	39
Analysis 3.1. Comparison 3 Analysis according to control treatment, Outcome 1 Mortality.	40
Analysis 3.2. Comparison 3 Analysis according to control treatment, Outcome 2 Rebleeding within 30 days.	41
Analysis 3.3. Comparison 3 Analysis according to control treatment, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.	42
Analysis 4.1. Comparison 4 Analysis according to route of PPI administration, Outcome 1 Mortality.	43
Analysis 4.2. Comparison 4 Analysis according to route of PPI administration, Outcome 2 Rebleeding within 30 days.	43
Analysis 4.3. Comparison 4 Analysis according to route of PPI administration, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.	44
Analysis 5.1. Comparison 5 Analysis according to the PPI used, Outcome 1 Mortality.	45
Analysis 5.2. Comparison 5 Analysis according to the PPI used, Outcome 2 Rebleeding within 30 days.	46
Analysis 5.3. Comparison 5 Analysis according to the PPI used, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.	47
Analysis 6.1. Comparison 6 Analysis according to report of endoscopic haemostatic treatment, Outcome 1 Mortality.	48
Analysis 6.2. Comparison 6 Analysis according to report of endoscopic haemostatic treatment, Outcome 2 Rebleeding.	49
Analysis 6.3. Comparison 6 Analysis according to report of endoscopic haemostatic treatment, Outcome 3 Surgery.	49
Analysis 7.1. Comparison 7 Analysis restricted to peptic ulcer patients, Outcome 1 Mortality.	50
Analysis 7.2. Comparison 7 Analysis restricted to peptic ulcer patients, Outcome 2 Rebleeding.	50
Analysis 7.3. Comparison 7 Analysis restricted to peptic ulcer patients, Outcome 3 Surgery.	51
APPENDICES	51
WHAT'S NEW	53
HISTORY	53

CONTRIBUTIONS OF AUTHORS	53
DECLARATIONS OF INTEREST	53
SOURCES OF SUPPORT	54
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	54
NOTES	54
INDEX TERMS	54

[Intervention Review]

Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding

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ABSTRACT

Background

There is conflicting evidence regarding the clinical efficacy of proton pump inhibitors (PPI) initiated before endoscopy for upper gastrointestinal bleeding.

Objectives

To systematically review evidence from randomised controlled trials (RCTs) of PPI treatment initiated before endoscopy for upper gastrointestinal bleeding.

Search methods

We searched CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE and CINAHL databases and major conference proceedings to September 2005, using the Cochrane Upper Gastrointestinal and Pancreatic Diseases model. Searches were re-run in February 2006 and October 2008.

Selection criteria

We selected randomised controlled trials (RCTs), of hospitalised participants with unselected upper gastrointestinal bleeding, undergoing active treatment with a proton pump inhibitor PPI (oral or intravenous) and control treatment with either placebo, histamine-2 receptor antagonist (H2RA) or no treatment prior to endoscopy. Outcomes were assessed at 30 days and included mortality, rebleeding and surgery. Also assessed were stigmata of recent haemorrhage (SRH; active bleeding, non bleeding visible vessel or adherent clot) at index endoscopy, length of hospital stay, blood transfusion requirements and requirement for endoscopic therapy at index endoscopy.

Data collection and analysis

At least two review authors assessed eligibility criteria and extracted data regarding outcomes and factors affecting methodological quality.

Main results

Six RCTs comprising 2223 participants were included. There was no statistical heterogeneity among trials for dichotomous outcomes. There were no statistically significant differences in mortality, rebleeding or surgery between PPI and control treatment. Unweighted pooled

Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding (Review)

1

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mortality rates were 6.1% and 5.5% respectively (odds ratio (OR) 1.12; 95% CI 0.72 to 1.73). Unweighted pooled rebleeding rates were 13.9% and 16.6% respectively (OR 0.81; 95% CI 0.61 to 1.09). Pooled rates for surgery were 9.9% and 10.2% respectively (OR 0.96 95% CI 0.68 to 1.35). PPI treatment compared to control significantly reduced the proportion of participants with SRH at index endoscopy; unweighted pooled rates were 37.2% and 46.5% respectively (OR 0.67; 95% CI 0.54 to 0.84). However, this result was not robust to sensitivity analysis. PPI treatment compared to control significantly reduced endoscopic therapy at index endoscopy; unweighted pooled rates were 8.6% and 11.7% respectively (OR 0.68; 95% CI 0.50 to 0.93). For continuous outcomes (length of hospital stay and blood transfusion requirements), quantitative analysis could not be performed.

Authors' conclusions

PPI treatment initiated before endoscopy for upper gastrointestinal bleeding might reduce the proportion of participants with SRH at index endoscopy and significantly reduces requirement for endoscopic therapy during index endoscopy. However, there is no evidence that PPI treatment affects clinically important outcomes, namely mortality, rebleeding or need for surgery.

PLAIN LANGUAGE SUMMARY

Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding

Bleeding from lesions in the oesophagus, stomach or duodenum is a common medical emergency. Research has suggested that reducing the amount of acid in the stomach may help to control the bleeding, but it is unknown if early initiation of such treatment (that is, before endoscopic diagnosis) is beneficial for patients.

This review compared the effect of one type of anti-acid drug (proton pump inhibitor) with either no treatment (placebo) or with another type of anti-acid drug (an Histamine-2 receptor antagonist) initiated prior to endoscopic diagnosis. Taking proton pump inhibitors 24 to 48 hours before endoscopy significantly reduced the proportion of patients with findings of recent serious bleeding on endoscopic examination and the need for treatment during endoscopy such as injecting medicines or cauterising blood vessels to stop bleeding. However, overall there was no effect of taking a proton pump inhibitor on further bleeding, need for surgery or risk of death.

BACKGROUND

Description of the condition

Upper gastrointestinal haemorrhage remains the most common reason for emergency hospital admission with a gastrointestinal problem and is a major cause of morbidity, mortality and medical care costs (Gilbert 1990; Longstreth 1997). Peptic ulcer is the most frequent source of acute upper gastrointestinal haemorrhage, accounting for around 50% of all cases (Laine 1994; Silverstein 1981). The prevalence of upper gastrointestinal haemorrhage is reported to be approximately 170 per 100,000 adults per year (Blatchford 1997), with a total estimated cost of \$750 million in the United States (Jiraneck 1996) and a substantial utilisation of resources and costs for each hospitalisation (Gralnek 1998; Gralnek 1997; Lee 1999; Longstreth 1995).

The mortality rates due to upper gastrointestinal haemorrhage have remained unchanged despite enormous advances in endoscopic and pharmacotherapy over the last 30 years. Epidemiological studies have shown a decrease in the incidence of peptic ulcer related upper gastrointestinal haemorrhage but without a significant decrease in rebleeding or mortality rates in recent years. This could be explained by the increased incidence in patients with advanced age, significant co-morbid illness and the increasing use of non-steroidal anti-inflammatory drugs (van Leerdaam 2003; Higham 2002; Paimela 2002).

Description of the intervention

Current management of bleeding ulcers includes fluid replacement, drug therapy with acid inhibitors, early endoscopic haemostasis and surgery. The cessation of bleeding from a peptic ulcer is inhibited by gastric acid by two mechanisms: firstly, inhibition of clot formation and promotion of clot lysis; and secondly, by ongoing tissue damage (Kolkman 1996). Drug therapy aimed at inhibition of gastric acid secretion increases gastric pH, facilitates clot formation, stabilises the clot and perhaps hastens the healing of lesions (Barkun 2006). This is based on data from in vitro studies that observed that an increase in pH > 6 would be required to inactivate pepsin and inhibit fibrinolysis (Green 1978; Low 1980). An open label randomised controlled trial (Brunner 1990) comparing omeprazole with ranitidine in critically ill patients with bleeding ulcers (Forest 1b) reported that significantly more patients stopped bleeding after omeprazole (84%) compared to ranitidine (15%).

How the intervention might work

A number of meta-analyses have assessed RCTs that studied the clinical effectiveness of PPI treatment in acute upper gastrointestinal bleeding (Khuroo 2005) and in acute peptic ulcer bleeding (Andriulli 2005; Bardou 2005; Khuroo 2005; Leontiadis 2005). These did not analyse RCTs that studied the clinical effectiveness of proton pump inhibitor (PPI) treatment initiated prior to endoscopy.

Evidence from recent cost-effectiveness studies suggests that PPI treatment after endoscopic haemostatic therapy reduces rebleeding rates and the requirement for surgery in patients with peptic ulcer haemorrhage (Barkun 2004; Lee 2003; Spiegel 2003). Guidelines on management of non variceal upper gastrointestinal bleeding from the British Society of Gastroenterology and, more recently, from ICON-UGIB multi-society consensus group,

recommend the use of high dose intravenous PPI in peptic ulcer bleeding with high risk stigmata on endoscopy (Barkun 2003; Barkun 2010; Palmer 2002).

Empirical acid suppression treatment using PPI or an H2RA is often used in clinical practice for patients presenting with upper gastrointestinal haemorrhage even before endoscopic confirmation of the cause of the bleed. Although empirical PPI treatment in this situation is regarded by many clinicians as reasonable, it appears to be a major challenge for formularies when judicious use of medications is required based on the evidence of benefit. In the absence of strong evidence, the indiscriminate use of PPIs could not be recommended for all patients presenting with upper gastrointestinal bleeding. The largest randomised study evaluating the role of PPI in acute, unselected upper gastrointestinal bleeding included 1147 patients. The authors found no significant difference in mortality, rebleeding rates or requirement for surgery between the PPI and control groups. The only significant difference between the groups was the reduction in endoscopic stigmata of haemorrhage in patients treated with PPI (Daneshmend 1992). In a more recent randomised controlled study, Lau et al (Lau 2007), randomised 631 patients to either high dose intravenous omeprazole or placebo before endoscopy in patients with acute unselected upper gastrointestinal bleeding. The authors found no significant difference in clinically relevant outcomes such as mortality, rebleeding or requirement for surgery between the omeprazole and the control groups. This study (Lau 2007) however, confirmed the observation that proton pump inhibitor treatment reduces the incidence of stigmata of recent haemorrhage and the requirement for endoscopic therapy on index endoscopy.

Previous studies have demonstrated some evidence that empirical PPI treatment before endoscopic confirmation could be cost effective (Enns 2003; Gagnon 2003). A more recent cost effectiveness study (Tsoi 2008) constructed a data analysis model of treatment pathways based on the data from their original randomised controlled trial (Lau 2007). The authors (Tsoi 2008) observed that pre-emptive PPI treatment reduces the need for endoscopic therapy by 7.4% and hence resulted in a lower cost per endoscopic therapy averted in the PPI group (US \$3561) compared to placebo group (US \$4117). Another study (Al-Sabah 2008) evaluated the cost effectiveness of high dose IV PPI before endoscopy in preventing rebleeding. The authors observed that this strategy was more cost effective than PPI use after endoscopy in the United States and in Canada. This strategy was more effective and less costly if the period of hospitalisation for high risk ulcer patients increased to more than 6 days or if the period of hospitalisation for low risk ulcer patients reduced to less than 3 days in Canadian hospitals.

Guidelines from the recent consensus group statement recommend the use of empirical PPI treatment in patients waiting for endoscopy. Although only 40% of the consensus panel agreed to this recommendation without any reservations (Barkun 2003), the more recent ICON-UGIB consensus considered the updated evidence for use of PPI prior to endoscopy and the consensus was near unanimous (Barkun 2010).

Why it is important to do this review

This is an update of a systematic review previously published in 2006, which aimed to ascertain the role of PPI therapy initiated prior to endoscopic diagnosis in reducing mortality in unselected

upper gastrointestinal haemorrhage. By systematically reviewing all studies in which a PPI has been directly compared with another acid-lowering agent (that is, an H2RA), placebo or no treatment in unselected patients with upper gastrointestinal bleeding prior to endoscopy, we aimed to assess whether PPIs show any overall benefit in reducing adverse clinical outcomes including mortality, rebleeding, requirement for surgery and endoscopic outcomes including stigmata of recent haemorrhage and requirement for haemostatic treatment during index endoscopy.

OBJECTIVES

This project aimed to assess the clinical effectiveness of PPI treatment initiated prior to endoscopy in acute upper gastrointestinal bleeding by systematic review and meta-analysis of randomised controlled trials.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that compared the relative effectiveness of pre-endoscopic PPI versus placebo or an H2RA were eligible for inclusion in this review. Published and unpublished studies, full articles and abstracts were considered for inclusion in this review. Only studies that evaluated PPI initiated prior to endoscopy upon presentation with upper gastrointestinal (GI) bleeding were included.

Types of participants

Trials were eligible for inclusion in the review if they recruited participants admitted to hospital with upper GI tract bleeding or inpatients who developed upper gastrointestinal bleeding after having been admitted for other reasons. The only studies included were those which enrolled unselected patients with upper GI bleeding before the cause of bleeding was ascertained by endoscopy, and those in which treatment groups were treated similarly regardless of the active therapies being compared.. Allocation to PPI or comparator treatment had to have been made before diagnostic upper endoscopy. Steps were taken to clarify whether participants with variceal bleeding had been excluded from the primary trials.

Types of interventions

To be included in the review, the tested regimen had to meet the following criteria:

The treatment group had to have received a PPI; the control group had to have received either placebo, an H2RA or no treatment prior to endoscopy and otherwise, the control group had to have been managed similarly to the active treatment group. The method of delivery of PPI and control treatment included both intravenous and oral routes of administration.

Types of outcome measures

Primary outcomes

The primary outcome measure in this review was all cause mortality, defined as any death occurring within 30 days (or mortality at the time point closest to 30 days) after the acute bleed.

Secondary outcomes

The secondary outcome measures were as follows:

1. rebleeding within 30 days;
2. surgery for continued or recurrent bleeding within 30 days of randomisation;
3. length of hospital stay, where available, expressed and compared as the mean and standard deviation;
4. transfusion requirements, where available, expressed and compared as mean number of units transfused per participant and standard deviation;
5. proportion of participants with high-risk stigmata at the time of endoscopy.
6. proportion of participants receiving endoscopic treatment at index endoscopy.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE and CINAHL databases up to September 2005 (using the search terms: (bleed or rebleed or haemorrhage or hemorrhage) and any of the generic names of proton pump inhibitors), using the Cochrane Upper Gastrointestinal and Pancreatic Diseases (UGPD) model ([Appendix 1](#)). We also searched the National Research Register (NRR) and the UGPD trials register. The search strategy was then re-run in February 2006 and in October 2008.

The search provided a comprehensive list of primary studies, both published and unpublished, that complied with the inclusion criteria. Free-text searches and medical subject headings were combined to identify papers concerned with PPIs and upper gastrointestinal bleeding.

Searching other resources

Reference lists from trials selected by electronic searching were handsearched to identify further relevant trials. Published Abstracts from Digestive Disease Week, United European Gastroenterology Week, American College of Gastroenterology annual meeting, World Congress of Gastroenterology and British Society of Gastroenterology annual meeting were also handsearched (1997 to October 2008). Authors of trial reports published only as abstracts were contacted and asked to contribute full data sets or completed papers. We handsearched the reference lists of identified articles for further relevant trials.

The following web based resources were also searched:

- <http://www.controlledtrials.com>
- <http://www.cancer.gov/cancerinformation>
- <http://clinicaltrials.gov>
- <http://www.eortc.be>
- <http://www.swog.org>
- <http://www.ctg.queensu.ca>
- <http://www.CenterWatch.com/>

In addition, members of the Cochrane UGPD Group and experts in the field were contacted and asked to provide details of outstanding clinical trials and any relevant unpublished materials.

Correspondence

Experts in the field who were registered with the Cochrane Collaboration Upper Gastrointestinal and Pancreatic Disease (UGPD) Review Group were contacted for leads on unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (AS and SD) independently checked trials and abstracts identified from the search for fulfilment of pre-defined inclusion criteria. One of the review authors (AS) was an expert in content matter. A third review author (GL) adjudicated in the event of discrepancies and a consensus view was taken. During the update of the review in 2008 two review authors (AS and JM) independently evaluated the studies for quality, methodology and collection of data. The full text of all relevant studies was obtained wherever possible. If it was not clear from the information presented whether the trial met the inclusion criteria, further information was sought from the original author. The inclusion of trials and grading of methodological quality were determined, and reasons for exclusion were documented. Authors were contacted to provide the relevant unpublished and missing data wherever required.

Data extraction and management

Data regarding the above-mentioned outcomes were extracted independently by two review authors (AS and SD for the initial version of the review; AS and JM during the update of the review in 2008). The data were collected using a pre-abstracted proforma. By a *post hoc* decision, a third review author (GL) independently extracted data. In the event of discrepancies a consensus view was taken. In the end, the agreement was 100% among the three authors.

Studies were summarised and, if appropriate, meta-analysis was undertaken.

The following features were also recorded:

- setting: single centre versus multicentre;
- geographical location;
- name of PPI;
- high dose PPI (equivalent to a dose of omeprazole or pantoprazole 80 mg bolus intravenous followed by an intravenous infusion of 8 mg/hr for 72 hours) versus lower dose PPI;
- intravenous PPI versus oral PPI;
- control group treatment - H2RA versus placebo;
- concomitant treatment - therapeutic endoscopy (subdivided by intervention - injection, thermal, injection plus thermal, clips, other) versus no therapeutic endoscopy;
- adverse reactions - actively sought versus not actively sought;
- proportion of participants eventually found to be bleeding from peptic ulcers.

Assessment of risk of bias in included studies

Assessment of risk of bias was based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Each included study was assessed regarding sequence generation,

allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias.

Other validity criteria used to assess studies included the following:

- baseline comparability of treatment groups;
- criteria for participant inclusion and exclusion;
- interventions described in detail;
- definition of outcomes;
- stated time for outcome assessment;
- stated indications for repeat endoscopy, initial and subsequent endoscopic treatment, surgery and transfusion;

Measures of treatment effect

Primary outcome

The primary outcome was mortality rate, defined as death from any cause within 30 days of randomisation. We expected dichotomous data for mortality and this was expressed as odds ratio (OR) with 95% confidence intervals (CI).

Secondary outcomes

We expected dichotomous data for secondary outcome measures including rebleeding rate, requirement for surgery within 30 days and proportion of participants with stigmata of recent haemorrhage (active bleeding, non bleeding visible vessel or adherent clot). These were also expressed as OR or with 95% CI.

We expected continuous data for secondary outcome measures including length of hospital stay and blood transfusion requirement. These were expressed as means and compared between the intervention groups. However, length of hospital stay was expected to be skewed and we admit that mean and standard deviation are not the ideal summary measures to express this outcome.

Unit of analysis issues

Studies with multiple treatment groups

A decision was made *a priori* to include such studies in the review, provided the study satisfied the inclusion criteria and the inclusion was limited to the interventions eligible to be included in this review, i.e., participants treated with PPI in the treatment group and participants either treated with H2RA, placebo or no-treatment in the control group. The other subgroups were excluded from this review.

Dealing with missing data

Details of missing values were requested from authors. Analyses were performed with an intention to treat basis. In the event of missing data such as standard deviation, these data were requested from authors in order to perform meta-analysis for continuous outcomes.

Assessment of heterogeneity

Heterogeneity was assessed using the Chi-squared test, I^2 statistic as a heterogeneity indicator along with visual inspection of the forest plots. A significance level less than 0.10 was interpreted as evidence of heterogeneity. We looked for an explanation for any heterogeneity and have reported this in the review. Sensitivity analysis was performed using the potential sources of

heterogeneity to test the robustness of the overall results. Where no significant heterogeneity was observed among study results, the fixed-effect model was used. Otherwise, the random-effects model was used.

The potential reasons for heterogeneity hypothesized a priori include:

1. study quality (open trial versus blinded trial);
2. study setting (multi centre versus single centre);
3. geographical location (Asian versus Western study);
4. PPI treatment (intravenous versus oral; conventional versus high dose PPI);

5. concomitant treatment (therapeutic endoscopy versus no therapeutic endoscopy);
6. control treatment used (H2RA versus placebo);
7. outcome measure for bleeding (recurrent bleeding versus persistent bleeding);
8. outcome measure of mortality, criteria stated (bleed-related mortality versus non bleed related mortality).

Assessment of reporting biases

The review was designed to include published and unpublished studies in all languages. Specialist translation help was sought to obtain data during data collection. Publication bias was explored using funnel plots ([Figure 1](#); [Figure 2](#); [Figure 3](#); [Figure 4](#); [Figure 5](#)).

Figure 1. Funnel plot of comparison: 1 Main analysis, outcome: 1.1 Mortality - 30 days or at point closest to 30 days.

Figure 2. Funnel plot of comparison: 1 Main analysis, outcome: 1.2 Rebleeding within 30 days.

Figure 3. Funnel plot of comparison: 1 Main analysis, outcome: 1.3 Surgery for continued or recurrent bleeding within 30 days of randomisation.

Figure 4. Funnel plot of comparison: 1 Main analysis, outcome: 1.5 Proportion of patients with stigmata of recent haemorrhage.

Figure 5. Funnel plot of comparison: 1 Main analysis, outcome: 1.8 Endoscopic haemostatic therapy at index endoscopy.

Data synthesis

All trials included in the systematic review were entered into Review Manager 5 (RevMan). An intention-to-treat approach was used in all analyses. Meta-analysis was performed only if two or more trials with similar comparisons and outcome measures were found.

Subgroup analysis and investigation of heterogeneity

We decided to perform sub group analyses *a priori* in the following categories:

- According to degree of allocation (A vs Non-A)
- According to control treatment (H2RA vs placebo vs no treatment)
- According to route of PPI administration
- According to the PPI used
- According to report of using endoscopic haemostatic treatment
- Restricted to participants to peptic ulcer bleeding

Sensitivity analysis

Sensitivity analyses for all outcomes were performed by excluding each study to assess the robustness of the results of the meta-analysis.

RESULTS

Description of studies

Results of the search

The search strategy used for CENTRAL, MEDLINE, EMBASE and CINAHL databases identified 94 articles. 33 further articles were identified during the update of the search strategy in October 2008. Handsearching reference lists from these articles and searching major conference proceedings identified no further trials. No further trials were identified by contacting members of the Cochrane UGPD Group, experts in the field of gastroenterology and pharmaceutical companies marketing PPIs.

After reviewing the abstracts of the above articles, 69 were excluded as they were clearly not relevant and three due to inadequate data. The main reason for exclusion was not being a RCT. We retrieved the full articles for the remaining 54 trials and obtained translations for those published in languages other than English. One trial was published only in the abstract form (Naumovski 2005). Of these trials, 49 did not meet the eligibility criteria and were excluded for the following reasons: randomisation had taken place after endoscopy, or the study had been restricted to peptic ulcer bleeding only (see table 'Characteristics of excluded studies').

The remaining six trials were included in our systematic review (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Lau 2007;

Naumovski 2005; Wallner 1996;) (see table 'Characteristics of included studies').

Of these, five were full peer-reviewed publications (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Lau 2007; Wallner 1996) and one was published as an abstract only (Naumovski 2005). Five of the trials were published in the English language and one in Turkish (Hulagu 1995). We were provided with additional information from the authors of two of the trials (Hulagu 1995; Lau 2007).

Included studies

Design

All included studies were RCTs with a parallel-group design. Other aspects of trial design are discussed in 'Risk of bias in included studies'.

Setting

Four of the studies had been conducted in a single centre (Hulagu 1995; Lau 2007; Naumovski 2005; Wallner 1996;) and two had been conducted in two centres (Daneshmend 1992, Hawkey 2001). All studies took place in a hospital setting.

Four trials had been conducted in Europe (Daneshmend 1992, Hawkey 2001; Naumovski 2005; Wallner 1996;) and two in Asia (Lau 2007; Hulagu 1995). (The trial by Hulagu et al had been conducted in the Asian part of Turkey).

Participants

All trials included participants with clinical signs of upper gastrointestinal bleeding. Three studies defined these as haematemesis or melaena or both (Daneshmend 1992; Hulagu 1995; Lau 2007).

The number of participants per trial ranged from 58 (Hulagu 1995) to 1147 (Daneshmend 1992). In one trial (Hawkey 2001), we included only two of the four treatment groups, the PPI-only group and the placebo group, in our analysis. One trial (Lau 2007) did report stigmata of haemorrhage only in the subgroup of participants with peptic ulcer disease and hence this study was not included in the main analysis for this outcome. Another study (Hulagu 1995) did not report requirement for surgery and hence was excluded from the analysis for this outcome.

The six trials that were included in the main analysis (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Lau 2007; Naumovski 2005; Wallner 1996) comprised a total of 2223 participants. Of these, 1114 were randomised to PPI treatment and 1109 to control treatment.

The mean age of participants was reported in three trials: 58.4 years with a standard deviation of 19.9 years (Hawkey 2001), 59.5 years with a standard deviation of 19 years (Daneshmend 1992) and 54 years (Naumovski 2005). Two trials reported only median age per treatment group: 54 years for PPI group and 56 years for the control group in one trial (Wallner 1996) and 58.1 years for the PPI group and 49.5 years for the control group in the other trial (Hulagu 1995). One trial (Lau 2007) reported mean age with standard deviation per treatment group, 61.7 (SD 17.9) in the PPI group and 62.3 (SD 17.5) in the control group.

Five studies reported the gender of participants; in all five there was a male predominance. The male to female ratios were 74/28

(Wallner 1996), 729/418 (Daneshmend 1992), 251/163 (Hawkey 2001), 409/222 (Lau 2007) and 52/28 (Naumovski 2005).

One trial specifically excluded participants who developed bleeding after being admitted to hospital for other reasons (Daneshmend 1992). It was not clear whether such participants had been excluded from the other studies.

None of the studies was confined to participants with peptic ulcer bleeding, although one only reported outcomes of stigmata of haemorrhage for participants with peptic ulcer bleeding (Lau 2007). The percentage of participants with peptic ulcer bleeding per trial was as follows: 43.9% (Daneshmend 1992), 42.4% (Hawkey 2001), 75.5% (Wallner 1996), 60.7% (Lau 2007) and 77.6% (Hulagu 1995).

Two of the studies did not exclude participants with bleeding from oesophageal varices. Such participants comprised 2.5% of total participants in one trial (Daneshmend 1992) and 3.9% of total participants in another trial (Hawkey 2001). One other trial attempted to avoid the inclusion of such patients by excluding patients with existing hepatic insufficiency (Wallner 1996). Hulagu et al did not state whether participants with variceal bleeding were deliberately excluded although no such patients were included in the study (Hulagu 1995). Lau et al did not exclude participants with varices and reported variceal bleeding in 3.2% of the PPI group and 4.4% in the control group (Lau 2007). Naumovski et al did not state any exclusion of variceal bleeding but mentioned that lesions considered were erosive gastritis, gastric and duodenal ulcers.

Co-morbidity was reported in detail in only one of the trials (Lau 2007). Lau et al reported co-morbid medical illness per treatment group. Of the 314 participants in the PPI group, 17 had cirrhosis, 32 had cancer, 18 had cardiovascular disease and two had chronic renal failure. In the control group, out of 317 participants, 19 had cirrhosis, 23 had cancer, 25 had cardiovascular disease and three participants had chronic renal failure. None of the other trials used a standardised grading system of co-morbidity. From information stated in the exclusion criteria, we presume that three of the trials (Daneshmend 1992; Hawkey 2001; Hulagu 1995) did not include severely ill participants (terminal illness and malignancy stated as examples). Naumovski et al (Naumovski 2005) reported eleven participants with renal and six participants with hepatic dysfunction in participants admitted to the Intensive Care unit. Wallner et al (Wallner 1996) did not include participants with hepatic insufficiency or malignancy. It is not possible to make comparisons about co-morbidity among the trials.

Two trials (Lau 2007; Wallner 1996) reported data on the haemodynamic condition of patients on admission: Lau et al (Lau 2007) reported a mean systolic blood pressure of 116.2 (SD 20.4) in the PPI group and 117.3 (SD 21.9) in the placebo group. The number of participants (%) with a systolic blood pressure of less than 90 mm Hg was 30 (9.6) in the PPI group and 28 (8.8) in the control group. In Wallner et al (Wallner 1996), 8.8% of total participants had haemodynamic shock, defined as systolic blood pressure < 80 mm Hg; 29.5% of participants had systolic blood pressure below 100 mm Hg or heart rate > 100 beats/min. One other study (Daneshmend 1992) stated the mean and standard deviation of systolic blood pressure and pulse rate per treatment group but did not report percentage of participants with shock.

Two trials (Lau 2007; Hawkey 2001) reported the proportion of participants on non-steroidal antiinflammatory drugs (NSAIDs). In

the Lau study, 70 (22.3%) participants in the PPI group and 74 (23.3) in the placebo group were on NSAIDs. In the Wallner study, 35% of all randomised participants used NSAIDs. Another trial (Hulagu 1995) reported that 62% of participants used such medications.

None of the trials reported *Helicobacter pylori* (*H pylori*) status of all randomised participants. One study (Lau 2007) reported 95/178 participants with peptic ulcer disease in the PPI group and 109/182 participants in the placebo group to be positive for *H pylori* either by biopsy urease (CLO test) or histology.

One study (Lau 2007) reported the proportion of participants using PPI or H2RA in the 4 weeks before admission. In the PPI group 38 (12.1%) had taken acid suppressant treatment compared to 40 (12.6%) in the placebo group.

Lau et al (Lau 2007) reported 80 (25.5%) to have had previous peptic ulcer disease in the PPI group compared to 80 (25.2%) participants in the placebo group. In the same study (Lau 2007), 68 (21.7%) participants had a previous GI bleed compared to 66 (20.8%) in the placebo group.

Baseline comparability of treatment groups

Hulagu et al (Hulagu 1995) reported baseline comparability of treatment groups regarding haemoglobin values, presentation with haematemesis and melaena, past history of peptic ulcer disease, past history of upper gastrointestinal bleeding, anti-ulcer therapy, cigarette smoking, alcohol abuse, postural haemodynamic compromise and use of NSAIDs.

Daneshmend et al (Daneshmend 1992) reported baseline comparability among the following characteristics for which raw data were provided: male to female ratio, age, systolic blood pressure, pulse, haemoglobin, presentation with haematemesis and melaena, history of peptic ulcer disease, history of previous upper gastrointestinal bleeding, previous gastric surgery and endoscopic haemostatic treatment.

In the trial of Hawkey et al (Hawkey 2001), both groups were well balanced for age, sex, past history of peptic ulcer disease and use of non-steroidal anti-inflammatory drugs. More participants had been receiving ulcer-healing medication on admission in the control group compared to the PPI group (14/55 versus 8/58). Also, fewer participants were classified as high risk (as classified in a non-standardised way by the admitting team) in the control group compared to the PPI group (7/55 versus 11/58).

In the study by Lau et al (Lau 2007), the two groups were comparable for age, gender, ASA status, haemodynamic status, comorbidity and proportion of participants with history of previous peptic ulcer disease or previous bleed. The two groups were similar for previous history of NSAIDs, warfarin use and the proportion of peptic ulcer participants with positive *H pylori* status.

Naumovski et al (Naumovski 2005) did not provide baseline characteristics in their abstract publication.

Wallner et al (Wallner 1996) reported that the two treatment groups were well balanced with respect to mean age, sex, haemodynamic shock and haemoglobin. There was a larger proportion of participants older than 65 years in the control group (18/52) compared to the PPI group (12/50).

Overall, there was good baseline comparability for the four trials (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Wallner 1996) that reported raw data and were available as full publications.

Presence of inclusion and exclusion criteria

All trials had well-defined inclusion criteria. Five trials also reported exclusion criteria in detail. The sixth trial, published as abstract only (Naumovski 2005), did not specify any exclusion criteria.

Intervention described in detail

Five trials provided detailed descriptions of the type, route and method of administration, dose and duration of medication used in both study groups. The fifth trial (Wallner 1996) was unclear regarding the dosing of both PPI and control treatment; three different dosage regimens were for each group but it was not clear how participants were allocated to each dose.

Also see table 'Characteristics of included studies' for details of intervention.

Interventions

1. Active treatment

Four trials used intravenous omeprazole as active treatment (Daneshmend 1992; Hulagu 1995; Lau 2007; Wallner 1996;). One study used oral lansoprazole (Hawkey 2001). Another study (Naumovski 2005) used intravenous pantoprazole. Only the Lau study (Lau 2007) used a high dose regimen as predefined in the methods of the review.

2. Control treatment

Three of the trials (Daneshmend 1992; Hawkey 2001; Lau 2007) used placebo as control treatment. Of these, one stated that placebo treatment consisted of intravenous mannitol (Daneshmend 1992). Two trials compared active treatment to an H2RA; Hulagu et al (Hulagu 1995) used intravenous ranitidine followed by oral famotidine, while Wallner et al (Wallner 1996) used intravenous ranitidine. The remaining study (Naumovski 2005) used no treatment in the control group as the study design was pre and post endoscopy PPI treatment. In this study (Naumovski 2005), participants in the control group were treated with IV pantoprazole 40mg IV bolus after endoscopy followed by 40mg tid for five days. Of note, Hawkey et al (Hawkey 2001) also randomised participants to an additional two treatment arms (four in total): tranexamic acid alone, and tranexamic acid plus lansoprazole. As mentioned above, these latter treatment arms were not included in our analysis.

Also see table 'Characteristics of included studies' for details of intervention including dose and duration of use.

Co-interventions

Endoscopic haemostatic treatment was offered in selected participants in three of the trials. Lau et al (Lau 2007) reported the mean duration between admission and index endoscopy to be 14.7 (SD 6.3) hours in the PPI group compared to 15.2 (SD 6.2) hours in the placebo group and administered endoscopic haemostatic treatment with adrenaline injection and heater probe thermocoagulation to participants with active bleeding, non-bleeding visible blood vessel or clots. Variceal bleeding was treated with cyanoacrylate glue or variceal ligation as decided appropriate by the treating endoscopist. In this study, 60 out of

314 participants underwent endoscopic therapy in the PPI group compared to 90 /317 in the control group. Daneshmend et al (Daneshmend 1992) reported performing the index endoscopy generally within 24 hours of admission and applied endoscopic haemostatic treatment to a minority of high risk participants (37 participants out of 164 participants with active bleeding or non-bleeding visible vessels, i.e. 22.5%). Hawkey et al (Hawkey 2001) reported performing index endoscopy on the morning following admission, or earlier if clinically indicated, and applied endoscopic haemostatic treatment only for actively bleeding lesions, which amounted to 40% of all participants with stigmata of haemorrhage. The remaining two trials (Hulagu 1995; Wallner 1996) did not mention the use of endoscopic haemostatic treatment. Hulagu et al (Hulagu 1995) reported performing the index endoscopy generally within 24 hours of admission and Wallner et al (Wallner 1996) reported performing the index endoscopy within the first 24 to 48 hours of admission. Information on the proportion of participants scoped before 24 hours from the onset of bleeding or admission, and the average duration of treatment with a PPI prior to index endoscopy were not available for either the whole study population or each study group from the published data or further unpublished data provided by the authors. Naumovski et al (Naumovski 2005) did not describe details of endoscopy or endoscopic treatment.

Excluded studies

49 did not meet the eligibility criteria and were excluded. The main reasons for exclusion included randomisation after endoscopy, or study restricted to peptic ulcer bleeding participants (see table 'Characteristics of excluded studies').

Risk of bias in included studies

Allocation

Sequence generation

Two trials (Lau 2007; Wallner 1996) adequately described the method of sequence generation. These have been described in the Risk of bias tables in the Characteristics of included studies.

Allocation concealment

One trial (Lau 2007) had adequate concealment (Grade A) and the remaining five trials (Daneshmend 1992; Hawkey 2001; Hulagu 1994; Naumovski 2005; Wallner 1996) had uncertain concealment (Grade B).

Blinding

Three trials were doubled blinded (Daneshmend 1992; Hawkey 2001; Lau 2007), one trial was described as unblinded (Wallner 1996), and another trial (Hulagu 1995) provided no information regarding blinding status. The sixth trial (Naumovski 2005) did not provide information about blinding, but was a comparison between PPI in the treatment arm and no treatment until endoscopy in the control arm.

Incomplete outcome data

Description of withdrawals and dropouts, and percentage dropouts

Five trials (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Wallner 1996; Lau 2007) described withdrawals and dropouts in detail. Of these, Wallner et al reported having no dropouts. Hawkey et al

and Daneshmend et al and Lau et al (Daneshmend 1992; Hawkey 2001; Lau 2007), clearly described the reasons for dropout for each treatment group at each stage of the study. All dropouts were assumed to have failed treatment and the clinical outcomes were analysed on an intention-to-treat basis. Hulagu et al (Hulagu 1995) report that two participants in the H2RA group could not get scoped at 30 days and had excluded them. However, these two participants had been included in the final analysis. The authors do not report whether the outcomes were imputed or last observation carried forward (LOCF) was used at 30 days. One remaining trial (Naumovski 2005) did not report the details of withdrawal and drop out data. The details of the withdrawals and dropouts for each study has been described in detail in the risk of bias table under characteristics of included studies

Selective reporting

Stated indications for repeat endoscopy, initial and subsequent endoscopic treatment, surgery and transfusion

Two trials (Hulagu 1995; Wallner 1996) offered scheduled repeat endoscopy to all participants at five days and at five to six days, respectively. Three trials (Daneshmend 1992; Hawkey 2001; Wallner 1996) offered the option of repeat endoscopy to participants with clinical suspicion of rebleeding, although the exact criteria were not specified. Lau et al (Lau 2007) clearly defined rebleeding which was treated with repeat endoscopy and retreatment with adrenaline injection and heater probe coagulation.

Wallner et al (Wallner 1996) stated that the indication for surgical treatment was ineffective conservative therapy or chronic ulceration with poor healing prognosis. Daneshmend et al (Daneshmend 1992) stated that participants were cared for by the admitting medical team, who made decisions about blood transfusion and surgery. In the Lau study (Lau 2007), surgery was deemed indicated for rebleeding if haemostasis could not be achieved by repeat endoscopy or at the second rebleeding episode. The other three trials did not state indications for surgery.

Within the Hulagu et al study, transfusions were offered with the aim of keeping the haemoglobin at least 10 g/dl (Hulagu 1995). The remaining five trials did not clarify indications for blood transfusions.

Stigmata of recent haemorrhage

Lau et al (Lau 2007) reported this outcome only for the subgroup of participants with peptic ulcer bleeding and not for all randomised participants.

Surgery

Hulagu et al (Hulagu 1995) did not report requirement for surgery.

Other potential sources of bias

Sample size estimation

Three trials (Daneshmend 1992; Hawkey 2001; Lau 2007) estimated an *a priori* sample size of the trials. The other three trials did not state this.

Definition of outcomes

Among the most important outcomes of the review: mortality, rebleeding and surgery, rebleeding was the only outcome that was difficult to define.

Primary Outcome

Naumovski et al (Naumovski 2005) did not define the time of assessment of mortality in their abstract. However, no mortality was found in either of the treatment groups in their study.

Secondary outcomes

Daneshmend et al (Daneshmend 1992) defined rebleeding by clinical or laboratory findings (fall in haemoglobin) or by endoscopic findings at repeat endoscopy. However, it was not clear if repeat endoscopy was offered to all participants with suspected rebleeding.

Hawkey 2001 defined rebleeding as a combination of clinical signs and a drop in haemoglobin or endoscopic evidence of rebleeding or both. However, repeat endoscopy was performed at the discretion of the managing team.

Hulagu 1995 did not define rebleeding. However, they did state that all participants were re-endoscoped five days following admission.

Wallner 1996 did not report rebleeding as this was not one of their study outcomes. Instead, they reported time required for cessation of bleeding as determined by clinical and endoscopic criteria.

Lau 2007 defined rebleeding as vomiting of fresh blood, hypotensive shock (defined as a systolic blood pressure ≤ 90 mm Hg or a pulse ≥ 110 beats per minute) with melaena after stabilization, or a decrease in the haemoglobin level of more than 2 g per deciliter and a decrease in the haematocrit of more than 6% within 24 hours after a transfusion, resulting in a haemoglobin level of 10 g per deciliter or less. The participants were followed up for 30 days and mortality, requirement for repeat endoscopy or surgery, were assessed at 30 days.

Naumovski 2005 did not provide details of the outcomes or time period of outcome assessment.

Regarding the definition of hospital stay, two trials (Daneshmend 1992; Wallner 1996) reported data on hospital stay but did not distinguish between hospital stay ended by death and hospital stay ended by discharge. Lau et al (Lau 2007) reported median length of stay according to treatment group and also the proportion of participants requiring more than three days stay in hospital. Naumovski 2005 reported mean length of stay in the intensive care unit for participants in both treatment groups.

Two studies (Naumovski 2005; Lau 2007), reported mean number of blood units transfused in each group whereas the remaining trials reported the number of participants requiring blood transfusion in both treatment groups.

There was a wide variation of reporting hospital stay among the studies. Naumovski et al (Naumovski 2005) measured and reported stay in intensive care unit. Lau et al (Lau 2007) reported median stay and also proportion of participants requiring stay less than three days per treatment group. Hence a pooled summary statistic could not be derived for this outcome.

Stated time for outcome assessment

Mortality

All trials reported mortality rates per treatment group. One trial (Wallner 1996) did not state the time of assessment. The four other

trials reported mortality at: 40 days (Daneshmend 1992), 30 days (Hawkey 2001; Lau 2007) and at both six and 30 days (Hulagu 1995). Naumovski 2005 did not report a time period for any of the outcomes apart from lesion stabilisation by repeat endoscopy after five days.

Rebleeding

One of the trials (Hulagu 1995) clarified that rebleeding was assessed at six and 30 days. Lau 2007 reported rebleeding rates at 30 days.

Surgery

Two trials (Hawkey 2001; Lau 2007) reported time for surgery assessment, namely at 30 days.

Stigmata of recent haemorrhage at index endoscopy

Timing of index endoscopy would have significantly affected this outcome. Of the four trials that reported the proportion of participants per treatment group with stigmata of recent haemorrhage (as opposed to not having any stigmata): two (Daneshmend 1992; Hawkey 2001) stated that index endoscopy took place within 24 hours of admission, one (Wallner 1996) stated that index endoscopy was performed within the first 24 to 48 hours of admission, and one (Lau 2007) reported the mean time to endoscopy in the PPI and control group. We could not extract the proportion of patients per treatment group with stigmata of recent haemorrhage from the trial by Hulagu et al, who performed endoscopy within 24 hours of admission (Hulagu 1995). Naumovski 2005 did not report timing of endoscopy or details of stigmata of haemorrhage.

Effects of interventions

Main analysis: all studies (Comparison 01)

Unweighted pooled rates and odds ratios with 95% confidence intervals were calculated for each of the outcomes and compared between the treatment and control groups.

Mortality - 30 days or at point closest to 30 days

Six trials reported mortality rates for all randomised patients (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Lau 2007; Naumovski 2005; Wallner 1996) comprising a total of 1114 participants in the PPI group and 1109 in the control group. There was no significant heterogeneity among the trials ($P = 0.60$, $I^2 = 0\%$). Unweighted pooled mortality rates were 4.9% for PPI treatment and 4.3% for control treatment. There was no statistically significant effect of PPI treatment on mortality (OR 1.12, 95% CI (fixed-effect model) 0.75 to 1.68; Analysis 1.1). The results remained non-significant when, in a sensitivity analysis, any of the four trials was removed. Of note, in the study by Daneshmend et al (Daneshmend 1992), all deaths occurred within 30 days although follow up was for a period of 40 days.

Visual inspection of a funnel plot indicated possible publication bias, missing small negative trials from the right bottom area of the plot (Figure 1).

Rebleeding

Rebleeding data for all randomised patients could be extracted from five trials (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Lau 2007; Naumovski 2005), comprising a total of 1064 patients in the

PPI group and 1057 in the control group. There was no significant heterogeneity in this analysis ($P = 0.45$, $I^2 = 0\%$). Unweighted pooled rebleeding rates were 11% for PPI treatment and 13.1% for control treatment. There was no statistically significant effect of PPI treatment on rebleeding (OR 0.81, 95% CI (fixed-effect model) 0.62 to 1.06; [Analysis 1.2](#)). The result remained non-significant when, in a sensitivity analysis, any of the trials was removed. Although the funnel plot was asymmetrical, it was not possible to conclude if there was evidence of publication bias due to the small number of studies ([Figure 2](#)).

Rebleeding rates could not be extracted from the trial by Wallner et al ([Wallner 1996](#)), since it was designed to assess the time needed for bleeding cessation. This trial found that the time required for bleeding cessation was shorter on omeprazole compared to control treatment, the difference being statistically significant.

Surgery

Five trials reported surgical intervention rates for all randomised patients ([Daneshmend 1992](#); [Hawkey 2001](#); [Wallner 1996](#); [Lau 2007](#); [Naumovski 2005](#)), comprising a total of 1084 patients in the PPI treatment group and 1081 in the control treatment group. Heterogeneity among trials was not statistically significant ($P = 0.53$, $I^2 = 0\%$). Unweighted pooled rates for surgery were 7.2% for PPI treatment and 7.9% for control treatment. PPI treatment did not significantly affect requirement for surgery (OR 0.90, 95% CI (fixed-effect model) 0.65 to 1.25; [Analysis 1.3](#)). The result remained non-significant when any of the trials was removed by sensitivity analysis. The funnel plot was asymmetrical (missing small negative studies in the bottom right area of the plot), suggesting possible publication bias ([Figure 3](#)).

Blood transfusion requirements

Two trials ([Lau 2007](#); [Naumovski 2005](#)) reported blood transfusion requirements as a continuous outcome. Lau et al ([Lau 2007](#)) reported mean (SD) units of blood transfused in the PPI group to be 1.54 (2.41) compared to 1.88 (3.44) in the placebo group. This difference was not statistically significant ($P = 0.12$). Naumovski et al ([Naumovski 2005](#)) reported mean units of blood transfused in the PPI group to be 2.5 compared to 4.2 in the placebo group and reported this to be significantly lower in the PPI group ($P = 0.001$). However, in the absence of standard deviation for these values or raw data, a meta analysis could not be undertaken for this outcome.

The other trials ([Daneshmend 1992](#); [Hawkey 2001](#); [Hulagu 1995](#); [Wallner 1996](#)) reported the proportion of patients requiring blood transfusion in the PPI and control groups. None of the trials found a statistically significant difference in blood requirements between the two groups. In a post hoc analysis, we were able to extract the percentage of patients per treatment group receiving blood transfusion from all four trials ([Daneshmend 1992](#); [Hawkey 2001](#); [Hulagu 1995](#); [Wallner 1996](#)). These trials comprised a total of 760 patients in the PPI treatment group and 752 in the control treatment group. There was no statistically significant heterogeneity among the trials ($P = 0.36$, $I^2 = 6.1\%$). A total of 53.2% of patients on PPI treatment and 54.5% on control treatment received blood transfusions. The proportion of patients requiring blood transfusion was not significantly affected by PPI treatment (OR 0.95, 95% CI (fixed-effect model) 0.78 to 1.16; [Analysis 1.4](#)). The result remained non-significant when, in a sensitivity analysis, any of the trials was removed.

Proportion of participants with stigmata of recent haemorrhage at index endoscopy

Four trials reported the proportion of participants per treatment group with stigmata of recent haemorrhage (active spurting or oozing, non bleeding visible vessel or adherent clot) at index endoscopy ([Daneshmend 1992](#); [Hawkey 2001](#); [Hulagu 1995](#); [Wallner 1996](#)). Lau et al ([Lau 2007](#)) reported this outcome only in participants with peptic ulcer disease and hence was excluded from the main analysis for this outcome. The other study ([Naumovski 2005](#)) did not report the details of stigmata of recent haemorrhage. The trials comprised 672 participants in the PPI arm and 660 in the control arm, in total. There was no significant heterogeneity among the trials ($P = 0.20$, $I^2 = 35\%$). A total of 37.2% of participants on PPI and 46.5% of participants on control treatment had stigmata of recent haemorrhage at index endoscopy. PPI treatment significantly reduced the proportion of participants with stigmata of recent haemorrhage (OR 0.67, 95% CI (fixed-effect model) 0.54 to 0.84; $P = 0.0005$; [Analysis 1.5](#)).

This result was not robust, that is, it became statistically non-significant with the exclusion of one of the trials ([Daneshmend 1992](#)). Furthermore, although the Chi-Square test did not show significant heterogeneity, the I^2 test indicated moderate heterogeneity; therefore a *post-hoc* sensitivity analysis was performed to assess whether the result would remain robust to the selection of the analysis model. When the random-effects model was applied, the result was rendered non significant (OR 0.80; 95% CI 0.52 to 1.21). Inspection of the funnel plot did not give any indication of publication bias ([Figure 4](#)).

Proportion of participants with blood in the stomach (post hoc analysis)

Three trials ([Daneshmend 1992](#); [Hawkey 2001](#); [Hulagu 1995](#)) reported the proportions of participants with blood in the stomach at index endoscopy. We conducted a post hoc analysis of the proportions of participants. These three trials comprised a total of 622 participants in the PPI group and 608 participants in the control group. A total of 20.6% of participants on PPI and 27.0% of participants on control treatment were found to have blood in the stomach at index endoscopy. Since there was statistically significant heterogeneity among the three trials ($P = 0.07$, $I^2 = 62.9\%$), a random-effects model was applied. There was no statistically significant effect of PPI treatment on the proportion of participants with blood in the stomach at index endoscopy (OR 0.64, 95% CI (random-effects model) 0.32 to 1.30; [Analysis 1.6](#)). On performing a sensitivity analysis, by excluding each trial, the results remained robust.

Proportion of participants with active bleeding

Four trials reported the proportions of participants per treatment group with active bleeding at index endoscopy ([Daneshmend 1992](#); [Hawkey 2001](#); [Hulagu 1995](#); [Wallner 1996](#)). The trials comprised 672 participants in the PPI arm and 660 in the control arm. There was no significant heterogeneity among the trials ($P = 0.52$, $I^2 = 0\%$). A total of 11.3% of participants on PPI and 14.7% of participants on control treatment had active bleeding at index endoscopy. PPI treatment had no significant effect on the proportion of participants with active bleeding (OR 0.74, 95% CI (fixed-effect model) 0.54 to 1.02; [Analysis 1.7](#)). When sensitivity analysis was performed by sequentially excluding each individual trial, the results remained

robust to the exclusion of two studies (Daneshmend 1992; Hawkey 2001) but a marginally significant result was obtained in favour of PPI treatment if either the Hulagu study (Hulagu 1995) or the Wallner study (Wallner 1996) was excluded.

The Lau study (Lau 2007) reported this outcome only in participants with peptic ulcer disease and hence could not be included in the main analysis.

Need for endoscopic haemostatic treatment at index endoscopy

Three trials (Daneshmend 1992; Hawkey 2001; Lau 2007) reported the proportions of participants who received endoscopic haemostatic treatment at index endoscopy. These three trials comprised a total of 985 participants in the PPI group and 998 participants in the control group. A total of 8.6% of participants on PPI and 11.7% of participants on control treatment required endoscopic haemostatic treatment at index endoscopy. There was no statistically significant heterogeneity amongst the trials ($P = 0.41$, $I^2 = 0\%$). The rate for endoscopic haemostatic treatment was significantly lower in the PPI group (OR 0.68, 95% CI 0.50 to 0.93; Analysis 1.8). This result was not robust to exclusion of the Lau study (Lau 2007) during sensitivity analysis, attributing the treatment effect to the results of this trial alone. However, considering current standards of care, the proportion of participants with high-risk stigmata treated with endoscopic therapy was low in both the studies, at 22.5% in the Daneshmend study (Daneshmend 1992) and 40% in the Hawkey study (Hawkey 2001). In comparison, in the more recent study by Lau et al (Lau 2007), all participants (100%) with high risk stigmata on endoscopy received endoscopic treatment amounting to 24% of all participants randomised. Hence, the results of this meta-analysis would appear to reflect a true treatment effect of PPI in reducing the need for haemostatic treatment during index endoscopy. Inspection of the funnel plot did not give any indication of publication bias (Figure 5)

Length of hospital stay

Three trials (Daneshmend 1992; Lau 2007; Wallner 1996) reported data on length of hospital stay for all randomised participants, but a quantitative analysis for pooled outcome was not possible as both the studies reported this outcome as a median. Daneshmend et al reported median time to discharge: five days in the PPI group and six days in the control group (not statistically significant); Wallner et al reported median time (range) to discharge: eight days (three to 26) in the PPI group and 7.6 (three to 20) in the control group (not statistically significant). Lau et al (Lau 2007) reported a significantly reduced median (range) stay in the PPI group three (one to 43) days compared to three (one to 54) days in the placebo group. Also, the authors reported (Lau 2007) a significant proportion had a hospital stay of fewer than three days in the PPI group 190 (60.5%) compared to 156 (49.2%) in the placebo group. The other study (Naumovski 2005) measured and reported the duration of stay in the intensive care unit and concluded this to be significantly shorter in the PPI group. Due to the wide variation in the manner that length of stay was reported in the above studies, a pooled analysis for the outcome was not possible and hence, an overall conclusion on the effect of PPI treatment on hospital stay could not be reached.

Analysis according to degree of adequate concealment (Comparison 02)

Mortality

Only one of the trials reporting mortality rates for all randomised participants was classified as being grade A regarding concealment of allocation (Lau 2007). There was no significant difference in the mortality rates between the PPI and placebo group (OR 1.16; 95% CI 0.41 to 3.23), $P = 0.78$; Analysis 2.1).

The other five trials that reported mortality rate for all randomised participants (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Naumovski 2005; Wallner 1996) were classified as being grade B regarding concealment of allocation. There was no statistically significant heterogeneity among the trials ($P = 0.44$, $I^2 = 0\%$). Mortality was not significantly affected by PPI treatment (OR 1.12, 95% CI 0.72 to 1.73, $P = 0.47$; Analysis 2.1).

The pooled odds ratio was not statistically significant (OR 1.12; 95% CI 0.75 to 1.68; Analysis 2.1).

Rebleeding

Of the five trials reporting rebleeding rates for all randomised participants, one (Lau 2007) was grade A regarding concealment of allocation. The difference in rebleeding rates was not statistically significant (OR 1.40, 95% CI 0.56 to 3.53; Analysis 2.2).

Four trials (Daneshmend 1992; Hawkey 2001; Hulagu 1995; Naumovski 2005) were grade B regarding concealment of allocation. There was no statistically significant heterogeneity among the trials ($P = 0.53$, $I^2 = 0\%$) and the pooled effect on rebleeding was not significant (OR 0.77, 95% CI 0.58 to 1.02, $P = 0.07$; Analysis 2.2).

Surgery

One trial (Lau 2007) of grade A concealment of allocation reported surgical intervention rates. The effect was not statistically significant (OR 0.67, 95% CI 0.19 to 2.39, $P = 0.54$; Analysis 2.3). Four trials (Daneshmend 1992; Hawkey 2001; Naumovski 2005; Wallner 1996) with grade B concealment of allocation also found a non-significant result (OR 0.92, 95% CI 0.66 to 1.29, $P = 0.63$; Analysis 2.3). There was no significant statistical heterogeneity between the trials ($P = 0.46$, $I^2 = 0\%$).

Analysis according to control treatment (Comparison 03)

Mortality

Three trials compared PPI to placebo (Daneshmend 1992; Hawkey 2001; Lau 2007). There was no statistically significant heterogeneity between them ($P = 0.38$, $I^2 = 0\%$). There was no statistically significant effect on mortality (OR 1.19, 95% CI (fixed-effect model) 0.78 to 1.81; Analysis 3.1).

Two trials (Wallner 1996; Hulagu 1995) compared PPI to an H2RA. There was no statistically significant heterogeneity among them ($P = 0.79$, $I^2 = 0\%$). They also found no significant effect on mortality (OR 0.66; 95% CI 0.18 to 2.44; Analysis 3.1).

One trial (Naumovski 2005) compared IV PPI treatment with no treatment before endoscopy and demonstrated no mortality during the period of the study in either group.

Rebleeding

Three trials compared PPI to placebo treatment ([Daneshmend 1992](#); [Hawkey 2001](#); [Lau 2007](#)). There was no statistically significant heterogeneity among the trials ($P = 0.51$, $I^2 = 0\%$). The pooled effect was not significant (OR 0.87; 95% CI 0.66 to 1.16; [Analysis 3.2](#)).

One trial compared PPI to an H2RA ([Hulagu 1995](#)) and found no significant effect on rebleeding (OR 0.56, 95% CI 0.14 to 2.26; [Analysis 3.2](#)).

One trial ([Naumovski 2005](#)) compared PPI treatment with no treatment prior to endoscopy. The OR for rebleeding was 0.39 (95%CI 0.14 to 1.12, $P = 0.08$; [Analysis 3.2](#)).

Surgery

Three trials compared PPI to placebo ([Daneshmend 1992](#); [Hawkey 2001](#); [Lau 2007](#)). There was no statistically significant heterogeneity among them ($P = 0.59$, $I^2 = 0\%$). There was no statistically significant effect on surgery (OR 0.90, 95% CI (fixed-effect model) 0.64 to 1.27; [Analysis 3.3](#)). One trial ([Wallner 1996](#)) compared PPI to H2RA and also found no significant effect on surgery (OR 1.53, 95% CI 0.45 to 5.18; [Analysis 3.3](#)). Another trial ([Naumovski 2005](#)) compared PPI treatment with no treatment prior to endoscopy and found no significant effect for PPI in reducing the requirement for surgery (OR 0.37, 95% CI 0.07, 2.02, $P = 0.25$; [Analysis 3.3](#)).

Analysis according to route of PPI administration (Comparison 04)

Mortality

Five trials used intravenous PPI treatment ([Daneshmend 1992](#); [Hulagu 1995](#); [Lau 2007](#); [Naumovski 2005](#); [Wallner 1996](#)) with no statistically significant heterogeneity among them ($P = 0.79$, $I^2 = 0\%$). The pooled effect on mortality was not statistically significant (OR 1.21; 95% CI 0.80 to 1.84; [Analysis 4.1](#)). One trial ([Hawkey 2001](#)) studied the effect of oral PPI treatment and also found no significant effect on mortality (OR 0.39, 95% CI 0.07 to 2.07; [Analysis 4.1](#)).

Rebleeding

Four trials used intravenous PPI ([Daneshmend 1992](#); [Hulagu 1995](#); [Lau 2007](#); [Naumovski 2005](#)) with no statistically significant heterogeneity among them ($P = 0.33$, $I^2 = 13\%$). The pooled effect on rebleeding was not statistically significant (OR 0.79, 95% CI (fixed-effect model) 0.60 to 1.05; [Analysis 4.2](#)).

One other trial used oral PPI treatment ([Hawkey 2001](#)) and also found a non-significant result (OR 1.01, 95% CI 0.40 to 2.54; [Analysis 4.2](#)).

Surgery

Four trials used intravenous PPI treatment ([Daneshmend 1992](#); [Lau 2007](#); [Naumovski 2005](#); [Wallner 1996](#)) with no statistically significant heterogeneity between them ($P = 0.56$, $I^2 = 0\%$). The pooled effect on surgery was not statistically significant (OR 0.93, 95% CI (fixed-effect model) 0.67 to 1.30; [Analysis 4.3](#)). One trial ([Hawkey 2001](#)) studied the effect of oral PPI treatment and also found no significant effect on surgery (OR 0.49, 95% CI 0.12 to 2.01; [Analysis 4.3](#)).

Analysis according to the PPI used (Comparison 05)

Mortality

Four trials used omeprazole ([Daneshmend 1992](#); [Hulagu 1995](#); [Lau 2007](#); [Wallner 1996](#)) with no statistically significant heterogeneity among them ($P = 0.79$, $I^2 = 0\%$). The pooled effect on mortality was not statistically significant (OR 1.21, 95% CI (fixed-effect model) 0.80 to 1.84; [Analysis 5.1](#)).

One trial ([Hawkey 2001](#)) studied the effect of oral lansoprazole and also found no significant effect on mortality (OR 0.39, 95% CI 0.07 to 2.07; [Analysis 5.1](#)).

The other trial ([Naumovski 2005](#)) used intravenous pantoprazole and demonstrated no mortality between their treatment groups.

Rebleeding

Three trials used omeprazole ([Daneshmend 1992](#); [Hulagu 1995](#); [Lau 2007](#);) with no statistically significant heterogeneity between them ($P = 0.46$, $I^2 = 0\%$). The pooled effect on rebleeding was not statistically significant (OR 0.84, 95% CI (fixed-effect model) 0.63 to 1.13; [Analysis 5.2](#)).

One other trial used oral lansoprazole treatment ([Hawkey 2001](#)) and also found a non significant result (OR 1.01, 95% CI 0.40 to 2.54; [Analysis 5.2](#)).

The other trial ([Naumovski 2005](#)) used intravenous pantoprazole and found no significant difference in rebleeding rates between their treatment groups (OR 0.39, 95% CI 0.14 TO 1.12; [Analysis 5.2](#)).

Surgery

Three trials used omeprazole treatment ([Daneshmend 1992](#); [Lau 2007](#); [Wallner 1996](#)) with no statistically significant heterogeneity among them ($P = 0.65$, $I^2 = 0\%$). The pooled effect on surgery was not statistically significant (OR 0.97, 95% CI (fixed-effect model) 0.69 to 1.37; [Analysis 5.3](#)). One trial ([Hawkey 2001](#)) studied the effect of lansoprazole and also found no significant effect on surgery (OR 0.49, 95% CI 0.12 to 2.01; [Analysis 5.3](#)).

Analysis according to report of endoscopic haemostatic treatment (Comparison 06)

Mortality

Three trials reported use of initial endoscopic haemostatic treatment ([Daneshmend 1992](#); [Hawkey 2001](#); [Lau 2007](#)) with no statistically significant heterogeneity among them ($P = 0.60$, $I^2 = 0\%$). The pooled effect on mortality was not statistically significant (OR 1.19; 95% CI 0.78 to 1.81; [Analysis 6.1](#)).

Three trials did not report use of initial endoscopic haemostatic treatment ([Hulagu 1995](#); [Naumovski 2005](#); [Wallner 1996](#)) with no statistical heterogeneity amongst them ($P = 0.79$, $I^2 = 0\%$) and also found no significant effect on mortality (OR 0.66, 95% CI 0.18 to 2.44; [Analysis 6.1](#)).

Rebleeding

Three trials reported the use of initial endoscopic haemostatic treatment ([Daneshmend 1992](#); [Hawkey 2001](#); [Lau 2007](#)) with no statistically significant heterogeneity between them ($P = 0.51$, $I^2 = 0\%$). The pooled effect on rebleeding was not statistically

significant (OR 0.87, 95 % CI (fixed-effect model) 0.66 to 1.16; [Analysis 6.1](#)).

Two trials did not report use of initial endoscopic haemostatic treatment ([Hulagu 1995](#); [Naumovski 2005](#)) with no statistical heterogeneity among them ($P = 0.69$, $I^2 = 0\%$) and found no significant difference in rebleeding rates between their treatment groups (OR 0.45, 95% CI 0.20 to 1.03; [Analysis 6.2](#)).

Surgery

Three trials reported the use of initial endoscopic haemostatic treatment ([Daneshmend 1992](#); [Hawkey 2001](#); [Lau 2007](#)) with no statistically significant heterogeneity among them ($P = 0.59$, $I^2 = 0\%$). The pooled effect on surgery was not statistically significant (OR 0.90, 95 % CI (fixed-effect model) 0.64 to 1.27; [Analysis 6.3](#)).

Two trials did not report use of initial endoscopic haemostatic treatment ([Naumovski 2005](#); [Wallner 1996](#)) with no statistical heterogeneity amongst them ($P = 0.59$, $I^2 = 0\%$) and found no significant difference in rebleeding rates between their treatment groups (OR 0.91, 95% CI 0.35 to 2.36; [Analysis 6.3](#)).

Outcomes for participants with peptic ulcer bleeding (Comparison 07)

Mortality

Two trials reported separate mortality rates for participants with peptic ulcer bleeding ([Daneshmend 1992](#); [Wallner 1996](#)). These trials comprised 282 participants in the PPI arm and 298 in the control arm in total. There was no statistically significant heterogeneity among the trials ($P = 0.20$, $I^2 = 39\%$). The pooled effect on mortality was not significant (OR 1.59, 95 % CI 0.85 to 2.97; [Analysis 7.1](#)).

Daneshmend et al also reported separate outcomes for participants bleeding from gastric and duodenal ulcers ([Daneshmend 1992](#)). For participants with gastric ulcer bleeding, mortality was 7% in the PPI group and 5% in the control group. In participants with bleeding duodenal ulcer, mortality was 11% in the PPI group compared to 5% in the control group (differences were not statistically significant).

Rebleeding

Two trials reported separate rebleeding rates for participants with peptic ulcer bleeding ([Daneshmend 1992](#); [Lau 2007](#)). These trials comprised 433 participants in the PPI arm and 447 in the control arm. There was no statistically significant heterogeneity between the trials ($P = 0.54$, $I^2 = 0\%$). The pooled effect on mortality was not significant (OR 0.86, 95 % CI 0.59 to 1.26; [Analysis 7.2](#)). The Daneshmend study ([Daneshmend 1992](#)) reported rebleeding rates separately for gastric and duodenal ulcer. The rebleeding rates were 27% in the PPI group compared to 25% in the placebo group in participants with bleeding gastric ulcer, and 21% in the PPI group compared to 29% in the placebo group for participants with bleeding duodenal ulcer. The results were not statistically significant.

Surgery

Two trials reported separate surgical intervention rates for participants with peptic ulcer bleeding ([Daneshmend 1992](#); [Lau 2007](#)). These trials comprised 433 participants in the PPI arm and 447 in the control arm. There was no statistically significant

heterogeneity between the trials ($P = 0.80$, $I^2 = 0\%$). The pooled effect for surgery was non-significant (OR 0.91, 95 % CI 0.59 to 1.40; [Analysis 7.3](#)).

The Daneshmend study ([Daneshmend 1992](#)) reported this outcome separately for gastric and duodenal ulcer participants. In participants with bleeding gastric ulcer, 19% in the PPI group underwent surgery compared to 17% in the placebo group. In participants with bleeding duodenal ulcer, 18% in the PPI group underwent surgery compared to 21% in the placebo group. The results were not statistically significant.

Hawkey et al ([Hawkey 2001](#)) provided outcomes on peptic ulcer participants (42.4% of total study population) but not per treatment group. The rates of rebleeding (13.9%), surgery (6.6%) and death (4.4%) in peptic ulcer participants did not differ significantly from the whole study population.

Proportion of participants with stigmata of recent haemorrhage at index endoscopy

One trial reported the proportion of participants with stigmata of recent haemorrhage at index endoscopy for participants with peptic ulcer bleeding ([Lau 2007](#)). In the PPI group, 67/187 participants were found to have stigmata of recent haemorrhage at index endoscopy compared with 100/190 participants in the placebo group ($P = 0.001$). The authors also observed that a significantly lower proportion of participants had actively bleeding ulcer in the PPI group (12/187) compared to the placebo group (28/190, $P = 0.01$). The proportion of non bleeding visible vessels, adherent clot or flat pigmented spots did not differ significantly between the groups.

Need for endoscopic haemostatic treatment at index endoscopy

One trial reported the proportion of participants with peptic ulcer bleeding who received endoscopic haemostatic treatment at index endoscopy ([Lau 2007](#)). This was 42/187 (22.5%) participants in the PPI group versus 70/190 (36.8%) participants in the placebo group. The difference between the PPI and placebo groups was statistically significant ($P = 0.002$). The authors ([Lau 2007](#)) also observed that the amount of adrenaline injected and the pulses of heater probe were significantly lesser in the PPI group in participants with peptic ulcer bleeding receiving endoscopic haemostatic treatment.

Blood transfusion requirements

None of the studies reported blood transfusion requirements in the subgroup of participants with peptic ulcer bleeding.

Length of hospital stay

None of the studies reported length of stay in the subgroup of participants with peptic ulcer bleeding.

DISCUSSION

Experimental data suggest that acid suppression and increased pH are important in clot stabilisation and hence potentially in reducing rebleeding ([Green 1978](#); [Low 1980](#)). However, evidence from clinical trials would suggest an adjunctive role for PPI in supplementing endoscopic haemostasis which is the cornerstone in the management of non variceal upper gastrointestinal bleeding ([Barkun 2003](#); [Cook 1992](#); [Sung 2003](#)).

The evidence for the use of PPI in acute upper GI bleeding has been evolving over the last decade. A meta-analysis of RCTs using acid suppressing drugs (either PPI or H2RA) compared to placebo for peptic ulcer bleeding showed a significant reduction in rates of rebleeding and surgery but no effect on mortality (Selby 2000). A meta-analysis of RCTs comparing PPI treatment to placebo found a significant reduction in rates of further bleeding but no effect on mortality or surgical intervention rates (Gisbert 2001).

More recently, several meta-analyses have studied the clinical effectiveness of PPIs compared to other available drug therapies in acute upper gastrointestinal haemorrhage (Khuroo 2005) or in acute peptic ulcer haemorrhage (Andriulli 2005; Bardou 2005; Leontiadis 2005)

Khuroo et al did not find a significant pooled effect of PPI treatment on clinical outcomes in patients with acute upper gastrointestinal bleeding (Khuroo 2005). However, the issue of time of initiation of PPI treatment was not addressed. Of the five trials included in that analysis, three (Orti 1995; Perez Flores 1994; Uribarrena 1994) randomised patients and initiated treatment after endoscopy. For this reason, these trials have been excluded from our systematic review.

The other three meta-analyses assessed the effectiveness of PPI treatment in RCTs confined to patients with peptic ulcer bleeding (Andriulli 2005; Bardou 2005; Leontiadis 2005). These meta-analyses are in broad agreement that PPI treatment significantly reduces rebleeding and largely surgery, compared with H2RA or placebo in patients with peptic ulcer bleeding. A Cochrane meta-analysis found no evidence of an overall effect of PPI treatment on mortality, although a significant reduction in mortality was found among patients with active bleeding or a non-bleeding vessel (Leontiadis 2005). The meta-analysis by Bardou et al (Bardou 2005) was confined to patients with peptic ulcer bleeding and high-risk endoscopic stigmata (active bleeding, a non-bleeding vessel, adherent clot) and found a significant reduction in mortality in the groups of trials that studied high dose intravenous PPI treatment versus placebo and non-high dose oral or intravenous PPI treatment versus placebo, but found no effect in mortality in trials that studied high dose oral PPI treatment versus placebo. Andriulli et al (Andriulli 2005) found no evidence of an overall effect of PPIs on mortality.

To our knowledge, this is the first updated systematic review and meta-analysis assessing the clinical effectiveness of PPI therapy initiated prior to endoscopic diagnosis in unselected patients with acute upper gastrointestinal haemorrhage.

Mortality is the single most important outcome of the present analysis. We found no evidence that initiation of PPI treatment prior to endoscopy had an effect on the 30 day all-cause mortality in unselected patients with acute upper gastrointestinal bleeding. The confidence interval of the pooled result is wide and is compatible with no difference in mortality rates between PPI and control groups, or may also suggest inadequate power to rule out clinically important differences in mortality. The quality of evidence regarding mortality is low due to an important inconsistency in the direction of the results among studies and also due to the wide confidence intervals to be consistent with conflicting clinical recommendations.

Rebleeding is a clinically important outcome that is related to poor prognosis. We found no evidence of an effect of PPI treatment initiated prior to endoscopy on rebleeding rates in unselected patients with upper gastrointestinal bleeding. The confidence interval for this result is consistent with no effect or a clinically insignificant reduction in rebleeding rates with PPI.

Surgery in patients with upper gastrointestinal bleeding can be associated with high mortality and is of considerable cost (Barkun 2003; Rockall 1995). Again, we found no evidence of an effect of PPI treatment initiated prior to endoscopy on surgical intervention rates in such patients. The confidence interval of this result is compatible with no difference in the requirement for surgery with PPI or control treatment.

An interesting observation is the effect of PPI treatment on findings at index endoscopy performed up to 24 hours (Daneshmend 1992; Hawkey 2001) or 48 hours (Wallner 1996) following admission. As first described by Daneshmend et al (Daneshmend 1992), an unexpected, but statistically significant reduction in stigmata of haemorrhage at index endoscopy was reported in patients treated with PPI (omeprazole) compared to placebo. Subsequent but smaller trials did not confirm this (Hawkey 2001; Wallner 1996), although one of these found that PPI treatment started prior to endoscopy significantly reduced the amount of blood in the stomach (Hawkey 2001).

Our meta-analysis of these trials showed a significant reduction in the proportion of patients with stigmata of haemorrhage (active spurting or bleeding, non bleeding visible vessel and adherent clot) at index endoscopy with PPI treatment, but the above analysis was dominated by one trial (Daneshmend 1992) and was not robust to its exclusion. Furthermore, this analysis became non-significant when a random effects model was used. There was no demonstrable effect on the proportion of patients with blood in the stomach or the proportion with active bleeding. However, the most recent of the trials (Lau 2007) found that PPIs prior to endoscopy significantly reduced both stigmata of haemorrhage at index endoscopy and rates of endoscopic haemostatic treatment, in patients with peptic ulcer bleeding. The authors did not report these outcomes for all randomised patients and hence this study could not be included in our meta analysis for this outcome.

Of note, Lau 2007 was the only study to have administered high dose intravenous PPI. None of the other studies (Daneshmend 1992; Hawkey 2001; Hurlag 1995; Naumovski 2005; Wallner 1996) used high dose intra venous PPI infusion. The biological rationale of high dose PPI infusion achieving sustained acid suppression (prolonged period of pH around 6) has been shown in gastric pH studies (Brunner 1996; Hasselgren 1998; Van Rensburg 2003) using 80mg bolus followed by 8mg/hr infusion of omeprazole or pantoprazole. However, a recent clinical trial in the US (Jensen 2006) was stopped prematurely due to slow recruitment of patients. This trial (Jensen 2006) was not powered to show significant differences between the groups and showed a trend for rebleeding rates to be lower in the high dose PPI group. A further multicentre trial (Sung 2009) has shown that high dose esomeprazole given after haemostatic treatment reduces rebleeding and endoscopic retreatment rates in patients with peptic ulcer bleeding

The rate of reduction of stigmata of haemorrhage seems plausible considering the findings of a study by Lau et al (Lau 1998). They

found a significant rate of reduction of stigmata per day for the first three days in patients treated with intravenous H2RA for acid suppression. Our meta-analysis showed a significant reduction in stigmata of recent haemorrhage and a reduced requirement for endoscopic haemostatic treatment in the PPI group. It is plausible that the overall costs of treatment and the need for experienced endoscopy personnel could be reduced if the need for endoscopic therapy is reduced. This might also reduce exposure of patients to the risks of interventional treatment. However, the clinical significance of the above effects of PPIs on endoscopic stigmata of haemorrhage and requirement for endoscopic treatment are unclear. The current meta-analysis found no evidence of an effect on mortality, rebleeding or surgery. In the Lau study (Lau 2007), among patients who did not have haemostatic treatment due to low risk stigmata on index endoscopy, 6/127 patients had rebleeding in the PPI group compared to 0/100 patients in the placebo group. Although not statistically significant, this increased rebleeding rate in the PPI group would raise concerns of spurious downstaging in ulcer stigmata at index endoscopy and could potentially lead to withholding of haemostatic treatment.

In this systematic review, planned subgroup analyses according to degree of allocation concealment, control treatment, route of PPI administration and application of initial endoscopic haemostatic treatment found no significant differences between pre-endoscopic initiation of PPI or control treatment regarding mortality, rebleeding or surgery. Based on the separate data for patients with peptic ulcer bleeding reported by three of the trials (Daneshmend 1992; Lau 2007; Wallner 1996), there was no evidence of an effect of PPI treatment initiated prior to endoscopy on mortality, rebleeding or surgery.

Two studies (Lau 2007; Naumovski 2005) demonstrated a shorter hospital and ICU stay and the latter study (Naumovski 2005) observed lower blood transfusion requirements in the PPI group. However, the other studies included in this review found no significant difference between the groups for this outcome (Daneshmend 1992; Hawkey 2001; Hurlag 1995; Wallner 1996). Also the presence of variation in the reporting of this outcome precluded a meaningful meta-analysis to estimate a pooled effect among the trials.

Summary of main results

In conclusion, PPI treatment initiated prior to endoscopy for upper gastrointestinal bleeding may reduce the proportion of patients with stigmata of recent haemorrhage. PPI treatment significantly reduces the need for haemostatic treatment at index endoscopy. However, we found no evidence that this improves mortality, rebleeding or the need for surgery.

Overall completeness and applicability of evidence

This systematic review and meta-analysis was designed to include trials performed all around the world and regardless of publication status or language of publication. Only three of the 127 studies identified by the search could not be retrieved in full. Hence, we believe this review is comprehensive and the results reflect the available evidence for the use of PPI before endoscopy in acute upper gastrointestinal bleeding.

Quality of the evidence

Of the six trials included, only one (Lau 2007) was assessed to be of methodologically high quality with a low risk of bias. However, this could be attributed to incomplete reporting of methodological data in the manuscript rather than methodology or design of the trials. The absence of statistical heterogeneity and the robustness of the results of all the analyses (with the exception of the analysis of the effect on stigmata of recent haemorrhage at index endoscopy) during sensitivity analysis excluding each study would support the quality and reliability of the evidence and conclusions reached by this review. The quality of the evidence could have been better if further details for outcomes such as blood transfusion requirement and stay in hospital had been available, to allow comparison of the pooled outcomes between the treatment groups.

Potential biases in the review process

Based on the available data, it is difficult to address several key issues which remain to be answered including the optimal duration of PPI treatment and time to endoscopy. Only the Lau study (Lau 2007) reported these data and the information was not available from the other studies included in this review to perform *post hoc* analyses.

An important limitation of the studies included in this review is the small proportion of patients receiving endoscopic haemostatic treatment (EHT). In the two studies that reported the proportion of patients undergoing EHT (Daneshmend 1992; Hawkey 2001), this was only applied in around 30% of patients with active bleeding or with other stigmata of recent haemorrhage. However, it is uncertain if the combination of high dose PPI in conjunction with a more aggressive endoscopic therapy would influence the outcome positively or negatively. Sung 2003 included patients with ulcers containing non-bleeding visible vessels or adherent clots and showed that combination therapy with endoscopic haemostasis and continuous intravenous omeprazole produced a lower rebleeding rate (1.1%) than intravenous omeprazole alone (11.6%). It would be difficult without individual patient data to determine confidently whether particular patient subgroups do benefit (for example based on 'severity' of initial bleed, likelihood of peptic ulcer, etc).

Another potential source of bias in the review would be the selection of the primary outcome. Although mortality is clinically the most important and significant outcome, the risk of mortality in most unselected patients with upper gastrointestinal bleeding is low (Longstreth 1998; Rockall 1996). Also, most RCTs reported rebleeding or requirement for retreatment as the primary outcome and hence would be inadequately powered to show a significant difference in mortality between the PPI and control groups. In our meta-analyses, a trend was observed for reduced rebleeding and active bleeding in the PPI group, with an adequate number of patients these results may have become statistically significant in favour of PPI for some of the clinically relevant outcomes.

Finally, cost effectiveness of PPI therapy in upper gastrointestinal haemorrhage was not considered in this review. In clinical practice, empirical PPI therapy is considered acceptable by many treating physicians (Andrews 2002; Andrews 2002a; Zandieh 2002), despite the lack of robust clinical evidence to support this practice. However, there is some evidence to suggest that this approach might be cost effective. A recent study utilised a decision analytical

model to estimate the incremental cost-effectiveness of empirical intravenous PPI treatment for upper gastrointestinal haemorrhage for the first 24 hours in 1000 hypothetical patients. Based on the expected reductions in rates of rebleeding and surgery over a period of 60 days, the authors concluded that this approach is cost effective with a potential saving of \$20,700 resulting from the prevention of 37 rebleeding episodes (Enns 2003). More recent evidence on the cost effectiveness of PPI prior to endoscopy raises uncertainty. Sung et al (Sung 2008) used a decision analysis model based on the data from the Lau study (Lau 2007) and found preemptive PPI treatment to be a cost effective strategy. However, another study (Al-Sabah 2008) found this strategy to be slightly more costly and effective. This strategy was found to be cost effective in Canada if high risk patients stay more than 6 days and low risk patients stay less than 3 days in hospital.

Agreements and disagreements with other studies or reviews

Recent consensus recommendations (Barkun 2003; Barkun 2010) support the use of PPI before endoscopy based on the cost effectiveness studies. However, our review has not found any evidence to support reduction in clinically significant adverse outcomes with the use of PPI before endoscopy in acute upper gastrointestinal bleeding.

AUTHORS' CONCLUSIONS

Implications for practice

PPI therapy is already widely initiated before endoscopy in patients with upper gastrointestinal bleeding. The present analysis did not find significant improvement with PPI treatment for

clinically important outcomes including rebleeding, surgery or mortality. The reduced rate of serious endoscopic stigmata of bleeding found at endoscopy among patients given PPI therapy before endoscopy and the reduced requirement for endoscopic haemostatic treatment are of uncertain clinical significance. However, PPI therapy may have a role if prompt endoscopy is not readily available. Among such patients in whom PPI therapy is initiated before endoscopy, therapy can obviously be discontinued if endoscopy finds no evidence of bleeding or evidence of bleeding from an alternate source (for example, oesophageal or gastric varices).

Implications for research

There is a need for further large trials using high dose PPI treatment prior to endoscopy in patients with upper gastrointestinal bleeding and concentrating on clinical outcomes. The comparator could be either post-endoscopic initiation of PPI treatment (among patients found to have had ulcer bleeding) or pre-endoscopic initiation of a control treatment (placebo or an H2RA).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Daneshmend 1992

Methods	Large multicentre (two centres) double blind RCT.
Participants	Country: UK. Included 1147 participants (578 on PPI; 569 on control treatment). PU 43.9%; oesophageal varices 2.5% of total. Excluded severe bleeding (that required surgery) and bleeding that developed in patients.
Interventions	1. Omeprazole 80 mgs IV immediately, then 3 doses of 40 mg IV at eight-hourly intervals, then 40 mg oral every 12 hours for 101 hours or until surgery, discharge, or death. 2. Identical regimen with mannitol. Post-intervention drug treatment at discretion of physician. Initial endoscopic treatment at discretion of endoscopist (received by a minority of high risk participants).
Outcomes	40-day mortality; rebleeding; surgery; stigmata of recent haemorrhage at index endoscopy; number of participants requiring blood transfusion. First three outcomes also reported by peptic ulcer site.
Notes	Only a few of the high-risk participants with PU received initial endoscopic treatment. Timing of assessment of rebleeding and surgery not clear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	The treatments were randomized in blocks of 10. No further description of sequence generation provided by authors.
Allocation concealment?	Unclear risk	No report from the authors on the methods to use adequate concealment.
Blinding? All outcomes	Low risk	Authors report that this study was double blind and that mortality assessors were blinded, but does not report who else was blinded. Authors also report that the appearances of study treatment and placebo were identical.
Incomplete outcome data addressed? All outcomes	Low risk	Initially 1154 participants randomised. Authors reported 4 participants were not given the study treatment (one omeprazole group and three placebo group) and in 3 the treatment given could not subsequently be clearly identified. Hence 1147 were successfully randomised (578 in omeprazole group and 569 to placebo group) Authors clearly reported protocol violations in 98 participants, (62 participants were prescribed concomitant H2RA, 18 more than 12 hours after admission, 3 were under age or pregnant). Authors have also reported Intention to treat and per protocol analysis separately. The results for each of the outcomes were comparable between the two analyses.
Free of selective reporting?	Low risk	No evidence of imputation or last observation carried forward.
Free of other bias?	High risk	Authors do not describe whether length of stay ended by discharge or death. Authors do not describe in detail the criteria for requirement of repeat endoscopy offered for participants with rebleeding.

Hawkey 2001

Methods	Multicentre (two centres) double blind RCT.
Participants	Country: UK. 414 participants in total (102 on PPI; 103 on placebo; 103 on tranexamic acid; 106 on tranexamic acid plus PPI). PU 42.4%; 3.9% oesophageal varices 2.5% of total. Excluded severe bleeding (that required immediate surgery).

Hawkey 2001 (Continued)

Interventions	1. Lansoprazole 60 mg orally (start), followed by 30 mg plus dummy medication four times daily for four days. 2. Placebo - double dummy technique. 3. Tranexamic acid 2g orally (start), followed by 1g orally plus dummy medication four times daily for four days. 4. Tranexamic acid and lansoprazole - both active drugs as above for four days. Post-intervention drug treatment not mentioned. Initial endoscopic haemostatic treatment offered for participants with active bleeding.
Outcomes	30 day mortality; 30 day surgery; rebleeding (timing unclear); stigmata of recent haemorrhage at index endoscopy; number of participants requiring blood transfusion.
Notes	For the current meta-analysis we included only group 1 (lansoprazole alone) as active treatment group and group 2 (placebo) as control group. participants that received tranexamic acid or the combination of PPI and tranexamic acid were not included. Timing of assessment of rebleeding not clear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Authors report no method for sequence generation.
Allocation concealment?	Unclear risk	Authors report no method for allocation concealment.
Blinding? All outcomes	Low risk	Authors mention double blind, double dummy comparison.
Incomplete outcome data addressed? All outcomes	Low risk	Authors provide a clear disposition of participants at each stage after randomisation. Of the 414 participants enrolled, 55 not endoscoped. Of the 298 endoscoped, 61 were not Gi bleed. 248 participants were eligible and 50 not eligible for further evaluation due to protocol violations (39 more than 72 hours after start of bleeding, 9 more than 8 hours from 1st dose to endoscopy, 2 participants with no trial data). 20 further participants were not evaluable (14 participants missed 2 or more doses, 4 endoscopy received before trial treatment, 3 prohibited drugs during trial and 1 previously in trial). The authors also report the withdrawals and dropouts within each treatment group.
Free of selective reporting?	Low risk	No evidence of selective reporting.
Free of other bias?	High risk	Authors report the decision to offer repeat endoscopy for rebleeding was left to the discretion of treating physician and do not describe in detail the criteria for requirement of repeat endoscopy.

Hulagu 1995

Methods	Single centred, open RCT.
Participants	Country: Turkey. Included 58 participants (30 omeprazole group, 28 control treatment group).
Interventions	1. Omeprazole 80mg IV as soon as possible after admission, followed by 40 mg IV once a day and 100mg IV 3 times a day for 6 days. Omeprazole 20mg once a day at end of 4 weeks. 2. Rantidine 100 mg as soon as possible after admission, followed by 100 mg IV 3 times a day for 6 days. Famotidine 40mg once a day at end of 4 weeks.
Outcomes	Mortality, rebleeding, stigmata of recent haemorrhage at index endoscopy, number of participants requiring blood transfusion.

Hulagu 1995 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Authors report no details of sequence generation.
Allocation concealment?	Unclear risk	Authors report no details of allocation concealment.
Blinding? All outcomes	Unclear risk	Authors report no details of blinding.
Incomplete outcome data addressed? All outcomes	Low risk	Authors provide clear disposition for all randomised participants. Among the 6 omeprazole group participants who were not endoscoped in the 1 st month; one participant died of massive upper gastrointestinal haemorrhage due to end stage liver disease, two participants moved to another city and could not come to control, one participant had appendicitis and operated at control date, and two participants refused control endoscopy. For the 1 st month endoscopy of ranitidine group, 20 of 28 participants(71%) were reexamined. Among the 8 ranitidine group participants who were not endoscoped in the 1 st month; one participant died of pancreas carcinoma with massive upper gastrointestinal bleeding, one participant had coronary by-pass surgery, one participant had unstable heart disease, 3 participants refused the endoscopy procedure and 2 participants with unknown reasons could not be reexamined. Authors report that these participants were omitted from the rest of the study.
Free of selective reporting?	High risk	No data regarding requirement for surgery. No data per treatment group for stigmata of recent haemorrhage.
Free of other bias?	High risk	No definition of rebleeding. Indications for surgery not stated.

Lau 2007

Methods	Single centre double blind randomised controlled trial.
Participants	Setting: Hongkong, Asia, 631 participants randomised (314 in the PPI group and 317 in the placebo group) 187 participants with Peptic ulcer disease in the PPI group and 190 in the placebo group. 3.8% participants with variceal bleed. Excluded long term aspirin users and participants with continued shock requiring emergency surgery.
Interventions	Intravenous omeprazole 80mg at randomisation and continuous infusion at 8mg/hour until endoscopy. Intravenous placebo 80mg bolus followed by infusion 8mg/hr until endoscopy. participants with high risk stigmata requiring endoscopic treatment were treated with PPI 8mg/hour infusion for 72 hours followed by 8 weeks of oral omeprazole 40mg. Omeprazole based standard Helicobacter eradication treatment for 7 days used as appropriate.
Outcomes	30 day mortality, rebleeding, surgery, proportion of participants requiring endoscopic therapy, length of hospital stay and mean units of blood transfusion reported according to treatment group. Stigmata of haemorrhage reported only in peptic ulcer disease participants.

Notes

Risk of bias

Lau 2007 (Continued)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Consecutive participants randomised according to computer generated random numbers in blocks of 20.
Allocation concealment?	Low risk	Sealed packs generated centrally in the pharmacy and sent to the wards with lowest numbered pack to be opened by the resident treating the participant.
Blinding? All outcomes	Low risk	Participants and all investigators were blinded to the treatment groups.
Incomplete outcome data addressed? All outcomes	Low risk	Clear reporting of disposition of participants at each stage of the study.
Free of selective reporting?	High risk	Stigmata of the recent haemorrhage reported only for peptic ulcer patients. The absence of this data for all randomised patients precluded the inclusion of this study from the main analysis which might have influenced the overall results for this outcome. The authors report that 5 patients in the omeprazole group excluded from analyses, (3 received the wrong diagnosis, 1 had small-bowel obstruction, 1 had a history of total gastrectomy, 1 had cholangitis, 2 withdrew voluntarily). 2 of the 314 patients did not undergo endoscopy. Of the 319 patients in the placebo group, 2 were excluded from the analysis, 1 because of wrong diagnosis and the other withdrew voluntarily.
Free of other bias?	Low risk	In the publication the authors did not distinguish length of stay ended by mortality or discharge; however, they provided separated data when requested.

Naumovski 2005

Methods	Single centre. Open RCT.
Participants	participants with acute UGI bleeding admitted to intensive care unit.
Interventions	IV Pantoprazole 80mg bolus after randomisation and 40mg tid for 5 days. control group received no treatment until endoscopy and then treated with pantoprazole 40mg iv bolus followed by 40mg tid for 5 days.
Outcomes	mortality, rebleeding, surgery, length of stay in ICU, mean number of blood units transfused and lesion stabilisation on repeat endoscopy at 5 days. No mention of follow up duration and time of outcome measurement.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Authors do not provide details of sequence generation.
Allocation concealment?	Unclear risk	Authors do not provide details of allocation concealment.
Blinding? All outcomes	Unclear risk	Authors do not provide details of blinding.

Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding (Review)

Naumovski 2005 (Continued)

Incomplete outcome data addressed? All outcomes	Unclear risk	Abstract publication. Authors do not provide disposition of participants at each stage of study. Hence difficult to ascertain the robustness of assessment of incomplete data. The authors do not report withdrawal or dropout data.
Free of selective reporting?	High risk	Length of stay limited to the intensive care unit. No stigmata of recent haemorrhage per treatment group.
Free of other bias?	High risk	Included participants admitted to ICU only. Authors do not report indications for surgery, timing of endoscopy, time period for assessment of any of the outcomes including mortality.

Wallner 1996

Methods	Single centred, open RCT.
Participants	Country: Poland. Included 102 participants (50 on PPI and 52 on placebo group). PU 75.5% of total; no participants with oesophageal varices (hepatic insufficiency was an exclusion criterion).
Interventions	1. Omeprazole IV bolus delivery, dosing regime unclear: stated as "40 mg" or "80 mg" or "120 mg" (presumably representing total daily doses). 2. Ranitidine IV bolus delivery, dosing regime unclear: stated as "150 mg" or "200 mg" or "300-400 mg" (presumably representing total daily doses). Unclear if participants within each treatment arm were allocated to each dosing group by a random method or not. Duration of treatment depending on continuation of bleeding. Initial endoscopic haemostatic treatment not mentioned.
Outcomes	Mortality; surgery; stigmata of recent haemorrhage at index endoscopy; number of participants requiring blood transfusion. Timing of outcome assessment not clear.
Notes	Timing of assessment of rebleeding not clear. Initial endoscopic haemostatic treatment not mentioned. Dosing of pharmacological treatments not clear. Rebleeding rates could be extracted because the study was designed to assess time needed for bleeding cessation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Series of random odd and even numbers generated by the computer.
Allocation concealment?	Unclear risk	No details of allocation concealment reported.
Blinding? All outcomes	High risk	Open study.
Incomplete outcome data addressed? All outcomes	Low risk	Reported disposition of all randomised participants and outcomes for all participants randomised. No withdrawal or dropouts were observed during the study period.
Free of selective reporting?	Low risk	No evidence of selective reporting.
Free of other bias?	Unclear risk	Did not distinguish length of stay ended by mortality or discharge. Rebleeding not reported as an outcome although the study was designed to assess cessation of bleeding at day 5 depending on clinical and laboratory criteria. No data

Wallner 1996 (Continued)

reported on the requirement for repeat endoscopy for persistence of bleeding. Authors did not report time of assessment of mortality.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Al-Sabah 2008	Cost effectiveness study. Not an RCT.
Andrews 2005	Not an RCT. Retrospective observation study.
Avgerinos 2005	Randomised controlled trial in participants with Peptic ulcer bleeding with outcome being serial gastric PH measurements over 24 hours, in response to treatment with somatostatin, PPI and placebo.
Bai 1995	Restricted to participants with bleeding from peptic ulcer and acute gastric mucosal lesions. Randomised after endoscopy.
Bajaj 2007	RCT comparing oral and IV PPI in NVUGIB. Does not satisfy the inclusion criteria of this review.
Brunner 1990	Limited to peptic ulcer bleeding. Randomisation after endoscopy.
Cheng 2005	Randomised after endoscopy. Comparison between low and high dose IV PPI. participants with peptic ulcer bleeding and comorbid illness.
Chu 1993	Restricted to peptic ulcer bleeding participants only and randomisation after endoscopy.
Colin 1993	Not randomised controlled trial.
Costamagna 1998	Randomised after endoscopy.
Dovas 1992	Unable to gain copy of publication.
Elphick 2007	Not an RCT. Letter to the editor.
Fasseas 2001	Restricted to endoscopically verified participants and only gastric ulcers, duodenal ulcers and erosions were included.
Felder 1998	Restricted to peptic ulcer bleeding participants only.
Fried 1999	Randomised after endoscopy. Restricted to peptic ulcer bleeding participants only.
Gao 1995	Unclear when randomisation took place.
Goletti 1994	Control group not being either placebo or H2RA alone; compared omeprazole alone versus the combination of ranitidine and endoscopic haemostatic therapy. Restricted to participants with ulcers or haemorrhagic gastritis. Randomisation post endoscopic diagnosis.
Hasselgren 1998	Study with main outcome of intra gastric PH studies. Limited to Peptic ulcer bleeding.
Hulagu 1994	Abstract publication, the trial was subsequently published in full (Hulagu 1995).
Hung 2007	Randomized post endoscopy in peptic ulcer bleeding.

Study	Reason for exclusion
Jensen 2006	RCT on bleeding peptic ulcer participants. Randomized post endoscopic haemostasis.
Keyvani 2006	Not an RCT. Retrospective observation study.
Kim 2007	Randomisation post endoscopy. RCT comparing oral PPI to endoscopic haemoclipping in peptic ulcer bleeding. Does not satisfy the inclusion criteria of this review.
Lau 2005	Abstract publication with results for Peptic ulcer disease participants only. The trial was subsequently published in full (Lau 2007).
Lee 2003	Cost effectiveness study.
Lin 2007	Not an RCT. Letter to the Editor.
Liu 2002	Randomised after endoscopy. Restricted to duodenal ulcer participants.
Maculotti 1995	Designed to assess healing rates. Not reporting any of the outcomes pre-determined in this systematic review. Randomisation post endoscopy.
Munkel 1997	Restricted to peptic ulcer bleeding participants only. Randomisation post endoscopy.
Murthy 2007	Not an RCT. Retrospective review of oral PPI versus IV PPI in peptic ulcer bleeding post endoscopic haemostasis.
Nehme 2001	Randomised after endoscopy.
Orti 1995	Restricted to participants suspected to have bleeding from peptic origin. It was not clear from the paper if the authors ascertained this before randomisation. Communications to obtain further details are ongoing.
Perez Flores 1994	Randomisation post endoscopy, restricted to participants with peptic ulcer bleeding
Savides 2001	Randomised after endoscopy, restricted to peptic ulcer bleeding.
Schaffalitzky 2007	Not an RCT. Letter to the editor.
Scheurlen 2000	Restricted to peptic ulcer bleeding participants only, not RCT.
Schonekas 1999	Restricted to peptic ulcer bleeding participants only; control group not either placebo or H2RA alone; compared two different regimens of PPI.
Srinath 1997	Not a randomised controlled trial. This article was a comment on another RCT (Khuroo 1997).
Sung 2003	Randomisation post endoscopy. participants with visible vessel and adherent clot.
Sung 2008	Randomisation post endoscopy. participants with Peptic ulcer bleeding only.
Tran 2007	Not an RCT. Letter to the editor.
Tsoi 2008	Not an RCT. Cost effectiveness study based on the data from the Lau study (Lau 2007).
Udd 2001	Control group not being either placebo or H2RA alone; compared to intravenous regimens of omeprazole at different doses.

Study	Reason for exclusion
Uribarrena 1994	Selected participants with bleeding from gastric ulcer, duodenal ulcer, erosions and peptic oesophagitis only. Participants with bleeding from non-peptic sources were excluded from the analysis.
Wei 2007	Randomization post endoscopic haemostasis. participants with peptic ulcer bleeding
Wu 2001	Unable to gain copy of publication.
Xuan 2003	Randomisation after endoscopy.
Yilmaz 2006	Randomization post endoscopy. participants with peptic ulcer bleeding with low risk stigmata.
Zargar 2006	Randomization post endoscopy. participants with peptic ulcer bleeding.

DATA AND ANALYSES

Comparison 1. Main analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality - 30 days or at point closest to 30 days	6	2223	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.75, 1.68]
2 Rebleeding within 30 days	5	2121	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.06]
3 Surgery for continued or recurrent bleeding within 30 days of randomisation	5	2165	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.25]
4 Patients requiring blood transfusion (post hoc analysis)	4	1512	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.16]
5 Proportion of patients with stigmata of recent haemorrhage	4	1332	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.54, 0.84]
6 Proportion of patients with blood in stomach (post hoc analysis)	3	1230	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.32, 1.30]
7 Proportion of patients with active bleeding	4	1332	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.54, 1.02]
8 Endoscopic haemostatic therapy at index endoscopy	3	1983	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.50, 0.93]

Analysis 1.1. Comparison 1 Main analysis, Outcome 1 Mortality - 30 days or at point closest to 30 days.

Analysis 1.2. Comparison 1 Main analysis, Outcome 2 Rebleeding within 30 days.

Analysis 1.3. Comparison 1 Main analysis, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.

Analysis 1.4. Comparison 1 Main analysis, Outcome 4 Patients requiring blood transfusion (post hoc analysis).

Analysis 1.5. Comparison 1 Main analysis, Outcome 5 Proportion of patients with stigmata of recent haemorrhage.

Analysis 1.6. Comparison 1 Main analysis, Outcome 6 Proportion of patients with blood in stomach (post hoc analysis).

Analysis 1.7. Comparison 1 Main analysis, Outcome 7 Proportion of patients with active bleeding.

Analysis 1.8. Comparison 1 Main analysis, Outcome 8 Endoscopic haemostatic therapy at index endoscopy.

Comparison 2. Analysis according to degree of allocation concealment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	2223	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.75, 1.68]
1.1 Degree of allocation concealment: A	1	631	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.41, 3.23]
1.2 Degree of allocation concealment: non-A	5	1592	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.72, 1.73]
2 Rebleeding within 30 days	5	2121	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.06]
2.1 Degree of concealment: A	1	631	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.56, 3.53]
2.2 Degree of concealment : non-A	4	1490	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.58, 1.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Surgery for continued or recurrent bleeding within 30 days of randomisation	5	2165	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.25]
3.1 Degree of concealment: A	1	631	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.19, 2.39]
3.2 Degree of concealment: non-A	4	1534	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.66, 1.29]

Analysis 2.1. Comparison 2 Analysis according to degree of allocation concealment, Outcome 1 Mortality.

Analysis 2.2. Comparison 2 Analysis according to degree of allocation concealment, Outcome 2 Rebleeding within 30 days.

Analysis 2.3. Comparison 2 Analysis according to degree of allocation concealment, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.

Comparison 3. Analysis according to control treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	2223	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.75, 1.68]
1.1 PPI versus placebo	3	1983	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.78, 1.81]
1.2 PPI versus H2RA	2	160	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.18, 2.44]
1.3 PPI versus No Treatment	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Rebleeding within 30 days	5	2121	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.06]
2.1 PPI versus placebo	3	1983	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.66, 1.16]
2.2 PPI versus H2RA	1	58	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.14, 2.26]
2.3 PPI versus No Treatment	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.14, 1.12]
3 Surgery for continued or recurrent bleeding within 30 days of randomisation	5	2165	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.25]
3.1 PPI versus placebo	3	1983	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.64, 1.27]
3.2 PPI versus H2RA	1	102	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.45, 5.18]
3.3 PPI versus No Treatment	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.07, 2.02]

Analysis 3.1. Comparison 3 Analysis according to control treatment, Outcome 1 Mortality.

Analysis 3.2. Comparison 3 Analysis according to control treatment, Outcome 2 Rebleeding within 30 days.

Analysis 3.3. Comparison 3 Analysis according to control treatment, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.

Comparison 4. Analysis according to route of PPI administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Oral PPI	1	205	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.07, 2.07]
1.2 Intravenous PPI	5	2018	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.80, 1.84]
2 Rebleeding within 30 days	5	2121	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.06]
2.1 Oral PPI	1	205	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.40, 2.54]
2.2 Intravenous PPI	4	1916	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.60, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Surgery for continued or recurrent bleeding within 30 days of randomisation	5	2165	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.25]
3.1 Oral PPI	1	205	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.12, 2.01]
3.2 Intravenous PPI	4	1960	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.67, 1.30]

Analysis 4.1. Comparison 4 Analysis according to route of PPI administration, Outcome 1 Mortality.

Analysis 4.2. Comparison 4 Analysis according to route of PPI administration, Outcome 2 Rebleeding within 30 days.

Analysis 4.3. Comparison 4 Analysis according to route of PPI administration, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.

Comparison 5. Analysis according to the PPI used

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	2223	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.75, 1.68]
1.1 IV Omeprazole	4	1938	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.80, 1.84]
1.2 IV Pantoprazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Oral Lansoprazole	1	205	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.07, 2.07]
2 Rebleeding within 30 days	5	2121	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.06]
2.1 IV Omeprazole	3	1836	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.13]
2.2 IV Pantoprazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.14, 1.12]
2.3 Oral Lansoprazole	1	205	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.40, 2.54]
3 Surgery for continued or recurrent bleeding within 30 days of randomisation	5	2165	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.25]
3.1 IV Omeprazole	3	1880	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.69, 1.37]
3.2 IV Pantoprazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.07, 2.02]
3.3 Oral Lansoprazole	1	205	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.12, 2.01]

Analysis 5.1. Comparison 5 Analysis according to the PPI used, Outcome 1 Mortality.

Analysis 5.2. Comparison 5 Analysis according to the PPI used, Outcome 2 Rebleeding within 30 days.

Analysis 5.3. Comparison 5 Analysis according to the PPI used, Outcome 3 Surgery for continued or recurrent bleeding within 30 days of randomisation.

Comparison 6. Analysis according to report of endoscopic haemostatic treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	2223	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.75, 1.68]
1.1 Report of using Endoscopic Haemostatic treatment	3	1983	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.78, 1.81]
1.2 No report of using endoscopic haemostatic treatment	3	240	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.18, 2.44]
2 Rebleeding	5	2121	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.06]
2.1 Report of using Endoscopic haemostatic treatment	3	1983	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.66, 1.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 No report of using endoscopic haemostatic treatment	2	138	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.20, 1.03]
3 Surgery	5	2165	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.25]
3.1 Report of using endoscopic haemostatic treatment	3	1983	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.64, 1.27]
3.2 No report of using endoscopic haemostatic treatment	2	182	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.35, 2.36]

Analysis 6.1. Comparison 6 Analysis according to report of endoscopic haemostatic treatment, Outcome 1 Mortality.

Analysis 6.2. Comparison 6 Analysis according to report of endoscopic haemostatic treatment, Outcome 2 Rebleeding.

Analysis 6.3. Comparison 6 Analysis according to report of endoscopic haemostatic treatment, Outcome 3 Surgery.

Comparison 7. Analysis restricted to peptic ulcer patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	580	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.85, 2.97]
2 Rebleeding	2	880	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.26]
3 Surgery	2	880	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.59, 1.40]

Analysis 7.1. Comparison 7 Analysis restricted to peptic ulcer patients, Outcome 1 Mortality.

Analysis 7.2. Comparison 7 Analysis restricted to peptic ulcer patients, Outcome 2 Rebleeding.

Analysis 7.3. Comparison 7 Analysis restricted to peptic ulcer patients, Outcome 3 Surgery.

APPENDICES

Appendix 1. Search strategy

- 1 randomized controlled trial.pt. (267272)
- 2 controlled clinical trial.pt. (80460)
- 3 randomized.ab. (175319)
- 4 placebo.ab. (110572)
- 5 drug therapy.fs. (1309262)
- 6 randomly.ab. (127249)
- 7 trial.ab. (182795)
- 8 groups.ab. (882077)
- 9 or/1-8 (2367276)
- 10 (animals not (humans and animals)).sh. (3277268)
- 11 9 not 10 (2008270)
- 12 exp stomach/ (96737)
- 13 stomach.tw. (73048)
- 14 gastr\$.tw. (329679)
- 15 exp duodenum/ (35151)
- 16 duoden\$.tw. (63673)
- 17 peptic\$.tw. (22791)
- 18 exp esophagus/ (35405)
- 19 esophag\$.tw. (77638)
- 20 oesophag\$.tw. (22091)
- 21 or/12-20 (509656)
- 22 exp peptic ulcer/ (70077)
- 23 exp peptic ulcer hemorrhage/ (6406)

- 24 exp gastrointestinal hemorrhage/ (37564)
- 25 (peptic adj5 ulcer\$).tw. (19919)
- 26 (stomach adj5 ulcer\$).tw. (3840)
- 27 (duoden\$ adj5 ulcer\$).tw. (19848)
- 28 (gastroduoden\$ adj5 ulcer\$).tw. (3900)
- 29 (bleed\$ adj5 ulcer\$).tw. (4193)
- 30 (rebleed\$ adj5 ulcer\$).tw. (154)
- 31 (recurrent adj5 bleed\$ adj5 ulcer\$).tw. (136)
- 32 (acute adj5 bleed\$ adj5 ulcer\$).tw. (269)
- 33 (gastrointestinal adj5 bleed\$).tw. (9453)
- 34 (gastrointestinal adj5 rebleed\$).tw. (43)
- 35 (gastrointestinal adj5 hemorrhag\$).tw. (4059)
- 36 (gastrointestinal adj5 haemorrhag\$).tw. (1077)
- 37 (ulcer adj5 hemorrhag\$).tw. (1229)
- 38 (ulcer adj5 haemorrhag\$).tw. (272)
- 39 (haemorrhagic adj3 gastritis).tw. (69)
- 40 (hemorrhagic adj3 gastritis).tw. (279)
- 41 (haemorrhagic adj3 duodenitis).tw. (2)
- 42 (hemorrhagic adj3 duodenitis).tw. (14)
- 43 exp melena/ (1659)
- 44 melena.tw. (1167)
- 45 melaena.tw. (434)
- 46 exp hematemesis/ (1708)
- 47 haematemesis.tw. (630)
- 48 hematemesis.tw. (1379)
- 49 (coffee adj1 ground).tw. (87)
- 50 or/22-49 (113582)
- 51 exp omeprazole/ (7383)
- 52 omeprazole.tw. (5588)
- 53 lansoprazole.tw. (1395)
- 54 pantoprazole.tw. (713)
- 55 rabeprazole.tw. (509)
- 56 esomeprazole.tw. (440)
- 57 (proton adj5 pump adj5 inhibitor\$).tw. (4880)
- 58 ppi\$.tw. (6568)

59 or/51-58 (16898)

60 21 and 50 and 59 (4178)

61 60 and 11 (3255)

62 limit 61 to ed=20050301-20081010 (573)

WHAT'S NEW

Date	Event	Description
13 February 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 4, 2006

Date	Event	Description
2 June 2010	New citation required but conclusions have not changed	The review is being republished to correct the citation version.
28 October 2009	New search has been performed	Updated.
30 October 2008	Amended	Converted to new review format.
17 August 2006	Amended	New studies sought but none found.
18 June 2006	Amended	Minor update.
7 January 2005	Amended	New studies found and included or excluded.

CONTRIBUTIONS OF AUTHORS

All review authors were responsible for conception of the review and protocol design. AS and SD performed eligibility checks on the search results, data extraction and contributed to the writing up of the initial version of the review. SD did not take any further part in this update. AS and JM performed eligibility checks on the search results. AS and JM carried out the data extraction. Statistical analyses were performed by AS. The manuscript was updated by AS, GL and JM; all review authors provided critical review. All review authors contributed to final editing of the review and gave final approval.

DECLARATIONS OF INTEREST

A Sreedharan - Has received speaker fees from Astra Zeneca and has accepted honoraria from Abbott for attending scientific meetings

Janet Martin - co-investigator in a partner grant between industry (Astra Zeneca) and CIHR, but does not receive any payment from this grant.

G Leontiadis - Has received speaker fees and reimbursement for expenses to attend scientific meetings from AstraZeneca, Sanofi-Aventis, Janssen-Cilag and GlaxoSmithKline.

D Forman - Has received speaker fees from Astra Zeneca

P Moayyedi - Chair is partly funded by an unrestricted donation from AstraZeneca to McMaster University.

Has been on the speaker's bureau for AstraZeneca, Altana and Janssen-Ortho

Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding (Review)

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Has been on the advisory boards of AstraZeneca and Janssen-Ortho

C Howden - Previously consulted for TAP Pharmaceutical Products Inc, Takeda Chemical Industries, and Altana Pharma

Currently consults for Santarus Inc., Takeda Pharmaceuticals North America, Procter & Gamble, Xenoport

Speaker's bureau for Santarus Inc, AstraZeneca and Takeda Pharmaceuticals North America

Previous research grant support from AstraZeneca

Was previously an investigator and speaker for Merck.

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Internal sources

- University of Leeds, UK.

External sources

- NHS R & D Health Technology Assessment Programme (Project 03/12/03), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A post hoc decision was made to include a third author to independently data extract. Two post hoc analyses were conducted; concerning blood transfusion requirements and proportion of participants with presence of blood in the stomach.

NOTES

Protocol Published as 'Proton Pump Inhibitors (before endoscopic diagnosis) in upper gastrointestinal bleeding'. Dorward S, Forman D, Howden CW, Leontiadis GI, Sreedharan A *The Cochrane Database of Systematic Reviews* Published in Issue 2, 2006. Copyright © 2005 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

INDEX TERMS

Medical Subject Headings (MeSH)

*Endoscopy, Gastrointestinal; Anti-Ulcer Agents [*therapeutic use]; Gastrointestinal Hemorrhage [*drug therapy] [mortality]; Histamine H2 Antagonists [therapeutic use]; Proton Pump Inhibitors; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Humans