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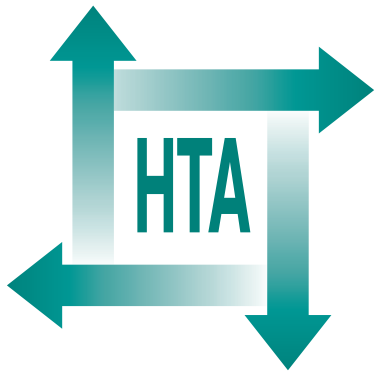

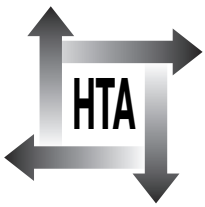

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The research reported in this monograph was commissioned by the HTA Programme as project number 03/12/03. The contractual start date was in August 2004. The draft report began editorial review in June 2006 and was accepted for publication in April 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding

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Objectives: To evaluate the clinical effectiveness and cost-effectiveness of proton pump inhibitors (PPIs) in the prevention and treatment of acute upper gastrointestinal (UGI) haemorrhage, as well as to compare this with H_2-receptor antagonist (H_2RA), *Helicobacter pylori* eradication (in infected patients) or no therapy, for the prevention of first and/or subsequent bleeds among patients who continue to use non-steroidal anti-inflammatory drugs (NSAIDs). Also to evaluate the clinical effectiveness of PPI therapy, compared with other treatments, for the prevention of subsequent bleeds in patients who had previously experienced peptic ulcer (PU) bleeding.
Data sources: Electronic databases and major conference proceedings were searched up to February 2006.
Review methods: Data were collected from the systematic reviews addressing each research objective. These were then entered into an economic model to compare the costs and quality-adjusted life-days of alternative management strategies over a 28-day period for patients who have had UGI bleeding. A Markov model with a Monte Carlo simulation used data from the systematic reviews to identify the most cost-effective treatment strategy for the prevention of UGI bleeding (first and subsequent) among NSAID users using an outcome of costs per quality-adjusted life-years (QALYs) over a lifetime from age 50 years.
Results: PPI treatment initiated after endoscopic diagnosis of PU bleeding significantly reduced re-bleeding and surgery compared with placebo or H_2RA. Although there was no evidence of an overall effect of PPI treatment on all-cause mortality, PPIs significantly reduced mortality in subgroups when studies conducted in Asia were examined in isolation or when the analysis was confined to patients with high-risk endoscopic findings. PPI treatment initiated prior to endoscopy in UGI bleeding significantly reduced the proportion of patients with stigmata of recent haemorrhage (SRH) at index endoscopy compared with

placebo or H_2RA, but there was no evidence that PPI treatment affected clinically important outcomes. Giving oral PPI both before and after endoscopy, with endoscopic haemostatic therapy (EHT) for those with major SRH, is preferred to all others on cost-effectiveness grounds at any threshold over £25,000 per QALY, even if only short-term effects are taken into account, and at any threshold over £200 per life-year gained if long-term effects are included. The risk of NSAID-induced endoscopic gastric and duodenal ulcers was reduced by standard doses of PPI and misoprostol, and double doses of H_2RAs. Standard doses of H_2RAs reduced the risk of endoscopic duodenal ulcers. PPIs reduced NSAID-induced dyspepsia. PPIs were superior to misoprostol in preventing recurrence of NSAID-induced endoscopic duodenal ulcers, but PPIs were comparable to misoprostol in preventing the recurrence of NSAID-induced endoscopic gastric ulcers. Full-dose misoprostol reduced bleeding, perforation or gastric outlet obstruction due to NSAID-induced ulcers, but misoprostol was poorly tolerated and associated with frequent adverse effects. *H. pylori* eradication treatment was equally effective with PPI treatment for the primary or secondary prevention of endoscopic ulcers in NSAID users. *H. pylori* eradication treatment was more effective than placebo for the primary prevention of endoscopic PU and for the prevention of re-bleeding from PU in NSAID users. With regard to primary and secondary prevention of bleeding PU in NSAID users, the two most cost-effective strategies are *H. pylori* eradication alone, and *H. pylori* eradication followed by misoprostol (substituted by a PPI, if misoprostol is not tolerated) at an additional £4810 per QALY. In patients who had previously experienced a bleed from a PU, re-bleeding was less frequent after *H. pylori* eradication therapy than after non-eradication antisecretory therapy, whether or not the latter was combined with long-term maintenance antisecretory therapy.

Conclusions: PPI treatment compared with placebo or H_2RA reduces mortality following PU bleeding among patients with high-risk endoscopic findings, and reduces re-bleeding rates and surgical intervention. PPI treatment initiated prior to endoscopy in UGI bleeding significantly reduces the proportion of patients with SRH at index endoscopy but does not reduce mortality, re-bleeding or the need for surgery. The strategy of giving oral PPI before and after endoscopy, with EHT for those with major SRH, is likely to be the most cost-effective. Treatment of *H. pylori* infection was found to be more effective than antisecretory therapy in preventing recurrent bleeding from PU. *H. pylori* eradication alone or eradication followed by misoprostol (with switch to PPI, if misoprostol is not tolerated) are the two most cost-effective strategies for preventing bleeding ulcers among *H. pylori*-infected NSAID users, although the data cannot exclude PPIs also being cost-effective. Further large randomised controlled trials are needed to address areas such as PPI administration prior to endoscopic diagnosis, different doses and administration of PPIs, as well as the primary and secondary prevention of UGI bleeding.

Contents

List of abbreviations

ARR	absolute risk reduction
BNF	British National Formulary
CC UGPD	Cochrane Collaboration Upper Gastrointestinal and Pancreatic Disease
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
COX-2	cyclooxygenase-2
CRD	Centre for Reviews and Dissemination
DDW	Digestive Disease Week
DU	duodenal ulcer
EHPSG	European *Helicobacter pylori* Study Group
EHT	endoscopic haemostatic therapy
GI	gastrointestinal
GU	gastric ulcer
H_2RA	H_2-receptor antagonist
ICER	incremental cost-effectiveness ratio
INAHTA	International Agencies for Health Technology Assessment
NBVV	non-bleeding visible vessel
NNT	number-needed-to-treat
NRR	National Research Register
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PA	prostaglandin analogue
PNI	Pharmaceutical News Index
PPI	proton pump inhibitor
PSSRU	Personal Social Services Research Unit
PU	peptic ulcer
QALD	quality-adjusted life-day
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
SD	standard deviation
SRH	stigmata of recent haemorrhage
UEGW	United European Gastroenterology Week
UGI	upper gastrointestinal
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Declared competing interests of authors

GI Leontiadis has received travel grants (support to attend scientific meetings) from AstraZeneca, Janssen-Cilag and GlaxoSmithKline. B Delaney has received speaker's honoraria and travel expenses from AstraZeneca, Wyeth, Reckitt Benckiser, AxCan Pharma and Takeda and consultancy fees from AstraZeneca, Wyeth and Merck. He has held small project grants from AstraZeneca and Wyeth. CW Howden has received speaker's honoraria from AstraZeneca, TAP Pharmaceutical Products, Santarus, Abbott (Canada), Abbott (Austria) and Negma-GILD and consulting fees from TAP Pharmaceutical Products, Altana, Eisai, Santarus, Allergan, Schwarz Pharma, Novartis Consumer Health, Meretek and Negma-GILD. He has also received research support from AstraZeneca. P Moayyedi is on the speaker's bureau and has acted as an independent medical adviser for AstraZeneca and Janssen Ortho. He has also received speaker's honoraria from Takeda, Axcan and Altana. His Chair is in part funded by an unrestricted donation given to McMaster University by AstraZeneca. D Forman has received speaker's honoraria and travel expenses from AstraZeneca, AxCan Pharma and TAP Pharmaceutical Products and consultancy fees from AstraZeneca.

Executive summary

Background

Upper gastrointestinal (UGI) haemorrhage is a major cause of morbidity, mortality and medical care costs, with peptic ulcer (PU) being the most frequent source of bleeding.

It has been estimated that approximately 2–3% of duodenal ulcer (DU) patients who are not receiving antisecretory therapy are likely to develop haemorrhage during each year of follow-up, giving a cumulative risk of haemorrhage after 5 years of approximately 10–14%. Furthermore, patients whose ulcers have bled once have an increased risk of further bleeding, compared with those with uncomplicated ulcer disease. Thus, among patients who present with a bleeding ulcer, approximately one-third will develop recurrent bleeding in the following 1–2 years, and 40–50% within the subsequent 10 years, if left untreated after initial healing.

Objectives

The objectives were as follows:

- to evaluate the clinical effectiveness and cost-effectiveness of proton pump inhibitors (PPIs) in the prevention and treatment of acute UGI haemorrhage
- to evaluate the clinical effectiveness and cost-effectiveness of PPI therapy, compared with H_2-receptor antagonist (H_2RA), *Helicobacter pylori* eradication (in infected patients) or no therapy, for the prevention of first and/or subsequent bleeds among patients who continue to use non-steroidal anti-inflammatory drugs (NSAIDs)
- to evaluate the clinical effectiveness of PPI therapy, compared with H_2RA, *H. pylori* eradication (in infected patients) or no therapy, for the prevention of subsequent bleeds in patients who had previously experienced peptic ulcer bleeding.

Methods

For the first objective, evidence was sought with the Cochrane Collaboration methodology from two systematic literature reviews of randomised controlled trials (RCTs) on the clinical effectiveness of oral or intravenous PPI treatment in patients with acute UGI bleeding. The first review concerned PPI use in patients with an endoscopic diagnosis of PU; trials were identified by searching CENTRAL, the Cochrane Library, MEDLINE, EMBASE and major conference proceedings up to November 2004. The second review concerned oral or intravenous PPI use prior to endoscopy in patients with UGI bleeding; trials were identified by searching CENTRAL, the Cochrane Library, MEDLINE, EMBASE, CINAHL and major conference proceedings up to September 2005. Subsequently, data from these systematic reviews and other sources, including a patient quality of life survey in Birmingham and Leeds using the EuroQoL questionnaire, were entered into an economic model to compare the costs and quality-adjusted life-days of alternative management strategies over a 28-day period for patients who have had UGI bleeding.

For the second objective, results were obtained from two further updated Cochrane systematic reviews to (a) compare the prophylactic effectiveness (including, as an outcome, UGI haemorrhage) of PPIs, H_2RAs and prostaglandin analogues in patients requiring chronic use of NSAIDs (trials were identified by searching MEDLINE to June 2002, Current Contents for 6 months prior to August 2004, EMBASE to August 2004 and CCTR to 2004; studies on cyclooxygenase-2 selective NSAIDs were not included) and (b) compare long-term rates of first or subsequent bleeding from PU in *H. pylori*-positive NSAID users with either eradication therapy alone or long-term prophylactic antisecretory therapy; trials were identified by searching the Cochrane Library, MEDLINE and EMBASE up to February 2006.

Data from these systematic reviews and other sources were then entered into a Markov model with a Monte Carlo simulation to identify the most cost-effective treatment strategy for the prevention of UGI bleeding (first and subsequent) among NSAID users using an outcome of costs per quality-adjusted life-years (QALYs) over a lifetime from age 50 years.

For the third objective, results were obtained from one further updated Cochrane systematic review comparing long-term re-bleeding rates from PU in *H. pylori*-positive patients with either eradication therapy alone or ulcer healing antisecretory therapy followed by long-term prophylactic antisecretory therapy. Trials were identified by searching the Cochrane Library, MEDLINE, EMBASE, CINAHL and major conference proceedings up to January 2005.

Results

PPI treatment initiated after endoscopic diagnosis of PU bleeding significantly reduced re-bleeding [odds ratio (OR) 0.49, 95% confidence interval (CI) 0.37 to 0.65; number-needed-to-treat (NNT) 13, 95% CI 9 to 25] and surgery (OR 0.61, 95% CI 0.48 to 0.78; NNT 33, 95% CI 20 to 50) compared with placebo or H_2RA. There was no evidence of an overall effect of PPI treatment on all-cause mortality (OR 1.01, 95% CI 0.74 to 1.40). However, PPIs significantly reduced mortality in subgroups when studies conducted in Asia were examined in isolation (OR 0.35, 95% CI 0.16 to 0.74) or when the analysis was confined to patients with high-risk endoscopic findings (i.e. spurting bleeding, oozing of blood or a non-bleeding visible vessel) (OR 0.53, 95% CI 0.31 to 0.91).

PPI treatment initiated prior to endoscopy in UGI bleeding significantly reduced the proportion of patients with stigmata of recent haemorrhage (SRH) at index endoscopy compared with placebo or H_2RA (OR 0.67, 95% CI 0.54 to 0.84; NNT 11, 95% CI 7 to 25). However, there was no evidence that PPI treatment affected clinically important outcomes, namely mortality, re-bleeding or need for surgery.

The strategy of giving oral PPI both before and after endoscopy, with endoscopic haemostatic therapy (EHT) for those with major SRH, is likely to be the most cost-effective. Under base-case assumptions, this strategy is preferred to all other modelled strategies on cost-effectiveness grounds at any threshold over £25,000 per QALY, even if only short-term effects are taken into account, and at any threshold over £200 per life-year gained if long-term effects are included.

The risk of NSAID-induced endoscopic gastric and duodenal ulcers was reduced by standard doses of PPI [relative risk (RR) 0.40, 95% CI 0.32 to 0.51 and RR 0.19, 95% CI 0.09 to 0.37, respectively] and misoprostol (RR 0.26, 95% CI 0.17 to 0.39 and RR 0.47, 95% CI 0.33 to 0.69, respectively) and double doses of H_2RAs (RR 0.44, 95% CI 0.26 to 0.74 and RR 0.26, 95% CI 0.11 to 0.65, respectively). Standard doses of H_2RAs reduced the risk of endoscopic duodenal ulcers (RR 0.36, 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73, 95% CI 0.50 to 1.09). PPIs reduced NSAID-induced dyspepsia. PPIs were superior to misoprostol in preventing recurrence of NSAID-induced endoscopic duodenal ulcers, but PPIs were comparable to misoprostol in preventing the recurrence of NSAID-induced endoscopic gastric ulcers. Full-dose misoprostol reduced bleeding, perforation or gastric outlet obstruction due to NSAID-induced ulcers (OR 0.60, 95% CI 0.36 to 0.98). However, misoprostol was poorly tolerated and associated with frequent adverse effects. PPIs and H_2RAs were well tolerated. However, further data comparing these agents directly with misoprostol are required to compare clinical outcomes including ulcer-related complications and prevention of NSAID-induced dyspepsia.

H. pylori eradication treatment was equally effective with PPI treatment for the primary or secondary prevention of endoscopic ulcers in NSAID users. *H. pylori* eradication treatment was more effective than placebo for the primary prevention of endoscopic PU and for the prevention of re-bleeding from PU in NSAID users.

With regard to primary and secondary prevention of bleeding PU in NSAID users, the two most cost-effective strategies are *H. pylori* eradication alone, and *H. pylori* eradication followed by misoprostol (substituted for a PPI, if misoprostol is not tolerated) at an additional £4810 per QALY. In a Monte Carlo analysis, *H. pylori* eradication strategy appears to be cost-effective compared with doing nothing for almost all patients at any level above £80/QALY. The *H. pylori* eradication followed by misoprostol strategy is 90% likely to be cost-effective compared with doing nothing for a willingness to pay of £500/QALY, rising to 99% at £1000/QALY. Under most reasonable assumptions, strategies involving PPI use (either alone or in combination with *H. pylori* eradication) are not cost-effective.

In patients who had previously experienced a bleed from a PU, re-bleeding was less frequent after *H. pylori* eradication therapy than after non-eradication antisecretory therapy, whether or not the latter was combined with long-term maintenance antisecretory therapy (OR 0.17,

95% CI 0.10 to 0.32 and OR 0.25, 95% CI 0.08 to 0.76, respectively). The NNT to prevent one episode of re-bleeding with eradication therapy was 7 (95% CI 5 to 11) compared with ulcer healing treatment alone, and 20 (95% CI 12 to 100) when compared with long-term maintenance antisecretory therapy.

Conclusions

PPI treatment compared with placebo or H_2RA reduces mortality following PU bleeding among patients with high-risk endoscopic findings. It also consistently reduces rates of re-bleeding and the need for surgical intervention. PPI treatment initiated prior to endoscopy in UGI bleeding significantly reduces the proportion of patients with SRH at index endoscopy but does not reduce mortality, re-bleeding or the need for surgery. The strategy of giving oral PPI before and after endoscopy, with EHT for those with major SRH, is likely to be the most cost-effective.

Treatment of *H. pylori* infection is more effective than antisecretory therapy (with or without long-term maintenance antisecretory therapy) in preventing recurrent bleeding from PU. *H. pylori* eradication alone or *H. pylori* eradication followed by misoprostol (with switch to PPI, if misoprostol is not tolerated) are the two most cost-effective strategies for preventing bleeding ulcers among *H. pylori*-infected NSAID users, although the data cannot exclude PPIs also being cost-effective.

Implications for healthcare

No specific recommendation either for or against PPI use before endoscopy can be made. PPI treatment should be administered to patients with endoscopically documented PU bleeding.

Based solely on the results of our meta-analysis, no specific conclusions can be drawn with regard to PPI dose or mode of administration. Nevertheless, if an oral PPI is used, the dose should be at least twice the standard clinical dose for that PPI. Based on the results of our economic modelling, the strategy of administering oral PPI both before and after endoscopy, with EHT for those with active bleeding or a non-bleeding visible vessel, is likely to be the most cost-effective.

It is suggested that *H. pylori*-infected NSAID users should receive appropriate eradication treatment, followed by misoprostol, at least 200 μg twice daily. If misoprostol is not tolerated, it should be substituted for standard clinical dose PPI. The above strategy is likely to be the most cost-effective.

Recommendations for further research

PPIs in the acute hospital management of patients with UGI bleeding

- The issue of PPI administration prior to endoscopic diagnosis needs to be explored further in large RCTs in which patients with acute UGI bleeding are randomised to PPI therapy before endoscopy.
- A large, multicentre trial is needed in Europe and North America that would randomise patients to high-dose intravenous PPI or control treatment after any appropriate endoscopic intervention and address mortality as the primary end-point. Unfortunately, there are major obstacles to such a trial.
- Randomised trials directly comparing different doses of PPIs and/or oral and intravenous administration of PPIs in patients with PU bleeding are also needed.
- There is very limited evidence on head-to-head clinical outcome comparisons between different PPIs in PU bleeding, so such trials may be relevant.

PPIs in the primary and secondary prevention of UGI bleeding

- Large-scale randomised trials in patients commencing long-term NSAID therapy of the effect of PPIs, misoprostol and *H. pylori* eradication on the primary prevention of actual UGI bleeds are urgently required. The efficacy of combination therapy with PPI plus low-dose misoprostol could also be studied.
- Similar randomised trials in secondary prevention among NSAID users who have had a UGI bleed are also required, but these should include the option of stopping NSAIDs altogether.
- In relation to *H. pylori* eradication in patients who have had a PU bleed, an assessment of the long-term beneficial results of *H. pylori* eradication and the role of other factors that could explain recurrence of bleeding despite *H. pylori* eradication (especially NSAID use and *H. pylori* re-infection) is needed.

Chapter 1

Introduction and background

The burden of peptic ulcer bleeding

Upper gastrointestinal (UGI) haemorrhage is a major cause of morbidity, mortality and medical care costs, with peptic ulcer (PU) being the most frequent source of bleeding.[1] It has been estimated that approximately 2–3% of duodenal ulcer (DU) patients who are not receiving antisecretory therapy are likely to develop haemorrhage during each year of follow-up, giving a cumulative risk of haemorrhage after 5 years of approximately 10–14%.[2] Furthermore, patients whose ulcers have bled once have an increased risk of further bleeding, compared with those with uncomplicated ulcer disease. Thus, among patients who present with a bleeding ulcer, approximately one-third will develop recurrent bleeding in the following 1–2 years, and 40–50% within the subsequent 10 years, if left untreated after initial healing.[3,4] The mortality rate among patients with bleeding ulcers has remained around 5–10% for the past 50 years, despite improved medical and surgical treatments, the development of diagnostic and therapeutic endoscopy and the availability of intensive care units.[1,5] The lack of a decline in mortality rates despite therapeutic advances may be due to a rise in the age of patients and to the prevalence of concomitant diseases.[6] In a recent UK prospective cohort study of 716 patients with UGI bleeding, the re-bleeding rate was 10% and the mortality rate was 14.6%.[7] Despite the reduction in re-bleeding rates compared with the national audit in 1995,[8] the mortality rate was not reduced. Only 29% had gastrointestinal (GI) bleeding stated in the death certificate as a contributing factor for death.[7]

Risk factors for adverse outcomes among patients with ulcer bleeding

Factors associated with a high risk of re-bleeding, surgery and mortality are the presence of shock on admission, concurrent medical illness, transfusion requirement of more than 5 units, age over 60 years and endoscopic appearances of stigmata of recent haemorrhage (SRH); ulcers that are actively bleeding or oozing, those with visible vessels and those with adherent clots are at high risk.[1] Ulcer size greater than 1 cm has also been found to be associated with an increased risk of re-bleeding.[9]

Management of peptic ulcer bleeding

Current management of bleeding ulcers includes fluid replacement, blood transfusion as necessary, drug therapy with an acid inhibitor, diagnostic endoscopy with endoscopic haemostasis if necessary and, in some patients, surgery. One of the most important treatment measures in the management of acute bleeding ulcers is prompt fluid restoration; mortality halved in the 1930s when this was introduced.[10] Endoscopic treatment of PU bleeding can control ongoing haemorrhage and also reduces rates of mortality, re-bleeding and surgical intervention.[11,12] However, delayed recurrent bleeding may still be a problem after initial endoscopic haemostasis and some patients may still require repeat endoscopic treatment or surgical intervention.

Rationale for acid suppression therapy in peptic ulcer bleeding

The cessation of bleeding from a PU is inhibited by gastric acid by two mechanisms: by inhibition of clot formation and promotion of clot lysis and by ongoing tissue damage.[13] *In vitro*, haemostasis has been shown not to occur at a pH of less than 5.4.[14] These factors were the main stimuli towards trials studying the effects of potent acid inhibitors in bleeding from PUs. Medical treatment has included H_2-receptor antagonists (H_2RAs) and, more recently, proton pump inhibitors (PPIs).

H_2RA treatment

The efficacy of H_2RAs had been studied for several years. In 1985, a meta-analysis by Collins and Langman found essentially no benefit of intravenous H_2RA therapy in bleeding DU but

small benefits in bleeding gastric ulcer (GU).[15] A more recent update of that meta-analysis of randomised controlled trials (RCTs) comparing intravenous H_2RA treatment with placebo in PU bleeding found no evidence of an effect on mortality.[16] Intravenous H_2RA treatment was associated with a marginally significant reduction in rates of re-bleeding and surgical intervention confined to patients with bleeding GU and not extended to patients with bleeding DU.[16]

PPI treatment

More recently, PPIs have been used in patients with PU bleeding. Since PPIs are more potent acid inhibitors than H_2RAs, they would seem to have a theoretical advantage over H_2RAs. In some study populations, PPIs have been shown to maintain intragastric pH over 6 for up to 72 hours when given in adequate doses (e.g. omeprazole or pantoprazole 80 mg intravenous bolus followed by continuous intravenous infusion of 8 mg/h for 72 hours).[17] On the other hand, H_2RAs, even when administered intravenously in high doses, cannot maintain intragastric pH over 6 for longer than 24 hours – probably due to the rapid development of pharmacological tolerance.[18] A previous meta-analysis of RCTs reported superiority of PPI therapy over H_2RA therapy in preventing ulcer re-bleeding.[19]

The initial Cochrane Collaboration systematic review and meta-analysis of 21 RCTs (that were published or presented before February 2003) comparing PPI treatment with placebo or H_2RA in PU bleeding found that PPI treatment reduced re-bleeding and surgical intervention rates, but found no evidence of an effect on all-cause mortality.[20,21] Following the publication of the initial Cochrane meta-analysis, three other meta-analyses,[22–24] and also an update of the Cochrane meta-analysis[25] (scheduled for the need of the current project) have been published. Among these meta-analyses, there are methodological differences and disagreements with regard to the overall effect of PPIs on mortality. However, the finding of favourable effects of PPIs on re-bleeding and, especially, on surgical intervention rates in patients with ulcer bleeding is consistent among different meta-analyses.

Intravenous PPI therapy, especially high-dose therapy, is expensive, whereas oral PPI therapy is relatively inexpensive. Cost-effectiveness analyses in patients with high-risk endoscopic findings who have received endoscopic haemostatic therapy (EHT) have shown that both oral and intravenous PPI therapy are more effective and less costly than intravenous H_2RA therapy[26] or placebo administration.[27] However, cost-effectiveness studies have yielded conflicting results regarding which of the two PPI administration strategies, oral[26] or intravenous,[27] is more cost-effective in high-risk patients. Guidelines on management of non-variceal UGI bleeding from the British Society of Gastroenterology[28] and, more recently, from a multi-society consensus group[12] recommend the use of high-dose intravenous PPI in PU bleeding with high-risk stigmata on endoscopy.

Empirical PPI treatment is often used in clinical practice for patients presenting with UGI haemorrhage even before endoscopic confirmation of the cause of the bleed. Although this approach is regarded by many clinicians as reasonable, it presents a major challenge for formularies. To our knowledge, there are no systematic reviews assessing the clinical effectiveness of PPI therapy initiated prior to endoscopic diagnosis in unselected patients with acute UGI haemorrhage.

Long-term prevention of re-bleeding

Prevention of re-bleeding from a PU remains a clinical challenge. Maintenance antisecretory therapy has been widely accepted as the standard long-term treatment for patients with a history of ulcer bleeding in order to prevent recurrent bleeding. However, only two randomised studies have specifically examined this in patients with PU haemorrhage and both of them used ranitidine.[29,30] The first study found no significant difference in the rate of recurrent bleeding between maintenance therapy with ranitidine and placebo, but the number of bleeding episodes was so small that a treatment benefit could not be demonstrated.[29] The second study reported significantly fewer episodes of haemorrhage among patients taking ranitidine than among those taking placebo.[30]

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are important agents in the management of arthritic and inflammatory conditions, and are among the most frequently prescribed medications

in North America and Europe.[31,32] However, there is overwhelming evidence linking these agents to a variety of GI toxicities.[32–43] Common side-effects such as nausea and dyspepsia correlate poorly with serious adverse GI events.[43] Although endoscopic ulcers can be documented in up to 40% of chronic NSAID users,[34] it is estimated that as many as 85% of these never become clinically apparent.[30,44] Serious NSAID-induced GI complications, such as haemorrhage, perforation or death, are much less common, occurring collectively with an incidence of about 1.5% per year.[43] However, the number of individuals prescribed NSAIDs and the potential for life-threatening adverse events make NSAID toxicity an important clinical and economic problem.

Large outcomes studies had suggested that the newer cyclooxygenase-2 (COX-2) selective NSAIDs carry a lower risk of GI toxicity than the more traditional non-selective NSAIDs.[45,46] However, more recent evidence has raised serious concerns about the cardiovascular safety profile of COX-2 selective agents.[47]

A Cochrane review[48] has examined 40 RCTs that compared the occurrence of endoscopic ulcers in patients given either placebo or misoprostol, H_2RA or PPI in conjunction with an NSAID. Only one RCT, the MUCOSA trial, evaluated the efficacy of misoprostol prophylaxis against clinically important NSAID-induced ulcer complications.[33] In this study of 8843 patients studied over 6 months, the overall incidence of definite or probable serious GI events (PU bleeding, PU perforation or gastric outlet obstruction) was about 1.5% per year. Misoprostol 800 μg/day was associated with a statistically significant 40% risk reduction [odds ratio (OR) = 0.598, 95% confidence interval (CI) 0.364 to 0.982] in definite serious GI events ($p = 0.049$), representing a risk difference of 0.38% (0.95% minus 0.57%). Overall, approximately 260 patients would have to be treated with misoprostol to prevent one clinically important GI event. This number-needed-to-treat (NNT) would drop if only higher risk patients were considered for this intervention. To set against this, misoprostol was associated with a small but statistically significant 1.6-fold excess risk of drop-out due to drug-induced side-effects. In the MUCOSA trial, 732 out of 4404 patients on misoprostol experienced diarrhoea or abdominal pain, compared with 399 out of 4439 on placebo for a relative risk of 1.82 associated with misoprostol ($p < 0.001$). Overall, 27% of patients on misoprostol experienced one or more side-effects. When analysed by dose, only misoprostol 800 μg daily showed a statistically significant excess risk of drop-outs due to diarrhoea [relative risk (RR) = 2.45, 95% CI 2.09 to 2.88], and abdominal pain (RR = 1.38, 95% CI 1.17 to 1.63). Both misoprostol doses were associated with a statistically significant risk of diarrhoea. However, the risk of diarrhoea with 800 μg/day (RR = 3.25, 95% CI 2.60 to 4.06) was significantly higher than that seen with 400 μg/day (RR = 1.81, 95% CI 1.52 to 2.16) ($p = 0.0012$).

In order to extrapolate from the endoscopic ulcers observed in the other RCTs to clinical events, it is necessary to model using the assumption that the relative effect observed for endoscopic ulcers will also apply, but with reduced absolute numbers, to clinical events.

A recent systematic review with economic modelling, also funded by the Health Technology Assessment Programme, examined the effectiveness and cost-effectiveness of five strategies for the prevention of NSAID-induced GI toxicity: non-selective NSAID plus H_2RA, non-selective NSAID plus PPI, non-selective NSAID plus misoprostol, COX-2 coxib NSAID or COX-2 preferential NSAID.[49–51] Regarding effectiveness, the results for the first three strategies were similar to the results of the Cochrane review.[48] COX-2 coxib NSAIDs reduced the risk of endoscopic ulcers, symptomatic ulcers and possibly serious GI events. COX-2 preferential NSAIDs reduced the risk of symptomatic ulcers. Cost-effectiveness analysis showed that non-selective NSAID plus H_2RA is the most cost-effective strategy for avoiding endoscopic ulcers in patients requiring long-term NSAID therapy.

Currently, there is evidence that misoprostol use has declined, presumably due to side-effects.[52,53]

Helicobacter pylori infection

H. pylori infection is the main aetiological factor for PU disease. However, although the role of this microorganism in uncomplicated PU has been definitively established,[54] its role in complicated ulcer disease has not been studied as extensively.[55] *H. pylori* eradication has been demonstrated to reduce dramatically the rate of ulcer recurrence.[37,56] Therefore, it would seem logical to assume that *H. pylori* cure would also represent an effective strategy to prevent recurrence of ulcer bleeding. In 1994, the National Institutes of Health (NIH) Consensus Conference panel stated that, although preliminary studies indicate that cure of *H. pylori*

infection prevents recurrent ulcer bleeding at rates equal to those of maintenance antisecretory therapy, until these studies can be confirmed, maintenance antisecretory "may be prudent" in such patients even after *H. pylori* eradication, in view of high risks associated with re-bleeding.[6] Two years later, in 1996, the American Digestive Health Foundation report stated that several trials indicate that *H. pylori* eradication also reduces the recurrence of ulcer complications, but "the magnitude of this reduction remains to be firmly established".[57]

Although several authors have administered *H. pylori* eradication treatment to patients with a history of PU haemorrhage with the intention of preventing re-bleeding, only a few studies have included a control group treated with 'traditional' antisecretory therapy (followed or not by long-term maintenance antisecretory therapy). Furthermore, the number of patients included in these 'eradication' studies has been small and, as the incidence of re-bleeding episodes is relatively low (especially when antisecretory maintenance treatment is prescribed and follow-up limited), efficacy differences between groups may not be demonstrated due to a problem of statistical power of individual studies. Consequently, the true efficacy of *H. pylori* eradication for the prevention of recurrent bleeding from peptic ulcer is unclear. The relevant randomised trials that have been included in Cochrane systematic reviews[58] were updated and summarised in this volume.

In addition to efficacy reasons, other relevant arguments may advocate the use of eradication therapy instead of maintenance antisecretory treatment. First, one disadvantage of maintenance antisecretory therapy is the requirement for long-term compliance, which may wane when symptoms are absent. Second, the cost of antibiotic therapy is lower than long-term management by antisecretory drugs, mainly because the financial outlay for medication in the former approach is not cumulative, as it is with the latter. Cost-effectiveness analysis comparing treatment of *H. pylori* infection with other approaches to prevent recurrent ulcer haemorrhage demonstrated that treatment of *H. pylori* infection was the least costly strategy unless the incidence of complicated recurrences after treatment was over 6%, or the cost of confirming eradication was over US$741.[59] Other authors have compared the cost per recurrent haemorrhage prevented for 11 strategies over 1 year.[60] The test/retest eradication strategy with maintenance proton pump inhibitor therapy for *H. pylori*-negative patients was most effective, and with maintenance H_2RA therapy was least costly. The test/retest strategies were dominant with average cost-effectiveness ratios of US$1118–1310 per recurrent haemorrhage prevented with maintenance antisecretory therapy.

Chapter 2

Aims and research questions

Aims

The first aim was to identify the role of PPI treatment in the hospital management of patients with UGI haemorrhage. We sought to enhance the existing literature in order to address the question by systematically considering all available evidence from RCTs relating to the management of haemorrhage for both diagnosed and presumed PUs. Second, we aimed to use existing Cochrane reviews to establish the efficacy of PPI therapy in preventing re-bleeding in those with previous PU bleeding. In both therapeutic and prophylactic situations, we sought to apply the clinical efficacy data in economic models in order to determine the relative cost-effectiveness of PPIs, in comparison with usual care, in the management and prevention of UGI bleeding.

Research questions addressed

What is the efficacy of PPI therapy in patients with endoscopically documented acute bleeding from a peptic ulcer?

In this updated systematic review and meta-analysis, we aimed to evaluate the efficacy of PPIs in the management of acute bleeding from PUs using evidence from RCTs. The main objective of the review was to compare all-cause mortality rates for PPI treatment with those following placebo or H_2RA treatment. We also aimed to assess re-bleeding and surgical intervention rates, adverse outcomes (defined as number of patients with any of re-bleeding, surgery, requirement for additional EHT and/or death), transfusion requirements and length of hospital stay. See Chapter 4.

What is the efficacy of PPI therapy initiated prior to endoscopy in unselected patients with acute upper gastrointestinal bleeding?

In this systematic review and meta-analysis, we aimed to evaluate the efficacy of PPIs initiated prior to endoscopy in the management of unselected patients with acute UGI bleeding using evidence from RCTs. The main objective of the review was to compare mortality rates for PPI treatment with those following placebo or H_2RA treatment. We also aimed to assess re-bleeding and surgical intervention rates, transfusion requirements and length of hospital stay and the proportions of patients with high-risk stigmata found at the subsequent index endoscopy. See Chapter 5.

What is the cost-effectiveness of PPI therapy in patients with acute upper gastrointestinal bleeding before and after the endoscopic diagnosis of bleeding peptic ulcer?

We aimed to compare the effects of PPI therapy (oral or intravenous) with H_2RA or no therapy for immediate management of patients who were haemodynamically stable following an episode of bleeding PU. Although the main difference between the strategies compared relates to management during the first 24 hours, the value of differences in outcome was to be achieved by modelling the detailed progress of patients for a period of 28 days and using an individual sampling model[61] to construct a large number of virtual patient histories. Comparison of different strategies allows the calculation of incremental cost-effectiveness ratios (ICERs) between strategies. See Chapter 6.

What is the efficacy of *H. pylori* eradication therapy in preventing recurrent bleeding from peptic ulcer in *H. pylori*-positive patients compared with ulcer-healing antisecretory therapy with or without subsequent long-term prophylactic antisecretory therapy?

This research question was addressed by two systematic reviews and meta-analyses. The first compared the long-term re-bleeding rate from PU in *H. pylori*-positive patients with *H. pylori* eradication therapy alone versus ulcer-healing antisecretory therapy (without subsequent long-term prophylactic antisecretory therapy). The second review compared the long-term re-bleeding rate from peptic ulcer in *H. pylori*-positive patients with *H. pylori* eradication therapy alone versus ulcer-healing antisecretory therapy followed by long-term prophylactic antisecretory therapy. See Chapter 7.

What is the efficacy of prophylactic PPI therapy in preventing peptic ulcer bleeds in patients taking NSAIDs compared with no treatment?

This research question was to be addressed partly by updating a Cochrane systematic review comparing the effectiveness of PPI, H_2RA and prostaglandin analogue (PA) therapies in the prevention of NSAID-induced UGI toxicity among patients requiring chronic NSAID use. The primary outcome of this review was the incidence of endoscopic ulcers or ulcer-related complications including haemorrhage, perforation, pyloric obstruction or death. The secondary objectives were the assessment of dose-related effectiveness, adverse effects, overall drop-outs and symptom-related drop-outs for each therapy. The strategy of substituting COX-2 inhibitors for non-selective NSAID as opposed to co-administering PPIs with non-selective NSAIDs has not been assessed here, as this is the focus of a separate HTA project.[49–51] See Chapter 8.

What is the cost-effectiveness of alternative strategies for the prevention of peptic ulcer bleeding in NSAID users?

This was to be addressed by construction of a Markov model representing the management of acute UGI bleeding and acute PU bleeding to compare PPI therapy (oral or intravenous) with H_2RA or no therapy with an outcome of cost per life-years saved from a health service perspective. In order to populate this model with clinical efficacy data, it was necessary to conduct a supplementary systematic review and meta-analysis to address the following question.

What is the role of *H. pylori* eradication versus proton pump inhibitors to prevent upper gastrointestinal bleeds in NSAID users?

We aimed to compare the efficacy of *H. pylori* eradication therapy compared with PPI maintenance therapy in the prevention of UGI bleeding in NSAID users. We intended to estimate RR both for the primary prevention of UGI bleeding and for secondary prevention in patients who already had a first bleed. See Chapter 9 and Appendix 6.

Chapter 3

Review methods for systematic reviews

What is the efficacy of PPI therapy in patients with endoscopically documented acute bleeding from a peptic ulcer?

Studies included in the review

RCTs that compared the relative effectiveness of a PPI with either placebo or an H_2RA in patients with endoscopically documented acute bleeding from peptic ulcer were included if they met all the following criteria:

- Use of a concurrent control group.
- Concomitant therapy was applied equally to both intervention arms.
- Diagnosis of acute bleeding from peptic ulcer was made endoscopically.
- At least one of the following outcomes was reported: mortality, re-bleeding, surgical intervention, endoscopic haemostatic treatment at some point after initial endoscopy.
- It was possible to isolate data for patients with bleeding peptic ulcers.

Types of participants

Patients admitted to hospital with acute UGI bleeding or inpatients who developed acute UGI bleeding after having been admitted for other reasons (including intensive care unit patients who developed stress-related ulcers) were included if they had an endoscopically confirmed diagnosis of bleeding PU. Patients with other causes of GI haemorrhage were not included in the analysis.

Types of interventions

The treatment group had to have received a PPI (either alone or in combination with some other treatment) and the control group had to have received either placebo or an H_2RA (alone or in combination with the same other therapy as the PPI group). Only studies in which treatment groups were treated similarly, apart from the active therapies being compared, were included. Method of delivery of PPI and control treatment included both intravenous and oral.

Types of outcome measures

Primary outcome measure

The primary outcome measure was the number of patients who died from any cause (30-day mortality or in-hospital mortality), analysed by treatment group.

Secondary outcome measures

Secondary outcome measures were as follows:

- number of patients with re-bleeding (as defined by the original authors) within 3 days, within 7 days and within 30 days of randomisation
- number of patients with re-bleeding within 30 days among those with actively bleeding ulcers at endoscopy
- number of patients requiring surgical intervention for bleeding during hospitalisation
- number of patients requiring additional endoscopic treatment at repeat endoscopy
- number of patients with any adverse outcomes, defined as one or more of re-bleeding, surgery, additional endoscopic haemostatic treatment and/or death, where it was possible to estimate those figures from reports without duplication of numbers.

Tertiary outcome measures

Tertiary outcome measures were as follows:

- blood transfusion requirements, reported as mean and standard deviation (SD) of number of units transfused.
- length of hospital stay, reported as mean and SD number of days in hospital.

Outcomes were short-term, defined as those occurring within 30 days of the acute bleed.

Search strategy for identification of studies

Trials were identified by searching CENTRAL, The Cochrane Library (Issue 4, 2004), MEDLINE (1966 to November 2004) and EMBASE (1980 to November 2004). We did not confine our search to English language publications. The following search strategy was constructed by using a combination of subject headings and text words relating to the use of PPIs for the treatment of bleeding PUs. The standard Cochrane search strategy filter for identifying RCTs was applied to all searches. The MEDLINE search strategy is listed in Appendix 1.

Reference lists from trials and review articles retrieved by electronic searching were handsearched to identify further relevant trials.

Published abstracts from the conference proceedings from Digestive Disease Week (DDW), United European Gastroenterology Week (UEGW), American College of Gastroenterology annual meeting, World Congress of Gastroenterology and British Society of Gastroenterology annual meeting, up to November 2004, were also handsearched.

Members of the Cochrane Collaboration Upper Gastrointestinal and Pancreatic Disease (CC UGPD) Group and experts in the field of gastroenterology were contacted and asked to supply details of any outstanding clinical trials and relevant unpublished materials.

Pharmaceutical companies which market PPIs in the USA or Europe were also contacted for any additional published or unpublished data.

Data synthesis

Two reviewers independently checked trials and abstracts identified from the search for fulfilment of predefined inclusion criteria. The full text of all relevant studies was obtained whenever possible. If multiple publications of the same patient groups were retrieved, only the most recent version was included. If it was not clear from the information presented whether the trial met the inclusion criteria, further information was sought from the original authors. The inclusion of trials and grading of methodological quality were determined by two reviewers independently and any disagreements were resolved by consensus. Original authors were contacted for further clarification whenever necessary.

Methodological quality assessment had emphasis on allocation concealment, which was ranked using the Cochrane approach:

- Grade A: adequate concealment
- Grade B: uncertain concealment
- Grade C: inadequate concealment
- Grade D: not randomised.

Other validity criteria used to assess studies included the following:

- baseline comparability of treatment groups
- presence of predefined inclusion and exclusion criteria
- *a priori* sample size estimation
- intervention described in detail
- definition of outcomes
- stated time for outcome assessment
- stated indications for repeat endoscopy, endoscopic treatment, surgery, transfusion and discharge from hospital
- description of drop-outs and percentage of drop-outs.

Data extraction and validity assessment were performed independently by two reviewers using a predesigned data extraction form and validity assessment form. Any disagreements were resolved by consensus.

The following data were extracted where possible:

- method of randomisation
- criteria for patient inclusion and exclusion
- details of intervention including dose and method of delivery
- duration of therapy and any co-interventions including initial endoscopic haemostatic treatment
- patient characteristics, including mean age or age range, sex ratio and ethnicity
- number of patients assigned to each treatment group
- number of patients with co-morbid conditions
- baseline comparison of treatment groups with respect to site of bleeding ulcer (duodenal or gastric) and stigmata of recent haemorrhage [spurting, oozing, non-bleeding visible vessel (NBVV) and adherent clot]
- outcome measures, including mortality, surgery, 'adverse' outcomes (defined as one or more of re-bleeding, surgery, additional endoscopic haemostatic treatment, and/or death), transfusion requirements and length of hospital stay
- blinding of outcome assessor, patients and carers
- number of patients withdrawn, with reasons
- outcomes reported by stigmata of haemorrhage at initial endoscopy
- adverse reactions.

Heterogeneity was assessed statistically. Clinical heterogeneity was discussed. A meta-analysis of outcomes was performed when appropriate.

Pooled outcomes were reported as OR with 95% CI for dichotomous outcomes and as weighted mean difference (WMD) with 95% CI for continuous outcomes.

When heterogeneity was significant ($p < 0.10$), a random effects model was used.

The influence of the following factors on the outcomes (mortality, re-bleeding and surgical intervention) was assessed with subgroup analyses where sufficient data were available:

- timing of outcome assessment
- study validity (adequate versus inadequate allocation concealment of randomisation)
- initial endoscopic haemostatic treatment (yes versus none)
- site of ulcer (gastric versus duodenal)
- presence of SRH at initial endoscopy
- mode of administration (oral versus intravenous)
- high-dose intravenous administration of PPI (equivalent to a dose of omeprazole or pantoprazole 80 mg intravenous bolus followed by an intravenous infusion of 8 mg/h for 72 hours) versus lower dose administration of PPI (intravenous or oral)
- type of control treatment used (placebo versus H_2RA)
- geographical location of the trials.

The influence of the following factors on the treatment effect (log OR for mortality, re-bleeding and surgical intervention) and on the heterogeneity of the analyses was also assessed with meta-regression analysis (random effects model, within-study variance estimated with the restricted maximum-likelihood method) where sufficient data were available:

- study validity (adequate versus inadequate allocation concealment of randomisation, double blinding)
- initial endoscopic haemostatic treatment (yes versus none)
- presence of SRH at initial endoscopy (percentage of participants with active bleeding)
- mode of PPI administration (oral versus intravenous)
- high dose intravenous administration of PPI (equivalent to a dose of omeprazole or pantoprazole 80 mg intravenous bolus followed by an intravenous infusion of 8 mg/h for 72 hours) versus lower dose administration of PPI (intravenous or oral)
- active treatment being omeprazole versus other PPI
- type of control treatment used (placebo versus H_2RA)
- geographical location of the trials.

In the main analyses with adequate number of trials, the presence of publication bias was investigated visually with the use of funnel plots. In the analyses for dichotomous outcomes (mortality, re-bleeding and surgical intervention rates), publication bias was additionally assessed statistically with the use of Egger's test. As proposed by Egger and colleagues,[62] we based evidence of asymmetry on $p < 0.10$, and we presented intercepts with 90% CIs.

All analyses were performed with the use of RevMan software (version 4.2.8), with the exception of Egger's test and meta-regression, which were preformed with Stata software (Intercooled Stata 8.2 for Windows, StataCorp LP, College Station, TX, USA).

Peer review

Once completed, the manuscript was peer reviewed by the following experts: Professor Joseph Sung, Shatin, Hong Kong, China; Professor Javier Gisbert, Madrid, Spain; Professor Alan Barkun, Montreal, Canada; and Ms Sarah Collin, Manchester, UK.

What is the efficacy of PPI therapy initiated prior to endoscopy in reducing mortality in unselected patients with acute upper gastrointestinal bleeding?

Studies included in the review

RCTs that compared the relative effectiveness of a PPI with placebo or an H_2RA were eligible for inclusion in this review. Published and unpublished studies, full articles and abstracts were considered for inclusion. Only studies that evaluated PPI treatment initiated prior to endoscopy upon presentation with UGI bleeding were included.

Types of participants

Participants were patients admitted to hospital with UGI tract bleeding or inpatients who developed UGI bleeding after having been admitted for other reasons. Only studies enrolling unselected patients with UGI bleeding before ascertaining the cause by endoscopy and studies in which treatment groups were treated similarly apart from the active therapies being compared were included. Allocation to PPI or comparator treatment would have been before diagnostic upper endoscopy. Steps were taken to clarify whether patients with variceal bleeding had been excluded from the primary trials.

Types of interventions

To be included in the review, the treatment group was to have received a PPI (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) and the control group was to have received either placebo or an H_2RA. Otherwise, the control group had to have been managed similarly to the active treatment group. Method of delivery of PPI/control included both intravenous and oral routes of administration. All doses of PPI were considered eligible.

Types of outcome measures

Primary outcome measure

The primary outcome measure was mortality, defined as deaths occurring within 30 days (or mortality at time point closest to 30 days) after the acute bleed.

Secondary outcome measures

Secondary outcome measures were the following:

- re-bleeding within 30 days
- surgery for continued or recurrent bleeding within 30 days of randomisation
- length of hospital stay
- transfusion requirements
- proportion of patients with high-risk stigmata at the time of endoscopy.

Search strategy for identification of studies

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 UGI bleeding.

A search was undertaken according to the Cochrane Upper Gastrointestinal and Pancreatic Diseases model using CCTR, MEDLINE, EMBASE and CINAHL databases up to September 2005 [(bleed or rebleed or hemorrhage or haemorrhage) and any of the generic names of PPIs]. The MEDLINE search strategy is listed in Appendix 2. The National Research Register (NRR) was also searched. Abstracts from DDW, UEGW, American College of Gastroenterology annual meeting, World Congress of Gastroenterology and British Society of Gastroenterology annual meeting were handsearched (1997 to September 2005). Experts in the field registered with the CC UGPD Group were contacted for leads on unpublished studies. The reference list of identified articles for further relevant trials was hand searched. Authors of trial reports published only as abstracts were contacted and asked to contribute full datasets or completed papers.

Data synthesis

Two reviewers (SD and AS) independently checked trials and abstracts identified from the search for fulfilment of predefined inclusion criteria. One of the reviewers was an expert in content matter. A third reviewer adjudicated in the event of discrepancies and a consensus view was taken. 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.

Two reviewers independently extracted data regarding the above-mentioned outcomes.

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

Validity of included studies was assessed by adequacy of

- method of randomisation
- criteria for patient inclusion and exclusion
- details of intervention including dose
- method of delivery.

Methodological quality assessment had emphasis on allocation concealment, which was ranked using the Cochrane approach:

- Grade A: adequate concealment
- Grade B: uncertain
- Grade C: inadequate concealment
- Grade D: not randomised.

Other validity criteria used to assess studies included the following:

- degree of blinding
- baseline comparability of treatment groups
- presence of inclusion and exclusion criteria
- intervention described in detail
- definition of outcomes
- stated time for outcome assessment
- stated indications for repeat endoscopy, initial and subsequent endoscopic haemostatic treatment, surgery and transfusion
- description of drop-outs and percentage of drop-outs.

The following features were also recorded:

- setting: single centre versus multicentre
- geographical location
- brand of PPI
- high-dose PPI (equivalent to a dose of omeprazole or pantoprazole 80 mg intravenous bolus followed by an intravenous infusion of 8 mg/h for 72 hours) versus lower dose PPI
- intravenous PPI versus oral PPI
- control group treatment – H_2RA versus placebo
- concomitant treatment – endoscopic haemostatic treatment (subdivided by intervention – injection, thermal, injection plus thermal, clips, other) versus no endoscopic haemostatic treatment
- adverse reactions – actively sought versus not actively sought
- proportion of patients eventually found to be bleeding from peptic ulcers.

All trials included in the systematic review were entered into Review Manager 4.2.8. An intention-to-treat approach was used in all analyses.

Meta-analysis was performed only if sufficient trials with similar comparisons and outcome measures were found.

Heterogeneity was assessed using the χ^2 test along with visual inspection of the forest plots. A significance level of less than 0.10 was interpreted as evidence of heterogeneity. We looked for an explanation for 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. If variation among studies was observed, a random effects model was used.

The potential reasons for heterogeneity hypothesised *a priori* included:

1. study quality [RCT versus controlled clinical trial (CCT); open versus blinded trial]
2. study setting (multicentre versus single centre)
3. geographical location (Asian versus Western study)
4. PPI treatment (intravenous versus oral; conventional versus high-dose PPI)
5. concomitant treatment (endoscopic haemostatic treatment versus no endoscopic haemostatic treatment)
6. type of control treatment used (H_2RA versus placebo)
7. outcome measure for bleeding (recurrent bleeding versus persistent bleeding)
8. outcome measure: mortality criteria stated (bleed-related mortality versus bleed-unrelated mortality).

Peer review

Once completed, the manuscript was peer reviewed by the following experts: Professor Alan Barkun, Montreal, Canada; Ms Sarah Collin, Manchester, UK; and Dr John Marshall, Hamilton, Canada.

What is the efficacy of *H. pylori* eradication therapy in preventing recurrent bleeding from peptic ulcer in *H. pylori*-positive patients compared with ulcer-healing antisecretory therapy with or without subsequent long-term prophylactic antisecretory therapy?

Studies included in the review

Controlled clinical trials that compared the long-term re-bleeding rate from PU in *H. pylori*-positive patients with *H. pylori* eradication therapy alone versus ulcer-healing antisecretory therapy (with or without subsequent long-term prophylactic antisecretory therapy) were included.

The trials had to fulfil the following criteria:

- clearly stated information about the number of patients treated and the number of patients with recurrent bleeding in each therapeutic group (*H. pylori* eradication group and non-eradication group)
- *H. pylori* eradication success confirmed (based on the negative results of two tests or one test repeated twice) at least 4 weeks after antibiotic treatment.

Studies designed to follow up patients for less than 6 months were excluded. Studies with all patients taking NSAIDs were excluded.

Two reviewers independently applied the selection criteria according to the prestated eligibility criteria. Where disagreements occurred, they were resolved by consensus.

Types of participants

Participants were *H. pylori*-positive patients with a previous episode of peptic ulcer bleeding.

Bleeding had to be severe enough to warrant hospitalisation, with evident haematemesis and/or melaena and/or a drop in haemoglobin level of more than 2 g/dl.

The presence of an ulcer had to be documented endoscopically and no other potential bleeding source had to be found during initial evaluation.

Types of interventions

Interventions were as follows:

- *H. pylori* eradication therapy versus antisecretory non-eradication therapy (without long-term maintenance antisecretory therapy)
- *H. pylori* eradication therapy versus antisecretory non-eradication therapy with long-term maintenance antisecretory therapy.

Types of outcome measures

Outcome was recurrence of bleeding during follow-up of more than 6 months. Re-bleeding during follow-up was assessed with the same criteria as used for initial evaluation.

Search strategy for identification of studies

Searches were conducted to identify all published and unpublished controlled clinical trials. Articles published in any language were included. Trials were identified by searching the Cochrane Library (Issue 4, 2003), MEDLINE (January 1966–January 2004), EMBASE (January 1980–January 2004) and CINAHL (January 1982–January 2004). The search strategy was re-run in January 2005, but no new trials were found.

The search strategy was constructed by using a combination of subject headings and text words relating to the use of antisecretory therapies in the prevention of re-bleeding in peptic ulcer patients (see Appendix 3). The standard Cochrane search strategy filter for identifying RCTs was applied to all searches.

Ms Iris Gordon, Trials Search Coordinator for the CC UGPD Group, scanned the results of the electronic searches and removed all the obviously irrelevant references. Two reviewers then independently assessed these results to ascertain if they were eligible for inclusion in the review.

Reference lists from the trials and review articles were also searched. We manually searched abstracts from 1995 to 2003 from the International Workshop on Gastroduodenal Pathology and European *Helicobacter pylori* Study Group (EHPSG), DDW and the UEGW.

Authors of trial reports published only as abstracts were contacted and asked to contribute full datasets or completed papers.

Assessment of study quality

The quality of the studies was assessed using the score proposed by Jadad and colleagues[63] based on three items: (1) randomisation, (2) degree of blinding and (3) description of withdrawals and drop-outs. Two reviewers independently assessed the quality of studies. Discrepancies in the interpretation were resolved by consensus.

Data extraction

The following variables were extracted in a predefined data extraction form: author, year of publication, type of publication (complete article or abstract), type of participants (DU or GU, or both), NSAID use prior to the inclusion in the study (yes/no; if yes, percentage of patients taking NSAIDs), intervention (*H. pylori* eradication treatment or antisecretory treatment, including drugs, dose, schedule and duration), maintenance antisecretory therapy (yes/no; if yes, drug, dose and schedule of administration), follow-up (months), quality score and re-bleeding rate (raw numbers and percentages in each therapeutic group).

Two reviewers independently extracted studies. Discrepancies in the interpretation were resolved by consensus.

Publications identified as duplicates were excluded; when more than one version of the same trial was retrieved, only the most recent data were considered.

Data synthesis

The main outcome considered in this study was 'percentage of patients having recurrence of bleeding' due to PU.

Drop-outs were considered as not having recurrent bleeding, as it is the most frequent outcome. In addition, it seems to be unlikely that patients having recurrent bleeding are lost to follow-up, so it is logical to assume that these patients will be finally included in the analysis.

The heterogeneity of effects throughout studies was appraised using a heterogeneity test based on the χ^2 test. Due to the low power of this test, a minimum cut-off p-value of 0.1 was established as a threshold of homogeneity.

Separate meta-analyses were performed for studies comparing (1) *H. pylori* eradication therapy versus non-eradication therapy with an anti-secretory but without subsequent long-term maintenance antisecretory therapy and (2) *H. pylori* eradication therapy versus non-eradication therapy with an antisecretory and followed by long-term maintenance antisecretory therapy.

Meta-analysis was performed combining the OR of the individual studies in a global OR, using both a random effects model (DerSimonian and Laird[66]) and a fixed effect model (Peto method). Significance and 95% CI were provided for the combined OR. All calculations were performed with the Cochrane freeware program Review Manager 4.2.

Absolute risk reduction (ARR) or risk difference, relative risk reduction (RRR) and NNT to prevent one episode of re-bleeding were also calculated for the pooled data.

Subanalysis/sensitivity analysis

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

What is the efficacy of prophylactic PPI therapy in preventing peptic ulcer bleeds in patients taking NSAIDs compared with no treatment?

RCTs of PA, H_2RA and PPI were eligible for inclusion if the following inclusion criteria were satisfied:

- If these drugs were used for prevention of NSAID-induced UGI toxicity in adults.
- If the duration of NSAID exposure was more than 3 weeks.

Studies in healthy volunteers were excluded.

Included studies were also classified into primary or secondary prophylaxis trials and by the periods of outcome measures.

Types of participants

Participants were eligible if they had taken NSAIDs for longer than 3 weeks and were enrolled for the prophylaxis of NSAID-induced ulcers.

Types of intervention

Interventions that were examined included H_2RA, PPI and misoprostol, each used for the prophylaxis of NSAID-induced gastroduodenal ulcers.

Double dose of H_2RA was defined to be the dose equivalent of $\geqslant$300 mg of ranitidine twice daily.

Types of outcome measures

Primary outcomes measure

The primary outcome measure was the number of patients with endoscopic ulcers or ulcer complications (haemorrhage, perforation, pyloric obstruction or death). Endoscopic ulcers were defined to be at least 3 mm in diameter and/or could be distinguished from erosions based on the authors' description.

Secondary outcome measures

Secondary outcome measures were symptoms (nausea, vomiting, dyspepsia, abdominal pain or diarrhoea), overall drop-outs and drop-outs due to symptoms.

Search strategy for identification of studies

RCTs of PA, H_2RA or PPIs for the prevention of NSAID-induced UGI toxicity were identified by a comprehensive search through electronic databases including MEDLINE (from 1966 to June 2002), Current Contents (for 6 months prior to August 2004), EMBASE (to August 2004) and CCTR (from 1973 to 2004). TOXFILE, Biosis Previews®, ADIS LMS Drug Alerts and Pharmaceutical News Index (PNI)® were searched to June 2002. Furthermore, International Agencies for Health Technology Assessment (INAHTA) websites, specialised databases [e.g. University of York NHS Centre for Reviews and Dissemination (CRD)] and Conference Papers Index, and also the Internet (e.g. Google), were searched in order to identify health technology assessment reports, meeting abstracts and other grey literature. Trial registries were searched for ongoing trials. Recent conference proceedings were consulted and content experts and companies were contacted. The reference lists of all potentially relevant articles including reviews were reviewed for the identification of other potential studies. New articles identified since the last search update were evaluated for inclusion into the review (2003 and

2004). The detailed search strategy is described in Appendix 4.

Assessment of quality of the studies

Methodological quality was assessed by two independent reviewers using Jadad's scale[63] with consideration of allocation concealment. A third reviewer was consulted to resolve any disagreement by consensus.

Data extraction

Data extraction was performed independently by two reviewers with standardised data extraction sheet and differences were resolved by consensus. Data regarding population characteristics, study design and number of patients with endoscopic ulcers, ulcer complications, symptoms, overall drop-outs and drop-outs due to symptoms were extracted.

Data synthesis

The dichotomous outcomes were analysed with MetaView 4.1, using the Mantel–Haenszel relative risk[64] using a fixed effect model. The risk difference was also presented. A global χ^2 test (one degree of freedom) was used to assess the difference between the estimated adjusted RR for high- and low-dose misoprostol.

Subanalysis/sensitivity analysis

Subgroup analyses were performed by:

- the dosages of the intervention used
- the length of follow-up.

Sensitivity analyses were performed by:

- the study quality, with the median quality score used as the cut-off to define lower and higher quality studies
- primary versus secondary prophylaxis trials
- varying the obtained point estimates from efficacy to intention-to-treat.

The presence of publication bias was explored through the use of an inverted funnel plot. Heterogeneity was tested using a χ^2 test at an α value of 0.10, and represented graphically with a L'Abbe plot.[65] Estimates of heterogeneous data were obtained using a random effects model[66] only if clinically and statistically appropriate.

Chapter 4

What is the efficacy of PPI therapy in patients with endoscopically documented acute bleeding from a peptic ulcer?

Description of studies

Results of search strategy

The search strategy in CENTRAL, the Cochrane Library, MEDLINE and EMBASE identified 181 articles. Handsearching reference lists from these articles and searching major conference proceedings identified a further 16 trials. No further trials were identified by contacting members of the CC UGPD Group, experts in the field of gastroenterology and pharmaceutical companies marketing PPIs.

Twenty-four trials were included in the systematic review (*Table 1*). Five trials were published as abstracts only;[67–71] all were in English. The remaining 19 trials were full peer-reviewed publications;[9,72–89] of these, two were published in French,[73,84] one in Spanish,[85] one in Chinese[89] and the remaining 15 in English. Of the 19 trials that were full peer-reviewed publications, only one was not indexed in MEDLINE.[89] Additional unpublished information for one trial published in abstract form[70] was obtained from Altana Pharma (Konstanz, Germany), which sponsored the trial. Dr. JYW Lau also provided us with additional unpublished data for a trial published as a full paper.[81]

A total of 143 RCTs were excluded from the review as they were clearly not relevant. Main reasons for exclusion were as follows: not being RCTs; control group not receiving either placebo or H_2RA; and only pH outcomes being assessed. We retrieved the full articles for the remaining 54 trials and obtained translations for those published in languages other than English. Of these 54 trials, 30 did not meet the eligibility criteria and were excluded for the following reasons: duplicate publications (seven trials), not possible to isolate data on outcomes for patients with bleeding from PUs (five trials); control treatment was neither placebo nor H_2RA alone (10 trials); not reporting any of the outcomes predetermined in this systematic review (six trials); and historical control group (two trials) (*Table 2*).

Design

All included studies were RCTs with a parallel group design.

Setting

All trials were conducted in hospital settings.

Fourteen trials had been performed in Europe.[67–69,72–76,79,80,84–86,88] One trial was conducted predominantly in Europe, but also included some patients from Canada and South Africa;[70] eight trials were conducted in Asia;[9,77,78,82,83,87,89] one trial was performed in the USA.[71]

Participants

Participants in each trial were patients with endoscopically confirmed recent or active bleeding from PU. Two trials included patients with UGI bleeding due to any cause but reported separate data for outcomes for patients with PU bleeding.[75,89] Characteristics of the participants are given in *Table 1*.

The classification of participants according to the baseline endoscopic appearance of the PU (which affected the baseline risk of adverse outcomes) varied among studies (*Table 3*).

Interventions

Active treatment

Five trials used oral PPI as active treatment, either omeprazole[9,74,77,78] or lansoprazole.[84] The remaining 19 trials studied the effects of intravenous PPI treatment; four trials used intravenous pantoprazole[68–71] and the others used intravenous omeprazole. Of the 19 trials that used intravenous PPIs, six used the high dose regimen defined previously.[70,71,76,81,82,86]

Control treatment

Seven trials compared PPI treatment with placebo;[9,75–78,81,86] three of these used intravenous mannitol as placebo.[75,76,86] Seventeen trials compared PPI treatment with H_2RA treatment: oral ranitidine;[84] intravenous ranitidine;[67–74,79,80,85,87,88] intravenous cimetidine;[82,83] intravenous famotidine.[89]

TABLE 1 *Characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Barkun, 2004[70]	Large multicentre double-blind RCT. Randomised after endoscopy	Countries: Europe, Canada and South Africa. 1244 patients with bleeding PU: spurting bleeding 10%, oozing bleeding 55%, NBVV 35%. Co-morbidity not reported	1. Pantoprazole 80 mg i.v. bolus followed by 8 mg/h continuous i.v. infusion for 72 hours. 2. Ranitidine 50 mg i.v. bolus followed by 13 mg/h continuous i.v. infusion for 72 hours. Post-intervention drug treatment not mentioned. All patients received initial endoscopic haemostatic treatment	Mortality (at day 3 and at day 14), re-bleeding (at day 3), surgery (at day 3)	Published as abstract only, but provided additional unpublished data. Baseline comparability of treatment groups could not be assessed	A
Brunner, 1990[72]	Single-centre, open RCT. Randomised after endoscopy	Country: Germany. 39 patients with oozing bleeding from PU. Nineteen (49%) were already in-hospital patients with serious co-morbidity	1. Omeprazole 80 mg i.v. bolus, then 40 mg i.v. bolus 12-hourly for 5 days. 2. Ranitidine 50 mg i.v. bolus, then 400 mg i.v. infusion/ 24 hours for up to 6 days. On day 6, all commenced on oral omeprazole 40 mg once daily or ranitidine 300 mg twice daily. Initial endoscopic treatment not performed. Some patients had endoscopic treatment (sclerotherapy) when acid suppression treatment failed to control bleeding	Mortality, surgery, post-randomisation endoscopic treatment, "treatment failure" (continued bleeding), "bad outcomes"	On inclusion all patients were actively bleeding, but no initial endoscopic treatment was offered apparently. Timing of outcomes not reported. Exclusion criteria not reported	B
Cardi, 1997[73]	Single-centre RCT, unclear if blinded. Randomised after endoscopy	Country: Italy. 45 patients, all with oozing bleeding from DU	1. Omeprazole 40 mg i.v. bolus, then 80 mg i.v. infusion/ 24 hours for 3 days. 2. Ranitidine 50 mg i.v. bolus, then 400 mg i.v. infusion/ 24 hours for 3 days. No post-intervention drug treatment. Initial endoscopic treatment not mentioned	Mortality, surgery	No apparent initial endoscopic treatment. Timing of outcomes not reported	B

continued

TABLE 1 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Coraggio, 1998[74]	Multicentre, RCT, unclear if blinded. Randomised after endoscopy	Country: Italy. 73 patients with PU bleeding. PPI group $n = 24$; H_2RA group $n = 24$. PPI and H_2RA groups combined: spurting bleeding 4%; oozing 19%; NBVV 71%; adherent clot 6%. In-hospital bleeding 13% in PPI group; 17% in H_2RA group	Three treatment groups. 1.Omeprazole 40mg orally every 12 hours for 5 days. 2.Ranitidine: 50 mg i.v. every 6 hours for 5 days. 3.Somatostatin 250 μg i.v. bolus followed by continuous infusion 250 μg/h for 5 days. Post-intervention drug treatment not mentioned. All received endoscopic treatment	Mortality, re-bleeding, surgery, further endoscopic treatment, blood transfusions, length of hospital stay	No times given for outcome assessments. Exclusion criteria not reported. For the purpose of our analysis, Group 1 served as the active treatment group and Group 2 as the control group	B
Daneshmend, 1992[75]	Large multicentre (two centres), double-blind RCT. Randomised before endoscopy	Country: UK. Included 1147 patients with acute UGI bleeding of any cause. Separate data for 503 patients with bleeding PU. Excluded severe bleeding (that required surgery) and bleeding that developed in inpatients	1. Omeprazole 80 mg i.v. immediately, then 3 doses of 40 mg i.v. at 8-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	40-day mortality; re-bleeding; surgery; outcomes reported by ulcer site	Not randomised for PU bleeding. Study designed to investigate the efficacy of PPI in unselected patients with UGI bleeding. Only a few of the high-risk patients with PU received initial endoscopic treatment. Timing of assessment of re-bleeding and surgery not clear	A
Desprez, 1995[67]	Single-centre RCT, unclear if blinded. Randomisation timing not clear; probably after endoscopy	Country: France. 76 patients with bleeding PU (oozing bleeding, NBVV or adherent clot)	1. Omeprazole 80 mg bolus i.v. followed by 40 mg bolus i.v. every 8 hours for 3 days. Then orally 40 mg daily. 2. Ranitidine 100 mg bolus i.v. followed by continuous i.v. infusion of 400 mg/day for 3 days. Then orally 600 mg daily. Initial endoscopic treatment not mentioned	Mortality, re-bleeding and surgery at day 4 and day 15	Published as abstract only. Exclusion criteria not reported. No apparent initial endoscopic treatment	B

continued

TABLE 1 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Duvnjak, 2001[68]	Single-centre RCT, unclear if blinded. Randomised after endoscopy. All patients had repeat endoscopy routinely at 72 hours	Country: Croatia. 62 patients with bleeding PU (spurting or oozing bleeding, NBVV or adherent clot)	1. Omeprazole 80 mg bolus i.v. followed by 40 mg bolus i.v. every 8 hours for 72 hours. 2. Ranitidine 150 mg i.v. every 6 hours for 72 hours. Post-intervention drug treatment not mentioned. Apparently all patients had initial endoscopic treatment	Re-bleeding in 3 days	Published as abstract only. Exclusion criteria not reported	B
Fried, 1999[69]	Multicentre, open RCT. Randomised after endoscopy	Countries: Switzerland and Germany. 113 patients with bleeding PU (spurting or oozing bleeding, NBVV or adherent clot). Mean age, male/female ratio, GU/DU ratio and co-morbidity not reported	1. Pantoprazole 40 mg i.v. bolus followed by 8 mg/h i.v. infusion for 2 days. 2. Ranitidine 50 mg i.v. bolus followed by 12.5 mg/h i.v. infusion for 2 days. Post-intervention drug treatment not mentioned. Apparently all patients had initial endoscopic treatment	Mortality and re-bleeding at 9 days	Published as abstract only. Exclusion criteria not reported. Withdrawals 24.4%. Previous publication, also as abstract (*Gastroenterology* 1999; **116**:A165), with slightly different results	B
Hasselgren, 1997[76]	Double-blind RCT. 20 centres in Sweden and 9 centres in Norway. Randomisation timing not clear; probably after endoscopy	Countries: Sweden and Norway. 322 patients aged over 60 with bleeding PU. Arterial spurting 7%; oozing 25%; NBVV 16%; adherent clot 52%. Significant co-morbidity in both groups. All participants were new admissions	1. Omeprazole 80 mg i.v. bolus, followed by continuous infusion 8 mg/h for 72 hours. 2. Identical placebo (mannitol) regimen for 72 hours. Then, all received omeprazole 20 mg oral daily until day 21. Initial endoscopic treatment only for spurting bleeding	"Overall outcome" (5-point scale ranking the outcome from worse to best as follows: death 5; surgery 4; endoscopic treatment 3; more than three units of blood transfused 2; 0–3 units of blood transfused 1). Mortality, surgery and endoscopic treatment in 3 and 21 days, treatment failure in 3 days, re-bleeding (from day 4 to 21), blood transfusions	Serious adverse events reported in detail. Very low mortality in the placebo group (0.6%); study stopped prematurely because of concerns regarding significantly higher mortality in PPI group. Imbalances in baseline characteristics	A

continued

TABLE 1 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Javid, 2001[77]	Single-centre double-blind RCT. Randomised after endoscopy	Country: India. 166 patients with bleeding PU (16% spurting bleeding; 25% oozing bleeding; 22% NBVV; 37% adherent clot)	1. Omeprazole 40 mg oral every 12 hours for 5 days. 2. Identical looking placebo for 5 days. Then all received oral omeprazole 20 mg daily for 3 weeks (with or without prior *H. pylori* eradication therapy). All had initial endoscopic treatment	Separately by SRH: mortality, re-bleeding and surgery (timing of outcome assessment not reported). Length of hospital stay	Five patients excluded because of continuing bleeding following initial endoscopy	A
Jensen, 2004[71]	Multicentre, double-blind RCT. Randomised after endoscopy	Country: USA. 149 "patients with stigmata of recent haemorrhage" who required endoscopic haemostasis; patients with spurting bleeding, oozing bleeding and NBVV were included, but it is not clear whether patients with adherent clots were also included	1. Pantoprazole 80 mg i.v. bolus followed by 8 mg/h continuous i.v. infusion for 72 hours. 2. Ranitidine 50 mg i.v. bolus followed by 6.25 mg/h continuous i.v. infusion for 72 hours. Then all patients received oral PPI. All patients received initial endoscopic treatment	Re-bleeding at days 3, 7 and 30. Rates of combined surgery or angiography. 30-day mortality was not reported by treatment group (total mortality was 4%; "none bleeding")	Published as abstract only. Provided additional data regarding the randomisation method	A
Kaviani, 2003[78]	Two-centre, double blind RCT. Randomised after endoscopy	Country: Iran. 149 patients with bleeding PU (8% spurting bleeding; 54% oozing bleeding; 38% NBVV) and haemostasis achieved on initial endoscopy	1. Omeprazole 20 mg every 6 hours oral, for 3–5 days 2. Identical placebo for 3–5 days. Then, all received oral omeprazole 20 mg twice daily plus *H. pylori* eradication therapy (if positive for the infection). All had initial endoscopic treatment	Assessed on day 21: mortality, re-bleeding, surgery and blood transfusions. Also length of hospital stay	Excluded those in whom initial haemostasis was not achieved	A

continued

TABLE I *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Khuroo, 1997[9]	Single-centre, double-blind RCT. Randomised after endoscopy	Country: India. 220 patients with PU bleeding (12% arterial spurting, 15% oozing, 16% NBVV, 57% adherent clot)	1. Omeprazole 40 mg orally every 12 hours for 5 days. 2. Identical looking placebo for 5 days. Both groups allowed liquid antacid 15 ml orally every 6 hours. Post-intervention drug treatment not mentioned. No initial endoscopic treatment	Mortality (30 days), continued bleeding, recurrent bleeding, surgery: reported by SRH. Blood transfusions, length of hospital stay	Excluded patients with severe bleeding and severe terminal illness	A
Labenz, 1997[79]	Single-centre RCT, unclear if blinded. Randomised after endoscopy	Country: Germany. 40 patients with bleeding PU (spurting or oozing bleeding, NBVV or adherent clot)	1. Omeprazole 80 mg i.v. bolus followed by 8 mg/h i.v. infusion for 24 hours. 2. Ranitidine 50 mg i.v. bolus followed by 0.25 mg/kg/h i.v. infusion for 24 hours. Post-intervention drug treatment not mentioned. Initial endoscopic treatment in 24 patients	Intragastric pH . Re-bleeding within 24 hours	Primary outcome was intragastric pH. None of the five patients that re-bled had shown clinical signs of re-bleeding; they were found to be bleeding on control endoscopy done at 24 hours	B
Lanas, 1995[80]	Single-centre open RCT. Randomised after endoscopy	51 patients with bleeding PU (18% oozing bleeding; 14% NBVV; 68% adherent red clot). Co-morbidity 55%. 74% male; 45% GU. Excluded: patients with spurting bleeding; severe bleeding needing surgery; bleeding in patients already hospitalised	1. Omeprazole 80 mg i.v. bolus followed by 40 mg i.v. every 12 hours. 2. Ranitidine 50 mg i.v. every 4 hours. Duration of omeprazole and ranitidine treatment not mentioned. No initial endoscopic treatment	Mortality, re-bleeding, surgery, blood transfusion requirements, length of hospital stay. Timing of outcome assessment not mentioned	No timing given for assessment of outcomes. No duration given for omeprazole/ranitidine treatment	B

continued

TABLE 1 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Lau, 2000[81]	Single-centre double-blind RCT. Randomised after endoscopy	Country: Hong Kong, China. 240 patients with bleeding PU (10% spurting bleeding; 41% oozing; 49% NBVV) and haemostasis achieved after endoscopic treatment	1. Omeprazole 80 mg i.v. bolus, then i.v. infusion 8 mg/h for 72 hours. 2. Identical placebo for 72 hours. After 72 hours, all were given oral omeprazole 20 mg daily for 8 weeks. All received initial endoscopic treatment	At 30 days: mortality, re-bleeding (also at 3 and 7 days), surgery, repeat endoscopic treatment, blood transfusions. Length of hospital stay. Provided additional unpublished data on outcomes by ulcer site and by initial endoscopic SRH	*A priori* power analysis: required $n = 320$; trial terminated at $n = 240$ due to significant differences in interim analysis in re-bleeding rates at 30 days	A
Lin, 1997[83]	Single-centre open RCT. Randomised after endoscopy	Country: Taiwan. 52 patients with bleeding PU (NBVV)	Four treatment groups: (A) cimetidine 300 mg i.v. bolus followed by short infusion 300 mg/6-hourly during hospitalisation. (B) heater probe coagulation plus cimetidine 300 mg i.v. bolus followed by short infusion 300 mg/6-hourly during hospitalisation. (C) Omeprazole 40 mg i.v. bolus followed by 40 mg short i.v. infusion daily for 2 days. (D) omeprazole 40 mg i.v. bolus followed by 40 mg i.v. short infusion every 12 hours for 2 days. No initial endoscopic treatment	Re-bleeding (timing of outcome assessment not clear)	No initial endoscopic treatment. Limited to NBVV. Small group size. For the purpose of our analysis, we combined Groups C and D as active treatment group and used Group A as control group	A
Lin, 1998[82]	Open, single-centre RCT. Randomised after endoscopy	Country: Taiwan. 100 patients with bleeding PU (21% spurting bleeding; 13% oozing bleeding; 66% NBVV) and initial haemostasis after endoscopic treatment	1. Omeprazole 40 mg i.v. bolus, then i.v. infusion 160 mg/day for 3 days, then 20 mg oral/day for 2 months. 2. Cimetidine 300 mg i.v. bolus, then i.v. infusion 1200 mg/day for 3 days, followed by 400 mg twice daily for 2 months. All received initial endoscopic treatment	At day 3 after entry: re-bleeding. At day 14: mortality, re-bleeding, surgery, blood transfusions	More patients with active bleeding in control group ($p = 0.09$). Mean haemoglobin concentration was lower in the omeprazole group than in the control group (not significant)	A

continued

TABLE 1 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Michel, 1994[84]	Multi-centre double-blind RCT. Timing of randomisation not clear (most probably after endoscopy)	Country: France. 75 patients with bleeding PU (spurting bleeding 13%; oozing 27%; NBVV 17%; adherent clot 43%). Excluded: patients presumed to need immediate surgery, patients developing bleeding while hospitalised for another reason	1. Lansoprazole 60 mg orally each morning for 6 days. 2. Ranitidine 300 mg orally twice daily for 6 days. Post-intervention drug treatment not mentioned. Patients with spurting bleeding received initial endoscopic treatment	At day 6: mortality, re-bleeding and surgery. Adverse reactions		B
Perez Flores, 1994[85]	Open, single-centre RCT. Timing of randomisation not clear	Country: Spain. 81 patients with bleeding PU (27% oozing bleeding; 7% NBVV; 66% adherent clot). Patients with concomitant severe diseases were excluded	1. Omeprazole 80 mg i.v. bolus, then 40 mg i.v. 8-hourly for 3 days, then 20 mg orally once daily. 2. Ranitidine 50 mg i.v. bolus, then 100 mg i.v. 6-hourly for 3 days, then 150 mg orally twice daily. The majority of high-risk patients did not receive initial endoscopic treatment	Mortality, re-bleeding, surgery, blood transfusions, length of hospital stay. Timing of outcome assessment not reported		C
Schaffalitzky, 1997[86]	Double-blind multicentre RCT (34 hospitals). Randomised after endoscopy	Countries: Denmark, The Netherlands and France. 265 patients with bleeding from PU that was severe enough to cause at least two of the following: systolic blood pressure <100 mmHg; heart rate >100/min; blood haemoglobin <11.3 g/dl for men or 10.5 g/dl. SRH: 7% spurting bleeding; 25% oozing bleeding; 21% NBVV; 47% adherent clot	1. Omeprazole 80 mg i.v. bolus, then infusion of 8 mg/h for 72 hours. 2. Identical placebo (mannitol) regimen. After 48 hours both groups received oral omeprazole 20 mg daily for 21 days. Initial endoscopic treatment to 192 patients	"Overall outcome" (5-point scale ranking the outcome from worse to best as follows: death 5; surgery 4; endoscopic treatment 3; more than 3 units of blood transfused 2; 0–3 units of blood transfused 1). Mortality (in 3, 21 and 35 days with causes of death by treatment group); re-bleeding (from day 4 to 21); surgery (in 3 and 21 days); "bad outcomes" (in 3 days); most severe episode of bleeding; duration of bleeding; "adjusted" number of transfused units of blood. Adverse events	Trial entry stopped prematurely because interim analysis revealed significantly higher mortality in PPI group when outcomes were polled together with a parallel study.[76] No pattern found to events preceding deaths. 35-day mortality results. Imbalances in baseline characteristics	A

continued

TABLE 1 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Sheu, 2002[87]	Single-centre RCT. Not clear if blinded. Randomised after endoscopy	Country: Taiwan. 175 patients with bleeding PU (36% with spurting, oozing or NBVV; 25% with adherent clot; 39% with clear base) and proven *H. pylori* infection. Excluded patients with severe debilitating medical conditions that interfered with oral intake	1. Omeprazole 80 mg i.v. bolus, then 40 mg i.v. twice daily for 3 days. 2. Ranitidine 50 mg infused i.v. every 8 hours for 3 days. Spurting, oozing, NBVV and vessels below clots received initial endoscopic treatment. All received triple eradication therapy from day 4 for 1 week. "Later", ranitidine 150 mg orally twice daily for additional 4 weeks	Re-bleeding at 3 days, 10 days and 6 weeks. Mortality and surgery. Re-bleeding also reported by severity of SRH	Only *H. pylori*-positive patients were included in the study. High proportion (39%) of patients with low-risk findings at index endoscopy. Timing of outcome assessment for mortality and surgery not clear (? 6 weeks)	B
Villanueva, 1995[88]	Open, single-centre RCT. Randomised after endoscopy	Country: Spain. 86 PU patients with active arterial bleeding (10% spurting; 90% oozing). Included patients with in-hospital onset of bleeding (16%)	1. Omeprazole 80 mg i.v. bolus followed by 40 mg i.v. every 8 hours for 4 days, then 20 mg/day orally (duration not stated). 2. Ranitidine i.v. 50 mg every 6 hours for 12–24 hours, then 150 mg oral twice daily (duration not stated). All received initial endoscopic treatment	Mortality, re-bleeding, surgery, blood transfusion requirements, length of hospital stay. Followed up until discharge or death	No times given for outcomes assessment. Imbalances in baseline characteristics	A
Xuan, 2003[89]	Single-centre RCT. Not clear if blinded. Timing of randomisation not clear	Country: China. Included 90 patients with acute UGI bleeding of any cause. Mortality rates could be calculated separately for 64 patients with bleeding PU. Not clear if included patients with bleeding that developed in hospital	1. Omeprazole 40 mg i.v. bolus every 12 hours for 3 days, then omeprazole 20 mg orally twice daily. 2. Famotidine 40 mg i.v. bolus every 12 hours for 3 days, then famotidine 20 mg orally twice daily. No initial endoscopic treatment was offered apparently	No separate outcomes for patients with bleeding PU, but mortality rates could be calculated separately for 64 patients with bleeding PU (timing of assessment not clear)	No times given for outcome assessments. Exclusion criteria not reported	B

[a] Cochrane ranking: Grades A–C.

TABLE 2 *Excluded studies*

Study	Reason for exclusion
Artal, 1996[90]	Only pH outcomes were assessed
Chilovi, 2003[91]	Control group not being either placebo or H_2RA alone; compared omeprazole with pantoprazole
Chu, 1993[92]	Did not report any of the outcomes predefined in this review; reported number of cases with cessation of bleeding within 48 hours, but these data could not be pooled with the re-bleeding data from the other trials because the definition of cessation of bleeding was not given and it was not clear whether all patients where actively bleeding at inclusion
Chua, 1996[93]	Dual publication [preliminary report of the Lin (1997) trial[83]]
Dokas, 2004[94]	Control group not being either placebo or H_2RA alone; compared two different regimens of omeprazole
Fasseas, 2001[95]	Not possible to isolate data on outcomes for patients with bleeding from PUs
Focareta, 2004[96]	Control group not being either placebo or H_2RA alone; compared omeprazole with esomeprazole
Fried, 1999[97]	Dual publication with Fried (1999)[69] (both published as abstracts of conference presentations)
Goletti, 1994[98]	Control group not being either placebo or H_2RA alone; compared omeprazole alone versus the combination of ranitidine and somatostatin
Grosso, 1995[99]	Control group not being either placebo or H_2RA alone; compared omeprazole alone versus the combination of ranitidine and endoscopic haemostatic therapy
Hawkey, 2001[100]	Not possible to isolate data on outcomes for patients with bleeding from PUs
Khuroo, 1997[9]	Preliminary report (abstract of conference presentation) of the Khuroo (1997) trial[9]
Lau, 1999[101]	Preliminary report (abstract of conference presentation) of the Lau (2000) trial[81]
Lin, 1996[102]	Preliminary report (abstract of conference presentation) of the Lin (1998) trial[82]
Lind, 1995[103]	Preliminary report (abstract of conference presentation) of the Hasselgren (1997) trial[76]
Maculotti, 1995[104]	Designed to assess healing rates. Not reporting any of the outcomes predetermined in this systematic review
Mohamed, 1996[105]	Historical control group; not randomised
Orti, 1995[106]	Not possible to isolate data on outcomes for patients with bleeding from PUs
Prassler, 1995[107]	Historical control group; not randomised
Schaffalitzky, 1996[108]	Preliminary report (abstract of conference presentation) of the Schaffalitzky (1997) trial[86]
Schonekas, 1999[109]	Control group not being either placebo or H_2RA alone; compared two different regimens of pantoprazole
Sofia, 2000[110]	Control group not being either placebo or H_2RA alone; compared various modalities of endoscopic haemostatic therapy alone or in combination with i.v. octreotide or i.v. omeprazole
Tang, 2001[111]	Designed to assess healing rates. Not reporting any of the outcomes predetermined in this systematic review
Tseng, 1999[112]	Control group not being either placebo or H_2RA alone; compared three i.v. regimens of omeprazole among themselves
Tsukamoto, 1997[113]	Designed to assess healing and relapsing rates. Not reporting any of the outcomes predetermined in this systematic review
Udd, 2001[114]	Control group not being either placebo or H_2RA alone; compared two i.v. regimens of omeprazole among themselves
Uribarrena, 1994[115]	Not possible to isolate data on outcomes for patients with bleeding from PUs
Wallner, 1996[116]	Not possible to isolate data on outcomes for patients with bleeding from PUs
Zhao, 1990[117]	Designed to assess healing rates. Not reporting any of the outcomes predetermined in this systematic review
Zhonglin, 2002[118]	Control group not being either placebo or H_2RA alone; compared omeprazole with pantoprazole

TABLE 3 *Baseline endoscopic appearance of peptic ulcers per study*

Study	Spurting bleeding	Oozing bleeding	NBVV	Clot	Clear base	Comments
Brunner, 1990[72]		✓				
Daneshmend, 1992[75]	?	?	?	?	?	Endoscopic staging not clear (patients randomised prior to endoscopy)
Michel, 1994[84]	✓	✓	✓	✓		
Perez Flores, 1994[85]		✓	✓	✓		
Desprez, 1995[67]		✓	✓	✓		
Lanas, 1995[80]		✓	✓	✓		
Villanueva, 1995[88]	✓	✓				
Cardi, 1997[73]		✓				
Hasselgren, 1997[76]	✓	✓	✓	✓		Reported separate surgical intervention rates for patients with oozing bleeding
Khuroo, 1997[9]	✓	✓	✓	✓		Reported separate outcomes per stage
Labenz, 1997[79]	✓	✓	✓	✓		
Lin, 1997[83]			✓			
Schaffalitzky, 1997[86]	✓	✓	✓	✓		
Coraggio, 1998[74]	✓	✓	✓	✓		
Lin, 1998[82]	✓	✓	✓			
Fried, 1999[69]	✓	✓	✓	✓		
Lau, 2000[81]	✓	✓	✓			Reported separate re-bleeding rates for patients with NBVV
Duvnjak, 2001[68]	✓	✓	✓	✓		
Javid, 2001[77]	✓	✓	✓	✓		Reported separate outcomes per stage
Sheu, 2002[87]	✓	✓	✓	✓	✓	
Kaviani, 2003[78]	✓	✓	✓	✓		
Xuan, 2003[89]	?	?	?	?	?	Endoscopic staging not reported
Barkun, 2004[70]	✓	✓	✓			Patients with an adherent clot were included if the clot was removed and the underlying lesion was reclassified
Jensen, 2004[71]	✓	✓	✓	?		Stated that they included "high-risk patients", defined as "patients with stigmata of recent haemorrhage" requiring endoscopic haemostasis; not clear whether patients with adherent clots were also included

See also *Table 1* for details of interventions, including dose and duration of therapy.

Co-interventions

Co-interventions (including EHT, the most important of the co-interventions) were applied equally to both treatment arms in all trials.

Fifteen trials allowed for the consistent application of some form of EHT to well-defined high-risk patients, before randomisation.[68–71,74,76–79,81,82,84,86–88] Nine trials[9,67,72,73,75,80,83,85,89] had not consistently managed patients with EHT before randomisation, although two[75,85] applied some form of EHT to a minority of the high-risk patients. With the exception of one trial,[89] all trials published in 1998 or later consistently used EHT before randomisation.

Methodological quality of included studies

All 24 included studies were RCTs with parallel group design.

Allocation concealment

Methodological quality assessment had emphasis on allocation concealment, which was ranked using the Cochrane approach:

- Grade A (adequate concealment), 12 trials.[9,70,71,75–78,81–83,86,88]
- Grade B (uncertain), 11 trials.[67–69,72–74,79,80,84,87,89]
- Grade C (inadequate concealment) in one trial,[85] where patients were allocated to control treatment or to PPI treatment depending on whether their age in years was an even or an odd number respectively.
- Grade D (not randomised), none of the trials.

Blinding

Ten trials were double-blinded[9,70,71,75–78,81,84,86] and seven were unblinded;[69,72,80,82,83,85,88] the remaining seven trials provided no information regarding blinding status.[67,68,74,79,87,89]

Baseline comparability of treatment groups

Overall, most trials were adequately balanced regarding baseline characteristics of treatment groups. No major imbalances were self-reported or seen in the tables of the raw data in any of the trials. However, not all trials reported such data.

Presence of predefined inclusion and exclusion criteria

In each trial, predefined inclusion criteria were reported in detail. In the majority of the trials, predefined exclusion criteria were also reported in detail, with the exception of the five trials published in abstract form[67–71] and three others.[72,74,89] Additional unpublished information regarding inclusion and exclusion criteria for the trial of Barkun and colleagues[70] was provided.

A priori sample size estimation

In 12 of the trials, sample size was estimated *a priori*.[9,70,71,75-78,81,82,84,86,88]

Detailed description of interventions in active and in control treatment groups

All trials provided detailed descriptions of the route and method of administration, dose and duration of medications used, in active and in control treatment groups, with the exception of one trial[80] that did not define the duration of drug intervention.

See also *Table 1* for details of intervention, including dose and duration of therapy.

Definition of outcomes

Of the main outcomes of the current systematic review, namely rates for mortality, surgical intervention and re-bleeding, the last was the only outcome difficult to define. Indeed, there were variations in the definition of re-bleeding among the trials.

First, not all trials made a distinction between re-bleeding (recurrence of bleeding following endoscopically confirmed haemostasis, whether spontaneous or resulting from EHT) and persistent bleeding (continuing bleeding in patients admitted to the trial actively bleeding with failed or unattempted endoscopic haemostasis). Furthermore, the means of identifying patients with re-bleeding (scheduled repeat endoscopy or repeat emergency endoscopy prompted by clinical suspicion of re-bleeding or clinical criteria or combinations of the above) varied among trials.

Stated causes of death by treatment group

Of the 20 trials that reported mortality rates by treatment group, three had no deaths in either treatment group, so reporting causes of death was not applicable.[73,85,89] Eight trials gave causes of death per treatment group;[72,76,77,81,82,84,86,88] three trials reported causes of death for the whole study

population but not separately by treatment group;[9,75,80] six trials did not report causes of death at all[67,69,70,74,78,87] (however, Barkun and colleagues[70] provided additional unpublished information about causes of death per treatment group).

Of note, only one trial[75] reported in detail a rigorous method of categorising causes of death, into eight categories according to the contribution bleeding had made to death; categorisation was performed before the randomisation code was broken. However, such data were not reported separately for patients with PU bleeding. Such an approach was not used by the eight trials (see above) that reported causes of death per treatment group for patients with PU bleeding. Therefore, we have not attempted to classify mortality as being related or unrelated to ulcer bleeding.

A detailed description of causes of death per trial is given in *Table 4*. There were no statistically significant differences in causes of death between the PPI group and the control group in any of the studies.

Stated time for outcome assessment

Timing for outcome assessment was not clear in some of the trials (see *Table 1*).

Description of withdrawals and dropouts

Only six trials reported detailed descriptions of withdrawals and dropouts[70,78,81,84,86,88] (Barkun and colleagues[70] with additional unpublished data).

Quantitative analysis

Mortality

Of the 24 RCTs, 20 provided data on mortality by treatment group[9,67,69,70,72–78,80–82,84–89] (Barkun and colleagues[70] with additional unpublished data). Of note, only one trial[75] specified that mortality was the main outcome and based accordingly to the calculation of the *a priori* sample size calculation. It must also be emphasised that the current pooled mortality analysis, and also the remaining subgroup analyses regarding mortality, refer to all-cause mortality (see the section 'Stated causes of death by treatment group', p. 26). These 20 trials comprised a total of 4082 patients (2020 randomised to PPI treatment and 2062 to control treatment). There was no significant heterogeneity among the trials ($p = 0.24$, $I^2 = 18.5\%$). The pooled mortality rate for PPI treatment was 3.91%; with a range from 0%[73,78,82,85,87,89] to 18.4%.[67] The pooled mortality rate for control treatment was 3.83% with a range from 0%[73,85,89] to 18.4%.[67] There was no statistically significant difference in mortality rates between PPI and control treatment (OR 1.01, 95% CI 0.74 to 1.40) (*Figure 1*); this result remained non-significant when, by sensitivity analysis, any one of the included trials was removed.

Visual inspection of the funnel plot for the outcome of mortality showed slight asymmetry suggesting the possibility of publication bias (small negative studies missing from the bottom right of the graph). However, Egger's test[62] showed no evidence of publication bias: coefficient for bias 0.219, 90% CI –1.066 to 1.503, $p = 0.77$.

Meta-regression was used to examine the influence of predefined study characteristics on the effect of treatment on mortality (see Chapter 3). The only study characteristic found to be significantly associated with the treatment effect (log OR for mortality) was the geographical location of the study; treatment effect was higher in favour of PPI treatment in studies that had been conducted in Asia compared with studies that had been conducted elsewhere: coefficient –1.91, 95% CI –2.18 to –0.21; constant 0.23 (results expressed in logarithmic form); $p = 0.02$; 14 studies analysed.

However, only 12 trials stated the time for mortality assessment and, of these, four assessed mortality over a period not exceeding 14 days post-admission (see the section 'Methodological quality of included studies', p. 26). The aim was to investigate the hypothesis that differences in mortality rates could become obvious only after a longer follow-up period, triggered by the finding of Daneshmend and colleagues[75] that a significant difference in mortality in favour of control (placebo) treatment was apparent at 21 days but not at 3 days. A *post hoc* sensitivity analysis was performed by pooling mortality rates from the six trials that assessed mortality for a period longer than 21 days following admission,[9,75,76,78,81,86] ranging from 21 days (in the trials of Kaviani and colleagues[78] and Hasselgren and colleagues[76]) to 40 days (in the trial of Daneshmend and colleagues[75]). Of note, no further deaths occurred after day 30 in the trial of Daneshmend and colleagues,[75] although mortality was monitored up to day 40. There was significant heterogeneity among these six trials ($p = 0.01$, $I^2 = 64.6\%$); heterogeneity remained significant when any one of the included studies was removed. Pooled mortality rates were 6.1% for PPI treatment and

TABLE 4 *Description of mortality per treatment group*

Study	Timing (days)	Mortality (PPI)	Mortality (control)	Causes (PPI)	Causes (control)	Comments
Brunner, 1990[72]	Not stated	1/19	1/20	1 death following surgery for bleeding from DU	1 death following surgery for bleeding from DU	
Daneshmend, 1992[75]	40	23/246	13/257	Not reported	Not reported, but stated that mortality was especially high in patients with bleeding duodenal ulcer in the PPI group	For the total study population (unselected patients with UGI bleeding randomised prior to endoscopy) detailed description of causes of death was given; patients in PPI group were more likely to have more complex surgical interventions, to die postoperatively, to have cancer or to be bleeding from the lower gut than those in the placebo group
Michel, 1994[84]	6	2/38	1/37	1 death due to ulcer bleed and 1 due to stroke	1 death due to stroke	
Desprez, 1995[67]	3 and 14	At 3 days 3/38; at 14 days 7/38	At 3 days 3/38; at 14 days 7/38	Not reported	Not reported	
Perez Flores, 1994[85]	Not stated	0/38	0/43	NA	NA	
Lanas, 1995[80]	Not stated	2/28	2/23	Not reported	Not reported	Stated that mortality occurred only in old patients with multiple severe concomitant diseases; was related to the bleeding episode only in one case
Villanueva, 1995[88]	Not stated	3/45	1/41	2 deaths following emergency surgery for peptic ulcer bleeding; 1 due to "unrelated cause"	1 death following emergency surgery for PU bleeding	
Cardi, 1997[73]	Not stated	0/21	0/24	NA	NA	

continued

TABLE 4 *Description of mortality per treatment group (cont'd)*

Study	Timing (day)	Mortality (PPI)	Mortality (control)	Causes (PPI)	Causes (control)	Comments
Hasselgren, 1997[76]	3 and 21	At 3 days 1/159; at 21 days 11/159	At 3 days 1/163; at 21 days 1/163	At 21 days: myocardial infarction (n = 5); cardiac failure (n = 2); stroke (n = 2); pulmonary embolism (n = 1); GI bleed (n = 1)	GI bleed (n = 1)	Very low mortality in the placebo group (0.6%); recruitment stopped prematurely because interim analysis revealed significantly higher mortality in PPI group
Khuroo, 1997[9]	30	2/110	6/110	Not reported	Not reported	Causes given (not separately per treatment group): continued GI bleeding (n = 4); chronic renal failure (n = 2); pulmonary embolism (n = 1); chronic obstructive pulmonary disease (n = 1)
Labenz, 1997[79]	NA	Not reported	Not reported	Not reported	Not reported	1 death due to massive re-bleeding from DU on day 2 (not mentioned which treatment group the patient belonged to)
Lin, 1997[83]	NA	Not reported	Not reported	NA	NA	
Schaffalitzky, 1997[86]	3, 21 and 35	At 3 days 2/130; at 21 days 8/130; at 35 days 10/130	At 3 days 0/135; at 21 days 8/135; at 35 days 11/130	At 35 days: cardiac failure (n = 2); stroke (n = 3); pulmonary embolism (n = 1); septic shock (n = 1); GI bleeding (n = 1); perforated GU (n = 1); not specified (n = 1)	At 35 days: cardiac failure (n = 3); myocardial infarction (n = 1); pulmonary embolism (n = 1); hepatic necrosis (n = 1); GI bleeding (n = 4); not specified (n = 1)	Recruitment stopped prematurely because interim analysis revealed significantly higher mortality in PPI group when outcomes were pooled together with a parallel study.[76] No pattern found to events preceding deaths
Coraggio, 1998[74]	Not stated	3/24	2/24	Not reported	Not reported	
Lin, 1998[82]	14	0/50	2/50	NA	1 death due to GI bleeding; 1 due to sepsis (both had advanced non-GI cancer)	
Fried, 1999[69]	9	1/66	1/67	Not reported	Not reported	

continued

TABLE 4 *Description of mortality per treatment group (cont'd)*

Study	Timing (day)	Mortality (PPI)	Mortality (control)	Causes (PPI)	Causes (control)	Comments
Lau, 2000[81]	30	5/120	12/120	Causes not reported but stated that none died from re-bleeding	4 died after surgery (performed in 3 for GI bleeding, and in 1 for perforation possibly due to thermo-coagulation), 2 due to re-bleeding, 6 due to concurrent illnesses (chest infection ($n = 3$), ischaemic stroke ($n = 2$), liver failure due to primary liver tumour ($n = 2$))	
Duvnjak, 2001[68]	NA	Not reported	Not reported	NA	NA	
Javid, 2001[77]	Not stated	1/82	2/84	1 death due to concurrent illness (5 days after recovery from the GI bleed)	2 deaths following surgery for recurrent GI bleed (1 due to uncontrolled bleeding and 1 due to ischaemic stroke)	
Sheu, 2002[87]	Not stated	0/86	2/89	Not reported	Not reported	
Kaviani, 2003[78]	21	0/71	1/78	Not reported	Not reported	Low mortality compared with other trials. 1 patient died (placebo group) on day 1. Low mean age of participants
Xuan, 2003[89]	Not stated clearly (at least 37)	0/31	0/33	NA	NA	
Barkun, 2004[70]	3 and 14	At 3 days 2/618; at 14 days 6/618	At 3 days 4/626; at 14 days 10/626	3 deaths (1 during 72 hours of drug infusion, 2 post-infusion) were related to re-bleeding	3 deaths (2 during 72 hours of drug infusion, 1 post-infusion) were related to re-bleeding	
Jensen, 2004[71]	30	Not reported	Not reported	NA	NA	Reported only total mortality (for both groups combined): 4% (none related to bleeding)

NA, not applicable.

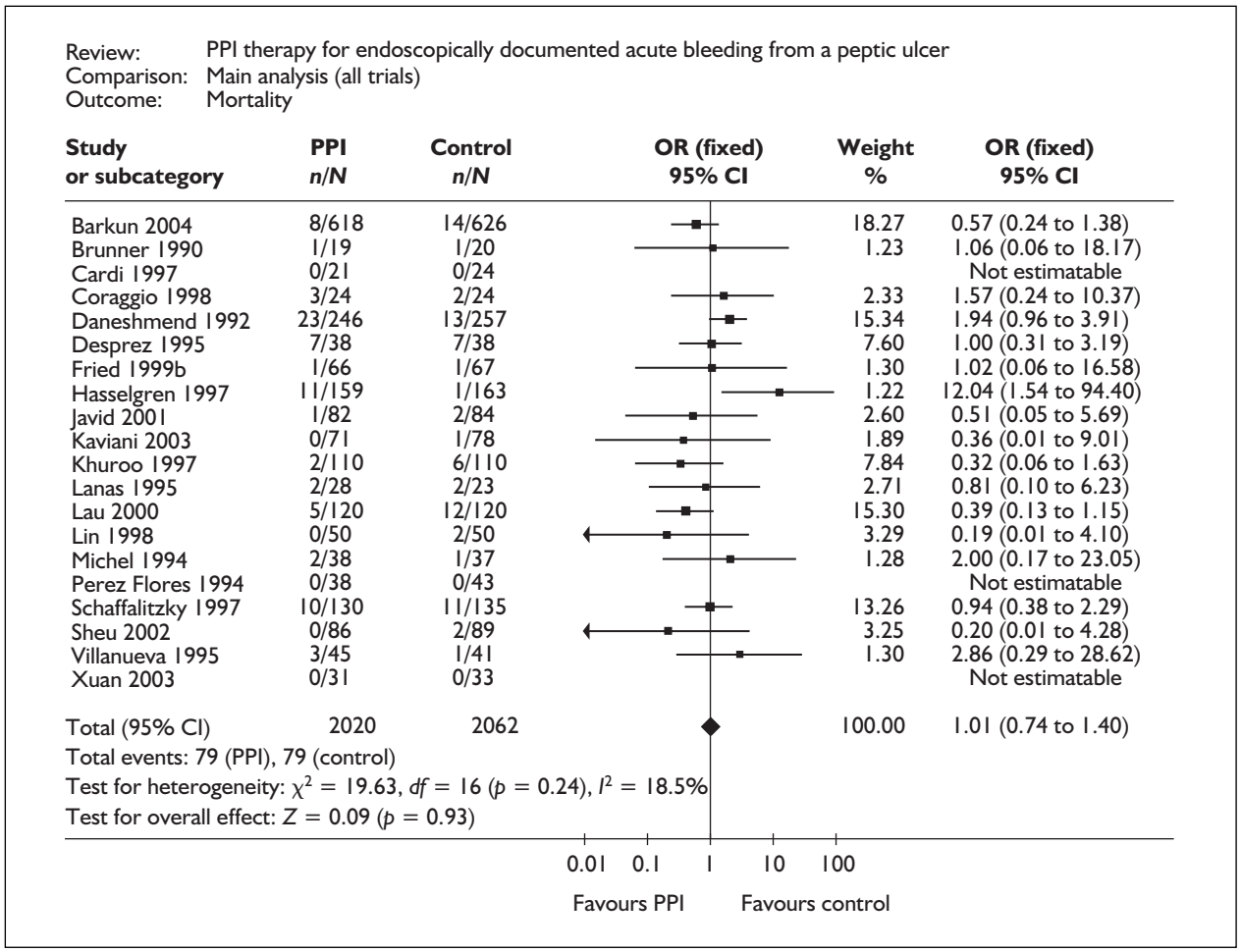

FIGURE 1 *Mortality with PPI versus H_2RA or placebo for endoscopically documented acute bleeding from a peptic ulcer*

5.1% for control. The difference in mortality rates between PPI and control treatment was not statistically significant (OR 1.01, 95% CI random effects 0.42 to 2.43); this result remained non-significant when, by sensitivity analysis, any one of the included trials was removed.

Re-bleeding

Twenty-one trials reported re-bleeding rates.[9,67–71,74–88] These trials comprised a total of 4224 patients: 2098 patients on PPI treatment and 2126 in the control arm. There was a statistically significant degree of heterogeneity among these trials ($p = 0.04$, $I^2 = 38.6\%$). The pooled re-bleeding rate was 10.6% for PPI treatment with a range from 0%[85] to 24.4%.[88] The pooled re-bleeding rate for the control group was 17.3% with a range from 2.3%[85] to 39.1%.[80] There was a highly significant difference in re-bleeding rates in favour of PPI treatment compared with control (OR 0.49, 95% CI random effects 0.37 to 0.65; NNT 13, 95% CI 9 to 25) (see *Figure 2*). This result remained significant when, by sensitivity analysis, any one of the included trials was removed.

Of note, the above-mentioned heterogeneity should not be considered a problem. Of course, according to our *a priori* statement that heterogeneity would be considered significant if *Q*-test >10, there is significant heterogeneity among the trials for the outcome of re-bleeding. However, with a large number of studies the *Q*-test can be significant even when heterogeneity is not a problem; this is suggested by the fact that I^2 is below 50%.

Visual inspection of the funnel plot for re-bleeding showed slight asymmetry, suggesting the possibility of publication bias (small negative studies missing from the bottom right of the graph). Nevertheless, this was not confirmed by Egger's test, which showed no evidence of publication bias: coefficient for bias –0.342, 90% CI –0.796 to 0.112; $p = 0.21$.

As mentioned in the section 'Methodological quality of included studies' (p. 26), three of the trials[67,76,86] did not report re-bleeding rates for the first 3 days but reported re-bleeding rates for the period from day 4 onwards. Since there was a

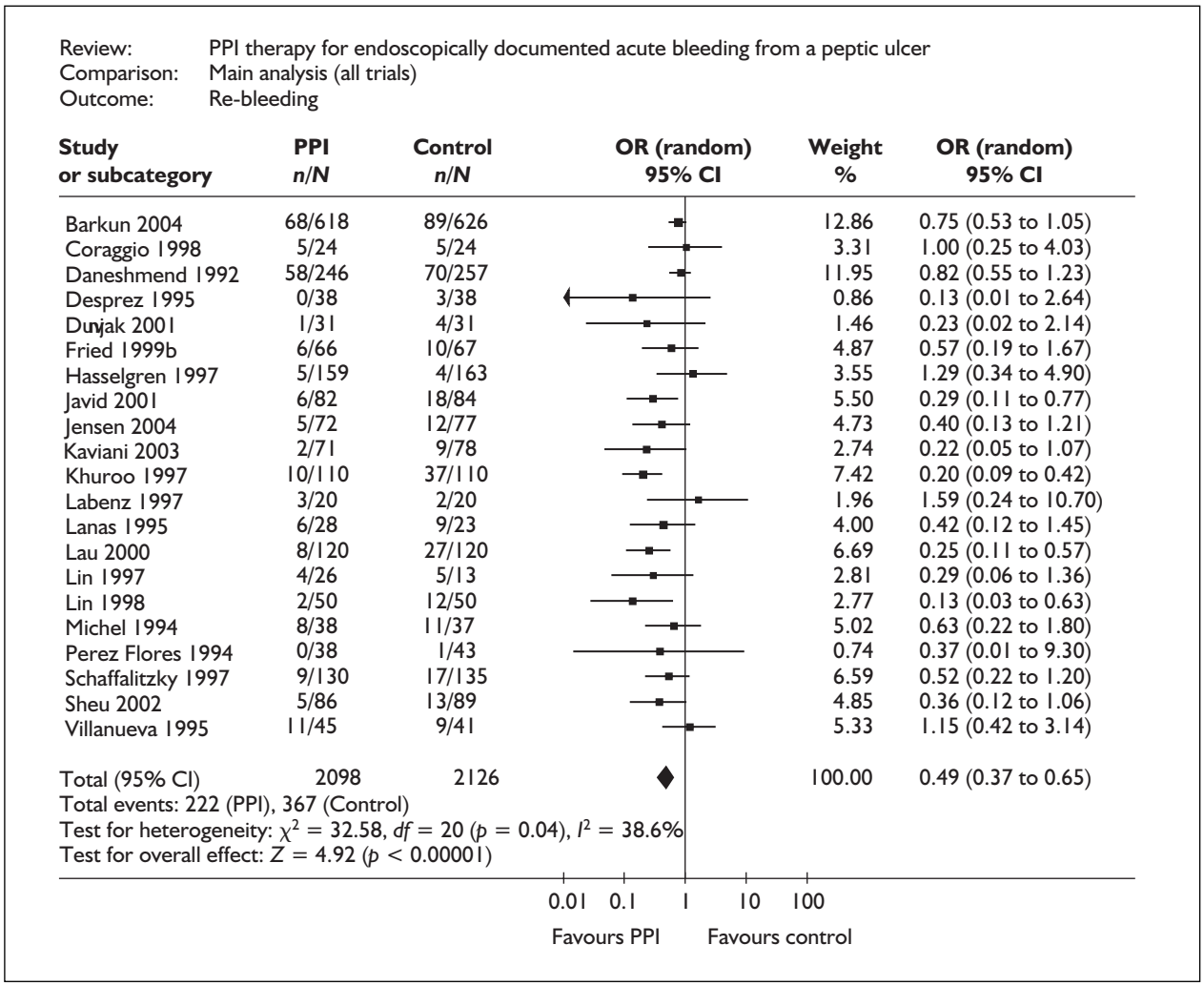

FIGURE 2 *Re-bleeding with PPI versus H_2RA or placebo for endoscopically documented acute bleeding from a peptic ulcer*

concern that this could bias the results of the analysis, we performed a *post hoc* sensitivity analysis by excluding these three trials; heterogeneity remained statistically significant ($p = 0.03$, $I^2 = 43.6\%$) and the overall effect did not change (OR 0.47, 95% CI random effects 0.34 to 0.64).

We aimed to investigate the potential causes of the statistical heterogeneity among the 21 trials reporting re-bleeding rates. As described in detail in the sections 'Description of studies' (p. 15) and 'Methodological quality of included studies' (p. 26), there was considerable clinical heterogeneity among the trials; there were differences among trials regarding the baseline SRH, the application of EHT, the dose and route of administration of PPI and the type of control treatment used (H_2RA or placebo). All of the above were addressed by predetermined subgroup analyses as reported below. Of these, only the subgroup analyses according to route of administration of PPI (oral or intravenous) and according to geographical location of trials resulted in two statistically homogeneous groups of trials regarding re-bleeding.

Furthermore, we assessed by meta-regression the influence of predefined study characteristics on the effect of treatment on re-bleeding (see Chapter 3). The only study characteristic that was found to be significantly associated with the treatment effect (log OR for re-bleeding) was the geographical location of the study. Treatment effect was higher in favour of PPI in Asian studies compared with studies that had been conducted elsewhere: coefficient –1.14, 95% CI –1.59 to –0.69; constant 0.29 (results expressed in logarithmic form); $p = 0.001$; 19 studies analysed.

Seven trials reported data separately, or exclusively, for re-bleeding within 3 days.[68,70,71,79,81,82,87] These

included a total of 2010 patients: 997 on PPI treatment and 1013 on control. There was significant heterogeneity among the trials ($p = 0.03$, $I^2 = 57.2\%$). Pooled re-bleeding rates within 3 days were 8.3% for PPI treatment and 14.2% for control. There was a highly significant difference in 3-day re-bleeding rates in favour of PPI treatment compared with control (OR 0.39, 95% CI random effects 0.19 to 0.80; NNT 13, 95% CI 8 to 33. This result remained statistically significant in favour of PPI treatment when, by sensitivity analysis, any one of the included studies was removed.

Persistent bleeding

Six trials[9,67,72–74,85] reported separately, or exclusively, the rates of persistent bleeding (continuing bleeding in patients admitted to the trial with active bleeding or with failed or unattempted EHT) as opposed to re-bleeding rates (recurrence of bleeding following endoscopically confirmed haemostasis, whether spontaneous or resulting from EHT). These six trials included a total of 509 patients: 250 on PPI treatment and 259 on control. There was significant heterogeneity among the trials ($p = 0.04$, $I^2 = 56.5\%$). Pooled rates for persistent bleeding were 6.8% for PPI treatment and 16.2% for control treatment. Persistent bleeding was significantly less common on PPI treatment than on control treatment (OR 0.29, 95% CI random effects 0.09 to 0.89). The above result was not robust to the exclusion of individual trials: exclusion of any of three trials[72,73,85] rendered the results non-significant. Consequently, the pooled results for persistent bleeding should be regarded with caution.

Surgical intervention

Nineteen trials reported rates of surgical intervention.[9,67,70–78,80–82,84–88] One trial offered the choice of either surgery or angiographic therapy and reported the total number of patients who received either of the two interventions;[71] we used these data for the surgical intervention analysis. These 19 trials comprised a total of 4034 patients: 1995 on PPI treatment and 2039 on control. Trials were statistically homogeneous (test for heterogeneity: $p = 0.45$, $I^2 = 0.1\%$). Pooled rates of surgical intervention were 6.1% for PPI treatment and 9.3% for control. Surgical interventions were significantly less common with PPI treatment than with control treatment (OR 0.61, 95% CI 0.48 to 0.78; NNT 33, 95% CI 20 to 50); this result remained significant when, by sensitivity analysis, any one of the included trials was removed.

Visual inspection of the funnel plot for surgical intervention showed asymmetry, suggesting the possibility of publication bias. Egger's test confirmed the presence of publication bias: coefficient for bias –0.920, 90% CI –1.727 to –0.113; $p = 0.06$.

Meta-regression was used to assess the influence of predefined study characteristics on the effect of treatment on surgical intervention rates. The only study characteristic found to be significantly associated with the treatment effect (log OR for surgical intervention) was again geographical location of the study; treatment effect was higher in favour of PPI treatment in studies that had been conducted in Asia compared with studies that had been conducted elsewhere: coefficient –0.96, 95% CI –1.63 to –0.29; constant 0.28 (results expressed in logarithmic form); $p = 0.01$; 17 studies analysed.

Further EHT post-randomisation

Seven trials (comprising a total of 939 patients: 468 on PPI treatment and 471 on control) allowed for the calculation of the number of patients who received further EHT post-randomisation.[74,78,80–82,86,88] Heterogeneity among these trials was not statistically significant ($p = 0.25$; $I^2 = 23.4\%$). Pooled rates were 5.5% for PPI treatment and 15.7% for control. Significantly fewer patients received further EHT post-randomisation with PPI treatment than with control treatment (OR 0.32, 95% CI 0.20 to 0.51; NNT 10, 95% CI 7 to 17); this result remained significant when any one of the studies was removed.

Adverse outcomes

Only three trials allowed for the calculation of patients with adverse outcomes (defined as the number of patients who had one or more of re-bleeding, repeat EHT, surgery or death).[72,76,88] These trials comprised a total of 447 patients (223 patients on PPI treatment and 224 on control). There was no significant heterogeneity among these trials ($p = 0.16$, $I^2 = 44.6\%$). Pooled rates were 11.2% for PPI treatment and 19.6% for control. There was a significant difference in rates of adverse outcomes in favour of PPI treatment compared with control treatment (OR 0.49, 95% CI 0.28 to 0.84; NNT 11, 95% CI 7 to 50); this result became non-significant when, by sensitivity analysis, one of the included studies[76] was removed.

Blood transfusion requirements

Mean (and SD) number of units of blood transfused per treatment group were reported in eight trials.[9,74,76,78,80,81,85,88] These trials comprised a total of 1197 patients: 595 on PPI treatment and

602 on control. There was statistically significant heterogeneity among these trials ($p < 0.00001$, $I^2 = 80.5\%$). Transfusion requirements in mean (SD) units of blood ranged from 1.00 (1.60)[85] to 2.70 (2.50)[81] for PPI treatment and from 1.30 (2.00)[85] to 4.10 (2.10)[9] for control treatment. Transfusion requirements were reduced with PPI treatment compared with control treatment, a difference of marginal statistical significance (WMD –0.6 units of blood, 95% CI random effects –1.1 to 0.0; test for overall effect $p = 0.05$). This result was not robust to the exclusion of individual trials; by sensitivity analysis, the effect became non-significant when any one of five trials was excluded. For this reason, and also because the precise criteria for administering blood transfusion were not given for three trials,[9,74,85] the strength of conclusion on the pooled effect of PPI treatment is limited.

We produced a funnel plot by plotting the WMD against the standard error of WMD. The plot was asymmetric. However, there was no evidence of publication bias (missing of small trials with negative effects) given that no trials were apparently missing from the right lower area of the graph. The asymmetry resulted from the trial of Khuroo and colleagues;[9] when this trial was removed, and not when any other trial was removed, the plot became symmetrical.

Length of hospital stay

Seven trials reported mean (and SD) number of days of hospital stay.[9,74,77,78,80,85,88] However, none of these had specified if the length of stay terminated by death was separated from length of stay ended by discharge. These trials included a total of 801 patients: 398 on PPI treatment and 403 on control. There was statistically significant heterogeneity among the trials ($p = 0.07$, $I^2 = 48.7\%$). A funnel plot showed no asymmetry, suggesting no publication bias. Length of hospital stay in mean (SD) days ranged from 2.60 (1.20)[78] to 14.00 (13.00)[88] for PPI treatment and from 3.10 (1.60)[78] to 15.00 (14.00)[88] for control treatment. The WMD for each of the seven trials was in favour of PPI treatment, although statistical significance was reached only in the three larger trials.[9,77,78] The pooled effect is not being reported, as it was agreed that a meta-analysis of this outcome would not have been appropriate for the following reasons. The statistical heterogeneity could not be adequately explained and, more importantly, there were serious concerns about the definition of this outcome (if patients who died were excluded, or time to death was included as though it was a length of stay then results could be misleading).

As the effect of treatment would be expected to be attenuated in patients with in-hospital onset of bleeding, we also performed a sensitivity analysis by excluding the two trials that included such patients;[76,88] the pooled result was unaffected (WMD = –1.1 days, 95% CI –1.6 to –0.6).

A further three trials[81–83] reported data on length of hospital stay although the SD could not be calculated. None of these trials specified if length of hospital stay ended by death was separated from length of stay ended by discharge. Of these, the only statistically significant result regarding length of hospital stay was reported by one trial;[81] this regarded patients admitted with bleeding (but not patients in whom bleeding developed in hospital), in whom PPI treatment was associated with shorter hospital stay.

Lau and colleagues[81] provided additional unpublished data for length of hospital stay (mean and SD of days) separately for patients successfully discharged and for patients who died in hospital; patients successfully discharged stayed in hospital for a mean of 14.14 days for the PPI group and 17.22 days for the control group; WMD = –3.1 days, 95% CI –5.0 to –1.1.

Overall, a conclusion on the effect of PPI treatment on the length of hospital stay could not be reached safely.

Adverse reactions to active and control treatment

Only 10 of the trials[70,71,75,76,79,81,84,86,88,89] reported data on adverse reactions to active and control treatment. Adverse reactions were actively sought, with the exception of four trials that did not state this clearly.[71,81,88,89] Two of the trials reported in detail the rigorous methods used to seek adverse reactions.[76,86] Overall, the reported information was not adequate for a formal meta-analysis for adverse events.

Of the 10 trials, one reported no adverse reactions to intravenous omeprazole (active treatment) or to intravenous ranitidine (control treatment).[88]

Lau and colleagues reported no adverse reactions to intravenous omeprazole (active treatment) or to placebo (control treatment).[81]

Daneshmend and colleagues reported that there was no evidence of any toxic effect of intravenous omeprazole (control treatment was placebo).[75]

Xuan reported no adverse events to intravenous omeprazole (active treatment) or to intravenous famotidine (control treatment).[89]

Labenz and colleagues reported that there were no generalised adverse reactions to intravenous omeprazole (active treatment) or to intravenous ranitidine (control treatment), but mild thrombophlebitis was noted at the site of drug infusion in two out of 20 patients on omeprazole and in six out of 20 on ranitidine (not statistically significant).[79]

Michel and colleagues found the following adverse reactions on oral lansoprazole (active treatment): headache ($n = 2$); confusion ($n = 1$); palpitation ($n = 1$); tachycardia ($n = 1$); leg pain ($n = 1$); and the following on oral ranitidine (control treatment): headache ($n = 1$); dyspnoea ($n = 1$); confusion ($n = 1$); back pain ($n = 1$); abdominal pain ($n = 1$); myalgia ($n = 1$); fever ($n = 1$).[84]

Jensen and colleagues reported that serious adverse events were more common in the control (intravenous ranitidine) group ($n = 19$; 24.7%) than in the PPI (intravenous pantoprazole) group ($n = 9$; 12.5%); $p = 0.063$. No further details were provided (the trial has been published only in abstract form), apart from the statement that no eye events occurred.[71]

Barkun and colleagues (published and unpublished data) reported adverse events in detail. Approximately 40% of the participants reported adverse events. The most common were headache, insomnia, hypertension, constipation and anxiety. Most were considered to be unrelated to the study medication. Significantly more patients in the intravenous ranitidine ($n = 19$) than in the intravenous pantoprazole group ($n = 7$) discontinued the study prematurely due to adverse events ($p = 0.03$); however, the investigator assessed most cases as "unrelated" to the study medication. The most common adverse events related to study medication were injection site reactions, primarily mild to moderate thrombophlebitis, which occurred in 5.3% of patients in the pantoprazole group and 0.5% in the ranitidine group. Only one case was rated as severe. The overall rate of serious adverse events was similar in both treatment groups (pantoprazole 7.5% and ranitidine 10.8%).[70]

The remaining two trials[76,86] reported very detailed descriptions of adverse events per treatment group. These trials had identical protocols (apart from the fact that Hasselgren and colleagues[76] recruited only patients older than 60 years of age, whereas Schaffalitzky and colleagues[86] recruited only patients with clinical signs of haemodynamic instability or severe blood loss) and were conducted in parallel to each other. Both trials compared intravenous omeprazole with intravenous placebo (mannitol). Of note, recruitment stopped prematurely in both trials because interim analysis revealed significantly higher mortality in the PPI treatment group when outcomes of the two trials were pooled together; see also the section 'Stated causes of death by treatment group' (p. 26) and *Table 5*. Serious adverse events per treatment group, pooled together for the two trials, are presented in *Table 5*. For each individual trial there was no statistically significant difference in the type of serious adverse event. A statistically significant difference was revealed when both trials were pooled together: cerebrovascular accidents (fatal and non-fatal) were more common [Fisher's exact test (two-tailed) $p = 0.01$] in the PPI group (six events in 289 patients) than in the control group (no events in 298 patients). In each of the two trials non-serious adverse events were equally distributed between the treatment groups (see *Table 5*).

TABLE 5 *Pooled serious adverse effects for the Schaffalitzky[86] and Hasselgren[76] studies (number of patients)*

Type of event	PPI (fatal)	PPI (non-fatal)	Placebo (fatal)	Placebo (non-fatal)
Myocardial infarction	5	–	–	3
Cardiac failure	2	2	3	5
Cerebrovascular accident	5	1	–	–
Pulmonary embolism	2	–	2	–
Cancer	–	3	–	2
GI bleeding/perforation	3	8	4	9
Miscellaneous	1	10	1	11
Total	18	24	10	30

TABLE 6 *Pooled summary data for trials of PPI treatment in ulcer bleeding: subgroup analyses according to concealment of allocation, geographical location of the trials, type of control treatment, route of PPI administration and dose of PPI*

Subgroup analyses and outcomes	Pooled rate (%)		Heterogeneity	OR (95% CI)
	PPI	Control		
Adequate concealment of allocation (12 trials; 3483 patients)				
Mortality	3.9	3.8	Yes	0.89 (0.47 to 1.68)
Re-bleeding	10.9	17.6	Yes	0.46 (0.31 to 0.67)
Surgical intervention	5.9	8.7	No	0.64 (0.49 to 0.84)
Trials conducted in Asia (8 trials; 1153 patients)				
Mortality	1.5	4.4	No	0.35 (0.16 to 0.74)
Re-bleeding	6.8	22.2	No	0.24 (0.16 to 0.36)
Surgical intervention	2.9	9.2	No	0.29 (0.16 to 0.53)
Trials conducted elsewhere (16 trials; 3219 patients)				
Mortality	4.8	3.6	No	1.36 (0.94 to 1.96)
Re-bleeding	11.9	15.5	No	0.72 (0.58 to 0.89)
Surgical intervention	7.2	9.4	No	0.73 (0.55 to 0.95)
H_2RA as control treatment (13 trials; 2507 patients)				
Mortality	2.5	3.0	No	0.82 (0.48 to 1.41)
Re-bleeding	10.5	15.7	No	0.63 (0.49 to 0.81)
Surgical intervention	3.9	5.3	No	0.73 (0.47 to 1.13)
Placebo as control treatment (7 trials; 1685 patients)				
Mortality	5.7	4.9	Yes	0.96 (0.43 to 2.15)
Re-bleeding	10.7	19.2	Yes	0.41 (0.23 to 0.72)
Surgical intervention	8.7	13.5	Yes	0.52 (0.32 to 0.84)
I.v. PPI versus placebo or H_2RA (19 trials; 3714 patients)				
Mortality	4.2	3.9	No	1.08 (0.77 to 1.52)
Re-bleeding	10.8	16.0	No	0.62 (0.50 to 0.75)
Surgical intervention	6.0	8.3	No	0.69 (0.52 to 0.91)
Oral PPI treatment versus placebo or H_2RA (5 trials; 658 patients)				
Mortality	2.5	3.6	No	0.67 (0.28 to 1.64)
Re-bleeding	9.5	24.0	No	0.32 (0.20 to 0.50)
Surgical intervention	6.5	14.4	No	0.38 (0.22 to 0.66)
'High-dose' i.v. PPI[a] versus placebo or H_2RA (6 trials; 2320 patients)				
Mortality	3.2	3.6	Yes	0.82 (0.33 to 2.06)
Re-bleeding	8.4	13.7	Yes	0.47 (0.28 to 0.82)
Surgical intervention	3.1	5.0	No	0.61 (0.40 to 0.93)
PPI (oral or i.v.) in doses other than 'high-dose' versus placebo or H_2RA (18 trials; 2320 patients)				
Mortality	4.8	4.0	No	1.22 (0.77 to 1.94)
Re-bleeding	13.2	21.6	No	0.53 (0.41 to 0.68)
Surgical intervention	10.0	15.0	No	0.61 (0.45 to 0.82)

[a] 'High dose' i.v. PPI = 80 mg bolus i.v., followed by 8 mg/h continuous i.v. infusion for 72 hours.

Subgroup analyses

The effect of trial characteristics on mortality and re-bleeding and surgical intervention rates was assessed with a series of predetermined subgroup analyses (in addition to meta-regression analyses presented above) (*Tables 6–8*).

In brief, the subgroup analyses showed no evidence suggesting that the effect of PPI treatment on mortality and re-bleeding was dependent on study quality, route of PPI administration (oral or intravenous: *Figures 3* and *4*), type of control treatment (H_2RA or placebo), choice of PPI (omeprazole, pantoprazole or lansoprazole) or application of initial endoscopic haemostatic treatment. PPIs significantly reduced surgery compared with placebo but not when compared with H_2RA. There was no evidence to suggest that study quality, route of PPI administration, choice of PPI or application of initial endoscopic haemostatic treatment influenced results on surgery.

TABLE 7 *Pooled summary data for trials of PPI treatment in ulcer bleeding: subgroup analyses according to administration of pre-randomisation EHT and dose of PPI*

Subgroup analyses and outcomes	Pooled rate (%)		Heterogeneity	OR (95% CI)
	PPI	Control		
Routine prerandomisation EHT (15 trials; 3245 patients)				
Mortality	3.0	3.3	No	0.89 (0.59 to 1.34)
Re-bleeding	9.4	14.7	No	0.60 (0.48 to 0.74)
Surgical intervention	3.9	6.2	No	0.60 (0.43 to 0.85)
Without routine prerandomisation EHT (8 trials; 1127 patients)				
Mortality	6.6	5.3	No	1.25 (0.75 to 2.09)
Re-bleeding	16.0	25.8	Yes	0.38 (0.18 to 0.81)
Surgical intervention	12.4	18.4	No	0.62 (0.44 to 0.88)
Routine prerandomisation EHT and use of 'high-dose' i.v. PPI[a] treatment (6 trials; 2320 patients)				
Mortality	3.2	3.6	Yes	0.82 (0.33 to 2.06)
Re-bleeding	8.4	13.7	Yes	0.47 (0.28 to 0.82)
Surgical intervention	3.1	5.0	No	0.61 (0.40 to 0.93)
Routine prerandomisation EHT and use of lower dose i.v. or oral PPI treatment (9 trials; 925 patients)				
Mortality	2.4	2.4	No	1.00 (0.42 to 2.35)
Re-bleeding	10.2	17.2	No	0.52 (0.35 to 0.78)
Surgical intervention	6.6	9.9	No	0.59 (0.33 to 1.05)

[a] 'High-dose' i.v. PPI = 80 mg bolus i.v., followed by 8 mg/h continuous i.v. infusion for 72 hours.

TABLE 8 *Pooled summary data for trials of PPI treatment in ulcer bleeding: subgroup analyses according to prerandomisation endoscopic findings*

Subgroup analyses and outcomes	Pooled rate (%)		Heterogeneity	OR (95% CI)
	PPI	Control		
Prerandomisation endoscopic findings of active bleeding or NBVV (12 trials)				
Mortality (2102 patients)	1.8	3.6	No	0.53 (0.31 to 0.91)
Re-bleeding (2057 patients)	10.8	18.3	Yes	0.40 (0.24 to 0.67)
Surgical intervention (2184 patients)	3.5	6.4	No	0.50 (0.33 to 0.77)
Prerandomisation endoscopic findings of active bleeding or NBVV; routine prerandomisation EHT (7 trials)				
Mortality (1923 patients)	1.8	3.3	No	0.54 (0.30 to 0.96)
Re-bleeding (1923 patients)	10.2	16.5	Yes	0.43 (0.23 to 0.80)
Surgical intervention (1923 patients)	2.8	3.9	No	0.68 (0.41 to 1.14)
Prerandomisation endoscopic findings of active bleeding or NBVV; without routine prerandomisation EHT (5 trials)				
Mortality (179 patients)	3.5	6.5	No	0.51 (0.12 to 2.12)
Re-bleeding (134 patients)	19.4	46.8	No	0.29 (0.13 to 0.63)
Surgical intervention (261 patients)	8.7	24.6	No	0.27 (0.12 to 0.57)

PPI treatment appeared more efficacious in studies conducted in Asia compared with studies conducted elsewhere. Mortality was reduced only in Asian studies; reductions in re-bleeding and surgery were quantitatively greater in Asian studies.

Among patients with high-risk endoscopic findings (i.e. spurting bleeding, oozing of blood or an NBVV), PPI treatment reduced all three main outcomes, namely mortality, re-bleeding and surgery.

Post hoc analyses

We performed additional analyses in order to estimate specific probabilities required for the cost-effectiveness model (Chapter 6).

For RR of re-bleeding and death with oral PPI treatment (initiated after endoscopy) versus

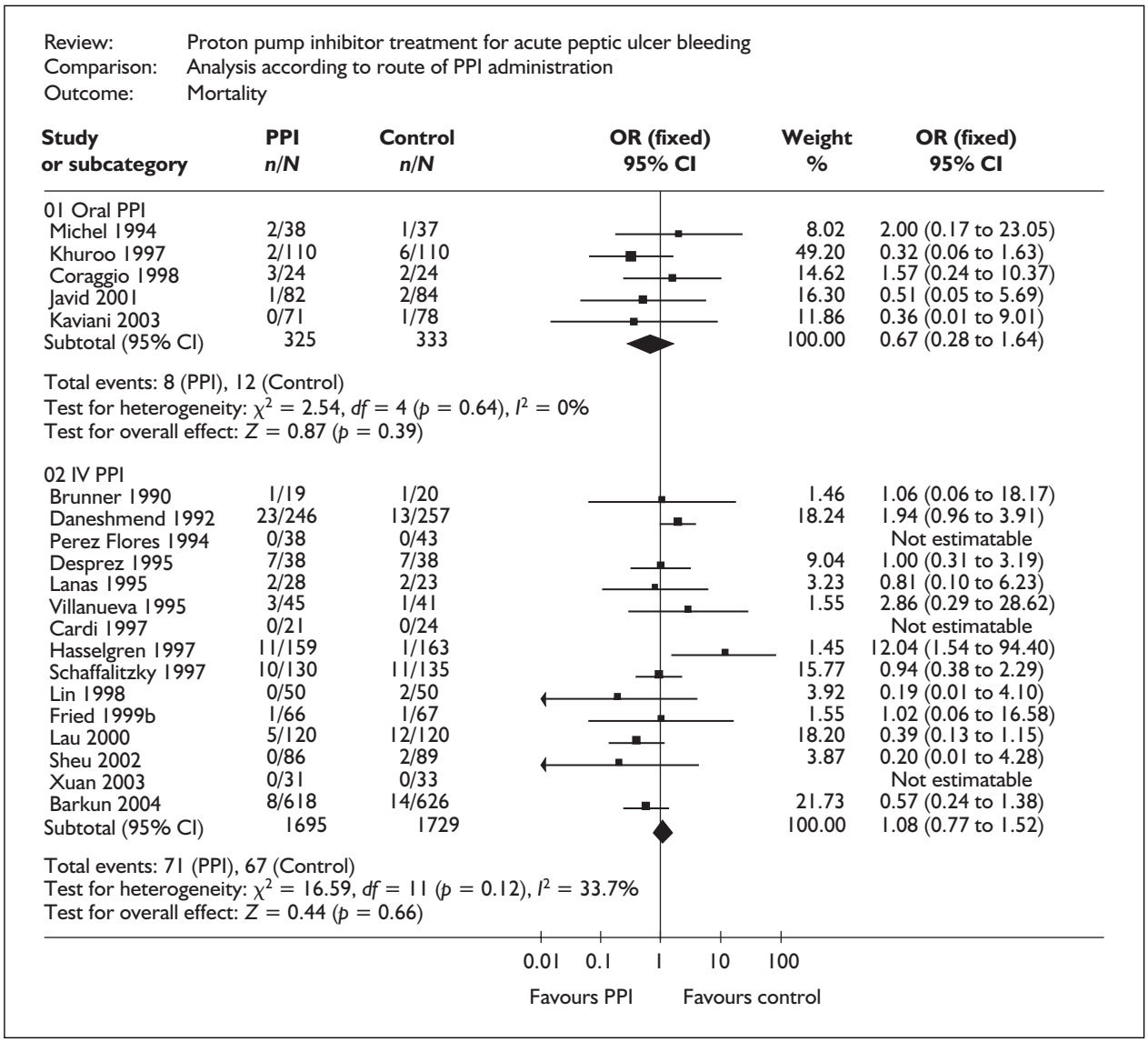

FIGURE 3 *Mortality with PPI versus H_2RA or placebo for endoscopically documented acute bleeding from a peptic ulcer: subgroup analysis according to route of PPI administration*

placebo in patients with endoscopically documented PU bleeding, three trials provided such information[9,77,78] comprising a total of 555 patients. Oral PPI treatment post-endoscopy significantly reduced re-bleeding (RR 0.29, 95% CI 0.18 to 0.47), but there was no evidence of an effect on mortality (RR 0.38, 95% CI 0.11 to 1.26).

For RR of re-bleeding and death with intravenous PPI treatment (initiated after endoscopy) versus placebo in patients with endoscopically documented PU bleeding, three trials provided such information[76,81,86] comprising a total of 827 patients. There was no evidence of an effect on mortality (RR 1.25, 95% CI 0.30 to 5.19, random effects model used due to significant heterogeneity, $p < 0.01$). Intravenous PPI treatment post-endoscopy significantly reduced re-bleeding (RR 0.47, 95% CI 0.29 to 0.76) when all three trials were pooled together. However, two of the trials[76,86] reported re-bleeding rates only for the period from days 4 to 21 post-randomisation, hence re-bleeding data for the critical first 72 hours were missing. Therefore, a safer estimation of the risk for re-bleeding for post-endoscopy intravenous PPI treatment can be obtained if these two trials are excluded from the analysis. This means that the above re-bleeding risk will be estimated from the results of the third trial[81] that reported re-bleeding rates for the period from day 0 to 21 (RR 0.30, 95% CI 0.14 to 0.63).

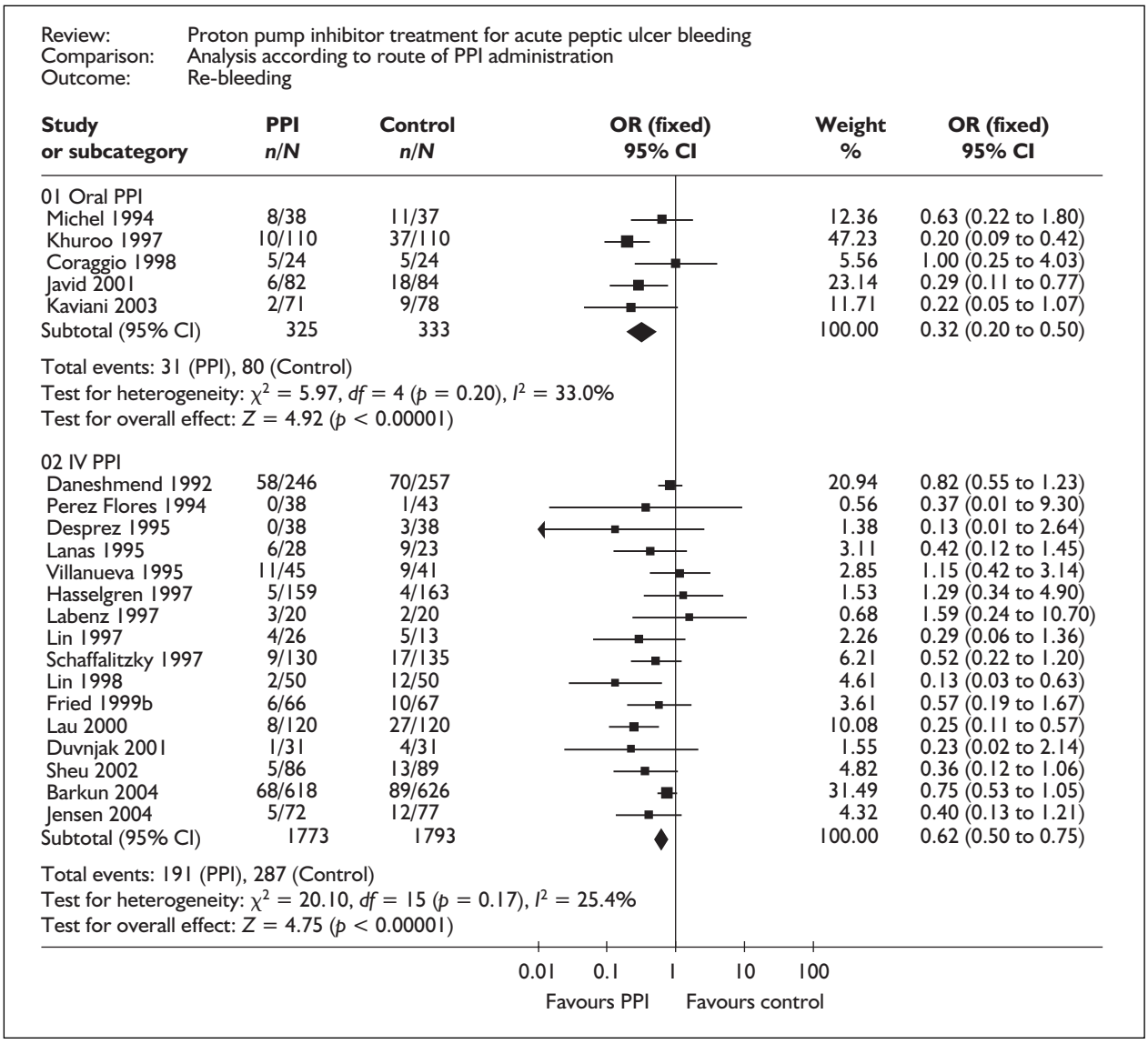

FIGURE 4 *Re-bleeding with PPI versus H_2RA or placebo for endoscopically documented acute bleeding from a peptic ulcer: subgroup analysis according to route of PPI administration*

Conclusion

PPI treatment has not been shown to reduce all-cause mortality following PU bleeding except when Asian studies were examined in isolation or when the analysis was confined to patients with high-risk endoscopic stigmata. It is, however, a remarkably consistent observation in subgroup analyses that PPI therapy reduces re-bleeding rates, whether only high-quality trials are examined in isolation, whether the PPI is administered orally or intravenously, and whether or not EHT is first administered. In general, the need for surgical intervention is also reduced by PPI treatment.

Chapter 5

What is the efficacy of PPI therapy initiated prior to endoscopy in reducing mortality in unselected patients with acute upper gastrointestinal bleeding?

Description of studies

Results of search strategy

The search strategy in the CCTR, MEDLINE, EMBASE and CINAHL databases identified 94 articles. 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 CC UGPD Group, experts in the field of gastroenterology and pharmaceutical companies marketing PPIs.

Of the 94 articles, 58 were excluded as they were clearly not relevant. The main reason for exclusion was not being an RCT. We retrieved the full articles for the remaining 36 trials and obtained translations for those published in languages other than English. Of these 36 trials, 31 did not meet the eligibility criteria and were excluded for the following reasons: randomisation had taken place post-endoscopy or the study had been restricted to PU bleeding only (*Table 9*).

The remaining five trials were included in our systematic review[75,100,116,119,120] (*Table 10*). Of these, four were published as full peer-reviewed publications[75,100,116,119] and one was published as an abstract only.[120] Four of the trials were published in English and one in Turkish.[119] We were provided with additional information from the authors of two of the trials.[119,120]

Design

All included studies were RCTs with a parallel group design. Other aspects of trial design are discussed in the section 'Methodological quality of included studies' (p. 26).

Setting

Three of the studies had been conducted in single centre[116,119,120] and two had been conducted in two centres each.[75,100] All studies took place in a hospital setting. Three trials had been conducted in Europe[75,100,116] and two in Asia[116,120] (the trial by Hulagu and colleagues[119] had been conducted in the Asian part of Turkey).

Participants

All trials included patients with clinical signs of UGI bleeding. Characteristics of the participants are given in *Table 10*.

The number of participants per trial ranged from 58[119] to 1147.[75] In one trial,[100] we included in our analysis only two of the four treatment groups, namely the PPI-only group and the placebo group. One trial[120] was included only in the subgroup analysis for patients with bleeding from PU, and was not included in the main qualitative analysis for all patients with UGI bleeding. This was because the trial (published as an abstract only) reported results only for 222 patients with PU bleeding and not for all randomised patients with all sources of UGI bleeding (n = 369).

The four trials that were included in the main analysis[75,100,116,119] comprised a total of 1512 patients. Of these, 760 were randomised to PPI treatment and 752 to control treatment.
The mean number of participants of these four trials was 378.

None of the studies was confined to patients with PU bleeding, although one reported outcomes only for patients with PU bleeding.[120] The percentages of patients with PU bleeding per trial were as follows: 43.9%,[75] 42.4%,[100] 75.5%,[116] 60.1%[120] and 77.6%.[119]

Two of the studies did not exclude patients with bleeding from oesophageal varices. Such patients comprised 2.5% of total participants in one trial[75] and 3.9% of the total participants in another trial.[100] One other trial avoided the inclusion of such patients by excluding patients with existing hepatic insufficiency.[116] Hulagu and colleagues did not state whether patients with variceal bleeding were deliberately excluded although, in the end, such patients were not present in the study.[119]

TABLE 9 *Characteristics of excluded studies: efficacy of PPI therapy initiated prior to endoscopy in unselected UGI bleeding*

Study	Reason for exclusion
Bai, 1995[121]	Restricted to patients with bleeding from PU and acute gastric mucosal lesions. Randomised after endoscopy
Barkun, 2004[70]	Randomised after endoscopy. Restricted to patients with PU-related bleeding
Brunner, 1990[72]	Randomised after endoscopy. Restricted to patients with PU-related bleeding
Chu, 1993[92]	Restricted to PU bleeding patients only and randomisation after endoscopy
Colin, 1993[122]	Not RCT
Costamagna, 1998[123]	Randomised after endoscopy. Abstract publication. Interim analysis of 49 of 64 originally evaluable cases with endoscopically verified forest I or IIa lesions only
Desprez, 1995[67]	Randomisation timing not clear; probably after endoscopy. Patients with bleeding PU
Dovas, 1992[124]	Unable to obtain copy of publication
Duvnjak, 2001[68]	Randomised after endoscopy. Restricted to patients with bleeding PU
Fasseas, 2001[95]	Restricted to endoscopically verified patients and only GUs, DUs and erosions were included
Felder, 1998[125]	Restricted to PU bleeding patients only
Fried, 1999[69]	Randomised after endoscopy. Restricted to PU bleeding patients only
Gao, 1995[126]	Unclear when randomisation took place
Goletti, 1994[98]	Control group not being either placebo or H_2RA alone; compared omeprazole alone versus the combination of ranitidine and EHT. Restricted to patients with ulcers or haemorrhagic gastritis. Randomisation post-endoscopic diagnosis
Hulagu, 1994	Abstract publication (Hulagu S, Demirturk L, Gul S, Yazgan Y, Altin M, Danaci M. The effect of omeprazole or ranitidine intravenous on upper gastrointestinal bleeding. *Endoscopy* 1994;**26**:404); the trial was subsequently published in full (Hulagu, 1995[119])
Javid, 2001[77]	Randomised after endoscopy. patients with bleeding PU
Liu, 2002[127]	Randomised after endoscopy. Restricted to DU patients
Maculotti, 1995[104]	Designed to assess healing rates. Not reporting any of the outcomes predetermined in this systematic review. Randomisation post-endoscopy
Michel, 1994[84]	Timing of randomisation not clear. Restricted to patients with bleeding PU
Munkel, 1997[128]	Restricted to PU bleeding patients only. Randomisation post-endoscopy
Nehme, 2001[129]	Randomised after endoscopy
Orti, 1995[106]	Restricted to patients suspected to have bleeding from peptic origin. It was not clear from the paper if the authors ascertained this before randomisation. Communication to obtain further details are ongoing
Perez Flores, 1994[85]	Timing of randomisation not clear (most probably after endoscopy). Restricted to patients with bleeding PU
Savides, 2001[130]	Randomised after endoscopy, restricted to PU bleeding
Scheurlen, 2000[131]	Restricted to PU bleeding patients only, not RCT
Schonekas, 1999[109]	Restricted to PU bleeding patients only; control group not being either placebo or H_2RA alone; compared two different regimens of PPI
Srinath, 1997[132]	Not an RCT. This article was a comment on another RCT[9]
Udd, 2001[114]	Control group not being either placebo or H_2RA alone; compared two i.v. regimens of omeprazole among themselves
Uribarrena, 1994[115]	Selected patients with bleeding from GU, DU, erosions and peptic oesophagitis only. Bleeding from non-peptic sources were excluded from the analysis
Wu, 2001[133]	Unable to obtain copy of publication
Xuan, 2003[89]	Randomisation after endoscopy

TABLE 10 *Characteristics of included studies: efficacy of PPI therapy initiated prior to endoscopy in unselected UGI bleeding*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Daneshmend, 1992[75]	Large multicentre (two centres) double-blind RCT	Country: UK. Included 1147 patients (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 inpatients	1. Omeprazole 80 mg i.v. immediately, then 3 doses of 40 mg i.v. at 8-hourly intervals, then 40 mg orally 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 patients)	40-day mortality; re-bleeding; surgery; SRH at index endoscopy; number of patients requiring blood transfusion. First three outcomes also reported by PU site	Only a few of the high-risk patients with PU received initial endoscopic treatment. Timing of assessment of re-bleeding and surgery not clear	A
Hawkey, 2001[100]	Multicentre (two centres) double-blind RCT	Country: UK. 414 patients 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)	1. Lansoprazole 60 mg orally (stat), followed by 30 mg plus dummy medication four times daily for 4 days. 2. Placebo – double dummy technique. 3. Tranexamic acid 2 g orally (stat), followed by 1 g orally plus dummy medication four times daily for 4 days. 4. Tranexamic acid and lansoprazole – both active drugs as above for 4 days. Post-intervention drug treatment not mentioned. Initial EHT offered for patients with active bleeding	30-day mortality; 30-day surgery; re-bleeding (timing unclear); SRH at index endoscopy; number of patients requiring blood transfusion	For the current meta-analysis we included only group 1 (lasoprazole alone) as active treatment group and group 2 (placebo) as control group. Patients that received tranexamic acid or the combination of PPI and tranexamic acid were not included. Timing of assessment of re-bleeding not clear	B

continued

TABLE 10 *Characteristics of included studies: efficacy of PPI therapy initiated prior to endoscopy in unselected UGI bleeding (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Hulagu, 1995[119]	Single-centre, open RCT	Country: Turkey. Included 58 patients (30 omeprazole group, 28 control treatment group)	1. Omeprazole 80 mg i.v. as soon as possible after admission, followed by 40 mg i.v. once a day and 100 mg i.v. 3 times per day for 6 days. Omeprazole 20 mg once per day at end of 4 weeks. 2. Rantidine 100 mg as soon as possible after admission, followed by 100 mg i.v. 3 times per day for 6 days. Famotidine 40 mg once per day at end of 4 weeks	Mortality; re-bleeding; SRH at index endoscopy; number of patients requiring blood transfusion		B
Lau, 2005[120]	Double-blind, placebo-controlled RCT	Country: China. Randomised 369 patients (omeprazole 179, placebo 190). Reported outcomes only for the patients with bleeding PU (110 omeprazole, 112 placebo)	1. Omeprazole 80 mg i.v. bolus followed by i.v. infusion 8 mg/h) 2. Equivalent placebo. After endoscopic haemostasis patients received omeprazole i.v. infusion 8 mg/h for 72 hours. Post-endoscopy pharmacological treatment for patients not requiring EHT was not stated	30-day mortality; surgery; 30-day re-bleeding; SRH at index endoscopy; number of patients requiring endoscopic treatment; blood transfusion requirements; length of hospital stay	This trial was included only into the subgroup analysis for patients with bleeding from PU	B
Wallner, 1996[116]	Single-centre, open RCT	Country: Poland. Included 102 patients (50 on PPI and 52 on placebo group). PU 75.5% of total; no patients with oesophageal varices (hepatic insufficiency was an exclusion criterion)	1. Omeprazole i.v. bolus delivery, dosing regime unclear: stated as "40 mg" or "80 mg" or "120 mg" (presumably representing total daily doses) 2. Ranitidine i.v. bolus delivery, dosing regime unclear: stated as "150 mg" or "200 mg" or "300–400 mg" (presumably representing total daily doses). Unclear if patients 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 EHT not mentioned	Mortality; surgery; SRH at index endoscopy; number of patients requiring blood transfusion. Timing of outcome assessment not clear	Timing of assessment of re-bleeding not clear. Initial EHT not mentioned. Dosing of pharmacological treatments not clear. Re-bleeding rates could be extracted because the study was designed to assess time needed for bleeding cessation	A

[a] Cochrane ranking: Grades A and B.

Lau and colleagues also did not mention whether patients with variceal bleeding were excluded, but reported data only for patients with PU bleeding.[120]

Interventions

Active treatment

Four trials used intravenous omeprazole as active treatment.[75,116,119,120] The fifth trial used oral lansoprazole.[100] None of the trials used a high-dose regimen as predefined in the methods of the review.

Control treatment

Three of the trials[75,100,120] used placebo as control treatment. Of these, one stated that placebo treatment consisted of intravenous mannitol.[75] Two trials compared active treatment with an H_2RA; Hulagu and colleagues[119] used intravenous ranitidine, followed by oral famotidine, whereas Wallner and colleagues[116] used intravenous ranitidine. Of note, Hawkey and colleagues[100] also randomised patients 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.

See also *Table 10* for details of interventions, including dose and duration.

Co-interventions

EHT was offered in selected patients in three of the trials. Lau and colleagues[120] treated endoscopically those patients with active bleeding, NBVV or adherent clots. Daneshmend and colleagues[75] applied EHT to a minority of high-risk patients (37 out of 164 with active bleeding or NBVV, i.e. 22.5%); Hawkey and colleagues[100] applied EHT only for active bleeding lesions, which amounted to 40% of all patients with SRH. The remaining two trials did not mention EHT.

Methodological quality of included studies

All five included trials were RCTs with a parallel group design.

Allocation concealment

According to the Cochrane Collaboration approach, methodological quality assessment had emphasis on allocation concealment. Two trials[75,116] had adequate concealment (Grade A) and three[100,119,120] had uncertain concealment (Grade B).

Blinding

Three trials were doubled blinded[75,100,120] one stated being unblinded[116] and the fifth[119] provided no information regarding blinding.

Baseline comparability of treatment groups

Overall, there was good baseline comparability for the four trials[75,100,116,119] that reported raw data and were also full publications.

The fifth trial,[120] which was published as an abstract only, did not report raw data, but stated having baseline comparability.

Presence of inclusion and exclusion criteria

All trials had well-defined inclusion criteria. Four trials also reported exclusion criteria in detail. The fifth trial, published as an abstract only,[120] did not specify any exclusion criteria.

Intervention described in detail

Four trials provided detailed description of the type of medication, route and method of administration, dose and duration of medications used in both study groups. The fifth trial[116] was unclear regarding the dosing of both PPI and control treatment.

Definition of outcomes

Among the most important outcomes of the review – mortality, surgery and re-bleeding – the last was the only outcome that was difficult to define.

Daneshmend and colleagues[75] defined re-bleeding 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 patients with suspected re-bleeding.

Hawkey and colleagues[100] defined re-bleeding as a combination of clinical signs and a drop in haemoglobin and/or endoscopic evidence of re-bleeding. However, repeat endoscopy was performed at the discretion of the managing team.

Hulagu and colleagues[119] did not define re-bleeding. Nevertheless, they did state that all patients were re-endoscoped 5 days following admission.

Wallner and colleagues[116] did not report re-bleeding 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 and colleagues[120] did not define re-bleeding.

Regarding the definition of hospital stay, two trials[71,114] reported data on hospital stay but did not distinguish between hospital stay ended by death and hospital stay ended by discharge.

Stated time for outcome assessment

Mortality

All trials reported mortality rates per treatment group. One trial[116] did not state time for assessment. The other four reported mortality at 40 days,[75] 30 days[100,120] and at both 6 and 30 days.[119]

Re-bleeding

Only one of the trials[119] clarified that re-bleeding was assessed at 6 and 30 days.

Surgery

Only one trial[100] reported time for surgery assessment, namely at 30 days.

SRH at index endoscopy

Timing of index endoscopy would have significantly affected this outcome. Of the four trials that reported proportion of patients per treatment group with SRH (as opposed to not having SRH), two[75,100] stated that index endoscopy took place within 24 hours from admission, one[116] stated that index endoscopy was performed within the first 24–48 hours after admission and one[120] did not state the timing of index endoscopy. The proportion of patients per treatment group with SRH could not be extracted from the trial by Hulagu and colleagues, who performed endoscopy within 24 hours of admission.[119]

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

Two trials[116,119] offered scheduled repeat endoscopy to all patients at 5 days and at 5–6 days, respectively. Two[75,100] offered the option of repeat endoscopy to patients with clinical suspicion of re-bleeding, although the exact criteria were not specified. Lau and colleagues[120] did not report indications for repeat endoscopy.

None of the trials reported indications for subsequent EHT.

Wallner and colleagues[116] stated that the indication for surgical treatment was ineffective conservative therapy or chronic ulceration with poor healing prognosis. Daneshmend and colleagues[75] stated that patients were cared for by the admitting medical team, who made decisions about blood transfusion and surgery. The other three trials did not state indications for surgery.

Within Hulagu and colleagues' study, transfusions were offered with the aim of keeping the haemoglobin at least 10 g/dl.[119] The remaining four trials did not clarify indications for blood transfusions.

Description of withdrawals and drop-outs and percentage of drop-outs

Three trials[75,100,116] described withdrawals and drop-outs in detail. Of these, Wallner and colleagues[116] reported having no drop-outs. Hawkey and colleagues[100] and Daneshmend and colleagues[75] clearly described the drop-outs with reasons for each treatment group for each stage of the study. Despite the drop-outs, clinical outcomes were analysed on an intention-to-treat basis.

Sample size estimation

Two trials[75,100] estimated *a priori* sample size of the trials. The other three did not state this.

Quantitative analysis

Main analysis: all studies

As mentioned previously, the trial by Lau and colleagues[120] reported mortality only for patients with PU bleeding, and not for all patients with UGI bleeding who were randomised in this trial. Therefore, this trial was not included in the main analysis.

Mortality at 30 days or at point closest to 30 days

Four trials reported mortality rates for all randomised patients[75,100,116,119] and comprised of a total of 760 patients in the PPI group and 752 in the control group. There was no significant heterogeneity among the trials ($p = 0.44$, $I^2 = 0\%$). Pooled mortality rates were 6.1% for PPI treatment and 5.5% for control treatment. There was no statistically significant effect of PPI treatment compared with control treatment on pooled mortality rates (OR 1.12, 95% CI 0.72 to 1.73); see *Figure 5*. The results remained statistically non-significant when, by sensitivity analysis, any of the four trials was removed. Of note, in the study by Daneshmend and colleagues,[75] all deaths occurred within 30 days although follow-up was for 40 days. Visual inspection of a funnel plot revealed evidence of publication bias (i.e. missing small negative trials from the right bottom area of the plot).

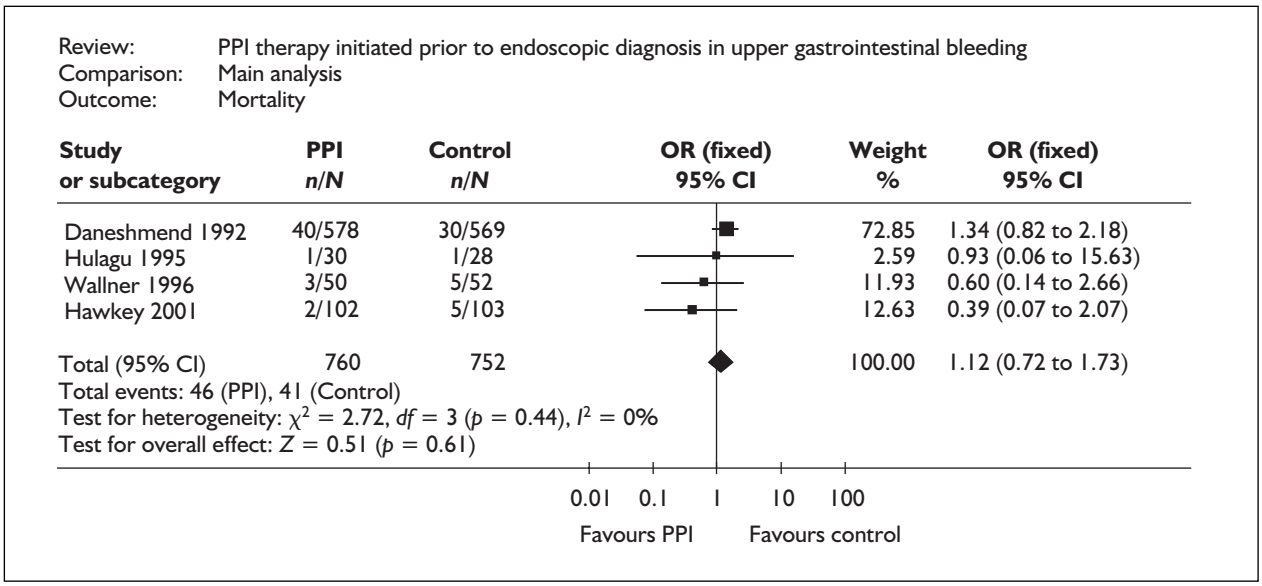

FIGURE 5 *Mortality with PPI versus H_2RA or placebo initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding*

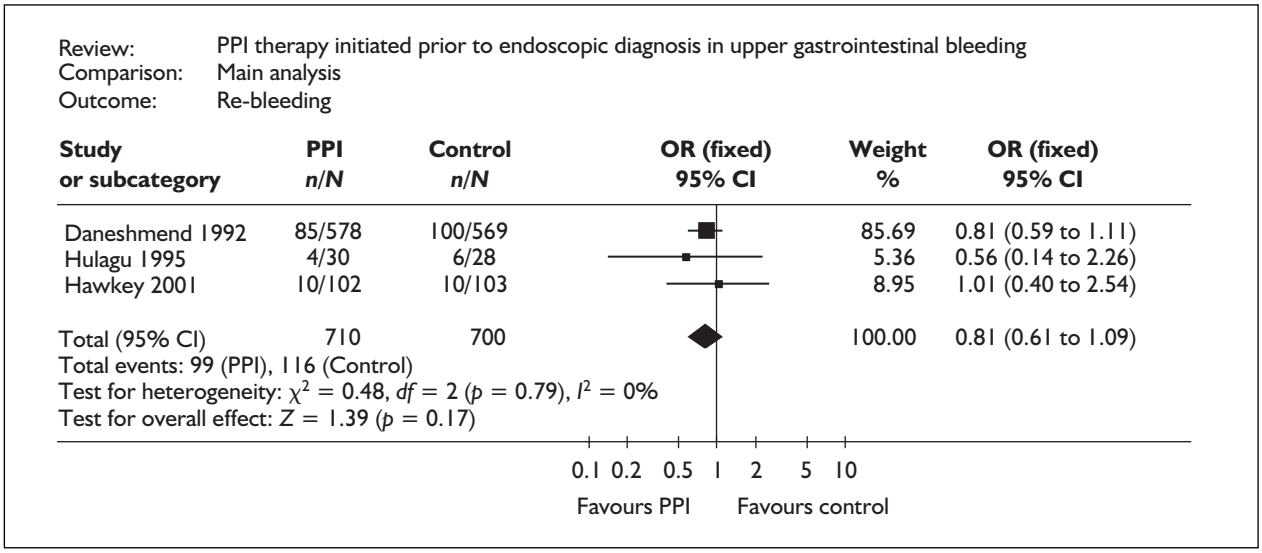

FIGURE 6 *Re-bleeding with PPI versus H_2RA or placebo initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding*

Re-bleeding

Re-bleeding data for all randomised patients could be extracted from three trials[75,100,119] comprising a total of 710 patients in the PPI group and 700 in the control group. There was no significant heterogeneity in this analysis ($p = 0.79$, $I^2 = 0\%$). Pooled re-bleeding rates were 13.9% for PPI treatment and 16.6% for control treatment. There was no statistically significant effect of PPI treatment compared with control treatment on pooled re-bleeding rates (OR 0.81, 95% CI 0.61 to 1.09) (see *Figure 6*). The result remained non-significant when, by sensitivity analysis, any of the trials was removed. The funnel plot was asymmetric but, due to the small number of studies, it was not possible to conclude if there was evidence of publication bias. Comparable re-bleeding rates could not be extracted from the trial by Wallner and colleagues[116] since it was designed to assess the time needed for bleeding cessation.

Surgery

Three trials reported surgical intervention rates for all randomised patients[75,100,116] and comprised a total of 730 patients in the PPI treatment group and 724 in the control treatment group. Heterogeneity among trials was not statistically significant ($p = 0.49$, $I^2 = 0\%$). Pooled rates for surgery were 9.9% for PPI treatment and 10.2%

for control treatment. PPI treatment compared with control did not significantly affect surgical intervention rates (OR 0.96, 95% CI 0.68 to 1.35) (see *Figure* 7). The result remained non-significant when, by sensitivity analysis, any of the trials was removed. The funnel plot was symmetrical providing no evidence of publication bias.

Proportion of patients with SRH at index endoscopy

Four trials reported proportion of patients per treatment group with SRH (as opposed to not having SRH) at index endoscopy.[75,100,116,119] The trials comprised 672 patients in the PPI arm and 620 in the control arm. There was no significant heterogeneity among the trials ($p = 0.20$, $I^2 = 34.6\%$). A total of 37.2% of patients on PPI and 46.5% of patients on control treatment were found to have SRH at index endoscopy. PPI compared with control treatment significantly reduced the proportion of patients with SRH (OR 0.67, 95% CI 0.54 to 0.84) (see *Figure 8*). This result became non-significant with the exclusion of one of the trials.[75] Inspection of the funnel plot did not give any indication of publication bias.

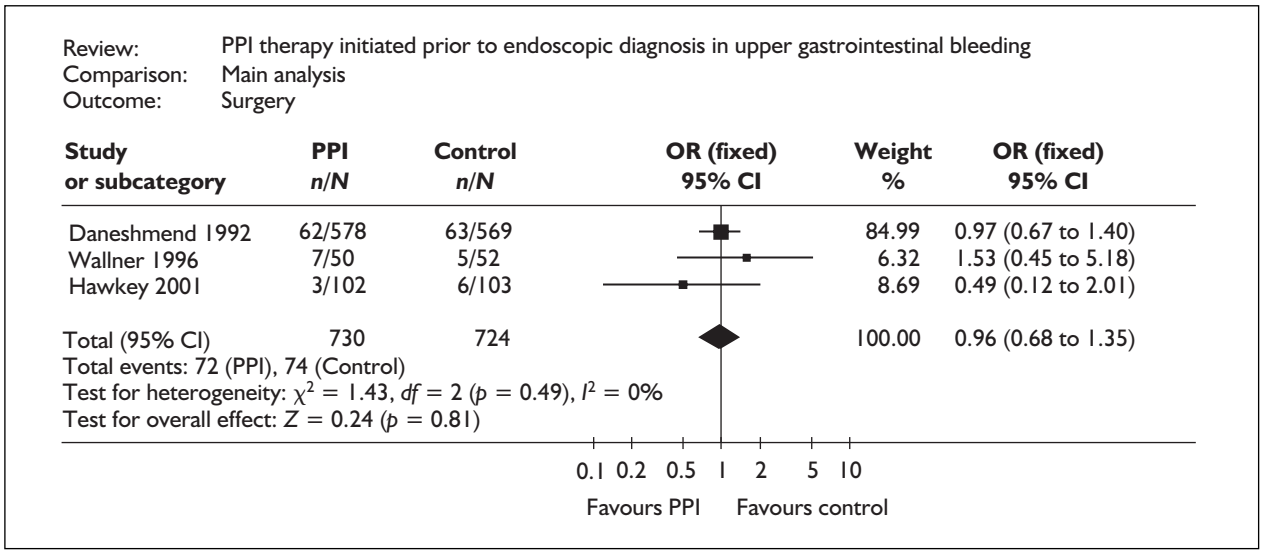

FIGURE 7 *Surgery with PPI versus H_2RA or placebo initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding*

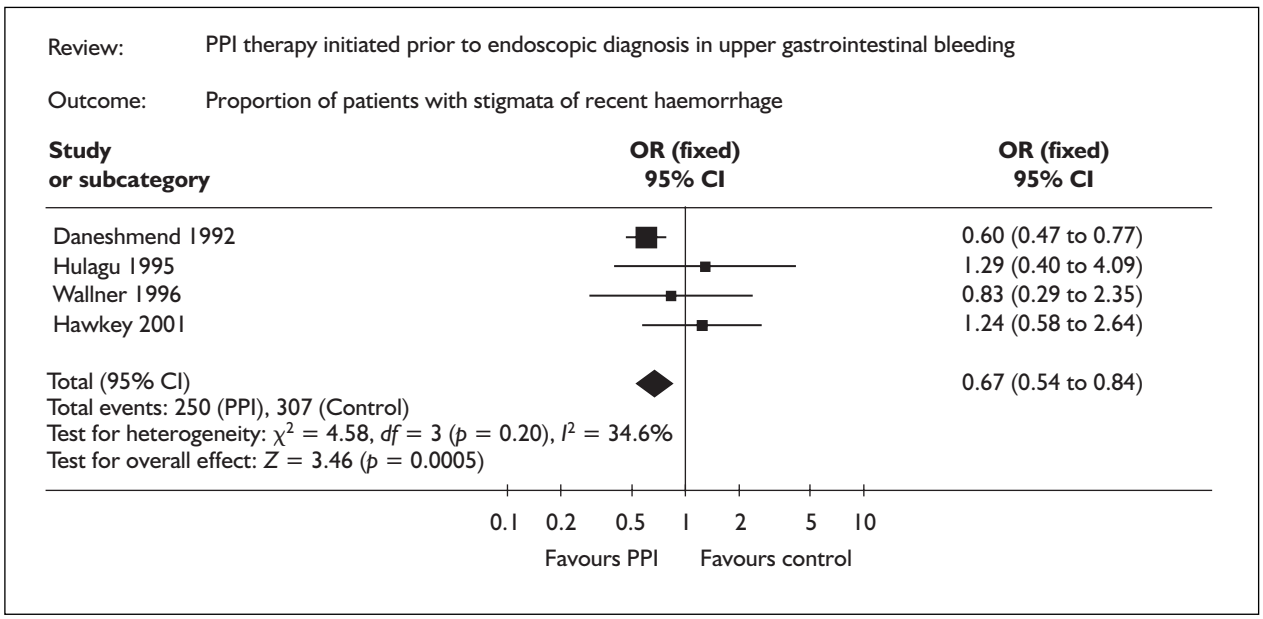

FIGURE 8 *Proportion of patients with stigmata of recent haemorrhage with PPI versus H_2RA or placebo initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding*

It must be emphasised that the reduction of SRH is of unknown clinical significance. It is plausible that it might be associated with reduced requirements for endoscopic haemostatic therapy. This presumed reduction of endoscopic haemostatic therapy could be considered as beneficial. However, it is equally plausible that it may actually be detrimental. PPI treatment could mask SRH which would have otherwise been present and might actually prevent the application of EHT, a treatment which is known to improve clinical outcomes.

Blood transfusion requirements

None of the trials reported blood transfusion requirements as means with SD per treatment group for all randomised patients. Hence a meta-analysis could not be performed for blood transfusion as a continuous outcome. None of the trials found a statistically significant difference in transfusion requirements between the two groups. In a *post hoc* analysis, we were able to extract the percentage of patients per treatment group requiring blood transfusion from three of the trials.[75,100,116] These three trials comprised a total of 730 patients in the PPI treatment group and 724 in the control treatment group. There was no statistically significant heterogeneity among these trials ($p = 0.31$, $I^2 = 13.7\%$). A total of 54% of patients on PPI treatment and 55.0% on control treatment received blood transfusions. The proportion of patients receiving blood transfusion was not significantly affected by PPI treatment compared with control treatment (OR 0.97, 95% CI 0.79 to 1.19). The result remained non-significant when, by sensitivity analysis, any of the trials was removed.

Need for EHT at index endoscopy

Two trials[75,100] reported the proportions of patients who required EHT at the index endoscopy and were pooled together in a *post hoc* analysis. These two trials comprised a total of 671 patients in the PPI group and 681 patients in the control group. A total of 37.3% of patients on PPI and 39.6% of patients on control treatment required EHT at the index endoscopy. There was no statistically significant heterogeneity between the two trials ($p = 0.83$, $I^2 = 0\%$). There was no statistically significant effect of PPI treatment on the proportion of patients who required EHT at the index endoscopy (OR 0.93, 95% CI 0.53 to 1.64). However, considering the current standards for administering EHT, the proportion of patients with high-risk SRH treated with EHT was low in both the studies – 22.5% in the Daneshmend study[75] and 40% in the Hawkey study.[100] This could probably undermine the results of the above analysis.

Length of hospital stay

Two trials[75,116] reported data on length of hospital stay for all randomised patients, but data could not be pooled. Daneshmend and colleagues[75] reported median time to discharge: 5 days in the PPI group and 6 days in the control group (not statistically significant). Wallner and colleagues[116] reported median time to discharge (range; SD): 8 days (3–26; 4.8) in the PPI group and 7.6 (3–20; 4.5) in the control group (not statistically significant). Hence, an overall conclusion on the effect of PPI treatment on hospital stay could not be reached.

Analysis according to degree of allocation concealment

Mortality

Two of the trials reporting mortality rates for all randomised patients were classified as being Grade A regarding allocation of concealment.[75,116] There was no statistically significant heterogeneity between the trials. The pooled OR was not statistically significant (OR 1.23, 95% CI 0.78 to 1.95).

The other two trials that reported mortality for all randomised patients[100,119] were classified as Grade B regarding allocation of concealment. There was no statistically significant heterogeneity between the trials. The mortality was not significantly affected with PPI treatment (OR 0.48, 95% CI 0.12 to 1.98).

Re-bleeding

Of the three trials reporting re-bleeding rates for all randomised patients, one trial[75] was Grade A regarding allocation of concealment. This trial did not find a significant effect on re-bleeding rates with PPI treatment compared with control (OR 0.81, 95% CI 0.59 to 1.11).

Two trials[100,119] were Grade B regarding allocation of concealment. There was no statistically significant heterogeneity between the trials and the pooled effect on re-bleeding was also non-significant (OR 0.84, 95% CI 0.39 to 1.81).

Surgery

Two trials[75,116] of Grade A degree of allocation of concealment reported surgical intervention rates. There was no statistically significant heterogeneity and the pooled effect was not statistically significant (OR 1.00, 95% CI 0.70 to 1.43). One trial[100] with Grade B allocation of concealment also found a statistically non-significant result (OR 0.49, 95% CI 0.12 to 2.01).

Analysis according to control treatment

Mortality

Two trials compared PPI with placebo.[75,100] There was no statistically significant heterogeneity. There was no statistically significant effect on mortality (OR 1.20, 95% CI 0.75 to 1.90). Two trials[116,119] compared PPI with an H_2RA (there was no statistically significant heterogeneity) and also found no significant effect on mortality (OR 0.66, 95% CI 0.18 to 2.44).

Re-bleeding

Two trials compared PPI with placebo.[75,100] There was no statistically significant heterogeneity between the trials. The pooled effect was non-significant (OR 0.83, 95% CI 0.61 to 1.12). One trial compared PPI with H_2RA treatment[119] and found no statistically significant effect on re-bleeding (OR 0.56, 95% CI 0.14 to 2.26).

Surgery

Two trials compared PPI with placebo.[75,100] There was no statistically significant heterogeneity. There was no statistically significant effect on surgery (OR 0.92, 95% CI fixed effect 0.64 to 1.32). One trial[120] compared PPI with H_2RA and also found no significant effect on surgery (OR 1.53, 95% CI 0.45 to 5.18).

Analysis according to route of PPI administration

Mortality

Three trials used intravenous PPI treatment[75,100,119] with no statistically significant heterogeneity among them. The pooled effect on mortality was not statistically significant (OR 1.22, 95% CI 0.78 to 1.93). One trial[100] 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).

Re-bleeding

Two trials used intravenous PPI[75,119] with no statistically significant heterogeneity between them. The pooled effect on re-bleeding was not statistically significant (OR 0.79, 95% CI 0.58 to 1.08). One other trial used oral PPI treatment[100] and also found a non-significant result (OR 1.01, 95% CI 0.40 to 2.54).

Surgery

Two trials used intravenous PPI treatment[75,116] with no statistically significant heterogeneity between them. The pooled effect on surgery was not statistically significant (OR 1.00, 95% CI 0.70 to 1.43). One trial[100] 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 according to brand of PPI used

The analysis is identical to the above-reported analysis according to route of PPI administration, since the three trials that used intravenous PPI treatment all used omeprazole[75,116,119] whereas the trial that used oral PPI treatment used lansoprazole.[100]

Analysis according to application of initial EHT

This analysis is identical to the above-reported analysis according to control treatment; the two trials that applied EHT were the ones that used placebo as control treatment[75,100] whereas the two trials that did not apply EHT[116,119] used H_2RA as control treatment.

Outcomes for patients with peptic ulcer bleeding

Mortality

Three trials reported separate mortality rates for patients with PU bleeding.[75,116,120] These trials comprised 392 patients in the PPI arm and 410 in the control arm in total. There was no statistically significant heterogeneity among the trials. The pooled effect on mortality was non-significant (OR 1.41, 95% CI 0.80 to 2.47).

Daneshmend and colleagues also reported separate outcomes for patients bleeding from GU and DU.[75] For patients with bleeding GU, mortality was 7% in the PPI group and 5% in the control group. In patients with bleeding DU, mortality was 11% in the PPI group compared with 5% in the control group (differences were not statistically significant).

Re-bleeding

Two trials reported separate re-bleeding rates for patients with PU bleeding.[75,120] These trials comprised 356 patients in the PPI arm and 369 in the control arm. There was no statistically significant heterogeneity between the trials. The pooled effect on mortality was non-significant (OR 0.84, 95% CI 0.57 to 1.23). The Daneshmend study[75] reported re-bleeding rates separately for GU and DU. The re-bleeding rates were 27% in the PPI group compared with 25% in the placebo group in GU-related bleeds and 21% in the PPI group compared with 29% in the placebo group for DU-related bleeds. The results were not statistically significant.

Surgery

Two trials reported separate surgical intervention rates for patients with PU bleeding.[75,120] These trials comprised 356 patients in the PPI arm and

369 in the control arm. There was no statistically significant heterogeneity between the trials. The pooled effect on mortality was non-significant (OR 0.87, 95% CI 0.56 to 1.34).

The Daneshmend study[75] reported this outcome separately for patients with bleeding GU and DU. In GU-related bleeds, 19% in the PPI group underwent surgery compared with 17% in the placebo group. In DU-related bleeds, 18% in the PPI group underwent surgery compared with 21% in the placebo group. The results were not statistically significant.

Hawkey and colleagues[100] provided outcomes on PU patients (42.4% of the total study population) but not per treatment group. The rate of re-bleeding (13.9%), surgery (6.6%) and death (4.4%) in PU patients did not differ from the whole study population.

Blood transfusion requirements

One trial reported blood transfusion requirements for patients with PU bleeding.[120] Mean units transfused (SD) were 1.9 (2.2) on PPI and 2.2 (3.1) on control treatment (statistically non-significant difference).

The above results did not show any evidence for clinical effectiveness of PPI in PU-related bleeds, namely mortality, surgery and re-bleeding. There was no evidence to suggest that PPI treatment has a different effect in GU- or DU-related bleeding.

Proportion of patients with SRH at index endoscopy

One trial reported the proportion of patients with SRH at the index endoscopy for patients with PU bleeding.[120] In the PPI group, 20/110 patients were found to have SRH at the index endoscopy, as opposed to 41/112 patients in the placebo group ($p = 0.003$).

Need for EHT at the index endoscopy

One trial reported the proportion of patients with PU bleeding who needed EHT at the index endoscopy.[120] This was 20% patients in the PPI group versus 45% patients in the placebo group ($p = 0.002$).

Length of hospital stay

One trial reported length of hospital stay for patients with PU bleeding.[120] The mean (SD) length of stay was 3.7 (3.8) days on PPI and 4.7 (5.9) days on control treatment (statistically non-significant difference).

Conclusion

In summary, PPI treatment initiated prior to endoscopy in UGI bleeding significantly reduces the proportion of patients with SRH at the index endoscopy. However, we found no evidence that PPI treatment initiated prior to endoscopy affects clinically important outcomes, namely mortality, re-bleeding or the need for surgery.

Chapter 6

Modelling and health economic evaluation – 1. What is the cost-effectiveness of PPI therapy in patients with acute upper gastrointestinal bleeding before and after the endoscopic diagnosis of bleeding peptic ulcer?

Bleeding peptic ulcer model

Purpose of the model

The purpose of the model is to compare the effects of a variety of different options for immediate management of patients who are haemodynamically stable after an episode of bleeding PU. Although the main difference between the strategies compared relates to management during the first 24 hours, it is important to assess the value of differences in outcome. This is done by modelling the detailed progress of patients for a period of 28 days, using an individual sampling model[61] to construct a large number of virtual patient histories; 28 days is the timescale over which the model should capture all relevant events from a UGI bleed.

Costs and quality-adjusted life-days (QALDs) are accumulated. Comparison of different strategies then allows for the calculation of ICERs between strategies – for convenience of interpretation, these are expressed in pounds per quality-adjusted life-year (QALY). The pathways through the model are shown in *Figure 9*.

Patients enter the model having had an acute UGI haemorrhage, but are haemodynamically stable. They then wait for endoscopy. At endoscopy, patients may or may not receive endoscopic haemostatic therapy. Patients then move to a 'post-endoscopy' state, after which they may be discharged home. At all times, patients are at risk of (non-fatal) re-bleed and death. Re-bleeds may result in haemodynamic stability or instability.

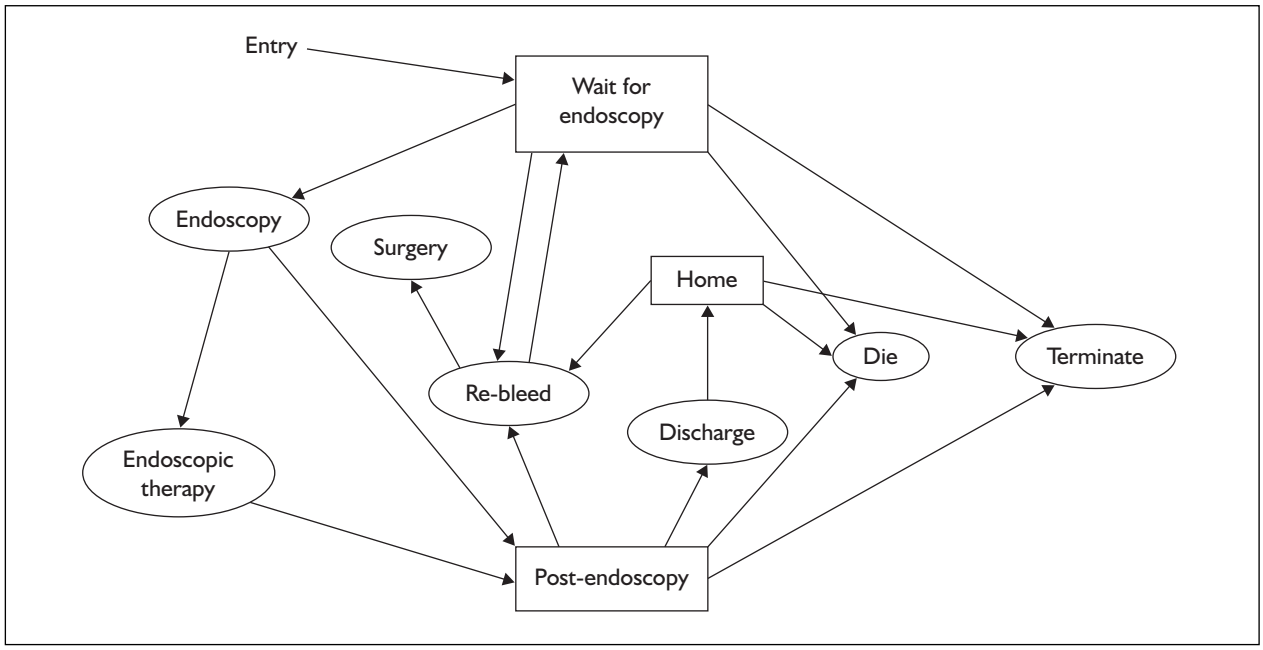

FIGURE 9 *Pathways through the model. Ellipses indicate events which take no time; rectangles indicate states in which patients remain for some time. Time taken for endoscopy and endoscopic therapy was considered negligible compared with the timescale of the model.*

Patients unstable after a bleed probably move to surgery and exit the model whereas patients stable after a bleed probably repeat the cycle starting at endoscopy. Patients surviving 28 days in the model exit the model through the 'Terminate' event at that time. (The arrow from 'Wait for endoscopy' to 'Terminate' allows for the possibility of a re-bleed just before the end of the 28-day period modelled.)

To allow for long-term effects, we have considered life expectancy at the end of the time modelled. We have done this in two ways: (1) by running the model for the full 28 days, and then including life expectancy for survivors, and (2) applying life expectancy immediately at discharge from hospital.

Basic assumptions in the model

Admissions are assumed to be uniformly distributed throughout the day (24 hours). The admission process for stable re-bleeds takes a few hours. Endoscopy occurs at the first opportunity after the admission process is completed. Endoscopies are assumed to be available only at 0900 each day (7 days per week).

Not all major SRHs will be detected at endoscopy. Stable re-bleeds are most likely to result from undetected major SRH, and thus require re-endoscopy. There were no 'false-positive' reports of SRH.

Strategies to be compared

There are three aspects of model strategy to be compared in this model. These relate to treatment before, at and after endoscopy.

Treatment before endoscopy may be any of:

- no treatment before endoscopy, in which case patients admitted for re-bleed stop taking oral PPI until re-endoscopy
- oral PPI on admission
- intravenous PPI on admission.

At endoscopy, endoscopic haemostatic therapy may be given to:

- no patients
- only patients with major SRH.

After endoscopy, two options are considered:

Option 1: variable treatment
Post-endoscopy treatment for patients with major SRH (if detected) consists of intravenous PPI for 72 hours, followed by a switch to oral PPI. If no major SRH is detected, treatment consists of oral PPI for the remainder of the modelled time.

Patients treated with intravenous PPI remain in hospital throughout intravenous PPI treatment (72 hours), and then for a further 24 hours if there is no co-morbidity or 72 hours if there is co-morbidity. If no re-bleed occurs within this time, patients are discharged.

Patients not treated with intravenous PPI remain in hospital for 24 hours if there is no co-morbidity or 48 hours if there is co-morbidity. Such patients are discharged if no re-bleed occurs.

All patients remain on oral PPI on discharge.

Option 2: fixed treatment
After endoscopy, all patients receive the same treatment as before endoscopy, except that, for strategies involving no treatment before endoscopy, all patients receive oral PPI after endoscopy. It is assumed that patients remain in hospital for the same length of time as for option 1 above, and that all patients receive oral PPI on discharge. Patients remain on oral PPI for rest of model.

These combinations give a total of 12 strategies to compare.

Data included in the model

Data are required in four areas.

Initial population characteristics

Prognosis in the model is largely dependent on a measure known as the Rockall score which has been adequately validated.[8] This is based on the following five characteristics on initialisation:

- *Age* (in years): *Age*: 0 = under 60, 1 = 60 to 79, 2 = 80 or over.
- *Shock*: 0 = no shock, 1 = tachycardia, 2 = hypotension.
- *Co-morbidity*: 0 = nil major, 2 = cardiac failure, ischaemic heart disease, any major co-morbidity, 3 = renal failure, liver failure, disseminated malignancy.
- *Diagnosis*: 0 = Mallory–Weiss tear, no lesion and no SRH, 2 = malignancy of UGI tract, 1 = all other.
- *Major SRH*: 0 = none, or dark spot, 2 = blood in UGI tract, adherent clot, visible or spurting vessel.

On initialisation, patients are given an age in years. As the model runs for a short period, this is given as an integer and is not updated during the

TABLE 11 *Baseline risk rates*

Rockall score	Base	Lower	Upper
Re-bleeding rates (per day at risk)			
0	0.015	0.006	0.037
1	0.015	0.008	0.026
2	0.021	0.014	0.034
3	0.034	0.025	0.047
4	0.036	0.027	0.048
5	0.058	0.047	0.073
6	0.071	0.056	0.090
7	0.090	0.070	0.115
8+	0.097	0.075	0.126
Death rates (per day at risk)			
0	0.0004	0.0000	0.0042
1	0.0007	0.0001	0.0039
2	0.0018	0.0005	0.0059
3	0.0121	0.0074	0.0197
4	0.0234	0.0166	0.0330
5	0.0283	0.0209	0.0384
6	0.0401	0.0297	0.0541
7	0.0711	0.0541	0.0935
8+	0.1426	0.1138	0.1787

Source: Vreeburg and colleagues[134] (see text for details).

model. Patients are given values of the other four characteristics from the possibilities shown above. The distribution of individual characteristics has been calibrated so that the overall distribution of Rockall scores matches the distribution of the combined Rockall and Vreeburg validation samples, as reported by Vreeburg and colleagues.[134]

Patient flow through the model

Patient flow is determined by time to events and by outcome of uncertain events.

Time to events

It is assumed that the main risk of re-bleeding and death occurs during the hospitalisation period. The baseline risks during this period are taken to vary according to the Rockall score, as shown in *Table 11*. The values are based on combining the Rockall and Vreeburg validation samples, as reported by Vreeburg and colleagues.[134] Small adjustments have been made to account for the cases in which there were no deaths reported. The data were given in the form of probabilities: these have been converted to risk per unit time by assuming that the probabilities applied for a period of 4 days.

The resulting risks have been taken to apply to the case where no PPI treatment was given, but endoscopic haemostatic therapy was given in the case of major SRH. To allow for variations in therapy, RRs are applied as shown in *Table 12*.

For the period post-hospital but during the 28 days modelled, the available data for the second to fourth weeks from admission have been used and converted into a daily risk rate. This is assumed to apply to all patients after discharge, all of whom will be on oral PPI treatment for the relevant period. The figures used are shown in *Table 13*.

TABLE 12 *Effects of therapy on risk of re-bleeding and death*

Parameter	Base	Lower	Upper	Source
RR re-bleed before endoscopy				
Oral PPI vs nothing	1.01	0.44	2.32	Hawkey, 2001[100]
I.v. PPI vs nothing	0.84	0.64	1.09	Daneshmend, 1992[75]
RR re-bleed after endoscopy				
Oral PPI vs nothing	0.29	0.18	0.47	Our re-analysis[a]
I.v. PPI vs nothing	0.30	0.14	0.63	Lau, 2000[81]
EHT	0.38	0.32	0.45	Cook, 1992[11]
RR death before endoscopy				
Oral PPI vs nothing	0.40	0.08	2.03	Hawkey, 2001[100]
I.v. PPI vs nothing	1.31	0.83	2.08	Daneshmend, 1992[75]
RR death after endoscopy				
Oral PPI vs nothing	0.38	0.11	1.26	Our re-analysis[a]
I.v. PPI vs nothing	1.25	0.30	5.19	Our re-analysis[a,b]
EHT	0.55	0.40	0.76	Cook, 1992[11]

[a] *Post hoc* analyses reported in the section '*Post hoc* analyses' (p. 37).
[b] This result was produced by random effects model due to significant heterogeneity ($p = 0.01$); if we apply the fixed effect model, then RR becomes 1.11 (95% CI 0.65 to 1.90).

TABLE 13 *Risk rates for re-bleed and death for the period after discharge*

Daily risk of	Base	Lower	Upper	Source
Re-bleed	0.0003	0.0000	0.0008	Lau, 2000;[81] Jensen, 2004[71]
Death	0.0023	0.0012	0.0037	Schaffalitzky, 1997[86]

TABLE 14 *Outcome of uncertain events*

Parameter	Base	Lower	Upper	Source
Sensitivity of endoscopy	0.90	0.83	0.95	Expert advice
Probability that re-bleed requires surgery	0.05	0.04	0.06	Rockall, 1997[135]
Mortality at surgery	0.21	0.13	0.30	Rockall, 1997[135]

TABLE 15 *Unit costs in the acute model*

Item	Unit cost (£)	Source
Day in hospital	227	PSSRU[136]
Endoscopy	340	NHS reference costs[137]
Endoscopic therapy	201	NHS reference costs[137]
Surgery	3468	NHS reference costs[137]
Oral PPI (per day)	0.46	BNF[138]
I.v. PPI (per day)	5.21	BNF[138]

Outcome of uncertain events

Table 14 gives the probability values for the outcome of uncertain events.

Costs

Costs were calculated from an NHS perspective. The main costs in the model relate to procedures and time in hospital. A basic cost per day in hospital was estimated from the Personal Social Services Research Unit (PSSRU). For surgical procedures, appropriate values were used from NHS reference costs. The values used in the model are shown in *Table 15*. These values were found to be as follows: cost of surgery is F61; cost of endoscopy is F65 minus 1 day's stay from PSSRU. For cost of endoscopic therapy, F62 minus 3 days' stay gives £541. Taking off the cost of endoscopy, the extra cost of endoscopic therapy is £541 less £340, which equals £201.

Outcomes

The average QALY of patients surviving a UGI bleed is uncertain. For the purposes of this model, additional information needs were obtained by using quality of life (QoL) data from patients with acute UGI bleeding. The EuroQoL EQ-5D instrument[139] was selected as it is a generic, single index measure that is validated in several countries that measures health for clinical and economic appraisal and is supported by an international research group.

The EuroQoL EQ-5D was given to 57 consecutive patients surviving a UGI bleed. The questionnaire was given at discharge or 7 days after the GI bleed, whichever was earlier. This did not give us baseline data, but indicated the immediate deterioration in QoL after a GI bleed. A further follow-up questionnaire at 4 weeks for comparison was completed by all patients. Appendix 5 contains full details of methods, inclusion/exclusion criteria and raw data results.

These QoL data were used to represent QoL at home and in hospital. The values are shown in *Table 16*. We made no adjustment for QoL in hospital while waiting for endoscopy or while on intravenous PPI.

TABLE 16 *Quality of life values used in the model*

Parameter	Base	Lower	Upper
QoL at home	0.78	0.70	0.85
QoL in hospital	0.45	0.34	0.57

TABLE 17 *Assumed life expectancy following discharge*

Age (years)	Base	Lower	Upper
50	24.15	22.38	25.94
55	20.06	18.42	21.73
60	16.21	14.72	17.75
65	12.75	11.44	14.12
70	9.65	8.54	10.84
75	7.03	6.12	8.02
80	4.98	4.27	5.76
85	3.38	2.86	3.97
90	2.29	1.92	2.71

Life expectancy among survivors was obtained by applying an RR of 2.1 (95% CI 1.7 to 2.6)[134] to general population life-tables (source: Government Actuary's Department). The results obtained are shown in the *Table 17*.

Bleeding peptic ulcer model results

The model was run with the base-case values of the data inputs described above, for a total of 100,000 (virtual) patients. Because of the sampling nature of the model, the results are given with a 'quasi-standard error'. This can be made as small as desired by running the model for sufficiently long, and is reported solely to show that sufficient replications of the model have been run. The results are shown in *Table 18*.

Results with short-term outcomes

All strategies without EHT are more costly and less effective than the corresponding strategies with EHT. Such strategies are said to be **strongly** or **simply dominated** and can be excluded. There is no simple dominance between the strategies involving EHT. Pairwise comparison between two strategies can be given as an ICER, which is calculated as the difference in cost divided by the difference in effectiveness. For convenience, the effectiveness is expressed in QALYs. The quasi-CI reflects the sampling within the model and is quoted to show that enough replications have been made. *Table 19(a)* lists the non-dominated options in ascending order of cost and effect. The ICERs between consecutive strategies can be seen to form an increasing sequence, except for 'Oral PPI – Variable'. This is an example of **weak** or **extended dominance**, and means that this strategy would never be preferred on cost-effectiveness grounds. *Table 19(b)* lists the strategies excluding the weakly dominated strategy. The ICERs now form an ascending sequence. *Table 19(b)* gives the strategies which are cost-effective at different threshold ICERs, subject to base-case assumptions, and only taking short-term effects into account. Of particular interest is the strategy of using oral PPI throughout, which has the highest clinical effectiveness in terms of both short- and long-term outcomes. Under baseline assumptions, this strategy is cost-effective on the basis of short-term outcomes alone, provided that the threshold ICER is at least £25,000 per QALY.

TABLE 18 *Base-case results for the acute model for peptic ulcer bleeding*

Strategy			Cost (£)		Short-term outcome (QALD)		Long-term outcome (LY)	
Rx before	End Rx	Option after	Mean	QSE	Mean	QSE	Mean	QSE
Nothing	No	Variable	846	2	18.31	0.02	9.84	0.02
Nothing	Yes	Variable	827	1	18.81	0.02	10.10	0.02
Oral PPI	No	Variable	857	2	18.46	0.02	9.92	0.02
Oral PPI	Yes	Variable	838	1	18.97	0.02	10.18	0.02
I.v. PPI	No	Variable	843	2	18.23	0.02	9.81	0.02
I.v. PPI	Yes	Variable	825	1	18.73	0.02	10.06	0.02
Nothing	No	Fixed	896	2	19.06	0.02	10.25	0.02
Nothing	Yes	Fixed	856	1	19.30	0.02	10.36	0.02
Oral PPI	No	Fixed	909	2	19.24	0.02	10.34	0.02
Oral PPI	Yes	Fixed	868	1	19.48	0.02	10.45	0.02
I.v. PPI	No	Fixed	836	1	17.41	0.02	9.38	0.02
I.v. PPI	Yes	Fixed	814	1	17.81	0.02	9.58	0.02

End Rx, endoscopic therapy; LY, life-year; QALD, quality-adjusted life-day; QSE, quasi-standard error; Rx before, treatment before endoscopy.

TABLE 19 *Comparison of non-dominated strategies for short-term outcomes*

Rx before	Option after	Mean difference[a]		ICER (£/QALY)[a]	
		Cost	QALD	Estimate	QCI
(a) Only simply dominated strategies excluded					
I.v. PPI	Fixed				
I.v. PPI	Variable	10	0.91	4,120	3,830 to 4,460
Nothing	Variable	3	0.08	13,000	10,700 to 16,600
Oral PPI	*Variable*	*11*	*0.16*	*23,900*	*21,800 to 26,500*
Nothing	Fixed	18	0.72	20,000	18,100 to 22,400
Oral PPI	Fixed	12	0.18	24,300	22,200 to 26,800
(b) Simply dominated and weakly dominated strategies excluded					
I.v. PPI	Fixed				
I.v. PPI	Variable	10	0.91	4,120	3,830 to 4,460
Nothing	Variable	3	0.08	13,000	10,700 to 16,600
Nothing	Fixed	28	0.48	21,300	20,200 to 22,600
Oral PPI	Fixed	12	0.18	24,300	22,200 to 26,800

QALD, quality-adjusted life-day; QALY, quality-adjusted life-year; QCI, quasi-confidence interval; Rx before, treatment before endoscopy.
[a] Mean difference and ICER compared with strategy defined in previous row.

Incorporating uncertainty in model inputs

In order to take into account the uncertainty in the model inputs, the model was re-run drawing 2000 parameter sets from appropriate distributions with the CIs as shown in the previous section, using 20,000 patients for each parameter set. The results of this analysis can be displayed in a cost-effectiveness acceptability curve (CEAC). This shows, for any given threshold ICER, the proportion of model runs that favour each option at that threshold. Although CEACs can be drawn for comparisons between multiple options, it is convenient to show a CEAC for a comparison between only two options. *Figure 10* shows the comparison between 'Oral PPI – Fixed' and the next best option, 'Nothing – Fixed'. At any threshold ICER of over £20,000/QALY, the majority of the model runs favour oral PPI.

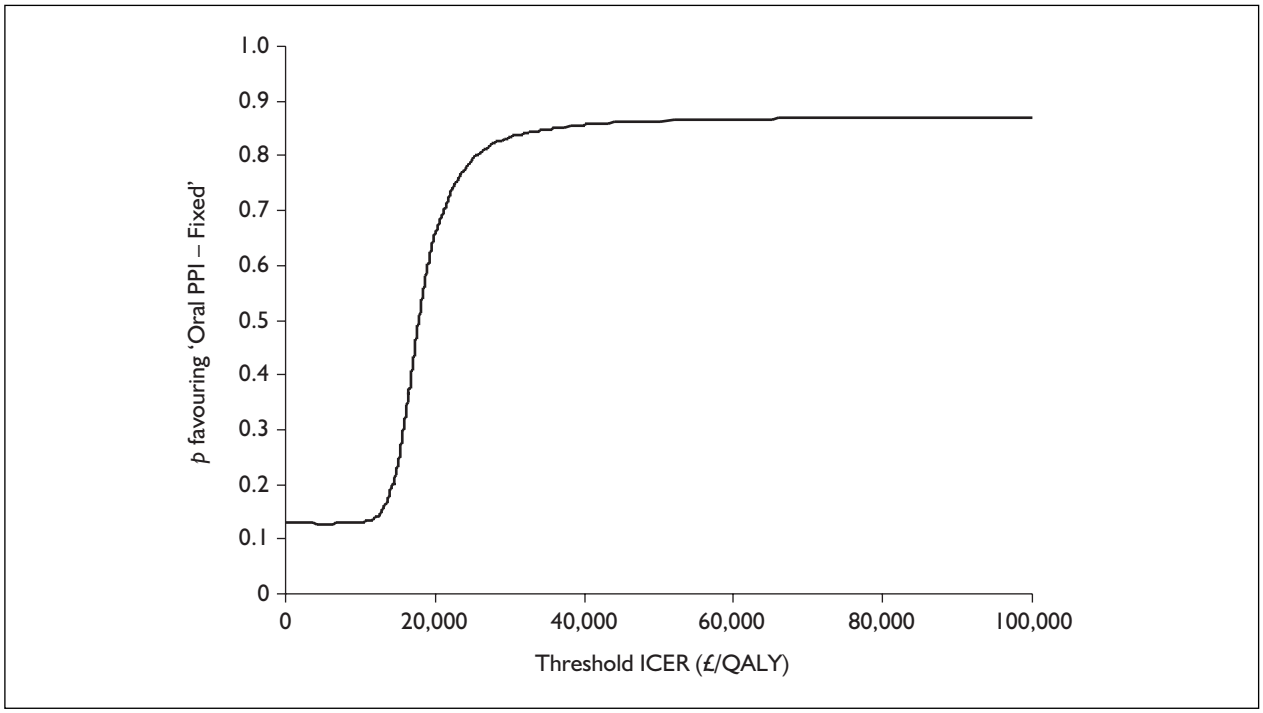

FIGURE 10 *CEAC for 'Oral PPI – Fixed' versus 'Nothing – Fixed'*

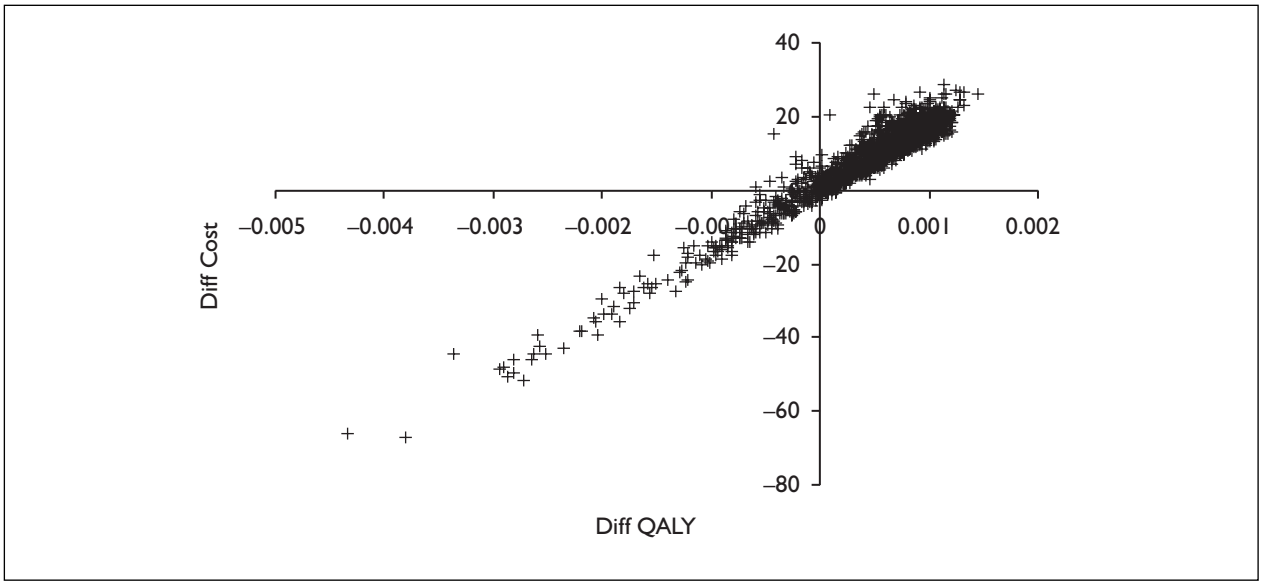

FIGURE 11 *Scatterplot for 'Oral PPI – Fixed' versus 'Nothing – Fixed'*

There is a non-negligible proportion of model runs favouring oral PPI at lower threshold ICERs, and a similar proportion favour no treatment before endoscopy at very high thresholds. This largely reflects the CIs for RR of re-bleed and death before endoscopy shown in *Table 12*. Particularly when the RR of death for oral PPI versus nothing takes a high value, there are higher expected costs and QALYs for not giving oral PPI before endoscopy. This is shown in the scatter plot in *Figure 11*, where approximately 11% of the points fall in the south-west quadrant.

Other important comparisons are 'Oral PPI – Fixed' against 'Oral PPI – Variable' and 'Oral PPI – Fixed' against 'Intravenous PPI – Fixed'. CEACs and corresponding scatterplots are shown in *Figures 12–15*. In each case, the majority of replications favour 'Oral PPI – Fixed' for thresholds above £20,000/QALY, but there is a

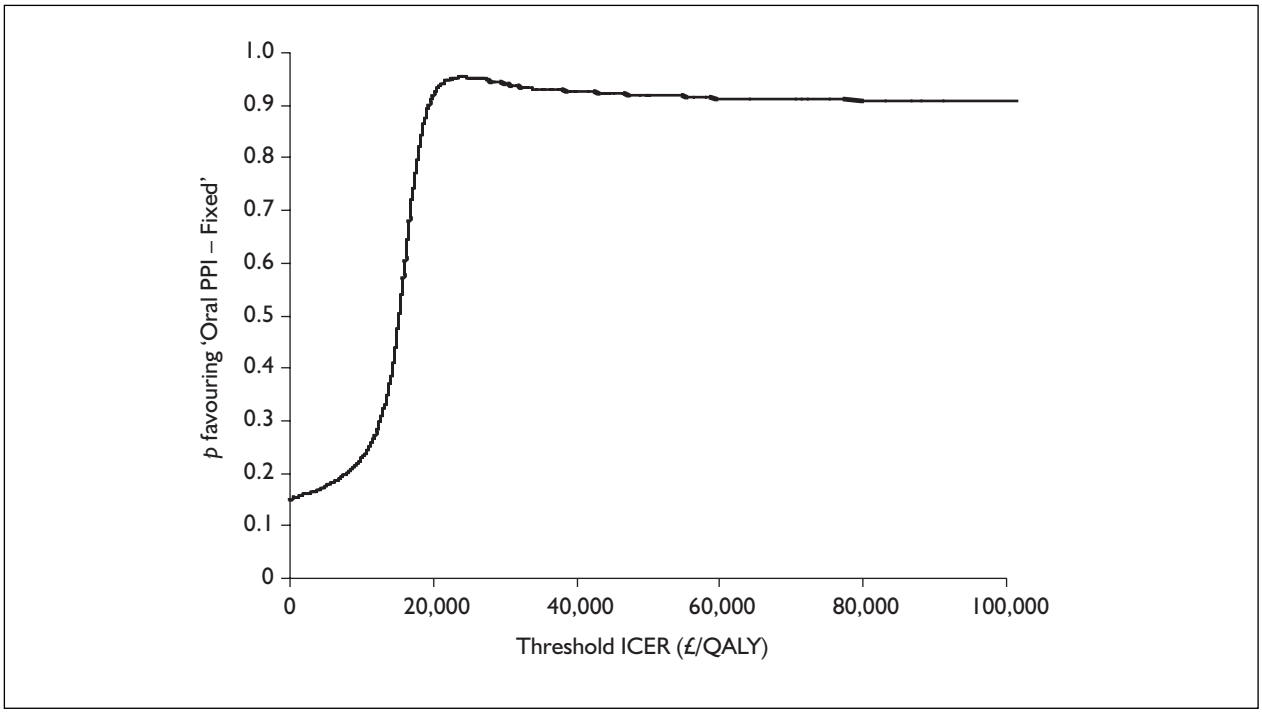

FIGURE 12 *CEAC for 'Oral PPI – Fixed' versus 'Oral PPI – Variable'*

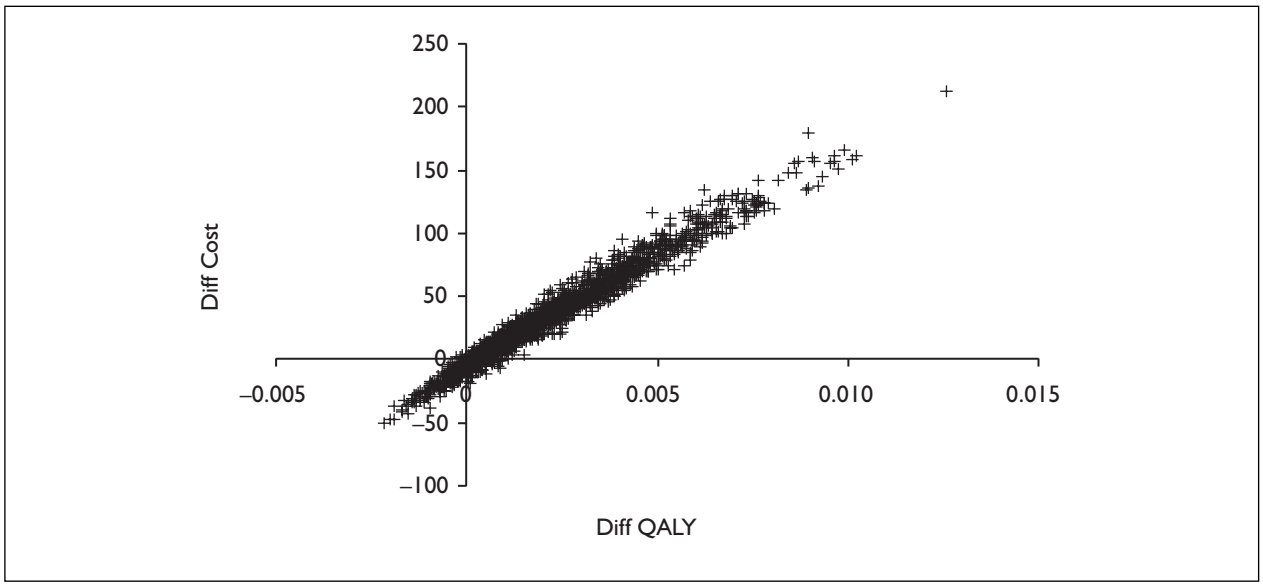

FIGURE 13 *Scatterplot for 'Oral PPI – Fixed' versus 'Oral PPI – Variable'*

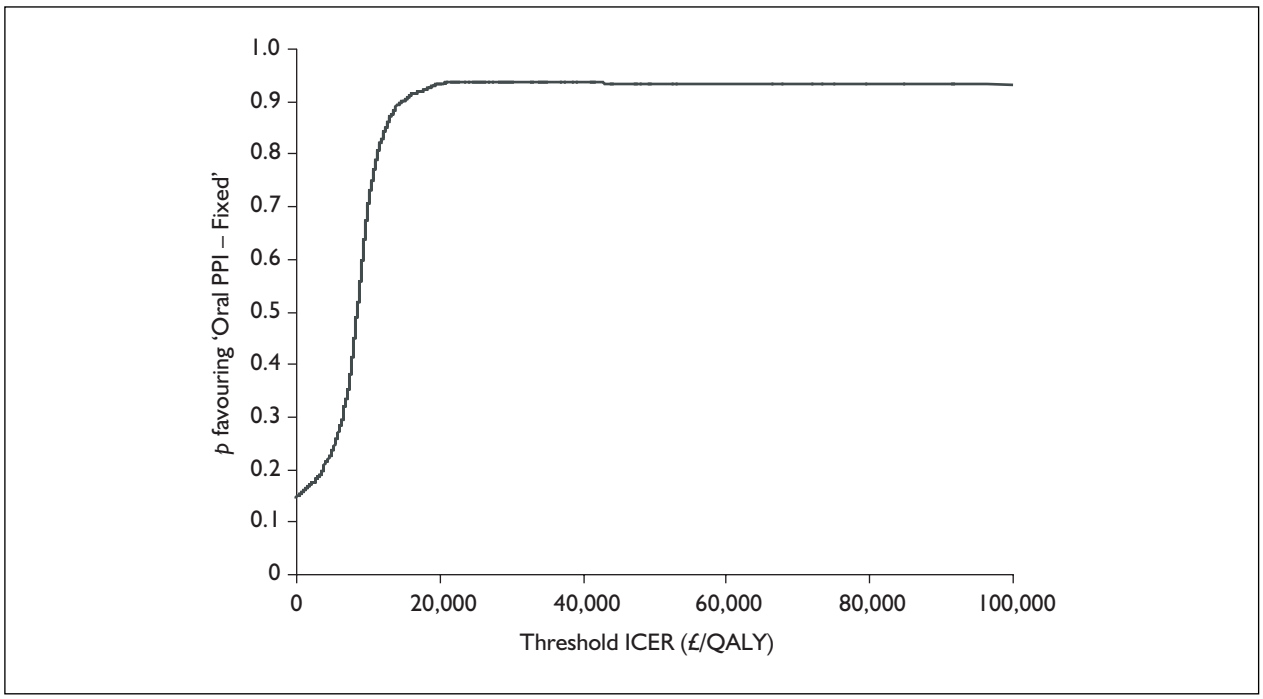

FIGURE 14 *CEAC for 'Oral PPI – Fixed' versus 'Intravenous PPI – Fixed'*

non-negligible proportion of replications in the south-west quadrant.

Results with long-term outcomes

The above analysis seriously underestimates the effect of differential mortality between the various strategies, because it gives no value to lifetime saved after the initial 28-day period. This analysis uses the long-term outcome obtained by ascribing the life expectancy to all survivors in the model. Using long-term outcomes, again all strategies not using EHT were simply dominated by the corresponding strategies with EHT. The comparison between the strategies involving EHT is shown in *Table 20*. As before, the strategy 'Oral PPI – Variable' is weakly dominated.

It is clear that, under the base-case assumptions in this analysis, oral PPI throughout (combined with endoscopic therapy) is highly cost-effective compared with any alternative strategy, namely intravenous PPI or do nothing.

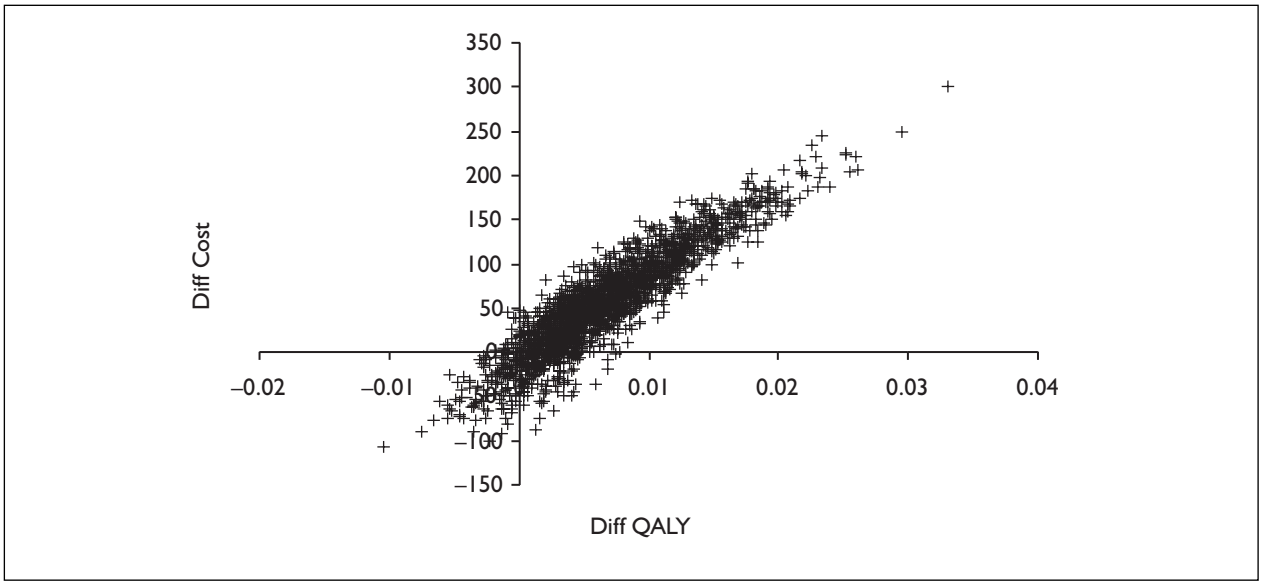

FIGURE 15 *Scatterplot for 'Oral PPI – Fixed' versus 'Intravenous PPI – Fixed'*

TABLE 20 *Comparison of non-dominated strategies for long-term outcomes*

Rx before	Option after	Mean difference		ICER (£/LY)		
		Cost	LY	Estimate	QCI	
Only simply dominated strategies excluded						
I.v PPI	Fixed					
I.v. PPI	Variable	10	0.48	22	20	23
Nothing	Variable	3	0.04	75	61	97
Oral PPI	*Variable*	*11*	*0.08*	*139*	*125*	*156*
Nothing	Fixed	18	0.18	99	89	111
Oral PPI	Fixed	12	0.08	140	127	157
Simply dominated and weakly dominated strategies excluded						
I.v. PPI	Fixed					
I.v. PPI	Variable	10	0.48	22	20	23
Nothing	Variable	3	0.04	75	61	97
Nothing	Fixed	28	0.26	111	104	118
Oral PPI	Fixed	12	0.08	140	127	157

LY, life-year; QCI, quasi-confidence interval; Rx before, treatment before endoscopy.

Incorporating parameter uncertainty

Parameter uncertainty has been explored for the same pairwise comparisons as was done for short-term outcomes. The resulting CEACs and scatter plots are shown in *Figures 16–21*. As before, there is a non-negligible probability that other strategies are more effective than "Oral PPI – Fixed", but, when long-term outcomes are included, the results strongly favour "Oral PPI – Fixed" even at threshold ICERs below £200 per life-year.

Alternative long-term analysis

For this analysis, the model was terminated on discharge from hospital, and life expectancies were applied immediately at this point. This meant no enhanced risk of death over the remainder of the first month. The base-case results are shown in *Table 21*. As expected, the costs for each strategy are slightly lower, whereas the life-years are slightly higher than the equivalents in *Table 18*. The incremental analysis shown in *Table 22* differs only very slightly from that in *Table 21*.

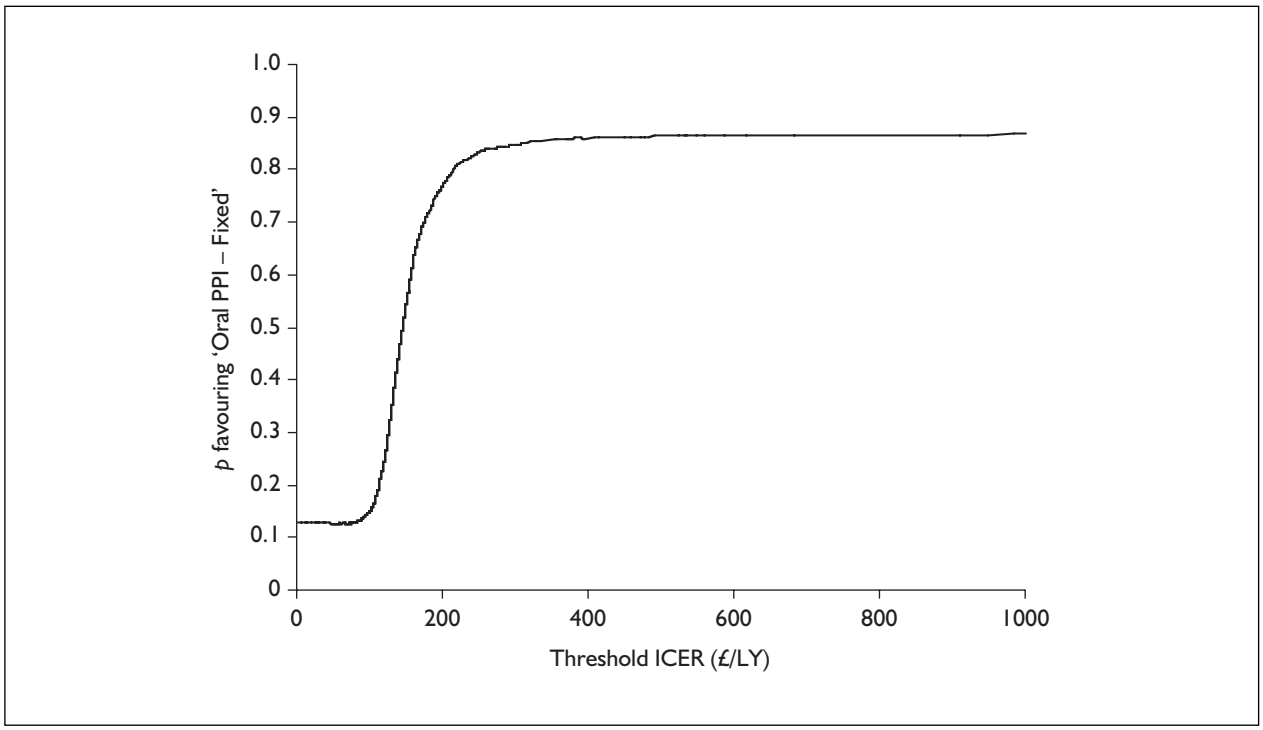

FIGURE 16 *CEAC for 'Oral PPI – Fixed' versus 'Nothing – Fixed' (long-term)*

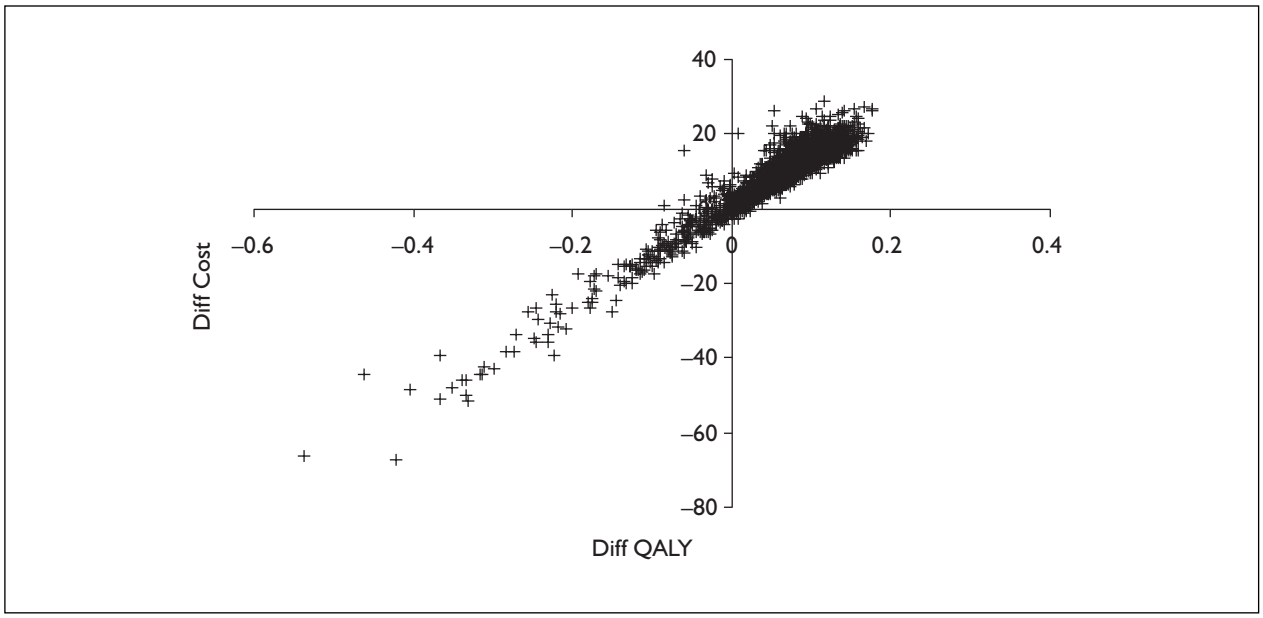

FIGURE 17 *Scatterplot for 'Oral PPI – Fixed' versus 'Nothing – Fixed' (long-term)*

We acknowledge that results from Asian studies may not be representative of a UK population. However, for the post-endoscopy comparison oral PPI versus nothing there were no other data available than data from Asian trials (see the section '*Post hoc* analyses', p. 37). Accordingly, we have used the data from Asian studies for this comparison.

Trials conducted in Asia demonstrate increased efficacy of PPI treatment in PU bleeding compared with trials conducted elsewhere (see the section 'Subgroup analyses', p. 36). Likely explanations for those findings have been discussed previously.[140] First, patients in the Asian trials had a higher mean age than those in the non-Asian trials. Therefore, Asian patients may

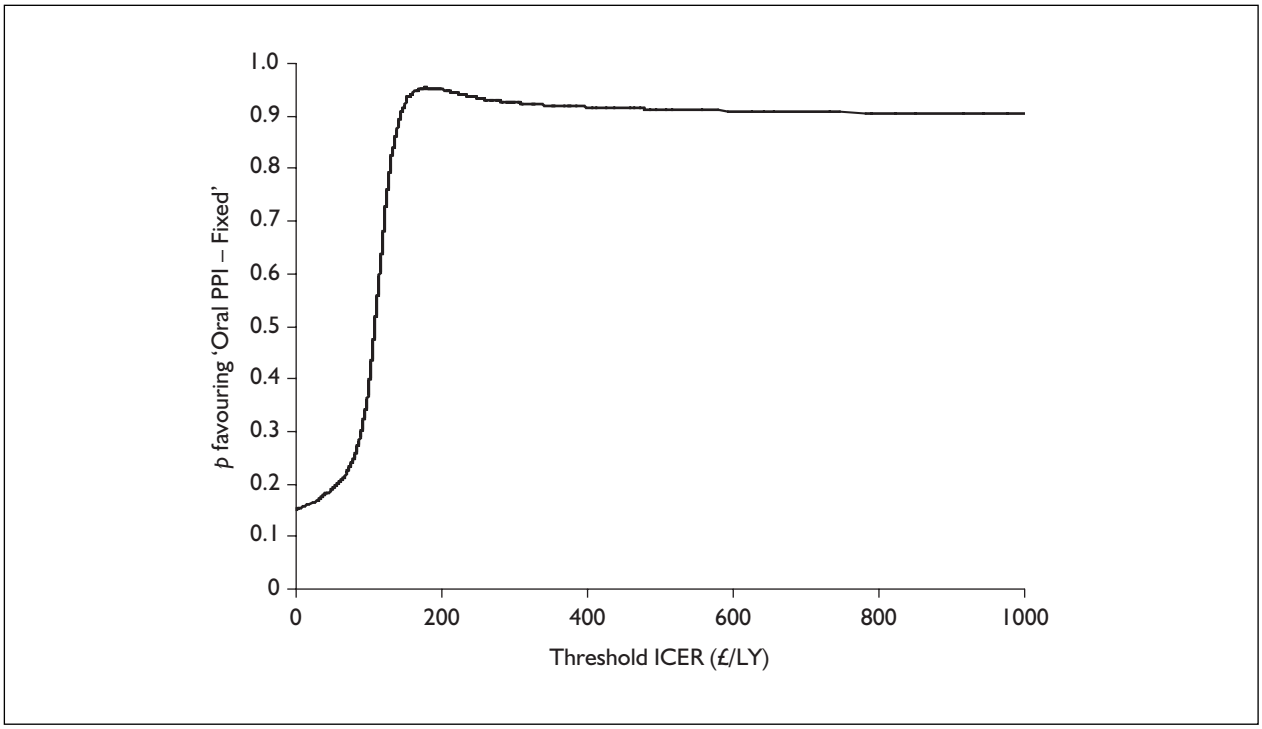

FIGURE 18 *CEAC for 'Oral PPI – Fixed' versus 'Oral PPI – Variable' (long-term)*

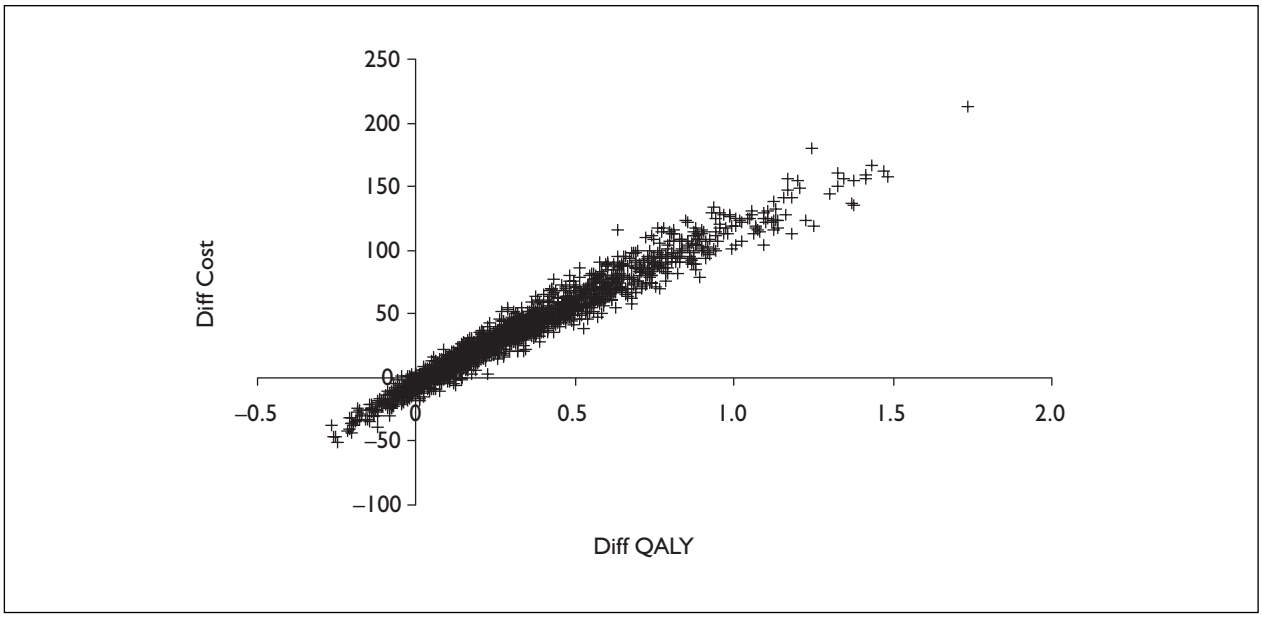

FIGURE 19 *Scatterplot for 'Oral PPI – Fixed' versus 'Oral PPI – Variable' (long-term)*

have had less co-morbidity, although a detailed analysis of this was not practicable from the information available. Furthermore, PPI treatment in Asian patients may produce a more profound reduction in acid secretion because of a lower parietal cell mass, a higher prevalence of *H. pylori* infection and a higher proportion of genetically determined slow metabolisers of PPIs. We acknowledge that the dependence on Asian studies for the post-endoscopy comparison may mean that these results are somewhat optimistic. However, given the robust nature of our results, we believe that the policy conclusions are not sensitive to this dependence.

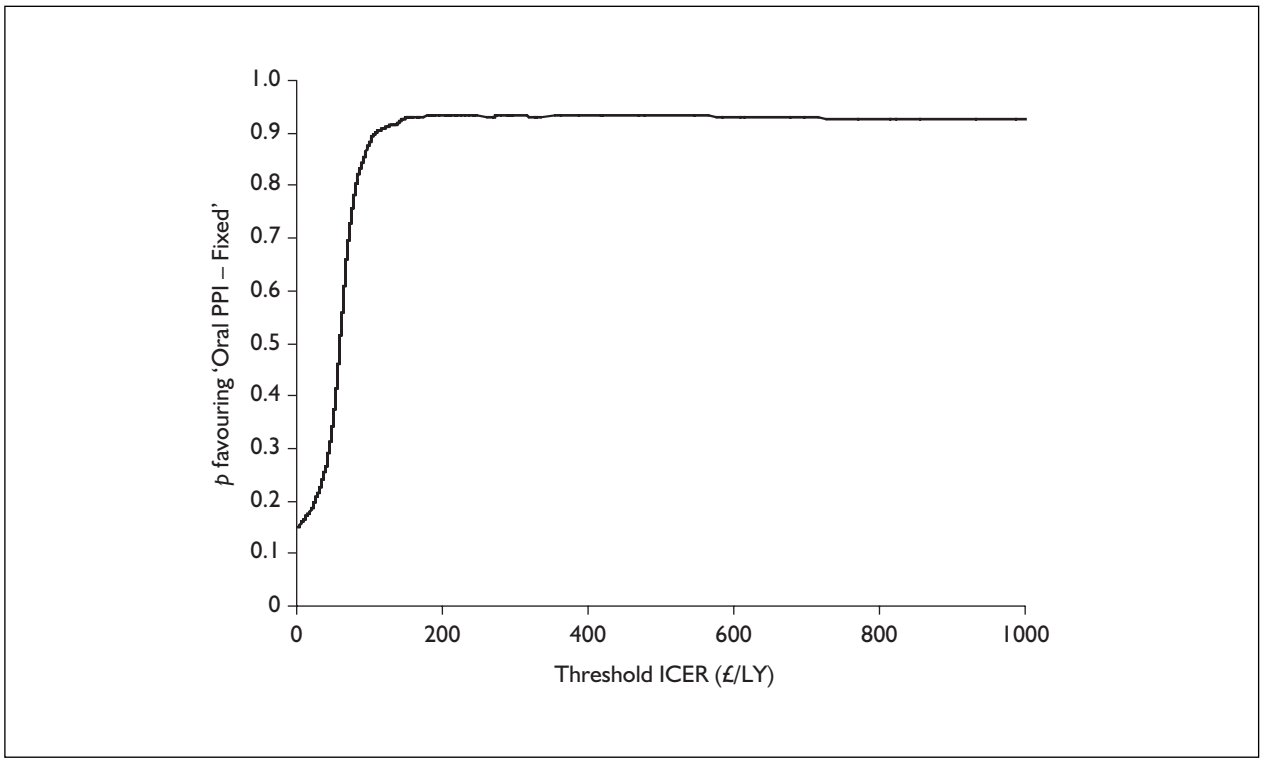

FIGURE 20 *CEAC for 'Oral PPI – Fixed' versus 'IV PPI – Fixed' (long-term)*

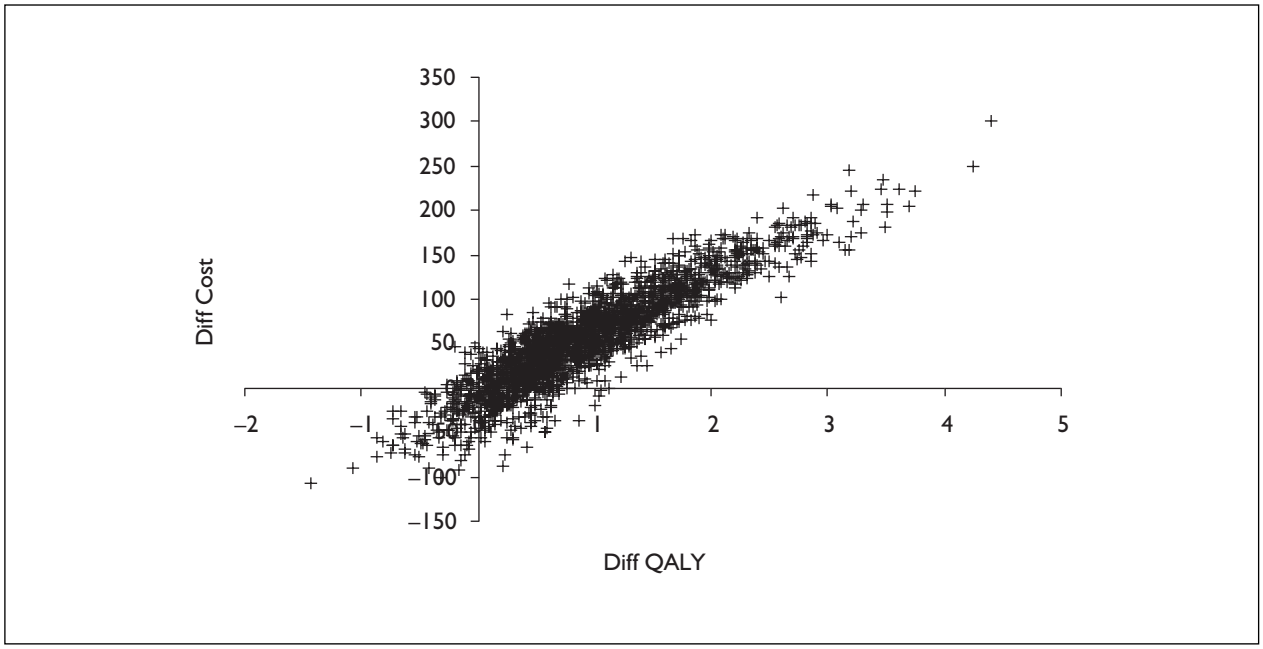

FIGURE 21 *Scatterplot for 'Oral PPI – Fixed' versus 'IV PPI – Fixed' (long-term)*

TABLE 21 *Base-case results for alternative version of the acute model*

Strategy			Cost (£)		Long-term outcome (LY)	
Rx before	**End Rx**	**Option after**	**Mean**	**QSE**	**Mean**	**QSE**
Nothing	No	Variable	834	2	9.99	0.02
Nothing	Yes	Variable	814	1	10.26	0.02
Oral PPI	No	Variable	845	2	10.06	0.02
Oral PPI	Yes	Variable	824	1	10.33	0.02
I.v. PPI	No	Variable	831	2	9.95	0.02
I.v. PPI	Yes	Variable	811	1	10.22	0.02
Nothing	No	Fixed	883	2	10.41	0.02
Nothing	Yes	Fixed	842	1	10.52	0.02
Oral PPI	No	Fixed	896	2	10.49	0.02
Oral PPI	Yes	Fixed	854	1	10.61	0.02
I.v. PPI	No	Fixed	825	1	9.53	0.02
I.v. PPI	Yes	Fixed	802	1	9.74	0.02

TABLE 22 *Comparison of non-dominated strategies for long-term outcomes*

Rx before	**Option after**	**Mean difference**		**ICER (£/LY)**		
		Cost	**LY**	**Estimate**	**QCI**	
Only simply dominated strategies excluded						
I.v PPI	Fixed					
I.v PPI	Variable	9	0.48	19	17	21
Nothing	Variable	3	0.04	73	59	96
Oral PPI	*Variable*	*11*	*0.08*	*141*	*127*	*159*
Nothing	Fixed	17	0.19	91	82	102
Oral PPI	Fixed	12	0.08	144	130	161
Simply dominated and weakly dominated strategies excluded						
I.v. PPI	Fixed					
I.v. PPI	Variable	9	0.48	19	17	21
Nothing	Variable	3	0.04	73	59	96
Nothing	Fixed	28	0.27	106	99	113
Oral PPI	Fixed	12	0.08	144	130	161

Chapter 7

What is the efficacy of *H. pylori* eradication therapy in preventing recurrent bleeding from peptic ulcer in *H. pylori*-positive patients compared with ulcer-healing antisecretory therapy with or without subsequent long-term prophylactic antisecretory therapy?

Description of studies

Seven studies fulfilled the inclusion criteria and contained data for the first planned meta-analysis: *H. pylori* eradication therapy versus non-eradication therapy with an antisecretory but without subsequent long-term maintenance antisecretory therapy.[141–147] Detailed characteristics of the studies are shown in the *Table 23*. A total of 375 patients were included in the eradication therapy group and 203 in the group receiving non-eradication therapy. Details of eradication and antisecretory treatment of included studies are summarised in *Table 24*. Three studies prescribed, as eradication regimen, a bismuth-based triple therapy; three other studies prescribed omeprazole plus amoxicillin; in one study, both eradication regimens were used. These eradication regimens were administered for 10–14 days.

With respect to the second planned meta-analysis (*H. pylori* eradication therapy versus non-eradication therapy with an antisecretory and followed by long-term maintenance antisecretory therapy), three studies fulfilled the inclusion criteria;[148–150] detailed characteristics are also shown in *Table 23*. A total of 257 patients were included in the eradication therapy group and 213 received long-term maintenance antisecretory therapy. Details of eradication and antisecretory treatment of included studies are summarised in *Table 24*. One study prescribed, as eradication regimen, a bismuth-based triple therapy; a second study prescribed omeprazole plus amoxicillin; in a third study, both regimens were used. These eradication regimens were administered for 7–12 days. Antisecretory maintenance therapy with ranitidine 150 mg once daily was administered in two studies; in a third study, ranitidine 150 mg once daily or omeprazole 20 mg once daily was used as maintenance regimen.

Forty-eight studies were excluded and reasons for exclusion are summarised in *Table 25*. Causes of exclusion were: re-bleeding not evaluated, less than 6-months' follow-up, no control group (all patients received *H. pylori* eradication therapy), no previous UGI bleeding, all patients had received NSAIDs, no *H. pylori* eradication group, control group included only *H. pylori*-negative patients or patients with unknown *H. pylori* status.

Quantitative analysis

Seven studies with a total of 578 patients were included in the first meta-analysis.[141–147] The mean percentage of re-bleeding in the *H. pylori* eradication therapy group was 2.9% (95% CI 1.6 to 5.2%); in the group given non-eradication antisecretory therapy without subsequent long-term maintenance antisecretory therapy, it was 20% (95% CI 14 to 25%). There was no statistically significant heterogeneity among the trials (test for heterogeneity: $p = 0.41$), so the fixed effect model was applied. The OR was 0.17 (95% CI 0.10 to 0.32) (*Figure 22*). The RR was 0.22 (95% CI 0.12 to 0.40). The ARR or 'risk difference' between the two groups was –0.15 (95% CI –0.21 to –0.09). The NNT with eradication therapy to prevent one episode of re-bleeding, compared with non-eradication therapy, was 7 (95% CI 5 to 11).

Three studies with a total of 470 patients were included in the second meta-analysis. The mean percentage of re-bleeding in the *H. pylori*

TABLE 23 *Characteristics of included studies*

Study	Methods	Participants	Interventions[a]	Outcomes	Notes	Allocation concealment[b]
Arkkila, 2003[141]	Randomised Not double-blinded	DU and GU Some patients used NSAIDs (19%) or ASA (35%)	OBAM/OA vs O No maintenance antisecretory therapy	Re-bleeding Follow-up 12 months in all patients	*Q* = 3 Eradication rates: 92% in eradication groups and 4% in antisecretory group	B
Bataga, 1997[142]	Randomised Not double-blinded	DU NSAID use unknown	BAM (with or without endoscopic haemostasis) vs H_2RA No maintenance antisecretory therapy	Re-bleeding Follow-up 12 months in all patients	*Q* = 1 Eradication rates not provided in any group Abstract form only (no complete article)	B
Graham, 1993[143]	Randomised Not double-blinded	DU and GU Some patients (28%) used NSAIDs	BMT vs ranitidine No maintenance antisecretory therapy	Re-bleeding Mean follow-up 12 months in eradication group and 9 months in antisecretory group	*Q* = 2 Eradication rates: 81% in eradication group and 0% in antisecretory group	B
Jaspersen, 1995[144]	Randomised Not double-blinded	DU No patient used NSAIDs	OA vs O No maintenance antisecretory therapy	Re-bleeding Follow-up 12 months in all patients	*Q* = 2 Eradication rates: 83% in eradication group and 5% in antisecretory group	B
Lai, 2000[145]	Randomised Not double-blinded	DU No patient used NSAIDs	BAM vs B No maintenance antisecretory therapy	Re-bleeding Mean follow-up 53 months	*Q* = 3 Eradication rates: 85% in eradication group and 2% in antisecretory group	A
Riemann, 1997[148]	Randomised Not double-blinded	DU and GU No patient used NSAIDs	OA vs ranitidine (as maintenance antisecretory therapy)	Re-bleeding Mean follow-up 19 months	*Q* = 2 Eradication rates: 89% in eradication group and not provided in antisecretory group	A

continued

TABLE 23 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions[a]	Outcomes	Notes	Allocation concealment[b]
Rokkas, 1995[146]	Randomised Not double-blinded	DU Some patients (6%) used NSAIDs	OA vs O No maintenance antisecretory therapy	Re-bleeding Follow-up 12 months in all patients	*Q* = 3 Eradication rates: 81% in eradication group and 13% in antisecretory group	A
Santander, 1996[149]	Not randomised Not double-blinded	DU and GU No patient used NSAIDs	OA/OC/BAM vs ranitidine/O (as maintenance antisecretory therapy)	Re-bleeding Follow-up 12 months in all patients	*Q* = 1 Eradication rates: 100% in eradication group (retreatment was prescribed in failures) and not provided in antisecretory group	B
Sung, 1997[150]	Randomised Not double-blinded	DU and GU No patient used NSAIDs	BAM vs ranitidine (as maintenance antisecretory therapy)	Re-bleeding Median follow-up 12 months	*Q* = 2 Eradication rates: 98% in eradication group and 6% in antisecretory group	B
Vcev, 1996[147]	Randomised Not double-blinded	DU NSAID use unknown	OA vs O No maintenance antisecretory therapy	Re-bleeding Follow-up 12 months in all patients	*Q* = 1 Eradication rates: 72% in eradication group, and 0% in antisecretory group	B

ASA, acetylsalicylic acid (taken by the patient previous to the inclusion in the study); NSAIDs, non-steroidal anti-inflammatory drugs (taken by the patient previous to the inclusion in the study); *Q*, quality score (Jadad scale, from 0 to 5 points; see appropriate section).

[a] Intervention (treatment): A, amoxicillin; B, bismuth; C, clarithromycin; M, metronidazole; O, omeprazole; T, tetracycline; details of eradication and antisecretory treatment are provided in additional *Table 23*.

[b] Cochrane ranking: Grades A and B.

TABLE 24 *Details of eradication and antisecretory treatments in included studies*

Study	Eradication treatment	Antisecretory treatment
Arkkila, 2003[141]	Bismuth subcitrate, 120 mg q.d.s., for 14 days, amoxicillin, 500 mg q.d.s., metronidazole, 400 mg t.d.s., and omeprazole, 40 mg o.d., for 28 days; amoxicillin, 500 mg q.d.s., for 14 days, and omeprazole, 40 mg o.d., for 28 days	Omeprazole, 40 mg o.d., for 28 days plus placebo q.d.s., for 14 days
Bataga, 1997[142]	H_2-antagonist (dose not stated) for 7 days, followed by bismuth subcitrate, 240 mg b.d., metronidazole, 500 mg t.d.s., and amoxicillin 500 mg t.d.s., for 10 days (with and without endoscopic haemostasis with pure ethanol)	H_2-antagonist (dose not stated) and antacids for 7 days
Graham, 1993[143]	Bismuth subsalicylate 5–8 tablets daily, metronidazole, 250 mg t.d.s., and tetracycline, 500 mg q.d.s., for 14 days, and ranitidine, 300 mg o.d., until ulcer healing	Ranitidine, 300 mg o.d., until ulcer healing
Jaspersen, 1995[144]	Omeprazole, 40 mg o.d. and amoxicillin, 1 g b.d., for 14 days	Omeprazole, 40 mg o.d., for 14 days
Lai, 2000[145]	Metronidazole, 300 mg q.d.s., and amoxicillin, 500 mg q.d.s., for 14 days, and tripotassium dicitratobismuthate, 120 mg q.d.s., until ulcer healing	Tripotassium dicitratobismuthate, 120 mg q.d.s., until ulcer healing
Riemann, 1997[148]	Omeprazole, 60 mg b.i.d, and amoxicillin, 750 mg t.d.s., for 10 days, followed by omeprazole, 20 mg o.d., for 30 days	Ranitidine, 300 mg o.d., for 6 weeks, followed by antisecretory maintenance therapy with ranitidine, 150 mg o.d.
Rokkas, 1995[146]	Omeprazole, 20 mg o.d. for 30 days, followed by omeprazole, 20 mg t.d.s., and amoxicillin, 500 mg q.d.s., for 14 days	Omeprazole, 20 mg o.d., for 30 days, followed by omeprazole, 20 mg t.d.s., for 14 days
Santander, 1996[149]	Omeprazole, 20 mg b.d., and clarithromycin, 500 mg t.d.s., for 12 days; or omeprazole, 20 mg b.d., and amoxicillin, 500 mg t.d.s., for 10 days; or bismuth subsalicylate, 240 mg b.d., for 30 days, metronidazole, 500 mg t.d.s., for 10 days, and amoxicillin, 500 mg t.d.s., for 10 days	Antisecretory maintenance therapy with ranitidine, 150 mg o.d., or omeprazole, 20 mg o.d.
Sung, 1997[150]	Bismuth subsalicylate, 120 mg q.d.s., metronidazole, 400 mg q.d.s., tetracycline, 500 mg q.d.s., and ranitidine, 300 mg o.d., for 7 days	Ranitidine, 300 mg o.d., for 6 weeks, followed by antisecretory maintenance therapy with ranitidine, 150 mg o.d.
Vcev, 1996[147]	Omeprazole, 20 or 40 mg o.d, and amoxicillin, 500 mg q.d.s. or 1 g b.d., for 14 days, followed by omeprazole, 20 mg o.d., for 14 days	Omeprazole, 20 mg o.d., for 30 days

b.d., two times per day; o.d., once per day; q.d.s., four times per day; t.d.s., three times per day.

eradication therapy group was 1.6% (95% CI 0.6 to 3.9%); in the group given non-eradication antisecretory therapy with subsequent long-term maintenance antisecretory therapy, it was 5.6% (95% CI 2.5 to 8.7%). There was no statistically significant heterogeneity (test for heterogeneity: $p = 0.52$; $I^2 = 0\%$), so the fixed effect model was applied. The OR was 0.24 (95% CI 0.09 to 0.67) (*Figure 23*). The ARR or 'risk difference' between the two groups was –0.05 (95% CI –0.08 to –0.01). The NNT with eradication therapy to prevent one episode of re-bleeding, compared with long-term maintenance antisecretory therapy, was 20 (95% CI 12 to 100).

Sub-analyses

Quality of studies

Regarding the first meta-analysis, when only the three high-quality studies (having a Jadad score of 3) were included (see *Table 23*), the OR was 0.27 (95% CI 0.12 to 0.61), RR 0.33 (95% CI 0.15 to 0.70), ARR –0.10 (95% CI –0.17 to –0.03) and NNT 10 (95% CI 6 to 33) (fixed effect model). When trying to perform separate comparisons depending on the quality of studies in the second meta-analysis, all studies were classified as low quality (one of which was non-randomised[149]) and therefore the influence of this variable could not be adequately assessed.

TABLE 25 *Characteristics of excluded studies*

Study	Reason for exclusion
Adamek, 1994[151]	Re-bleeding not evaluated
Altorjay, 2000[152]	Re-bleeding not evaluated
	Less than 6 months' follow-up
Amendola, 1999[153]	No control group (all patients received *H. pylori* eradication therapy)
Arkkila, 2001[154]	Insufficient data (no response from the authors)
Capurso, 2001[155]	No previous UGI bleeding
	No control group (all patients received *H. pylori* eradication therapy)
Chan, 1997[156]	All patients received NSAIDs
Chan, 1998[157]	Re-bleeding not evaluated
Chan, 2001[158]	All patients received NSAIDs
Chan, 2002[159]	All patients received NSAIDs
Chan, 2002[160]	All patients received NSAIDs
	No previous UGI bleeding in one group
Chen, 1996[161]	No control group (all patients received *H. pylori* eradication therapy)
	Less than 6 months' follow-up
Chen, 1998[162]	No control group (all patients received *H. pylori* eradication therapy)
	Less than 6 months' follow-up
Di Mario, 1997[163]	No control group (all patients received *H. pylori* eradication therapy)
Fakhreih, 1995[164]	No control group (all patients received *H. pylori* eradication therapy)
Gisbert, 1995[165]	No control group [all patients (one) received *H. pylori* eradication therapy]
Gisbert, 1999[166]	No control group (all patients received *H. pylori* eradication therapy)
Hsieh, 2001[167]	Re-bleeding not evaluated
Huelin Benitez, 1998[168]	No control group (all patients received *H. pylori* eradication therapy)
Jaspersen, 1994[169]	No control group (all patients received *H. pylori* eradication therapy)
Jaspersen, 1994[170]	No control group (all patients received *H. pylori* eradication therapy)
	Less than 6 months' follow-up
Jaspersen, 1995[171]	No control group (all patients received *H. pylori* eradication therapy)
Krizman, 1997[172]	No control group (all patients received *H. pylori* eradication therapy)
Kung, 1997[173]	No control group (all patients received *H. pylori* eradication therapy)
	Less than 6 months' follow-up
Labenz, 1994[174]	No control group (all patients received *H. pylori* eradication therapy)
Lai, 1998[175]	No control group (all patients received *H. pylori* eradication therapy)
Lai, 2000[176]	Re-bleeding not evaluated
Lee, 1998[177]	Re-bleeding not evaluated
Lee, 1999[178]	No control group (all patients received *H. pylori* eradication therapy)
Lin, 1999[179]	No *H. pylori* eradication group
Loperfido, 2001[180]	No control group (all patients received *H. pylori* eradication therapy)
Macri, 1998[181]	No control group (all patients received *H. pylori* eradication therapy)
Martino, 1998[182]	No control group (all patients received *H. pylori* eradication therapy)
	No previous UGI bleeding
Pamos, 1998[183]	Control group included only *H. pylori*-negative patients or patients with unknown *H. pylori* status
Pauly, 1997[184]	No control group (all *H. pylori*-positive patients received eradication therapy)
Pazzi, 1996[185]	No control group (all patients received *H. pylori* eradication therapy)
Pazzi, 1999[186]	No control group (all patients received *H. pylori* eradication therapy)
Pellicano, 2001[187]	No control group (all patients received *H. pylori* eradication therapy)
Pica, 1996[188]	No control group (all patients received *H. pylori* eradication therapy)
Romero Gomez, 2000[189]	Re-bleeding not evaluated
Ruiz Gomez, 2002[190]	Re-bleeding not evaluated
Seppala, 1995[191]	Insufficient data (no response from the authors)
Sheu, 1996[192]	Re-bleeding not evaluated
Sheu, 1999[193]	Re-bleeding not evaluated
Sheu, 2002[87]	No control group (all patients received *H. pylori* eradication therapy)
	Less than 6 months' follow-up
Siu, 1999[194]	No control group (all patients received *H. pylori* eradication therapy)
Sonnenberg, 1999[195]	No previous UGI bleeding
van der Voort, 2001[196]	Stress ulcer bleeding
	No previous UGI bleeding
Vergara, 2000[197]	No control group (all patients received *H. pylori* eradication therapy)

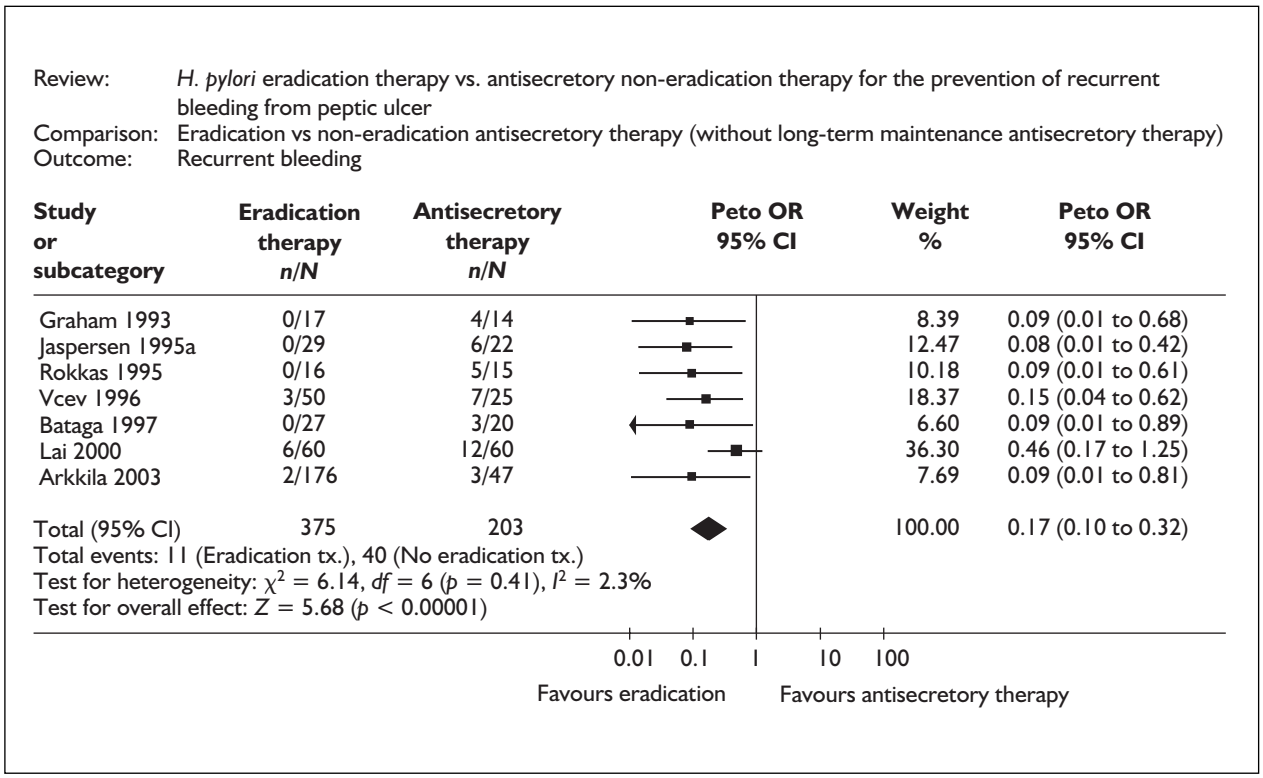

FIGURE 22 *Recurrent bleeding from peptic ulcer with* H. pylori *eradication therapy versus antisecretory non-eradication therapy without long-term maintenance antisecretory therapy*

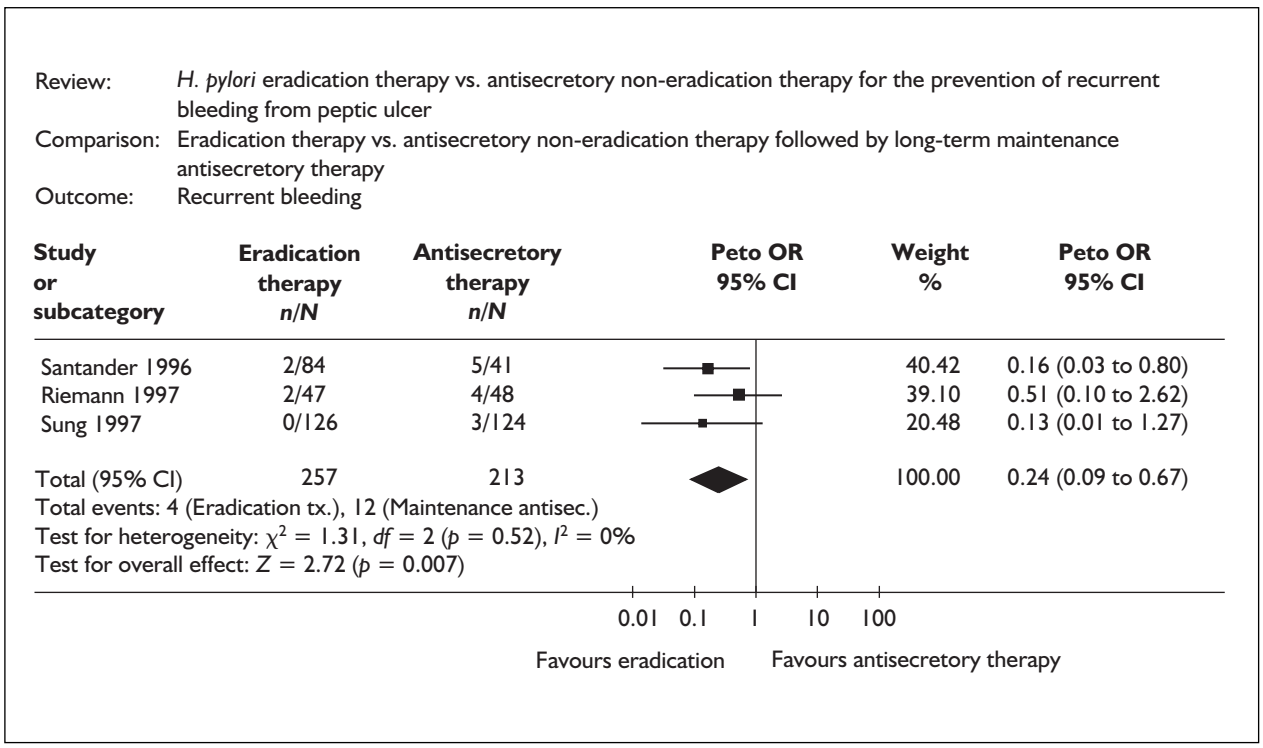

FIGURE 23 *Recurrent bleeding from peptic ulcer with* H. pylori *eradication therapy versus antisecretory non-eradication therapy followed by long-term maintenance antisecretory therapy*

Location of ulcer disease

In the first meta-analysis of seven studies,[141–147] all but two studies included patients with only DUs (see *Table 23*), thus precluding adequate subanalysis of the results depending on the ulcer location (duodenal or gastric). Furthermore, in the second meta-analysis, the three studies[148–150] included patients with both DU and GU, again precluding this planned subanalysis.

Duration of follow-up

From the 10 studies included in the two meta-analyses, all but two had a similar follow-up of 12 months (see *Table 23*). Therefore, the influence of this variable on the outcome of the review (e.g. rate of re-bleeding) could not be adequately assessed.

NSAID use

In the first meta-analysis, one of the patients who had recurrence of haemorrhage in the study by Lai and colleagues[145] took NSAIDs at the time of re-bleeding. Thus, subanalysis of the data excluding this patient resulted in a re-bleeding rate of 2.7% (95% CI 1.5 to 5%) in the group receiving *H. pylori* eradication therapy (OR 0.17, 95% CI 0.08 to 0.33), RR 0.20 (95% CI 0.11 to 0.38), ARR –0.15 (95% CI –0.21 to –0.10) and NNT 7 (95% CI 5 to 10) (fixed effect model).

In the second meta-analysis, the two patients suffering from recurrence of haemorrhage in the study by Riemann and colleagues[148] had taken NSAIDs at the time of re-bleeding (and were *H. pylori* negative). Subanalysis of the data excluding these two patients in the group receiving *H. pylori* eradication therapy gave a re-bleeding rate of 0.78% (95% CI 0.22 to 2.8%), RR 0.16 (95% CI 0.04 to 0.58), OR 0.15 (95% CI 0.04 to 0.55), ARR –0.05 (95% CI –0.09 to –0.02) and NNT 20 (95% CI 11 to 50) (fixed effect model).

H. pylori *eradication failure*

In the study by Lai and colleagues,[145] four out of the six patients with a re-bleeding episode in the eradication treatment group failed eradication of *H. pylori* infection. In the study by Vcev and colleagues,[147] all three patients with recurrence of bleeding had failed eradication of *H. pylori* infection with antibiotic therapy. Therefore, when these seven patients were excluded from the analysis, re-bleeding occurred in 1.1% of patients (95% CI 0.4 to 2.7%) in the *H. pylori* eradication therapy group; the OR was 0.10 (95% CI 0.05 to 0.19), RR 0.10 (95% CI 0.05 to 0.24), ARR –0.17 (95% CI –0.23 to –0.12) and NNT 6 (95% CI 3 to 7) (fixed effect model).

Recurrence of H. pylori *infection*

In the first meta-analysis, one of the patients who had recurrence of haemorrhage in the study by Lai and colleagues[145] had recurrence of *H. pylori* infection at the time of re-bleeding, and in the second meta-analysis *H. pylori* recurrence occurred in the two patients having recurrence of haemorrhage in the study by Santander and colleagues.[149]

Re-bleeding in patients with successful eradication of H. pylori *infection*

Re-bleeding in patients in whom *H. pylori* eradication was achieved (and did not receive maintenance antisecretory therapy) in studies included in the meta-analysis and in other uncontrolled studies from the literature are summarised in *Table 26*. Overall, from 1370 patients in whom *H. pylori* infection had been eradicated, the weighted mean rate of re-bleeding was 1.24% (95% CI 0.8 to 2%). However, as the follow-up time varied markedly among studies, this factor needs to be taken into account. Thus, follow-up periods in each study, measured in patient-years, and respective yearly bleeding (in patient-years^{-1}), are also included in *Table 26*. A total of 2179 patient-years of follow-up was calculated from all studies. A total of 17 episodes of re-bleeding was observed among patients with *H. pylori* eradication success, yielding a yearly recurrence of 0.78% (95% CI 0.5 to 1.2) patient-years^{-1}.

Conclusion

The present meta-analysis showed that re-bleeding was less frequent after *H. pylori* eradication therapy than after non-eradication antisecretory therapy, either with or without subsequent long-term maintenance antisecretory therapy, with ORs of 0.17–0.25. This advantage is expressed by an NNT with eradication therapy to prevent one episode of re-bleeding of only seven compared with ulcer healing treatment alone, and 20 when compared with long-term maintenance antisecretory therapy (mainly because the risk of re-bleeding with maintenance antisecretory therapy was relatively low).

TABLE 26 *Re-bleeding in* H. pylori *patients cured of* H. pylori *infection and no maintenance antisecretory treatment*

Study	No. of patients	Mean follow-up (months)	Re-bleeding (%)	Notes	Follow-up (patient-years)	Yearly re-bleeding (%)
Arkkila, 2003[141]	176	12	2 (1.1%)	The two patients had Dieulafoy's ulcer	176	1.1
Bataga, 1997[142]	–	12	0 (0%)			
Graham, 1993[143]	13	12	0 (0%)		13	0
Jaspersen, 1995[144]	24	12	0 (0%)		24	0
Lai, 2000[145]	41	53	2 (4.9%)	One of these patients took NSAIDs at the time of re-bleeding; another patient had recurrence of *H. pylori* infection at the time of re-bleeding	177	3.4
Riemann, 1997[148]	42	19	2 (4.8%)	The two patients took NSAIDs at the time of re-bleeding (and were *H. pylori* negative)	66	3
Rokkas, 1995[146]	13	12	0 (0%)		13	0
Santander, 1996[149]	84	12	2 (2.4%)	The two patients had recurrence of *H. pylori* infection at the time of re-bleeding	84	2.4
Sung, 1997[150]	108	12	0 (0%)		108	0
Vcev, 1996[147]	36	12	0 (0%)		36	0
Studies not included in the meta-analysis						
Amendola, 1999[153]	42	24	0 (0%)		84	0
Di Mario, 1997[163]	40	21	0 (0%)		70	0
Fakhreih, 1995[164]	61	12	3 (4.9%)		61	4.9
Gisbert, 1999[166]	111	12	0 (0%)		111	0
Huelin Benitez, 1998[168]	80	18	1 (1.2%)	This patient took NSAIDs at the time of re-bleeding	120	0.8
Jaspersen, 1995[171]	29	12	1 (3.4%)	This patient had recurrence of *H. pylori* infection at the time of re-bleeding	29	3.4
Krizman, 1997[172]	33	17	0 (0%)		47	0
Labenz, 1994[174]	42	17	0 (0%)		59	0
Lai, 1998[175]	29	11	0 (0%)		27	0
Lee, 1999[178]	92	15	0 (0%)		115	0
Loperfido, 2001[180]	38	24	0 (0%)		76	0
Macri, 1998[181]	21	48	0 (0%)		84	0
Pamos, 1998[183]	31	18	0 (0%)		46	0
Pazzi, 1999[186]	39	47	4 (10.3%)		153	2.6
Pellicano, 2001[187]	46	47	0 (0%)		180	0
Pica, 1996[188]	6	12	0 (0%)		6	0
Vergara, 2000[197]	93	27	0 (0%)		209	0
Total	1370		17 (1.24%)		2179	0.78

Chapter 8

What is the efficacy of prophylactic PPI therapy in preventing peptic ulcer bleeding in NSAID users?

Description of studies

The initial search strategy resulted in a total of 970 references, of which 33 RCTs met the inclusion criteria: 18 misoprostol trials; nine standard dose H_2RA trials; three double-dose H_2RA trials; and four PPI trials. At the July 2001 update, four potentially relevant articles were found and two of these fulfilled the inclusion criteria. At the July 2002 update, a further five studies out of 200 potentially relevant articles fulfilled the inclusion criteria.[48] Further updated searches in August 2003 and August 2004 did not reveal any further new studies. Therefore, this updated review included a total of 40 RCTs. Some studies considered more than one active intervention. The characteristics of included studies are described in *Table 27*).

Fourteen RCTs were excluded from the meta-analysis for the following reasons: duplicate publication (two studies), inability to extract required data (two studies), not reporting the outcomes predetermined in this review (three studies), acute, healing or treatment only studies (six studies) or study and control groups different to those predetermined in this review (one study). The characteristics of excluded studies are described in *Table 28*).

Quantitative analysis

PPIs

Eight RCTs with 2181 patients assessed the effect of PPIs on the prevention of NSAID-induced UGI toxicity.[201,205,207,210,214,215,218,235]

PPIs compared with placebo

Endoscopic ulcers

Two RCTs compared omeprazole with placebo.[207,210] Two studies compared a PPI with placebo and with misoprostol. Of these, one used lansoprazole[214] and the other used omeprazole.[215] One study compared pantoprazole with placebo.[201]

Five RCTs that included 1216 patients reported the incidence of total endoscopic ulcers between 3 and 12 months. PPIs significantly reduced the incidence of endoscopic ulcers compared with placebo (Peto OR 0.23, 95% CI 0.18 to 0.31). Four trials that included 840 patients reported this outcome between 3 and 12 months. PPIs significantly reduced the risk of endoscopic duodenal ulcers (Peto OR 0.18, 95% CI 0.10 to 0.34) (see *Figure 24*).

In the five RCTs including 1187 patients, PPIs significantly reduced the risk of endoscopic gastric ulcers compared with placebo (Peto OR 0.29, 95% CI 0.21 to 0.40) (see *Figure 25*).

Adverse effects, drop-outs and symptoms

Two RCTs[214,215] reported the overall drop-out rate in 833 patients, which was significantly different between the PPI and placebo groups (Peto OR 0.88, 95% CI 0.57 to 1.35). Four RCTs reported drop-outs due to side-effects in 1113 patients. This was not different between the two groups, the Peto OR being 1.21 (95% CI 0.65 to 2.22). Individual side-effects such as diarrhoea, abdominal pain and flatulence were comparable between PPI and placebo. However, in two RCTs[207,215] including 345 patients, PPIs significantly reduced "dyspeptic symptoms" as defined by the authors. The Peto OR was 0.43 (95% CI 0.24 to 0.77).

PPI (omeprazole) compared with H_2RA (ranitidine)

In one RCT of 425 patients, comparing omeprazole 20 mg daily with ranitidine 150 mg twice daily for NSAID prophylaxis,[235] PPI was superior to standard-dose ranitidine for the prevention of both GUs (RR 0.32, 95% CI 0.17 to 0.62) and DUs (RR 0.11, 95% CI 0.01 to 0.89). PPI was superior in preventing total endoscopic ulcers (RR 0.28, 95% CI 0.15 to 0.51). However, the total clinical ulcer-related events (RR 3.07, 95% CI 0.13 to 74.97) and drop-outs due to adverse effects (RR 1.90, 95% CI 0.77 to 4.67) were comparable for PPI and H_2RA.

PPI compared with misoprostol

Endoscopic ulcers

Two secondary prophylaxis trials with a total of 838 patients[214,215] compared a PPI with

TABLE 27 *Characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Agrawal, 1991[198]	Randomised, double-blind controlled Sample size at entry: Misoprostol: 179 Sucralfate: 177 Study duration: 12 weeks	Patients: OA Setting: clinic outpatients Median age: 60 years Range: 30–82 years Sex: 56% female Length on NSAIDs? Type of NSAID: ibuprofen, naproxen, piroxicam Dose of NSAID: 22.4% Previous PUs: 22% Previous abdominal pain: inclusion criteria *H. pylori* positive?	Misoprostol 200 μg × 4 = 800 μg Sucralfate 1 g × 4 = 4 g	Endoscopic GUs (>3 mm) Endoscopic DUs (>3 mm) GUs (>5 mm) Withdrawals overall Withdrawals due to side-effects Drop-out due to diarrhoea Drop-out due to dyspepsia	Quality = 2	D
Agrawal, 1995[199]	Randomised, single-blind	Patients: RA and OA Length on NSAID: 2.5 years Previous PUs: all, secondary prophylaxis study Type of NSAID: diclofenac 50 mg 2–3/day	Misoprostol 200 μg 2–3/day (400–600 μg) + diclofenac Placebo + diclofenac	Endoscopic GUs Endoscopic DUs Total gastroduodenal ulcers Drop-outs due to side-effects Abdominal pain Diarrhoea Dyspepsia Nausea	Quality = 1	D
Berkowitz, 1987[200]	Randomised, double-blind, placebo-controlled Sample size at entry: Ranitidine: 25 Placebo: 25 Study duration: 4 weeks	Patients? Setting: clinic outpatients Mean age: 28.5 years SD: 2.2 years Sex: all male Length of NSAIDs: 4 at end Type of NSAIDs: aspirin Dose of NSAIDs: 50 mg q.d.s. Previous PUs? Previous abdominal pain? *H. pylori* positive?	Ranitidine 150 mg b.d. and 650 mg aspirin q.d.s. Placebo b.d. and 650 mg aspirin q.d.s.	Endoscopic GU (>3 mm) Endoscopic DU (>3 mm) Withdrawals overall Withdrawals due to side-effects	Quality = 3	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Bianchi Porro, 2000[201]	Randomised double-blind, placebo controlled 12-week study Pantoprazole : 70 Placebo: 34	Patients: OA + RA outpatients NSAIDs: diclofenec, ketoprofen, indocid	Placebo vs pantoprazole 40 mg/day	Lanza Score 4 = endoscopic ulcer adverse effects	Quality = 3	B
Bocanegra, 1998[202]	Randomised, double-blind, placebo controlled	Patients: OA Setting: clinics, outpatients with past ulcers Mean age: 62 years Type of NSAID: diclofenac	(1) Diclofenac 75 mg b.d. (2) Diclofenac 75 mg + misoprostol 200 μg b.d. (3) Diclofenac 50 mg + misoprostol 200 μg t.d.s. (4) Placebo	Endoscopic GUs (>3 mm) Endoscopic DUs (>3 mm) Side-effects Side-effects causing withdrawal Withdrawal overall	Quality = 3	D
Bolten, 1992[203]	Randomised controlled trial	Patients: OA Setting: outpatient Median age: 59.2 years SD: 12.4 years Sex: 76% female Length on NSAIDs: ? Type of NSAID: diclofenac Dose of NSAID: 50 mg b.d. or t.d.s. Previous PUs: ? Previous abdominal pain: inclusion criteria *H. pylori* positive: ?	Misoprostol 400–600 μg/day (Arthrotec) Placebo	Endoscopic ulcers (gastric, duodenal, total) at 1 month Drop-outs overall	Quality = 4	D
Chan, 2001[204]	Randomised, double-blind study of misoprostol + naproxen vs nabumatone 24-week study after initial healing phase	Participants: high-risk patients with NSAID ulcers recently healed with PPI	Naproxen + misoprostol 200 μg b.d. vs nabumatone 1000–1500 mg	Ulcers or bleeding Adverse events	Quality = 4	A
Chan, 2001 (abstract)[205]	Randomised, double-blind Omeprazole + diclofenac vs celecoxib	Participants *H. pylori* negative arthritis patients after ulcer healing	Diclofenac 75 mg b.d. + omprazole 20 mg daily vs celecoxib 200 mg b.d.	Recurrent ulcer bleeding	Quality = 3	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Chandrasekaran, 1991[206]	Randomised, placebo controlled Sample size at entry: Placebo: 45, Misoprostol: 45	Participants: RA, OA and spondyloarthropathy patients Mean age 39.9 years, 47% male, 1 month on NSAID prophylaxis Free of GI symptoms Normal UGI endoscopy at baseline No CVD, renal disease, hepatic disease, IBD, malignancy, history of GI surgery	Misoprostol 200 μg t.d.s. Placebo	Outcomes endoscopic ulcers	Quality = 4	D
Cullen, 1998[207]	Randomised, placebo-controlled Sample size at entry: Omeprazole: 83, Placebo: 85	Not available as presented as poster	Omeprazole 20 mg daily Placebo	Endoscopic ulcers	Quality = 2	D
Delmas, 1994[208]	Randomised controlled trial	Patients with rheumatic disease No prior NSAID use in last 10 days	Misoprostol 400 μg Misoprostol 800 μg Placebo (any NSAID)	GUs DUs	Quality = 3	D
Ehsanullah, 1988[209]	Randomised, placebo-controlled Sample size at entry: Ranitidine: 137, Placebo: 126	RA and OA patients Mean age: 57 years Male:female ratio: 58:79 No NSAIDs in last week, no ulcers at baseline, no treatment for ulcers in last 30 days No DMARDs No liver/kidney impairments, GI malignancy, dysphagia, RA of cervical spine	Ranitidine 150 mg b.d. Placebo	Endoscopic ulcers Adverse events	Quality = 5	D
Ekstrom, 1996[210]	Randomised, placebo-controlled Sample size at entry: Omeprazole: 86, Placebo: 91	Patients with dyspepsia or history of PUD Mean age: 58 years Male female ratio: 31:54 Previous PUs: 27% *H. pylori* positive: 53%	Omeprazole 20 mg daily Placebo	Endoscopic ulcers	Quality = 3	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Elliott, 1994[211]	Randomised, double-blind, placebo-controlled Sample size at entry: Misoprostol: 40 Placebo: 43 Study duration: 12 months	Patients: rheumatic Setting: clinic outpatients Mean age: 65 years SD: 6.5 years Sex: 38% female Length on NSAIDs: >3 months Type of NSAID? Dose of NSAID? Previous PUs: 28% Previous abdominal pain? *H. pylori* positive?	Misoprostol 200 μg q.d.s. or b.d. or t.d.s. depending on frequency of NSAID use Placebo (same protocol as misoprostol, with NSAID)	Endoscopic GUs (>3 mm), mean size 6 mm Endosopic DUs (>3 mm) Clinical ulcers Withdrawals overall Withdrawals due to side-effects Drop-out due to diarrhoea	Quality = 4	D
Graham, 1988[212]	Randomised, double-blind, placebo-controlled Sample size at entry: Placebo: 138 Misoprostol 100 μg: 143 Misoprostol 200 μg: 110 Study duration: 12 weeks	Patients: OA Setting: clinic outpatients Mean age: 58.9 years Range: 22–90 years Sex: 35% female Length on NSAIDs: >1 year Type of NSAID: Ibuprofen 36% Piroxicam 28% Naproxen 36% Dose of NSAID? Previous PUs? Previous abdominal pain: inclusion criteria *H. pylori* positive?	Placebo ×4 Misoprostol 100 μg × 4 Misoprostol 200 μg × 4	Endoscopic GUs (>3 mm) Endoscopic GUs (>5 mm) Clinical ulcers? Withdrawals overall Withdrawals due to side-effects	Quality = 3	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Graham, 1993[213]	Randomised, double-blind, placebo-controlled Sample size at entry: Misoprostol: 319 Placebo: 319 Study duration: 12 weeks	Patient RA, OA, Reiter syndrome, psoriatic arthritis, ankylosing spondylitis Setting: clinic outpatients Median age: 59 years Sex: 53% female Length on NSAIDs: 36 weeks Type of NSAID? Dose of NSAID? Previous PUs: 25% Previous abdominal pain? *H. pylori* positive?	Misoprostol 800 μg (200 μg × 4) Placebo	Endoscopic GUs (>5 mm) Endoscopic DUs (>5 mm) Clinical ulcers Withdrawals overall Withdrawals due to side-effects Diarrhoea drop-out Nausea drop-out Abdominal pain drop-out	Quality = 3	D
Graham, 2002[214]	Randomised, double-blind, active and placebo-controlled Sample size at entry: Misoprostol:134 Lansoprozole 15 mg: 136 Lansoprazole 30 mg: 133 Placebo: 134 Study duration: 12 weeks	*H. pylori* negative Previously healed GUs	Placebo Misoprostol 800 μg Lansoprazole 15 mg Lansoprazole 30 mg	Endoscopic GUs	Quality = 4	B
Hawkey, 1998[215]	Randomised, double-blind, placebo-controlled Sample size at entry: Omeprazole: 274 Misoprostol: 296 Placebo: 155 Study duration: 6 months	Patients: RA, OA Setting: clinic outpatients Mean age: 58 years Sex: 63% female Length on NSAIDs: >6 months Type of NSAID: diclofenac, ketoprofen, naproxen Dose of NSAID: >50 mg diclofenac, >100 mg ketoprofen, >500 mg naproxen Previous PUs: 29% Previous abdominal pain? *H. pylori* positive: 42%	Omeprazole 20 mg Misoprostol 200 μg b.d. = 400 μg Placebo	Endoscopic GUs (>3 mm) Endoscopic GUs (>5 mm) Endoscopic DUs (>3 mm) Endoscopic DUs (>5 mm) Clinical ulcers Withdrawals overall Withdrawals due to side-effects	Quality = 3	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Henriksson, 1993[216]	Randomised, double-blind	RA patients with long-term (median 36 months) NSAID therapy, no treatment for ulcers in last 30 days, no symptomatic ulcer	Misoprostol 200 μg t.d.s. Placebo t.d.s.	Endoscopic GUs Endoscopic DUs Drop-outs overall Abdominal pain Diarrhoea GI symptoms	Quality = 4	D
Hudson, 1997[217]	Randomised, placebo controlled. Sample size at entry: Famotidine: 39, Placebo: 39	RA or OA patients Those with ulcers went into healing phase, then secondary prophylactic phase Those with no ulcers at baseline started prophylaxis phase Mean age? Male:female ratio: 14:25 Previous PUD: 12/39 *H. pylori* positive: 18/39		Famotidine 40 mg b.d. (high dose) Placebo b.d. Outcomes: endoscopic ulcers	Quality = 3	D
Jensen, 2000 (abstract)[218]	Prospective. Randomised, parallel Group. Sample size: Omeprazole: 23 Misoprostol: 23	High-risk patients with previous NSAID or ASA ulcer who need continuation of NSAID	Omeprazole 20 mg b.d. vs misoprostol 200 μg q.d.s.	UGI bleeding, symptomatic ulcer recurrence, unrelieved UGI symptoms	Abstract: cannot determine	D
Levine, 1993[219]	Randomised, placebo-controlled Sample size at entry: Nizatidine: 248, Placebo: 248	Randomised, placebo-controlled Sample size at entry: Nizatidine: 248, Placebo: 248	Nizatidine 150 mg b.d. Placebo	Endoscopic ulcers Symptoms	Quality = 3	D
Melo Gomes, 1993[220]	Randomised, controlled, double-blind	Patients: OA Setting: outpatients PUs: no UGI damage as confirmed by endoscopy NSAID use: no use of NSAIDs in 10 days prior to study	Diclofenac/misoprostol: 216 patients Piroxicam: 217 patients Naproxen: 210 patients	Endoscopic ulcers Endoscopic GUs Endoscopic DUs Abdominal pain Diarrhoea Dyspepsia Nausea	Quality = 3	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Raskin, 1995[221]	Randomised, double-blind, placebo-controlled Sample size at entry: Placebo: 454 Misoprostol 400 μg: 462 Misoprostol 600 μg: 474 Misoprostol 800 μg: 228 Study duration: 3 months	Patients: RA, OA, psoriatic arthritis, ankylosing spondylitis, reiter syndrome Setting: clinic outpatients Median age: 58 years Sex: 59% female Length on NSAIDs? Type of NSAID: various Dose of NSAID: diclofenac >50, ketoprofen >150, naproxen >750 Previous PUs: no Previous abdominal pain: inclusion criteria *H. pylori* positive?	Placebo: 4 × day Misoprostol 200 μg × 2 = 400 μg Misoprostol 200 μg × 3 = 600 μg Misoprostol 200 μg × 4 = 800 μg	Endoscopic GUs (>3 mm) Endoscopic DUs (>3 mm) Clinical ulcers? Withdrawals overall Withdrawals due to side-effects All adverse events	Quality = 5	D
Raskin, 1996[222]	Randomised, double-blind, controlled Sample size at entry: Misoprostol: 269 Ranitidine: 269 Study duration: 8 weeks	Patients: RA, OA, psoriatic arthritis, ankylosing spondylitis, Reiter syndrome Setting: clinic outpatients Median age: 61 years Range: 23–85 years Sex: 53% female Length on NSAIDs: chronic Type of NSAID: ibuprofen, naproxen, piroxicam, sulindac Dose of NSAID? Previous PUs: 23% Previous abdominal pain? *H. pylori* positive?	Misoprostol 200 μg q.d.s. Ranitidine 150 mg b.d.	Endoscopic GU (>3 mm) Endoscopic DUs (>3 mm) Clinical ulcers? Withdrawals overall Withdrawals due to side-effects Nausea	Quality = 3	A

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Robinson, 1989[223]	Randomised, double-blind, placebo controlled Sample size at entry: Ranitidine 150 mg b.d.: 72 Placebo: 72	Patients: arthritis Setting: clinic outpatients Mean age (SD): 50.1 (3.1) years Sex: 60% female Length on NSAIDs: 0 at entry Type of NSAID: naproxen, sulindac, ibuprofen, piroxicam, indomethacin Dose of NSAID: set by protocol >1600 mg/day ibuprofen Previous PUs: not reported Exclusion: current gastroduodenal erosions, previous gastric surgery, use of NSAIDs in last 48 hours Corticosteroid use: exclude if use of prednisone >10 mg/day Previous abdominal pain: not mentioned *H. pylori* positive: not reported	Ranitidine 150 mg b.d. Placebo b.d.	Endoscopic DUs Endoscopic GUs Adverse events	Quality = 3	D
Robinson, 1991[224]	Report of unpublished data from trial by Glaxo Randomised, placebo-controlled Sample size at entry: 246 Reported sample: 227 Placebo: 115 Ranitidine: 112	Patients with no ulcers, confirmed by endoscopy	Ranitidine 150 mg b.d. Placebo	DUs (unspecified criteria)	DUs (unspecified criteria) Quality = 2	D
Roth, 1987[225]	Randomised, double-blind, placebo-controlled Sample size at entry: 36 Completed placebo: 14 Completed cimetidine: 12	Patients: RA, OA Secondary prophylaxis (ulcers healed during 2-month healing phase) NSAIDs: currently taking Exclude: high-dose corticosteroid, prior gastric surgery, grade IV ulcers	Cimetidine 400 mg/day Placebo	Total endoscopic ulcers	Quality = 1	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Roth, 1993[226]	Randomised, double-blind, controlled Sample size at entry: Nabumetone: 58 Ibuprofen: 53 Ibuprofen and misoprostol: 60 Study duration: 12 weeks	Patients: OA Setting: clinic outpatients Patients aged >60 years Sex: 52% female Length on NSAIDs: >12 months Type of NSAID: nabumetone, ibuprofen Dose of NSAID: 600 mg × 4 Previous PUs: 17% Previous abdominal pain? *H. pylori* positive?	Nabumetone 1000 mg × ? Ibuprofen 600 mg × 4/day Ibuprofen and misoprostol 600 mg/200 mg × 4/day	Endosopic GUs (>3 mm) Endoscopic DUs (>3 mm) Clinical ulcers Withdrawals overall Withdrawals due to side-effects GI side-effects	Quality = 2	D
Saggioro, 1991[227]	Randomised, placebo controlled Sample size at entry: Misoprostol: 82 Placebo: 84	Patients with RA or OA Mean age: 56 years Sex: 40.5% male Free of UGI symptoms Free of gastroduodenal lesions at baseline No NSAID use in previous 30 days No CVD, renal disease, DMARDs, steroids, history of GI surgery	Misoprostol 200 μg q.d.s. Placebo	Endoscopic ulcers Symptoms	Quality = 3	D
Silverstein, 1995[33]	Randomised, double-blind, placebo-controlled Sample size at entry: Misoprostol: 4404 Placebo: 4439 Study duration?	Patients: RA Setting: clinic outpatients Mean age: 67.6 years SD: 6.9 years Sex % F: ? Length on NSAIDs: >24 weeks Type of NSAID: any Dose of NSAID: diclofenac >100 mg Indomethacin >75 mg Ketoprofen >150 mg Naproxen >750 mg Piroxicam >20 mg Sulindac >200 mg Previous PUs: 14.6% Previous abdominal pain? *H. pylori* positive?	Misoprostol 200 μg × 4/day or 100 μg × 4 if poorly treated Placebo	Endoscopic GUs (>3 mm) Endoscopic DUs (>3 mm) Clinical ulcers: categories 1–6 Withdrawals overall Withdrawals due to side-effects	Quality = 4	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Simon, 1994[228]	Randomised, controlled Sample size at entry: Nizatidine 150 mg daily: 116 Nizatidine 150 mg b.d.: 121	Rheumatic patients with an ulcer and on NSAIDs for >3 weeks Mean age?	Nizatidine 150 mg daily Nizatidine 150 mg b.d.	Endoscopic ulcers	Quality = 2	D
Swift, 1989[229]	Randomised, double-blind	Patients: rheumatology clinic Placebo = 8 Ranitidine = 16	Ranitidine 150 mg b.d. for 7 weeks then ranitidine 300 mg b.d. for 7 weeks Placebo for 14 weeks	Gastritis Lanza score GUs Faecal blood loss	Quality = 4	D
Taha, 1996[230]	Randomised, controlled study Sample size at entry: Famotidine 20 mg b.d.: 95 Famotidine 40 mg b.d.: 97 Placebo: 93	Randomised, controlled study Sample size at entry: Famotidine 20 mg b.d.: 95 Famotidine 40 mg b.d.: 97 Placebo: 93	Famotidine 20 mg b.d. Famotidine 40 mg b.d. Placebo	Endoscopic ulcers Symptoms	Quality = 4	D
ten Wolde, 1996[231]	Randomised, double-blind	RA patients PU history: all	Ranitidine 300 mg b.d. + NSAIDs Placebo b.d. + NSAIDs	Gastric DUs Endoscopic DUs Total endoscopic ulcers	Quality = 3	D
Valentini, 1995[232]	Randomised, single-blind (endoscopist), controlled	Cancer patients	Misoprostol 200 μg b.d. and diclofenac 200 mg/day Ranitidine 150 mg b.d. and diclofenac 200 mg/day	GUs >6 mm DUs >6 mm Gastric erosions Duodenal erosions Nausea, abdominal pain, vomiting, diarrhoea	Quality = 2	D

continued

TABLE 27 *Characteristics of included studies (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment[a]
Van Groenendael, 1996[233]	Randomised, placebo-controlled 3 arms: Group A (n = 58): no gastroduodenal lesions at baseline; Group B (n = 36): gastric and duodenal lesions present at baseline but no ulcers; Group C (n = 30): gastric/duodenal ulcer at baseline entered into healing study Only Group B used for prophylaxis since Group A patients were only endoscoped at end of study if they had symptoms	Patients using NSAID at baseline with GI complaints eligible for study Patients classified into Group A, B or C according to baseline UGI endoscopy Mean age 52 years, 25% male, RA and OA patients	Ranitidine 150 mg b.d. Placebo b.d.	Endoscopic ulcers and erosions GI symptoms	Quality = 1	D
Verdickt, 1992[234]	Randomised, double-blind, placebo-controlled Sample size at entry: Diclofenac and misoprostol: 164 Diclofenac and placebo: 175 Study duration: 12 weeks	Patients: RA Setting: clinic outpatients Mean age: 51.3 years SD: 13.5 years Sex: 33% female Length on NSAIDs: 0 Type of NSAID: diclofenac Dose of NSAID: 50 mg diclofenac Previous PUs? Previous abdominal pain? *H. pylori* positive?	50 mg diclofenac and misoprostol (200 μg) 50 mg diclofenac and placebo	Endoscopic GUs (>3 mm), ulcer of any size Endoscopic DUs (>3 mm), ulcer of any size Clinical ulcers? Withdrawals overall Withdrawals due to side-effects Worse arthritis withdrawal	Quality = 3	D
Yeomans, 1998[235]	Randomised, controlled Sample size at entry: Omeprazole: 210 Ranitidine: 215	Participants: RA and OA patients Mean age: 56 years Male:female ratio: 64:146 *H. pylori*: 50% positive	Omeprazole 20 mg Ranitidine 150 mg b.d.	Endoscopic ulcers	Quality = 3	D

ASA, acetylsalicylic acid; CVD, cardiovascular disease; DMARDs, disease-modifying anti-rheumatic drugs; IBD, inflammatory bowel disease; OA, osteoarthritis; PUD, peptic ulcer disease; RA, rheumatoid arthritis.

[a] Cochrane ranking: Grades A, B and D.

TABLE 28 *Characteristics of excluded studies*

Study	Reason for exclusion
Agrawal, 1999[236]	Compared dicolfenac + misoprostol with nabumetone – study differences partially due to NSAID differences
Agrawal, 2000[237]	NSAID ulcer treatment not prophylaxis
Bianchi Porro, 1997[238]	Acute – only 14 days of treatment
Bianchi Porro, 1998[239]	Acute – only 3-week study
Caldwell, 1989[240]	Healing study
Daneshmend, 1990[241]	Acute, <2 weeks of NSAID exposure
Donnelly, 2000[242]	Only assessed erosions and not ulcers
Geis, 1991[243]	Required data could not be extracted
Geis, 1992[244]	Duplicate data
Melo Gomes, 1992[245]	Duplicate publication of Bolten, 1992[203] in osteoarthritis patients and Verdikt, 1992[234] in rheumatoid arthritis patients
Rose, 1999[246]	Abstract incomplete, group sizes not stated. May be included in future revision when published in full
Rugstad, 1994[247]	No ulcer outcomes, only GI symptoms
Ryan, 1987[248]	<3 weeks of prophylaxis
Walan, 1989[249]	Prophylaxis phase cannot be extracted

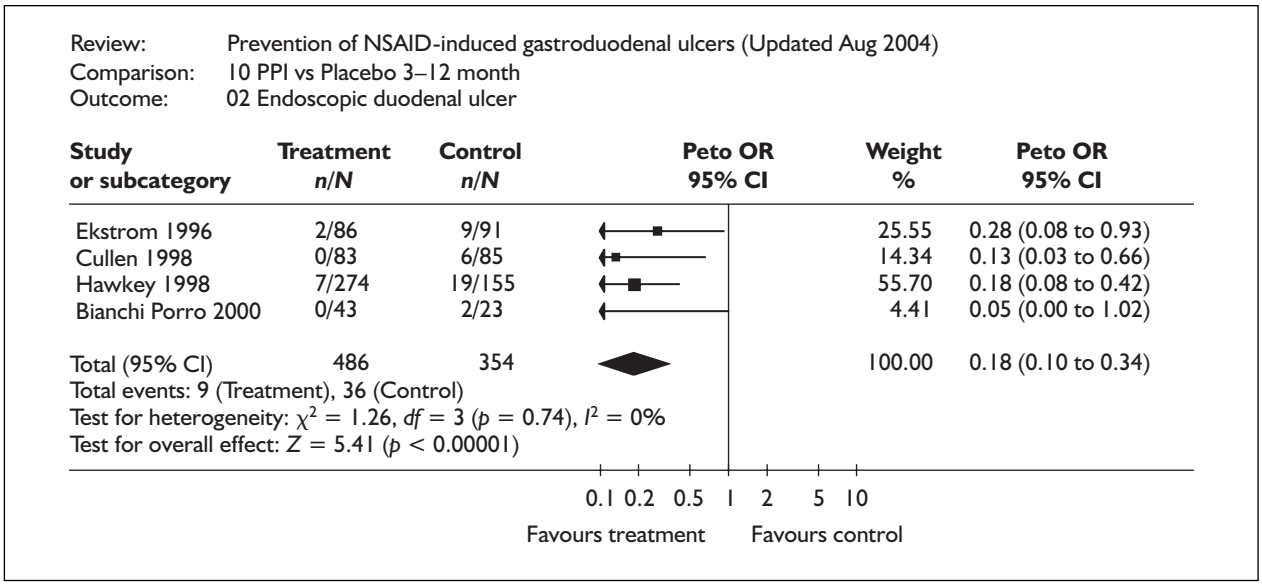

FIGURE 24 *Primary efficacy comparison of PPI versus placebo in reducing the incidence of endoscopic duodenal ulcer after at least 3 months of NSAID exposure*

misoprostol. Hawkey and colleagues[215] compared low-dose misoprostol (400 μg daily) with omeprazole (20 mg daily), whereas Graham and colleagues[214] compared high-dose misoprostol (800 μg daily) with lansoprazole (15 or 30 mg daily). PPIs were statistically superior to misoprostol for the prevention of DUs (RR 0.29, 95% CI 0.15 to 0.56).

However, no significant difference was observed in the prevention of GUs. Individually, the Hawkey trial showed a non-significant trend towards greater benefit with misoprostol over omeprazole for the prevention of GUs, whereas the Graham study actually showed that misoprostol is superior to lansoprazole for the prevention of GUs. The pooled results mirror these findings, but statistical

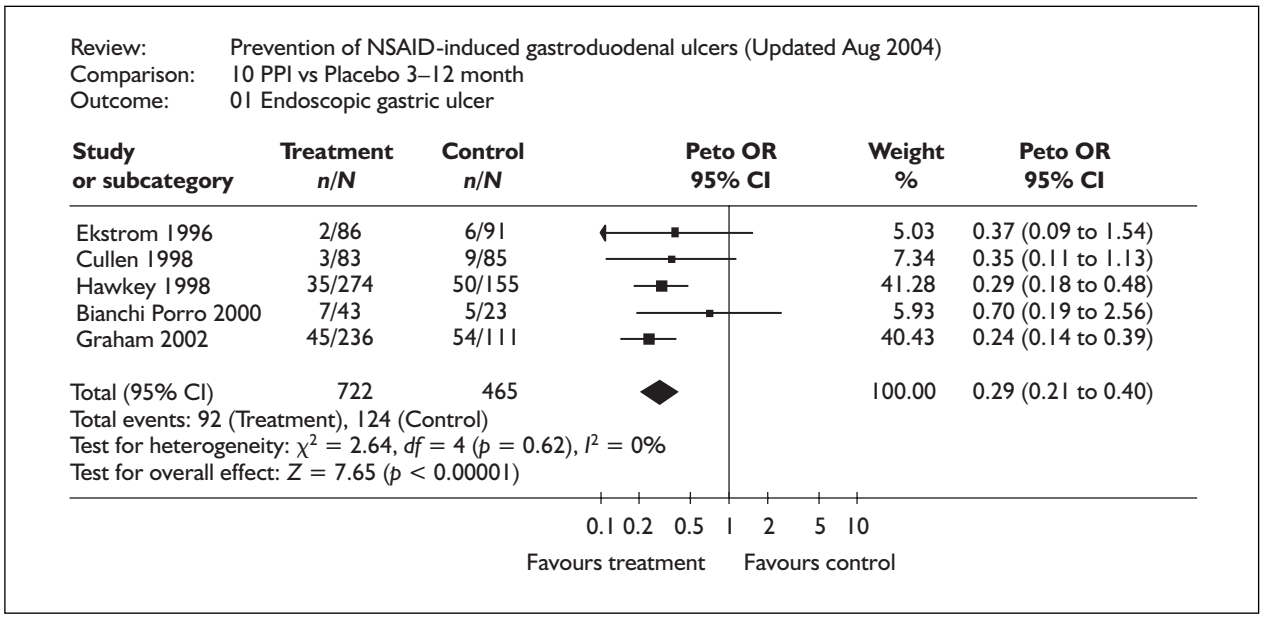

FIGURE 25 *Primary efficacy comparison of PPI versus placebo in reducing the incidence of endoscopic gastric ulcer after at least 3 months of NSAID exposure*

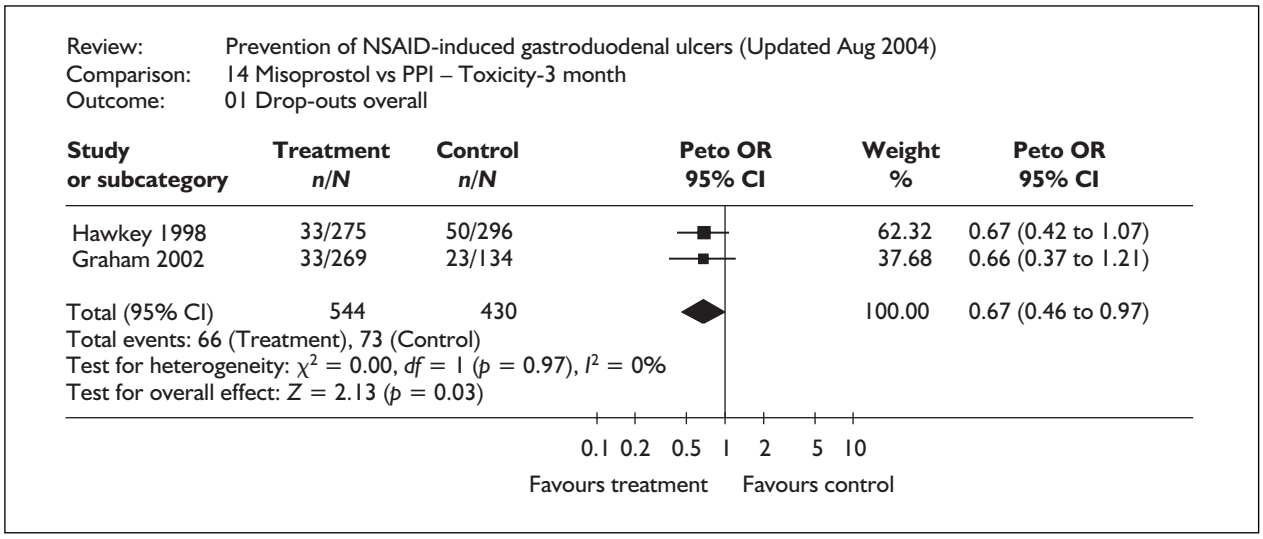

FIGURE 26 *Head-to-head comparison of PPI (treatment) versus misoprostol (control) for overall drop-outs after at least 3 months' exposure to NSAIDs*

heterogeneity existed and the use of a random effects model failed to demonstrate a statistically significant benefit of misoprostol over PPIs for GU prevention (RR 0.59, 95% CI 0.27 to 1.25).

Adverse effects, drop-outs and symptoms

PPI was better tolerated than misoprostol in two RCTs including 974 patients,[214,215] the Peto OR being 0.67 (95% CI 0.46 to 0.97) for overall dropouts (see *Figure 26*).

Three RCTs[214,215,218] including 1019 patients observed a significantly lower drop-out rate due to side-effects with PPI compared with misoprostol (Peto OR 0.45, 95% CI 0.27 to 0.76) (see *Figure 27*).

Other studies

Jensen and colleagues[218] presented an abstract of a prospective, randomised parallel group study comparing omeprazole (20 mg twice daily) with to misoprostol (200 μg four times daily) in high-risk patients who required continued use of NSAIDs or acetylsalicylic acid (ASA). In this study, patients had a previously documented severe GI haemorrhage while on NSAIDs. Treatment failures were defined as ulcer bleeding, severe adverse effects or

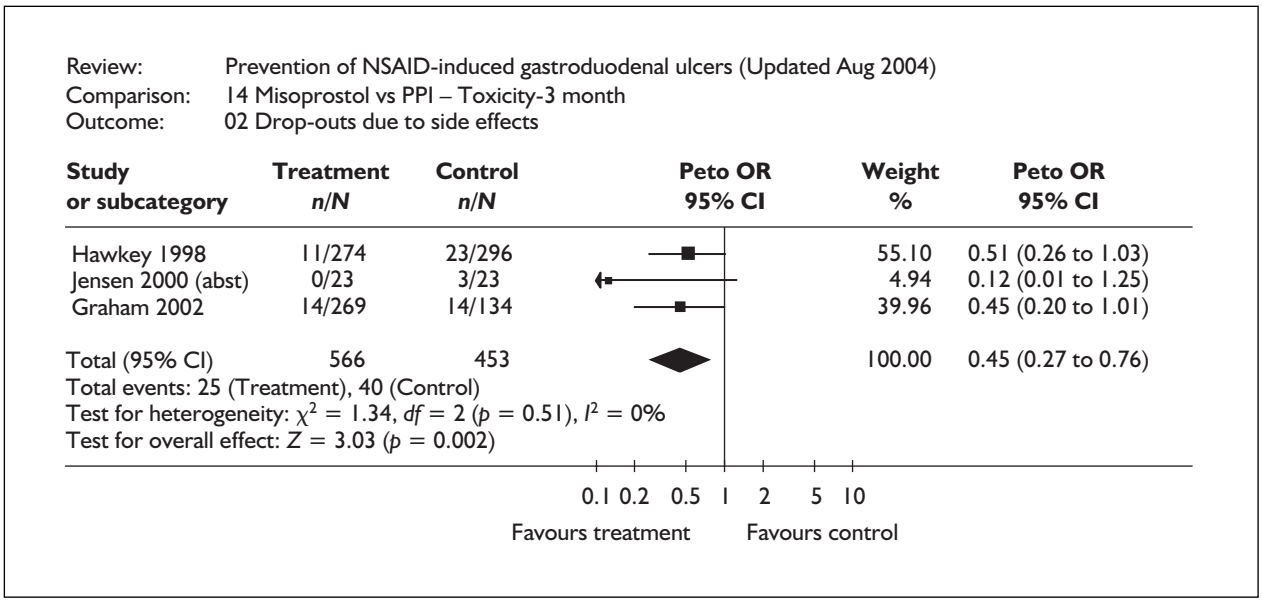

FIGURE 27 *Head-to-head comparison of PPI (treatment) versus misoprostol (control) for drop-outs due to side-effects after at least 3 months' exposure to NSAIDs*

symptomatic ulcers. Although the sample size of 46 patients was small, the authors found fewer treatment failures with omeprazole than with misoprostol (4.4% versus 30.4%, $p = 0.02$). However, if only ulcer bleeding or symptomatic ulcers were considered, a statistical difference was not seen (RR 0.25, 95% CI 0.03 to 2.07).

In a recent abstract of 130 patients comparing omeprazole and diclofenac with celecoxib, Chan and colleagues enrolled arthritic patients who had presented with an endoscopically proven GI bleed, and required the continued use of an NSAID.[205] Six patients in the omperazole group versus three in the celecoxib group developed recurrent bleeding at the 24-week interim analysis (RR 2.03, 95% CI 0.49 to 8.51; p = not significant).

The results were similar for both primary and secondary prophylaxis trials. No significant differences were observed with analysis by quality. No statistical heterogeneity was observed amongst the trials.

In summary, the above analyses demonstrate that PPI is superior to placebo and H_2RA in reducing the risk of NSAID-induced endoscopic GUs and DUs. PPIs are superior to misoprostol in the prevention of DUs (whereas there was no evidence of a difference regarding GUs) and are better tolerated. However, no study is available in the literature to suggest that PPI is superior in reducing clinical end-points such as ulcer-related complications.

Misoprostol

Misoprostol compared with placebo

Twenty-two studies (included through the update in August 2004) assessed the long-term effect of misoprostol on the prevention of NSAID ulcers.[202–204,206,208,211,212,214–216,220,222,226,227,232,234,237,250]

Endoscopic ulcers

Eleven studies with 3641 patients compared the incidence of endoscopic ulcers after at least 3 months of misoprostol with placebo.[37,205,212–215,226,234,236] Misoprostol significantly reduced the RR of DUs by 53%. The Peto OR was 0.47 (95% CI 0.33 to 0.67). Significant statistical heterogeneity was noted amongst the studies (χ^2 12.23, $df = 7$, $p = 0.09$ and $I^2 = 42.8$) (see *Figure 28*). However the result remained robust on applying a random effects model to evaluate the RRR (RR 0.47, 95% CI 0.33 to 0.69, random effects). This RR corresponded to a 3% ARR for DUs.

Misoprostol significantly reduced the RR of GU by 74% (RR 0.26, 95% CI 0.17 to 0.39, random effects) at 3 months or more compared with placebo. The Peto OR was 0.24 (95% CI, 0.19 to 0.30) (see *Figure 29*). This RR corresponded to a 12.0% ARR for GUs.

The observed heterogeneity in these estimates was due to inclusion of all misoprostol doses in the analyses. Analysis of the misoprostol studies stratified by dose eliminated this heterogeneity.

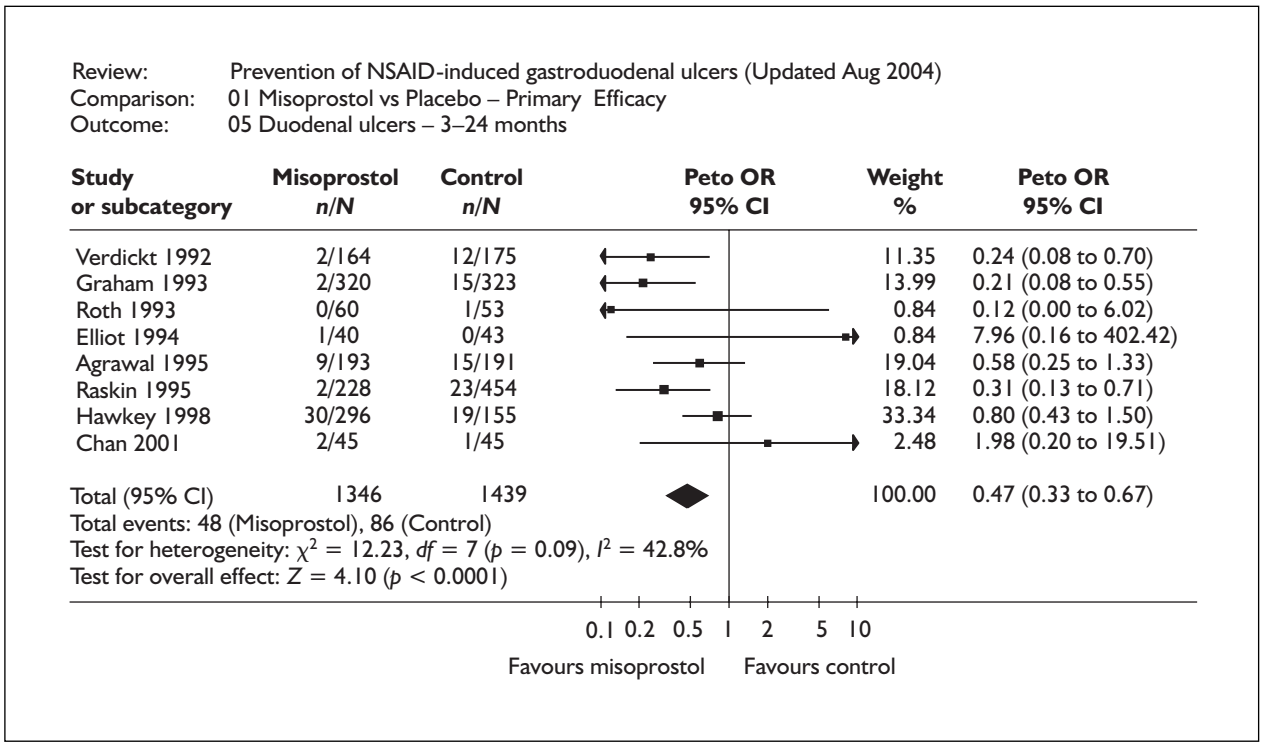

FIGURE 28 *Primary efficacy comparison of misoprostol versus placebo in reducing the incidence of endoscopic duodenal ulcer after at least 3 months of NSAID exposure*

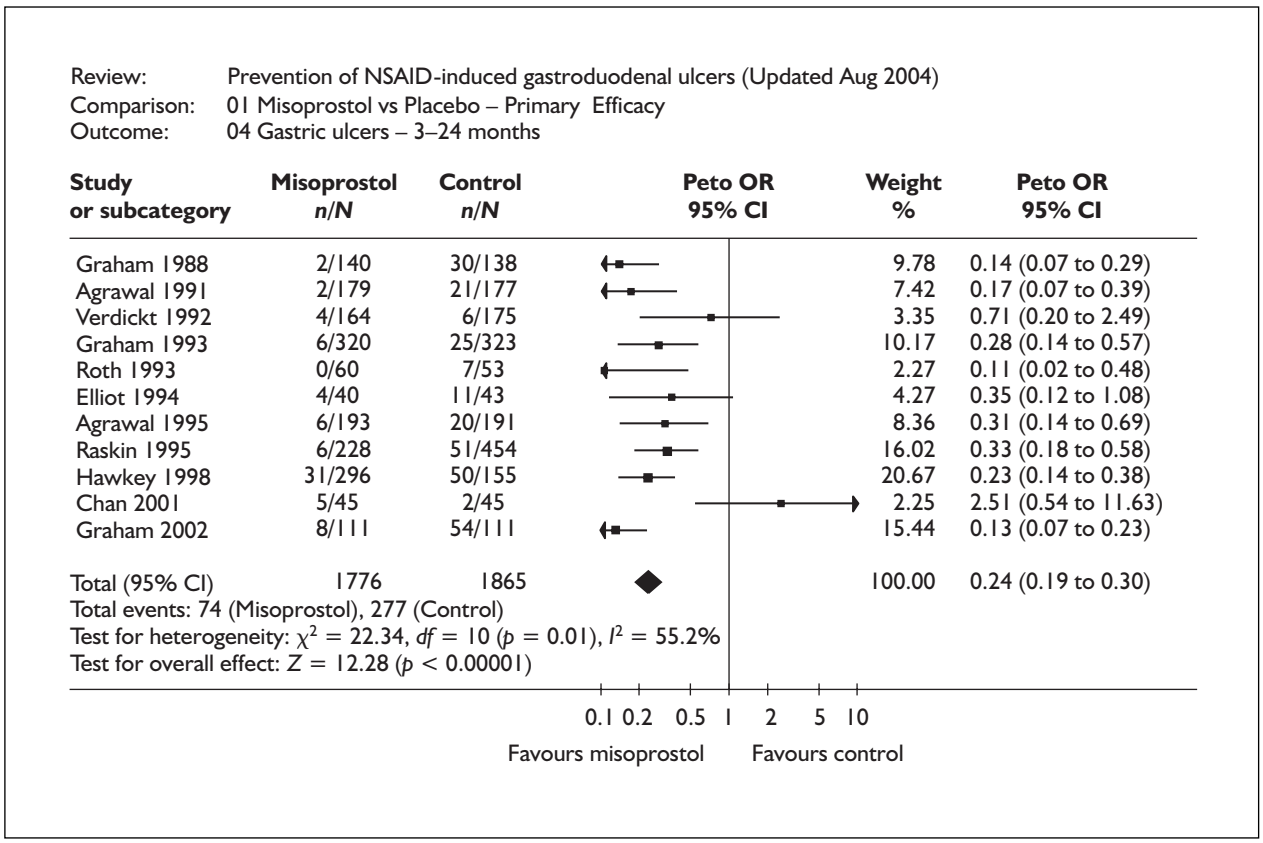

FIGURE 29 *Primary efficacy comparison of misoprostol versus placebo in reducing the incidence of endoscopic gastric ulcer after at least 3 months of NSAID exposure*

Clinical ulcers

To date, the only agent that has been assessed in a clinical outcome study (bleeding, perforation, obstruction) is misoprostol. All the other agents have been assessed only in endoscopic NSAID ulcer trials. The exact relationship between the endoscopic ulcer and a clinical ulcer event such as bleeding is unknown. Clinical events occur much less frequently (1.5% per year) than endoscopic ulcers (up to 40% per year). One RCT[33] evaluated the efficacy of misoprostol prophylaxis against clinically important NSAID-induced ulcer complications. In this study, 8843 patients were studied over 6 months. Misoprostol 800 μg/day was associated with a statistically significant 40% RR (OR 0.598, 95% CI 0.364 to 0.982) in combined GI events ($p = 0.049$), representing a risk difference of 0.38% (reduced from 0.95% to 0.57%).

Overall, approximately 260 patients would have to be treated with misoprostol to prevent one clinically important GI event. Misoprostol appeared to be ineffective at preventing endoscopically proven GI haemorrhage alone. However, a Type II error is likely since the study was not powered to detect a difference in this end-point.[34]

Adverse effects, drop-outs and symptoms

Misoprostol was associated with a small but statistically significant 1.6-fold excess risk of drop-out due to drug-induced side-effects, and an excess risk of drop-outs due to nausea (RR 1.30, 95% CI 1.08 to 1.55), diarrhoea (RR 2.36, 95% CI 2.01 to 2.77) and abdominal pain (RR 1.36, 95% CI 1.20 to 1.55) (see *Figures 30* and *31*). The incidence of dyspepsia as an adverse effect was comparable between the two groups.

The overall drop-out rate was significantly higher in the misoprostol group, the Peto OR being 1.35 (95% CI 1.25 to 1.46, χ^2 121.36, $df = 14$, $I^2 = 88.5$), as were the drop-outs due to side-effects (Peto OR 1.55, 95% CI 1.41 to 1.69) (*Figure 32*).

In the MUCOSA trial,[33] 732 out of 4404 patients on misoprostol experienced diarrhoea or abdominal pain, compared with 399 out of 4439 on placebo for an RR of 1.82 associated with misoprostol ($p < 0.001$). Overall 27% of patients on misoprostol experienced one or more side-effects.

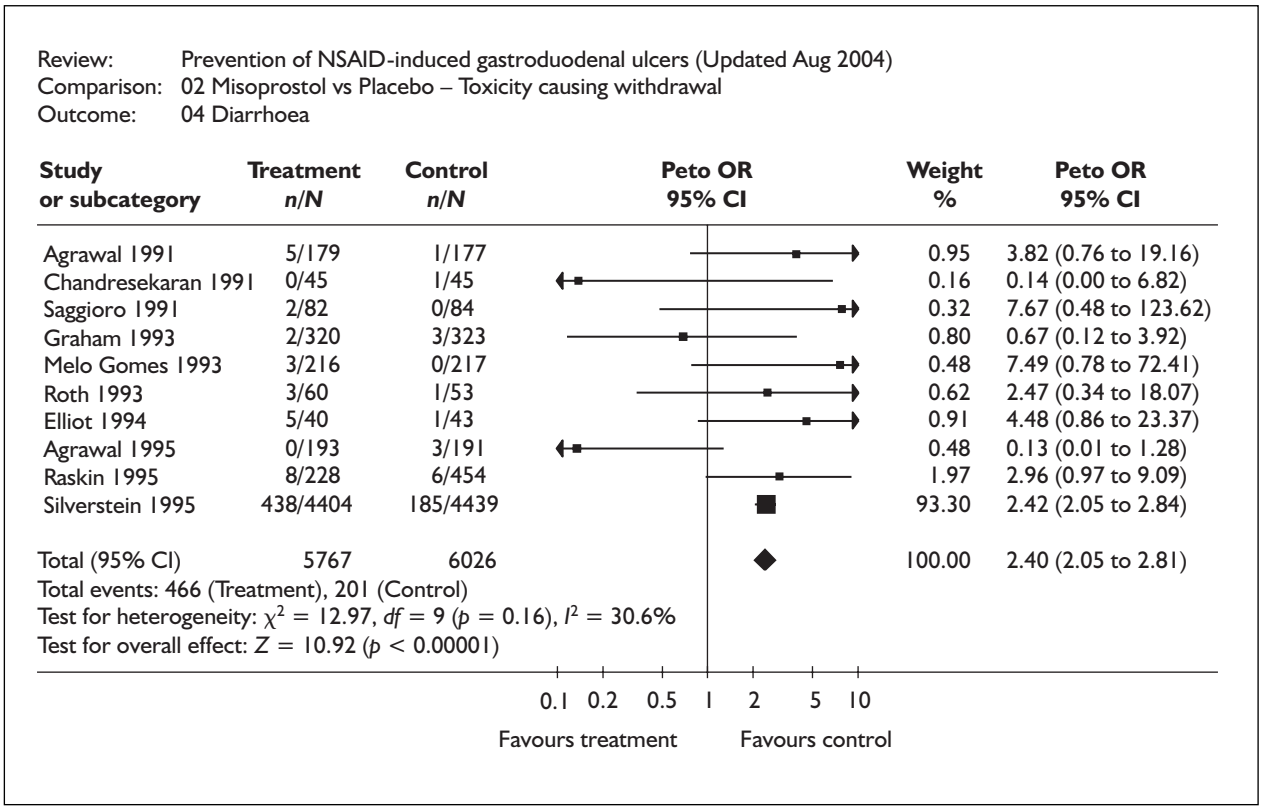

FIGURE 30 *Comparison of misoprostol (treatment) versus placebo (control) causing withdrawal due to diarrhoea*

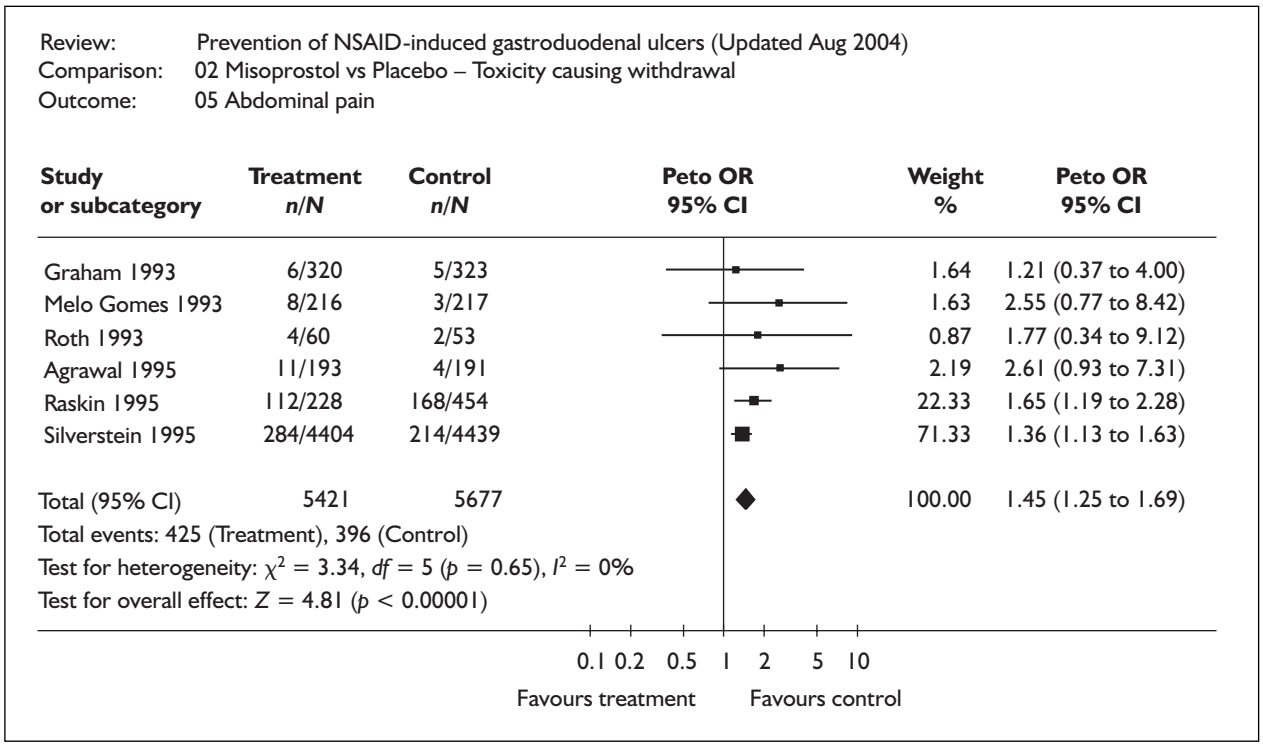

FIGURE 31 *Comparison of misoprostol (treatment) versus placebo (control) causing withdrawal due to abdominal pain*

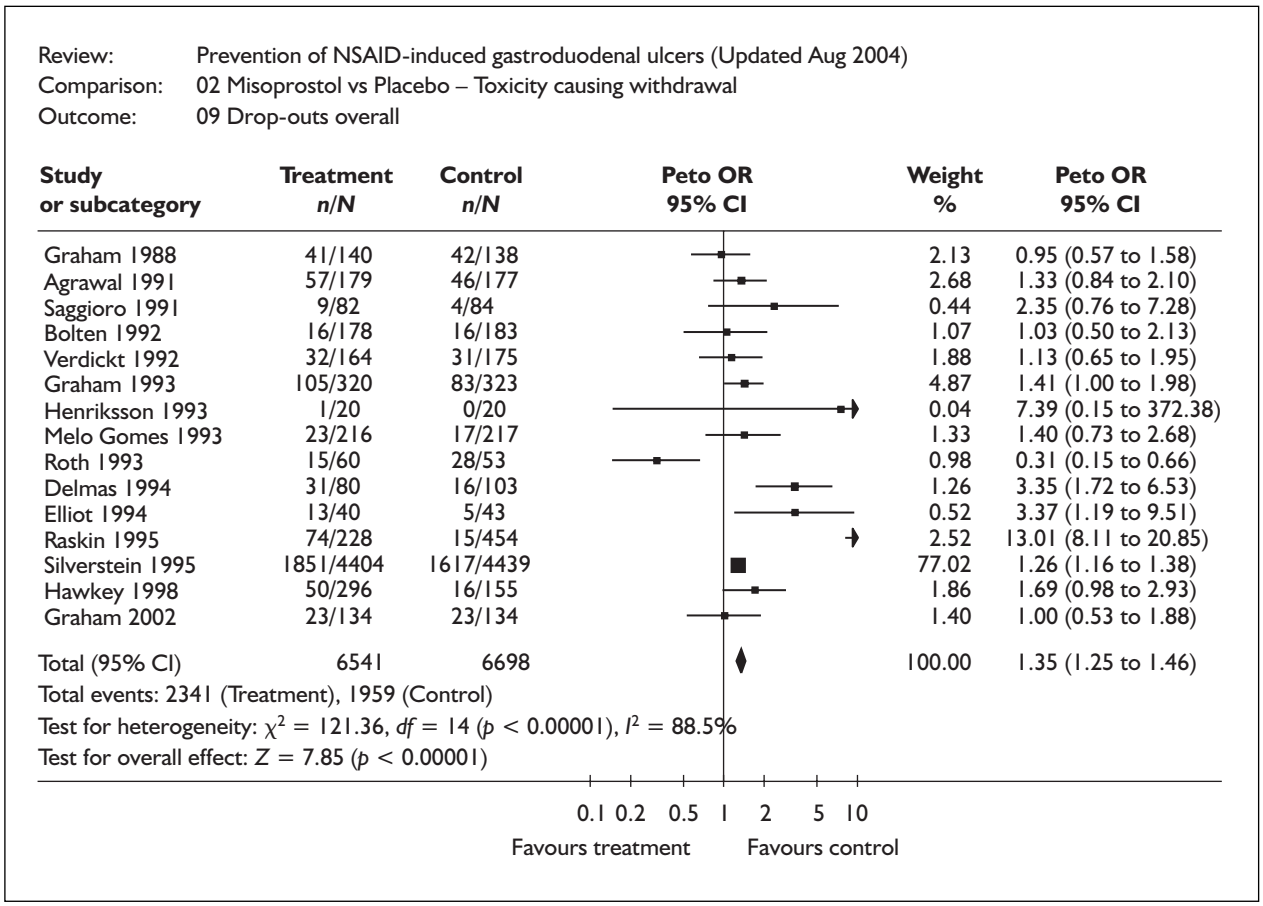

FIGURE 32 *Comparison of misoprostol (treatment) versus placebo (control): toxicity causing withdrawal: overall drop-outs*

Subanalysis by duration of follow-up

Studies including data with less than 3 months of NSAID exposure

Eight studies, with 2206 patients, assessed the rates of endoscopic ulcers with misoprostol compared with placebo at 1–1.5 months.[202,203,206,208,211,216,220,227] The pooling of these studies revealed an 81% RRR of GUs with misoprostol (RR 0.17, 95% CI 0.09 to 0.31) and a 72% RRR of DUs (RR 0.28, 95% CI 0.14 to 0.56).

One study compared misoprostol with a newer cytoprotective agent, dosmalfate, for NSAID prophylaxis and found no statistically significant difference in ulcer rates between the two agents.[250]

Analysis by dose

All the studied doses of misoprostol significantly reduced the risk of endoscopic ulcers, and a dose–response relationship was demonstrated for endoscopic gastric ulcers. Six studies with 2461 patients used misoprostol 400 μg,[199,202,212,215,221,234] one study with 928 patients used 600 μg daily[221] and seven with 2423 patients used 800 μg daily.[198,211–214,221,226] Misoprostol 800 μg daily was associated with the lowest risk (RR 0.17, 95% CI 0.11 to 0.24) of endoscopic gastric ulcers when compared with placebo, whereas misoprostol 400 μg daily was associated with an RR of 0.42 (95% CI 0.28 to 0.67, random effects model for heterogeneity). The observed heterogeneity in the 400-μg dose group was the result of the addition of the Chan study [$\chi^2 = 10.97$, $df = 5$ ($p = 0.05$), $I^2 = 54.4$].[205] This study compared the relatively more toxic naproxen with low-dose misoprostol with nabumatone alone. In this study, the risk of ulcers was greater in the misoprostol group, which could have been due to the differences between the safety of the comparator NSAIDs rather than the prophylactic agent. As a sensitivity analysis, removal of the Chan study eliminated the observed heterogeneity without significantly altering the results, giving low-dose misoprostol prophylaxis an RR of 0.39 (95% CI 0.3 to 0.51), [$\chi^2 = 5.85$, $df = 4$ ($p = 0.21$), $I^2 = 31.6$)]. This difference between high- and low-dose misoprostol reached statistical significance ($p = 0.0055$). The intermediate misoprostol dose (600 μg daily) was not statistically different from either the low or high dose. The pooled RRR of 78% (4.7% ARR, RR 0.21, 95% CI 0.09 to 0.49) for DUs with misoprostol 800 μg daily was not statistically different from those of the lower daily misoprostol dosages.

When analysed by dose, both misoprostol doses were associated with a statistically significant risk of diarrhoea. However, the risk of diarrhoea with 800 μg/day (RR 3.25, 95% CI 2.60 to 4.06) was significantly higher than that seen with 400 μg/day (RR 1.81, 95% CI 1.52 to 2.16). Only high-dose misoprostol showed a statistically significant excess risk of drop-outs due to diarrhoea (RR 2.45, 95% CI 2.09 to 2.88) and abdominal pain (RR 1.38, 95% CI 1.17 to 1.63). The overall drop-out rate and drop-outs due to adverse effects were not significant for low-dose misoprostol but were significantly higher with high-dose misoprostol, the Peto OR being 1.30 (95% CI 1.21 to 1.40) and 1.55 (95% CI 1.41 to 1.70), respectively (see *Figure 33*).

Subanalysis

Subanalysis by duration of follow-up (studies including data with less than 3 months of NSAID exposure)

Eight studies, with 2206 patients, assessed the rates of endoscopic ulcers with misoprostol compared with placebo at 1–1.5 months.[202,203,206,208,211,216,220,227] The pooling of these studies revealed an 81% RRR of GUs with misoprostol (RR 0.17, 95% CI 0.09 to 0.31) and a 72% RRR of DUs (RR 0.28, 95% CI 0.14 to 0.56).

One study compared misoprostol with a newer cytoprotective agent, dosmalfate, for NSAID prophylaxis and found no statistically significant difference in ulcer rates between the two agents.[250]

Misoprostol compared with H_2RAs

Endoscopic ulcers

Two trials with 600 patients compared misoprostol with ranitidine 150 mg twice daily.[221,232] Misoprostol appears superior to standard-dose ranitidine for the prevention of NSAID-induced GUs but not for DUs. The Peto ORs were 0.19 (95% CI 0.08 to 0.48) (see *Figure 34*) and 1.00 (95% CI 0.14 to 7.14), respectively.

Adverse effects, drop-outs and symptoms

The overall drop-out rate was similar between the two groups. However, the drop-outs due to adverse effects were significantly higher with misoprostol (Peto OR 2.09, 95% CI 1.19 to 3.66) (see *Figure 35*).

Only one RCT[222] reported the incidence of individual adverse effects in 538 patients. Abdominal pain, flatulence and diarrhoea were significantly higher with misoprostol. Dyspepsia was reported as an outcome in both RCTs[222,232] and was observed to be significantly higher in the misoprostol group (Peto OR 1.68, 95% CI 1.02 to 2.77) (see *Figure 36*).

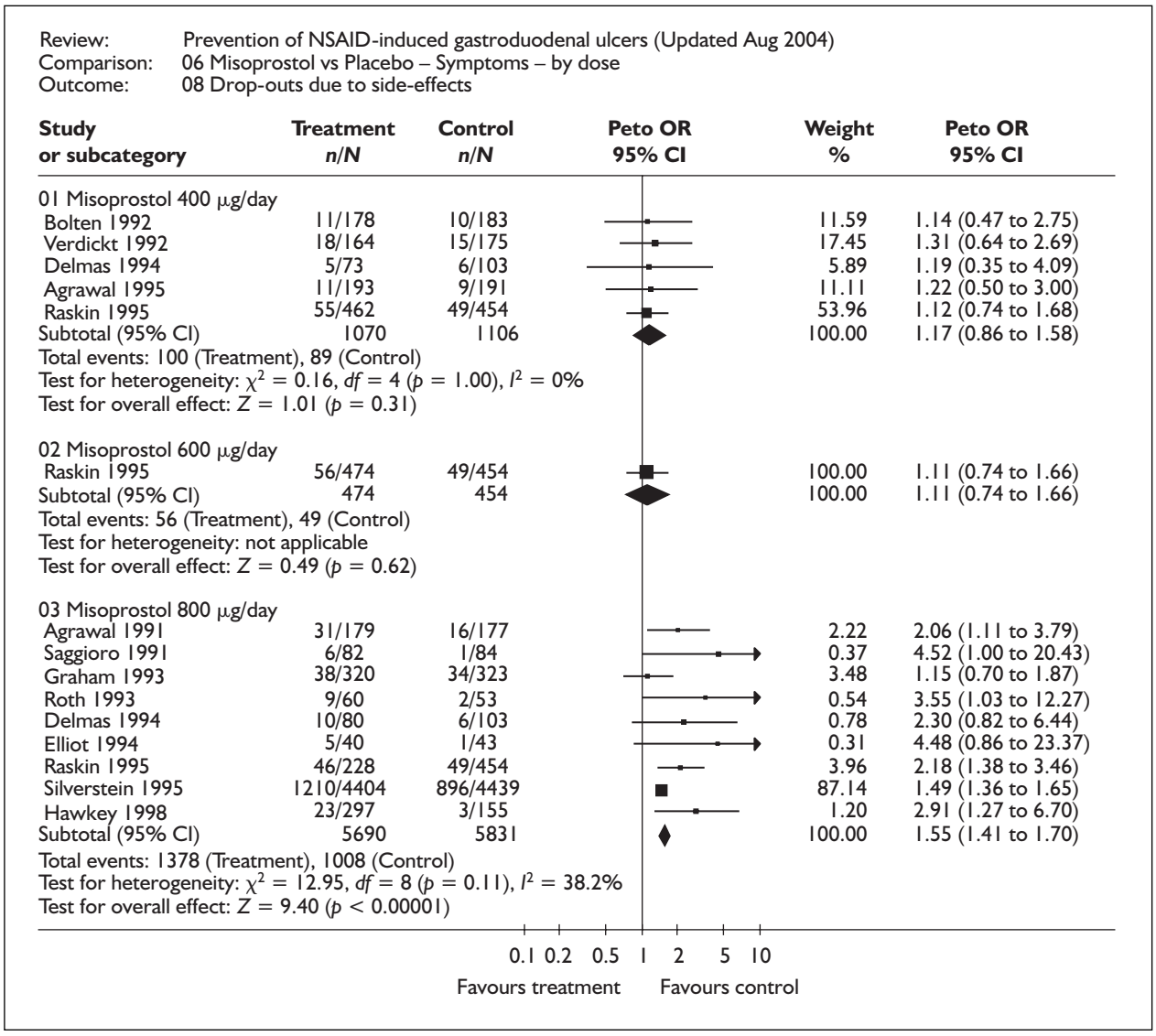

FIGURE 33 *Comparison by dose of misoprostol (treatment) versus placebo (control) causing symptoms: drop-outs due to side-effects*

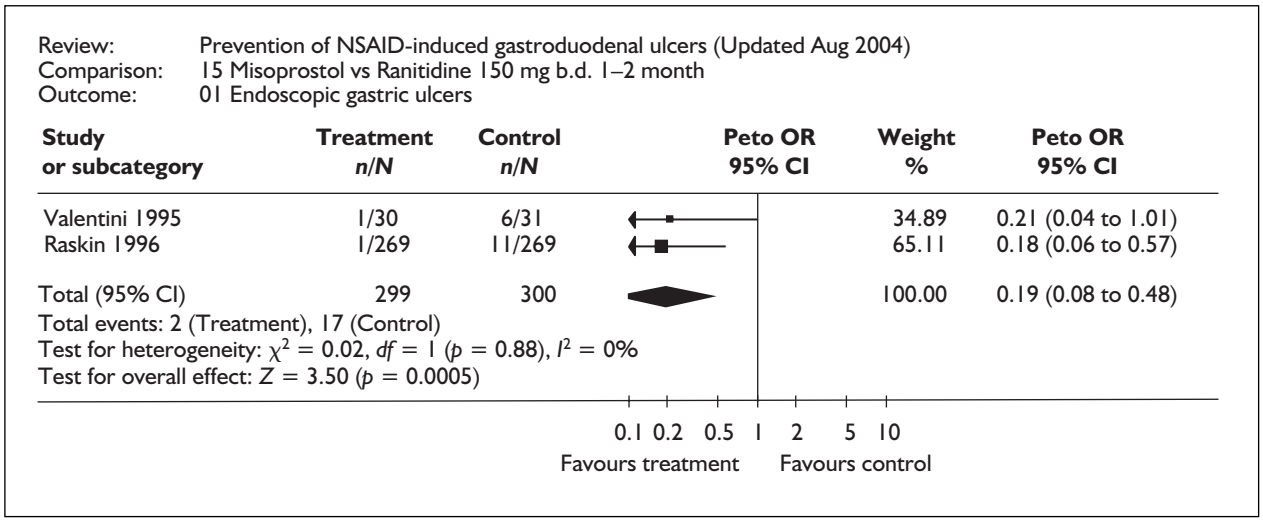

FIGURE 34 *Head-to-head comparison of misoprostol (treatment) versus H_2RA (control) in reducing endoscopic gastric ulcers at less than 3 months' exposure to NSAIDs*

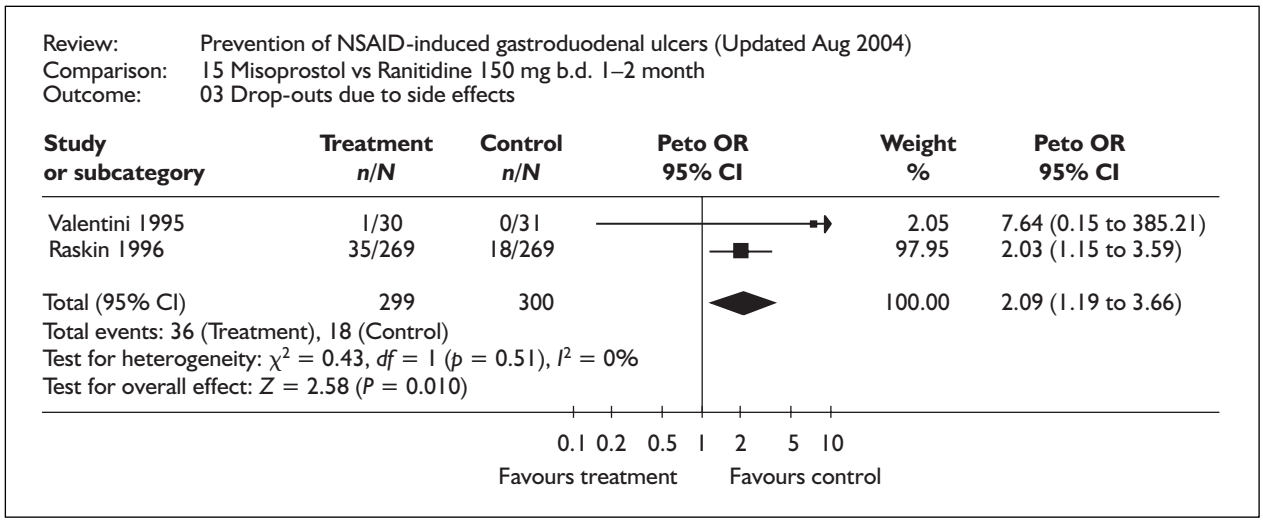

FIGURE 35 *Head-to-head comparison of misoprostol (treatment) versus H_2RA (control) for drop-outs due to side-effects at less than 3 months' exposure to NSAIDs*

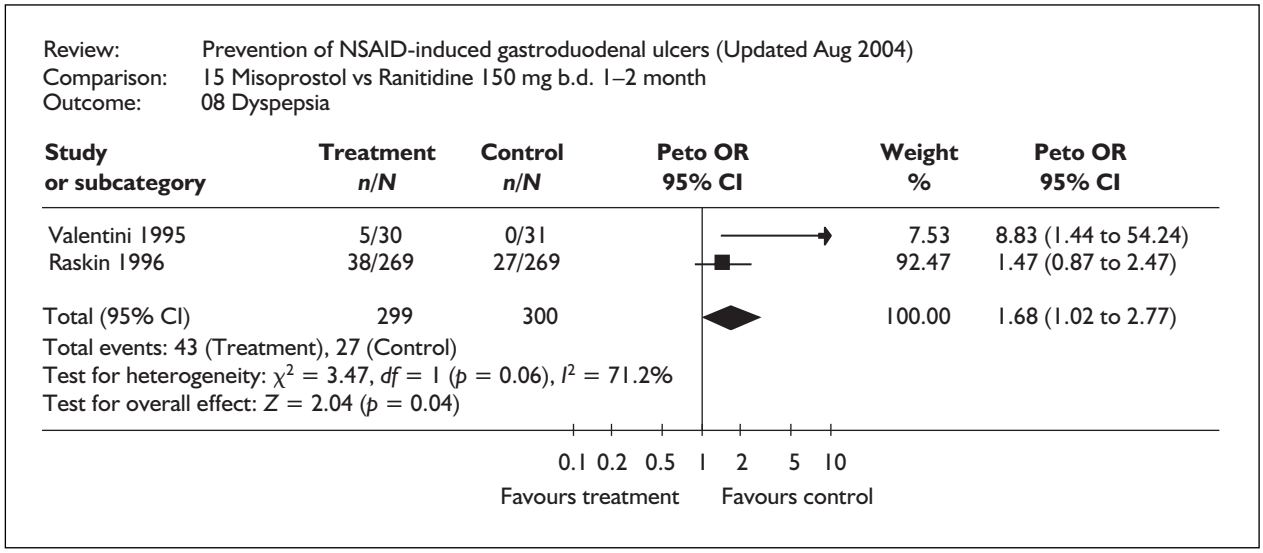

FIGURE 36 *Head-to-head comparison of misoprostol (treatment) versus H_2RA (control) for dyspepsia as a symptom outcome at less than 3 months' exposure to NSAIDs*

Both high- and low-quality misoprostol trials demonstrated a statistically significant reduction of endoscopic ulcers.

In summary, the above analyses demonstrate that both low- and high-dose misoprostol are effective in reducing the risk of NSAID-induced endoscopic GUs and DUs. However, the higher dose of 800 μg is associated with greater side-effects. High-dose misoprostol is the only prophylactic agent to show a reduction in ulcer-related complications. Misoprostol is comparable to PPI in preventing GUs but inferior in preventing DUs. Misoprostol is superior to H_2RA in preventing GUs but not DUs. However, both high- and low-dose misoprostol are associated with excessive adverse effects and are poorly tolerated compared with both PPI s and H_2RAs.

H_2RAs

H_2RAs compared with placebo

Endoscopic ulcers

Seven trials with 1188 patients assessed the effect of standard-dose H_2RAs on the prevention of endoscopic NSAID ulcers at 1 month[200,209,223,224,230,233,238] and five trials with

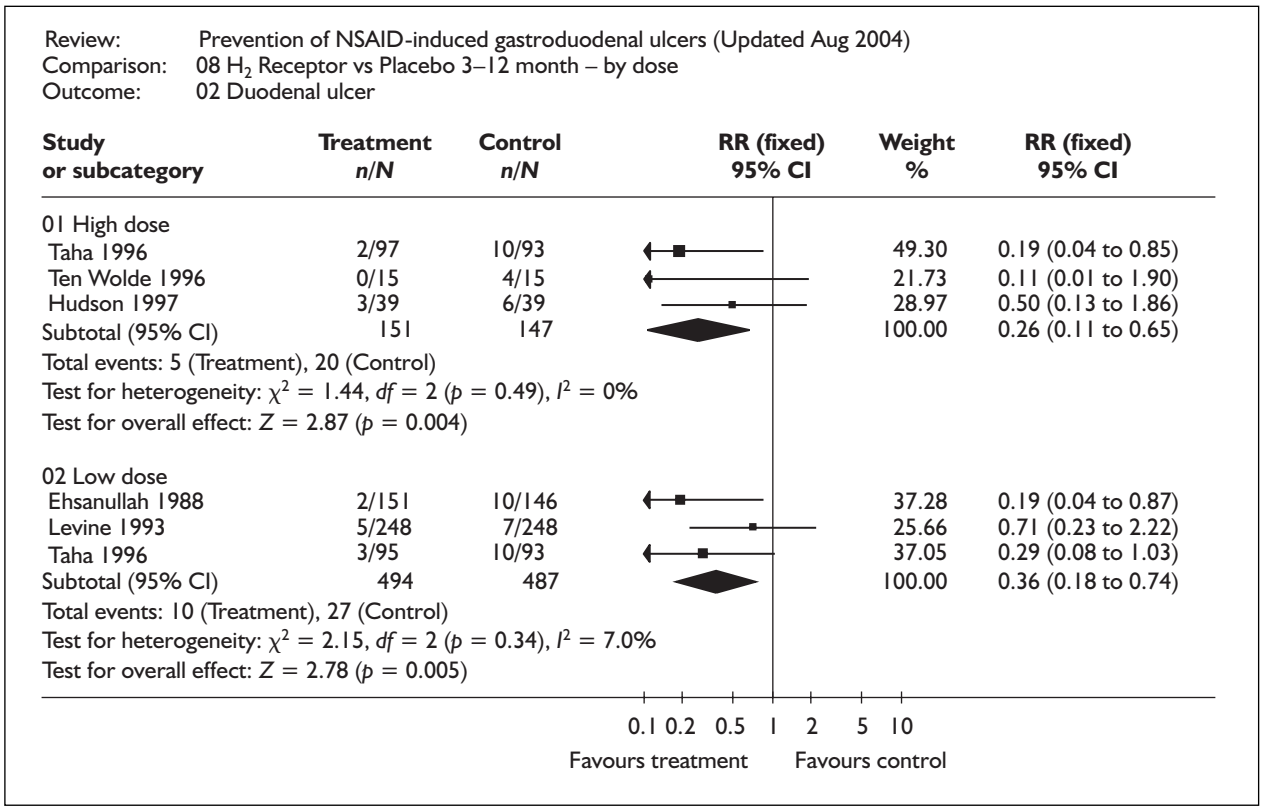

FIGURE 37 *Primary efficacy comparison of H_2RAs (treatment) versus placebo (control) in reducing the incidence of endoscopic duodenal ulcer after at least 3 months of NSAID exposure*

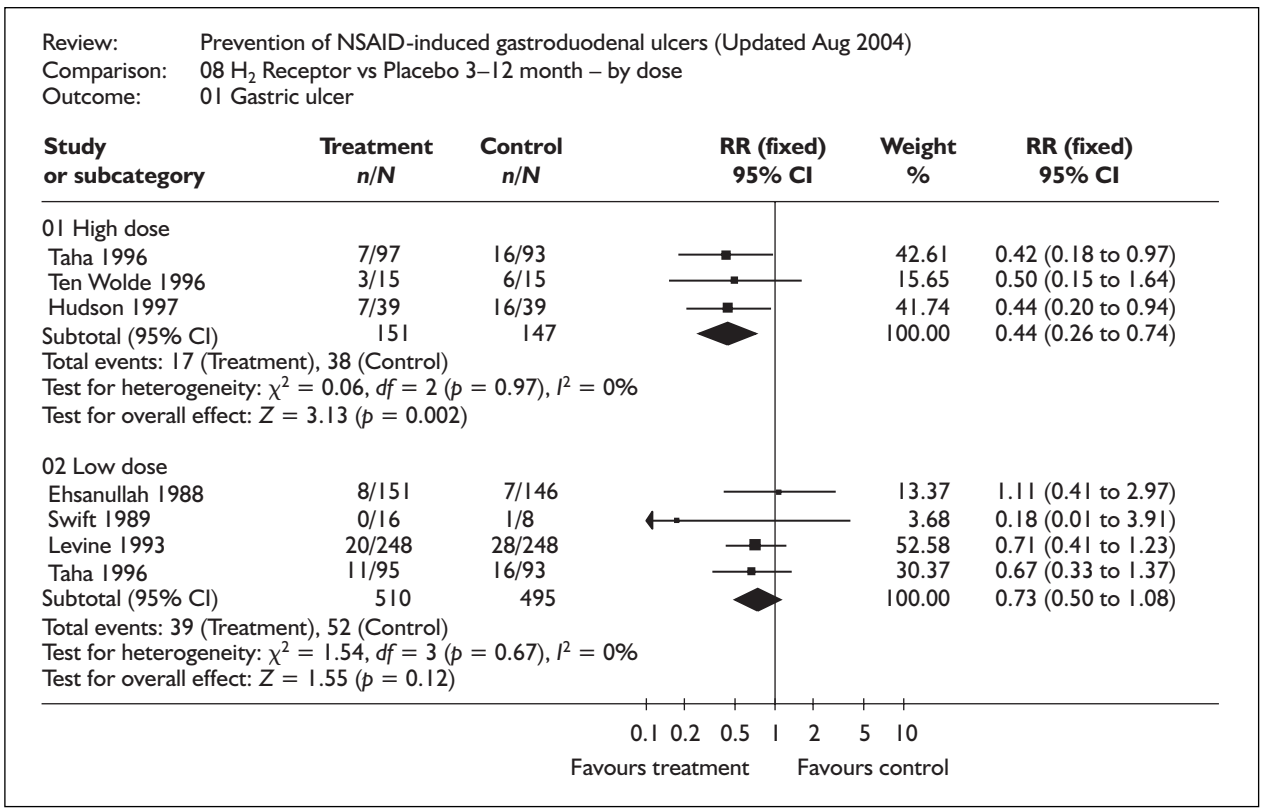

FIGURE 38 *Primary efficacy comparison of H_2RA (treatment) versus placebo (control) in reducing the incidence of endoscopic gastric ulcer after at least 3 months of NSAID exposure*

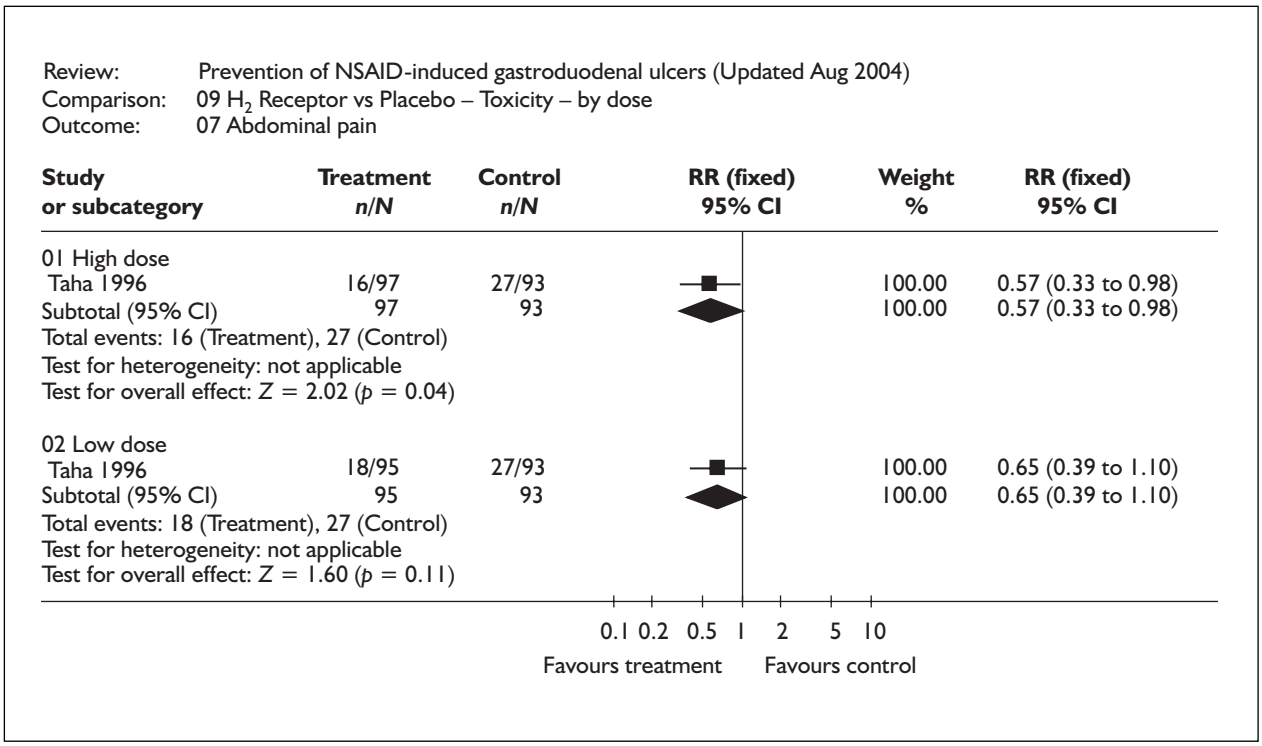

FIGURE 39 *Comparison of H_2RA by dose (treatment) versus placebo (control) causing toxicity: abdominal pain*

1005 patients assessed these outcomes at 3 months or longer.[209,219,228–230] Three RCTs including 981 patients assessed standard-dose H_2RA[209,219,230] and three RCTs[217,230,231] with 298 patients assessed the efficacy of double-dose H_2RAs for the prevention of NSAID-induced UGI toxicity. At 3 months or longer, standard-dose and double-dose H_2RAs are effective at reducing the risk of DUs (RR 0.36, 95% CI 0.18 to 0.74 and RR 0.26, 95% CI 0.11 to 0.65, respectively) (see *Figure 37*).

However, only double-dose H_2RAs when compared with placebo were associated with a statistically significant reduction in the risk of gastric ulcers (RR 0.44, 95% CI 026 to 0.74) (see *Figure 38*). This 56% RRR in GUs corresponds to a 12% absolute risk difference (from 23.1% to 11.3%). Analysis of the secondary prophylaxis studies alone yielded similar results.

Adverse effects, drop-outs and symptoms

H_2RAs, in standard or double doses, were not associated with an excess risk of total drop-outs, drop-outs due to side-effects or symptoms when compared to placebo. However, high-dose H_2RAs significantly reduced symptoms of abdominal pain when compared with placebo (RR 0.57, 95% CI 0.33 to 0.98) (see *Figure 39*).

In contrast to high-quality trials, low-quality trials failed to demonstrate a benefit of standard-dose H_2RAs for the prevention of endoscopic DUs. No significant differences were observed by quality for drop-outs and symptoms.

Conclusion

In summary, the above analyses demonstrate that double-dose H_2RAs are effective in reducing the risk of NSAID-induced endoscopic GUs and DUs whereas standard-dose H_2RAs are effective only in reducing the risk of NSAID-induced DUs. Standard-dose H_2RAs are inferior to PPIs in reducing endoscopic GUs and DUs and inferior to misoprostol in reducing endoscopic GUs. No study has compared double-dose H_2RAs with PPIs or misoprostol. Misoprostol reduces clinically important complications of NSAID-induced ulcers. There are no studies assessing clinical ulcer-related events with H_2RAs or PPIs in patients receiving NSAID therapy. An indirect comparison could be made between PPIs and misoprostol, but this would be using the endoscopic ulcer end-point. Therefore, a meaningful indirect comparison with misoprostol is not possible.

Chapter 9

Modelling and health economic evaluation – 2. What is the cost-effectiveness of alternative strategies for the prevention of peptic ulcer bleeding in NSAID users?

Introduction

In order to identify the most cost-effective treatment strategy for the prevention of first bleeds and subsequent bleeds amongst NSAID users, a Markov model with a second-order Monte Carlo simulation was constructed. The economic perspective was that of a third-party payer and the results were expressed as costs per QALY over a lifetime from age 50 years.

The strategies considered were as follows:

1. do nothing
2. PPI
3. misoprostol
4. *H. pylori* eradication
5. *H. pylori* eradication followed by PPI
6. *H. pylori* eradication followed by misoprostol.

We did not model the use of COX-2 inhibitors as these agents are no longer in routine use.

Methods and assumptions

Model structure

Within each strategy was outlined the possible health states through which a patient could transit:

- well
- recurrence of bleeding
- death.

The choice of transition states depends on the current health state. After a cycle in 'Well', a patient could transit to any of 'Well', 'Recurrence (of bleeding)' or 'Death' (*Figure 40*).

Transition following recurrence would only be to Well or Death; an assumption was made that, after a cycle of bleeding, a patient would not directly re-enter into that same state, i.e. continued bleeding. There was no transition from Death.

The model was run as a microsimulation, individual patients being tracked through the model using a 'tracker variable' for the number of bleeds and deaths from bleeding in each arm. When a first bleed occurred the tracker variable was used to switch that patient to a higher risk of rebleeding to incorporate the value of 'secondary prevention' strategies into the model.

Treatment strategies

1. **Do nothing**: No prophylactic therapy was provided either before or after an NSAID-related UGI bleed.
2. **PPI**: Omeprazole 20 mg once daily on an ongoing basis.
3. **Misoprostol 200 μg twice daily**: Misoprostol 200 μg twice daily on an ongoing basis. In recognition of misoprostol intolerance[251] due to severity of side-effects (diarrhoea and abdominal pain), the patients who did not tolerate misoprostol were put through the PPI regime.
4. ***H. pylori* eradication alone**: In the first month of the model, all patients are tested for *H. pylori* and given eradication therapy if positive. All treated patients are re-tested with the non-invasive [^{13}C]urea breath test (sensitivity 95%, specificity 96%). One week of triple therapy based on the National Dyspepsia Guidelines comprising omeprazole 20 mg twice daily,

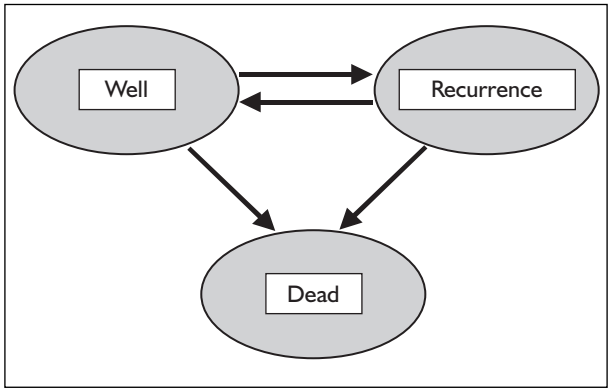

FIGURE 40 *Basic model structure*

amoxicillin 1000 mg twice daily, clarithromycin 500 mg twice daily was used.[252] If still positive, a second course of treatment with 1 week of triple therapy including one antibiotic change[138] (metronidazole 400 mg instead of clarithromycin) was given. In subsequent months, the do nothing strategy applied. *H. pylori*-negative patients received no further treatment (identical with the do nothing arm).

5. ***H. pylori* eradication followed by PPI**: In the first month, testing and triple therapy as above were carried out, followed by omeprazole 20 mg once daily for the rest of the month. Re-testing and re-treatment followed by Omeprazole 20 mg once daily for the rest of the month was carried out if necessary. In subsequent months Omeprazole 20 mg once daily was given. *H. pylori*-negative patients received PPI alone (identical with the PPI arm).
6. ***H. pylori* eradication followed by misoprostol**: In the first month, testing and triple therapy as above were carried out, followed by misoprostol 200 μg twice daily for the rest of the month. Re-testing and re-treatment followed by misoprostol 200 μg twice daily for the rest of the month were carried out if necessary. In subsequent months misoprostol 200 μg twice daily was given. *H. pylori*-negative patients received misoprostol alone (identical to the misoprostol arm). If patients failed to tolerate misoprostol they were switched to the PPI strategy.

The detailed structure of the model is shown in *Figure 41*.

Model process

The population profile was determined to reflect those patients most likely to use long-term NSAIDs such as for arthritis. Patients entered the model at age 50 years using age- and sex-dependent life expectancy.[253,254] Each cycle was 1 month (one-twelfth of a year) to reflect the biological process being modelled. In order to capture the full life span of the cohort, the termination condition was set it at 600 cycles (50 years). QoL, bleeding mortality and all-cause mortality were fixed for age and sex using a look-up table. All-cause mortality was not adjusted for bleeding as UGI bleeding is a minor cause of mortality. QALY values were applied to four age bands: 45–54, 55–64, 65–74 and 75 years and older.[255]

It was assumed that every patient would start each model as 'Well', giving a probability of starting the model in each transition health state of 1, 0 and 0, respectively. Following a cycle, the monthly likelihood of any particular outcome occurring (transitional probability, Tp) for an event rate r over a time interval t (1 year) can be estimated using the following equation:

$$Tp = 1 - e^{-rt/12}$$

It was assumed that none of the treatment strategies would affect the mortality rate due to other causes over the term of the model, and that patients remaining alive after a bleed would be subject to the same non-bleeding mortality as the rest of the population. It was also assumed that the treatment strategies would affect only the risk of bleeding but not the risk of death from bleeding. Also assumed is that the transitional probabilities of recurrence (Tp_Recurr) and death from recurrence (MR_Bl) remained unchanged by the number and frequency of transitions through the bleed state.

Outcomes

The outcomes were costs incurred and QALY gained per cycle (from EQ-5D index). Benefits considered are those directly to the patient's QoL. Dyspepsia was not used as an outcome as insufficient studies were found that had considered dyspepsia as a primary or secondary outcome of prophylaxis for bleeding.

Mortality due to other causes was determined from look-up tables which predicted the risk of dying in any stage of the cycle and any year, adjusted for age and sex. The RR of bleeding was assumed to be unchanged for all subsequent bleeds.

Direct health care costs included:

- primary care drug costs and cost of [^{13}C]urea breath tests, including GP consultations
- hospital-based inpatient treatment costs
- the excess cost of death due to bleeding, included as an incremental cost during the Bleed state.

Sources include the Prescription Pricing Authority, the BNF and the National Reference Costs website.[138,256] Both costs and effectiveness were discounted to present value at an annual rate of 3%.

The variables needed for second-order simulation were generated using the probability density function around assigned distributions based on prior knowledge of the variable. Counts and prevalence rates were given a beta distribution and costs were given a gamma distribution. A log-normal distribution was applied to the RRs.

TABLE 29 *Assumed annual rates and relative risks*

Name	Description	Source	Value	Distribution
CER	Baseline rate of first bleed	This report – Chapter 8	1.5%	Beta α 15 β 985
CER	Baseline rate of subsequent bleed	Sharma, 2001[59]	22 (95% CI 18 to 33)	Beta α 220 β 780
H. pylori prevalence	Age-related *H. pylori* prevalence	Consensus	(Age – 15)%	Beta α Age – 15% β 100 – (Age – 15)%
RR_PPI	RR 1 year PPI compared with placebo	This report – Chapter 8	0.42 (95% CI 0.32 to 0.51)	Log-normal μ – 0.87 σ 0.12
RR_misoprostol	RR 1 year misoprostol compared with placebo	This report – Chapter 8	0.4 (95% CI 0.37 to 0.98)	Log-normal μ – 0.92 σ 0.25
RR_*H. pylori*	RR 1 year *H. pylori* eradication compared with placebo	This report – Appendix 6	0.35 (95% CI 0.18 to 0.73)	Log-normal μ – 1.02 σ 0.357
RR_HP + PPI	RR 1 year *H. pylori* eradication followed by PPI compared with placebo	This report – Appendix 6	0.19 (95% CI 0.09 to 0.77)	Log-normal μ – 1.66 σ 0.79
MR_BI	Age-specific mortality rate of PU bleeding	Rockall, 1997[135]	$\leqslant$60 (4% mortality per bleed) 61–79 (12% mortality per bleed) $\geqslant$80 (35% mortality per bleed)	Table
MR_OC	Mortality rate – other causes	Government Actuary's Department,[253] Office for National Statistics[254]	Life expectancy table adjusted for age–sex profile	Table
Costs				
C_HP	Cost of 1 week triple therapy plus 20% re-treat	UK Drug Tariff[256]	£30.62	Fixed
C_PPI	Cost of PPI for 1 month	UK Drug Tariff[256]	£10.51	Fixed
Cameos	Cost of misoprostol for 1 month	UK Drug Tariff[256]	£10.17	Fixed
C_UBT	Cost of [^{13}C]urea breath test plus 100% re-test	UK Drug Tariff[256]	£41.50	Fixed
C_UBT_negative	Cost of single [^{13}C]urea breath test	UK Drug Tariff[256]	£20.75	Fixed
C_HP_PPI	Cost for eradication therapy followed by PPI for rest of month	UK Drug Tariff[256]	£46.97	Fixed
C_HP_PPI	Cost of eradication therapy followed by misoprostol for rest of month	UK Drug Tariff[256]	£38.45	Fixed
C_Recurrence	Cost of a recurrence	National Reference Tables[137] (F17, F18)	£1000	Gamma α 1 λ 0.0011
C_Death_BI	Cost of death from a bleed	National Reference Tables[137] (F13, F14, F17, F18)	£3000	Gamma α 1 λ 0.0011
C_Death_OC	Cost of death from another cause	NA	0	NA

NA, not applicable.

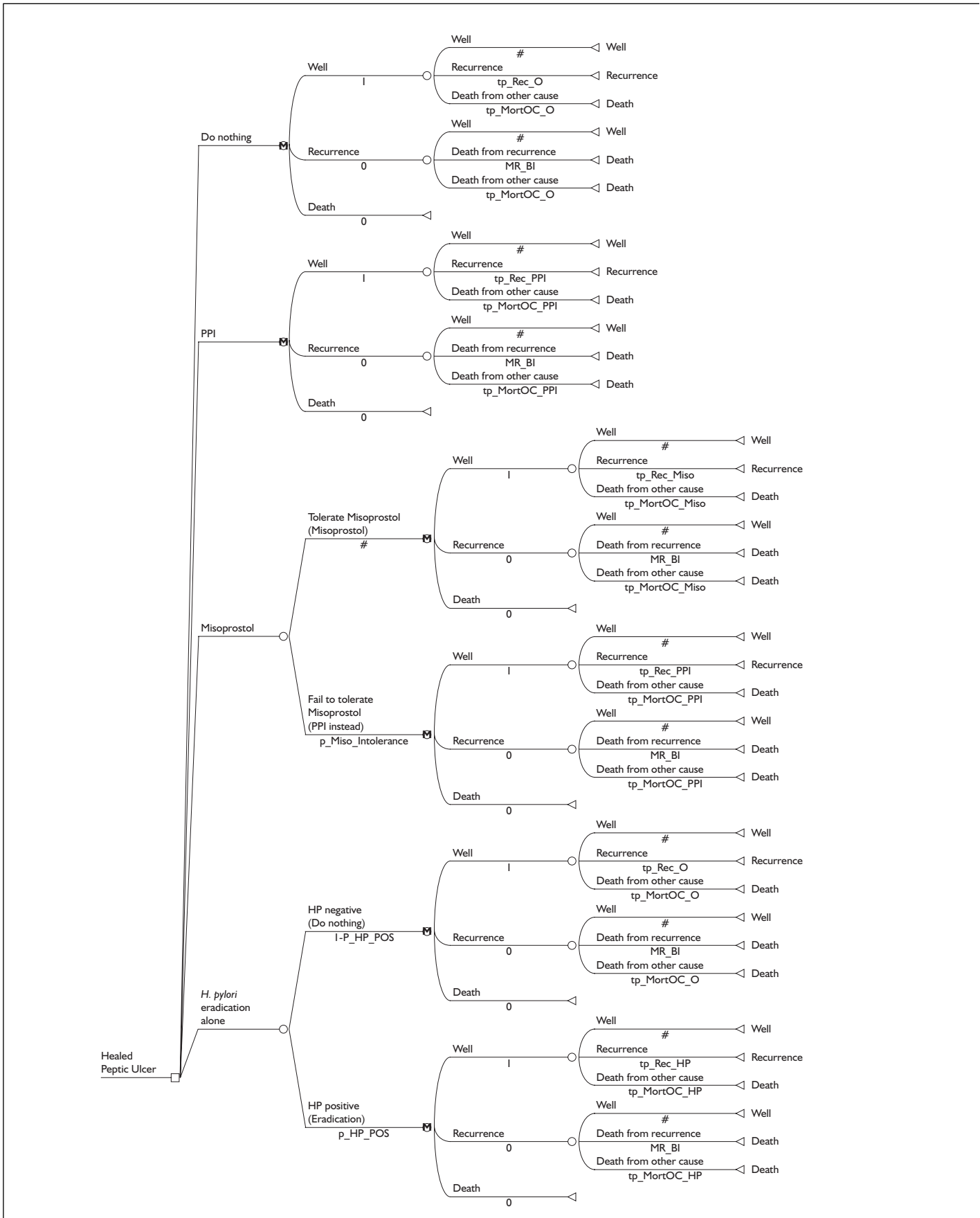

FIGURE 41 *Detailed model structure*

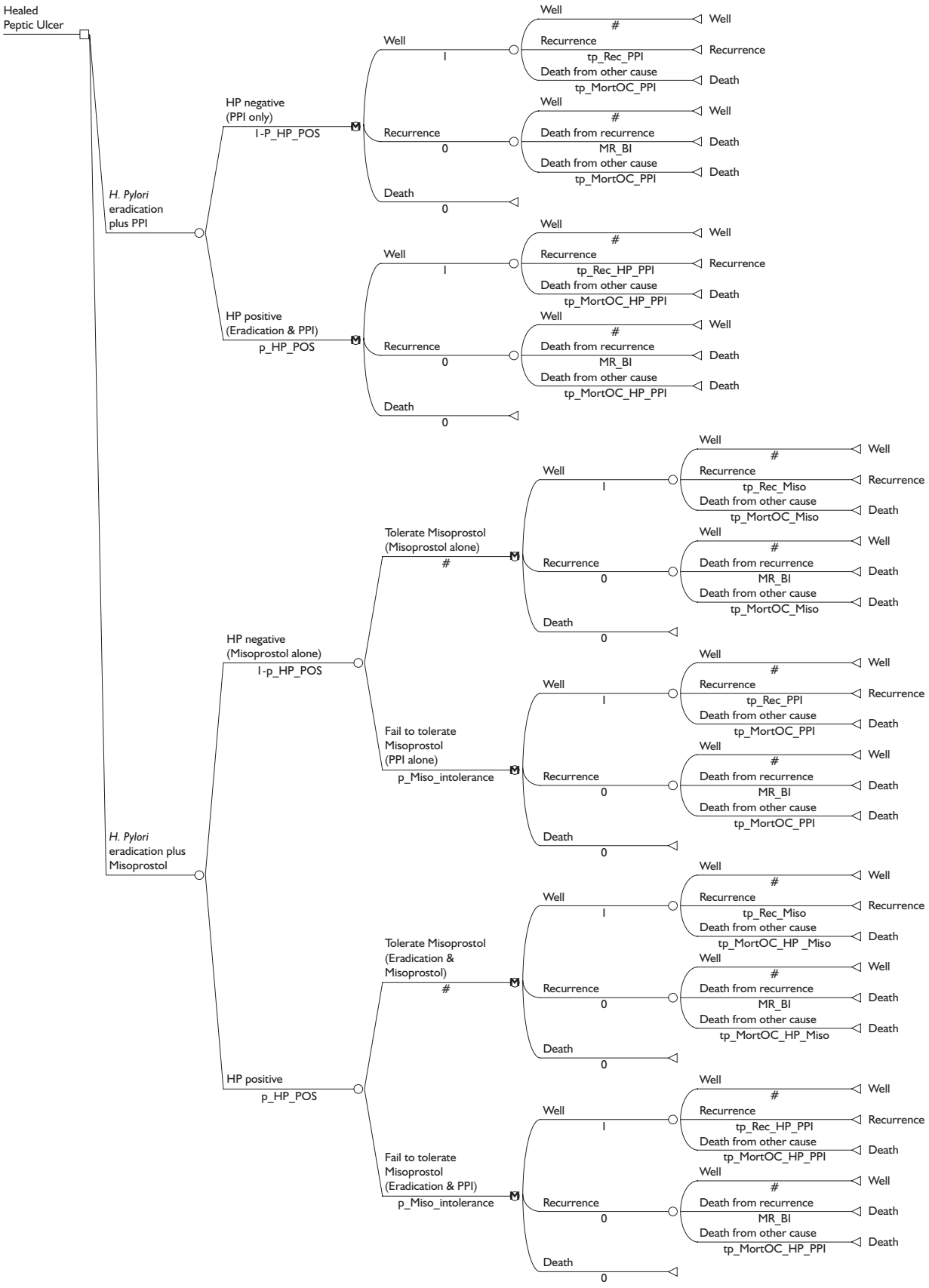

FIGURE 41 *Detailed model structure (cont'd)*

Model assumptions

The rates, RRs and assumed costs used in the model, together with ranges used in sensitivity analyses and the source information, are summarised in *Table 29*. As outcome data from the trials and meta-analyses relate to endoscopic ulcer recurrence, we assumed that the same RRRs would apply to actual bleeding events, but related to the much lower base rates for clinical events. In order to establish RRs for *H. pylori* eradication, compared with placebo and PPI, in reducing primary and secondary bleeds among NSAID users, it was necessary to conduct a supplementary systematic literature review and meta-analysis. This is described in Appendix 6.

Analysis

Probabilistic sampling was carried out with a run of 1000 simulations of 100. This provided estimates of the variability of the outcome measure. The primary outcome was cost per QALY. The software used was Data Pro 2005 v 1.0 (DATA™) from TreeAge Software (Williamstown, MA, USA). Results were first expressed on the cost-effectiveness plane and then uncertainty was explored using pairwise comparisons as CEACs. Multiple CEACs or frontiers were not plotted as their interpretation and production are problematic. A full multiple CEAC plot assumes that all the possible correlations between model parameters are accurately captured. In addition, removal of one dominated strategy may affect the placement of the other curves. We prefer instead to present the more conservative display of pairwise CEACs.

Results

Primary prevention of NSAID-related UGI bleeds

The first analysis was for primary prevention of NSAID-induced peptic ulcers, the base rate of bleeding being set at 1.5% per annum. The cost-effectiveness frontier, the line between the most cost-effective alternatives, ran between *H. pylori* eradication and *H. pylori* followed by misoprostol. The four strategies to the left and above the cost-effectiveness frontier were dominated, that is, they were more expensive and less effective (*Figure 42*).

Table 30 shows that if there were no limit on what one was willing to pay, then the most cost-effective strategy would be *H. pylori* eradication followed by misoprostol. The threshold for this choice is £5235 per QALY (*Table 31*). This point estimate is well below the limit of currently acceptable adoption.

A Monte Carlo simulation run of 1000 produces 6000 dots that appear as two clusters (*Figure 43*). The lower cluster represents do nothing and *H. pylori* eradication strategies with considerable

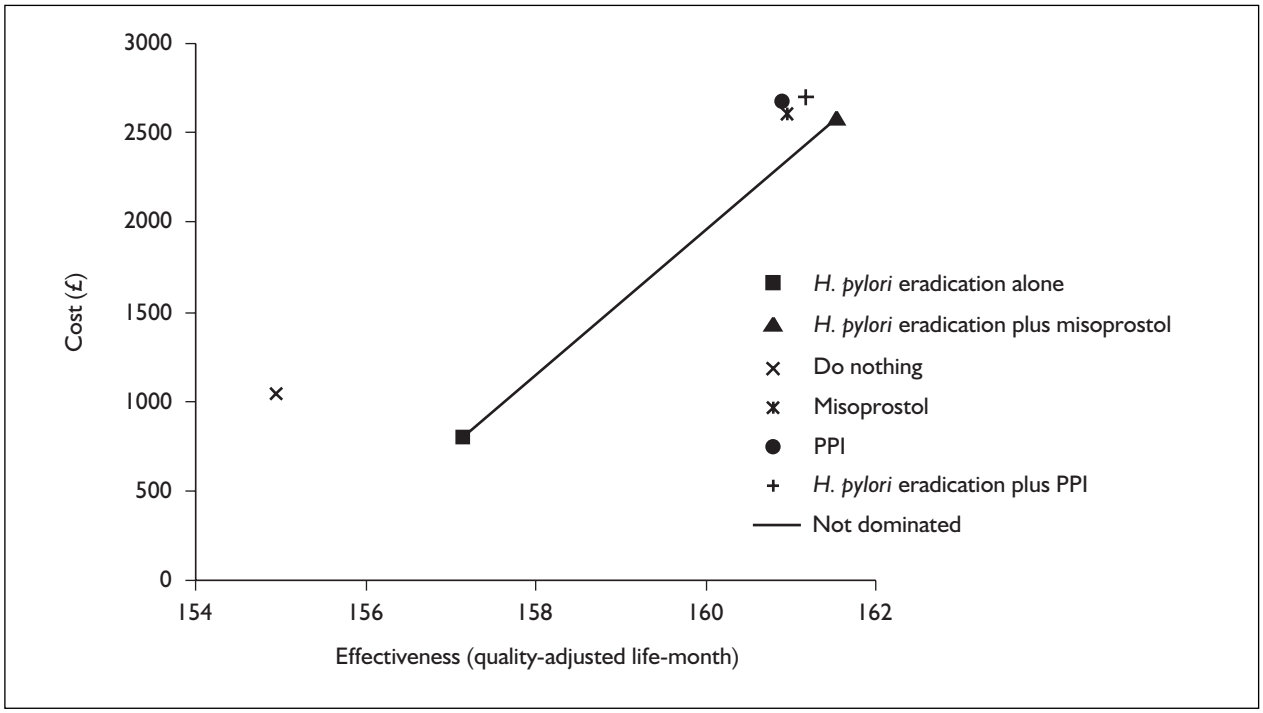

FIGURE 42 *Preventive strategies for NSAID-induced UGI bleeding on the cost-effectiveness plane*

TABLE 30 *Incremental cost-effectiveness of prophylaxis*

Strategy	Incremental cost (£)	Incremental effectiveness (QALY)	ICER (£/QALY)
H. pylori eradication alone	–	–	–
Do nothing	235	–0.18	Dominated
Misoprostol	20	0.05	Dominated
H. pylori plus misoprostol	1780	0.37	4810
PPI	94	–0.05	Dominated
H. pylori plus PPI	109	–0.029	Dominated

TABLE 31 *Comparative cost-effectiveness of non-dominated strategies*

Strategy	Cost (£)	Incremental cost (£)	Effectiveness	Incremental effectiveness (QALY)	ICER (£/QALY)
H. pylori eradication alone	804	–	13.08	–	–
H. pylori eradication followed by misoprostol	2584	1780	13.42	0.34	5235

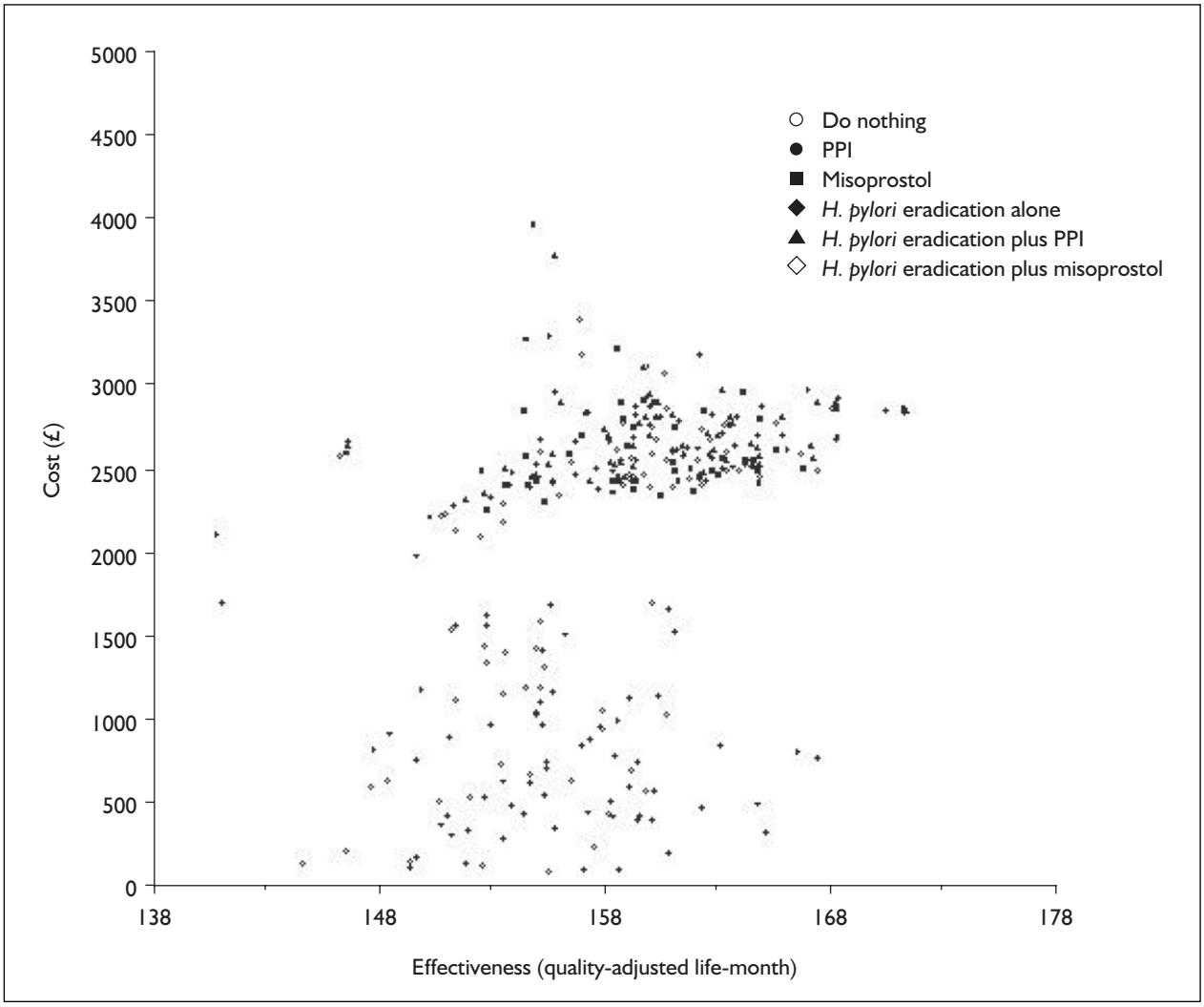

FIGURE 43 *Cost-effectiveness scatter plot for alternative strategies for the prevention of peptic ulcer bleeding in NSAID users*

overlap. The upwards and left-sided drift of do nothing suggests that it may be both more expensive and less effective than *H. pylori* eradication.

The second cluster, a clear distance apart, represents the other four strategies; this is more compact, indicating less variation within them. The clear distance from the lower cluster on the cost axis indicates that these four strategies are consistently more expensive. The overlap on the effectiveness axis shows that they are at least as effective as *H. pylori* eradication and do nothing.

The spread of the dots shows the distribution of losses and gains about the mean for each strategy but it does not take into account the relative position of points in a particular simulation that are correlated with each other.

Next, a series of CEACs were plotted. Using non-dominated strategies as comparators, this shows the proportion of patients for whom the comparator strategy would be cost-effective plotted against maximum willingness to pay. *H. pylori* eradication strategy appears to be cost-effective compared with do nothing for almost all patients at any level above £80/QALY (*Figure 44*).

The *H. pylori* followed by misoprostol strategy is 90% likely to be cost-effective compared with do nothing at a willingness to pay of £500/QALY, rising to 99% at £1000/QALY (*Figure 45*).

Direct comparison using *H. pylori* eradication as the baseline and *H. pylori* followed by misoprostol as the comparator shows that the latter strategy would be cost-effective in most patients treated at £2000/QALY (*Figure 46*).

Sensitivity analysis

In order to test the robustness of the model, a series of parameters were tested within a range of plausible values.

***H. pylori* prevalence**

In addition to being a variable in the Monte Carlo simulation with a baseline of 35%, the mean prevalence was changed from 5 to 50%. PPI and *H. pylori* eradication followed by PPI were dominated at all levels of *H. pylori* prevalence.

Age

The age at entry to the model was 50 years and this was sequentially increased by 10-year intervals. The results were unchanged for cohorts aged 60, 70, 80 and 90 years. For a cohort age of 90 years, PPI alone and misoprostol alone came under extended dominance (extended dominance refers to the situation where one strategy is less cost-effective than a mixture of two other strategies, one cheaper and one more expensive).

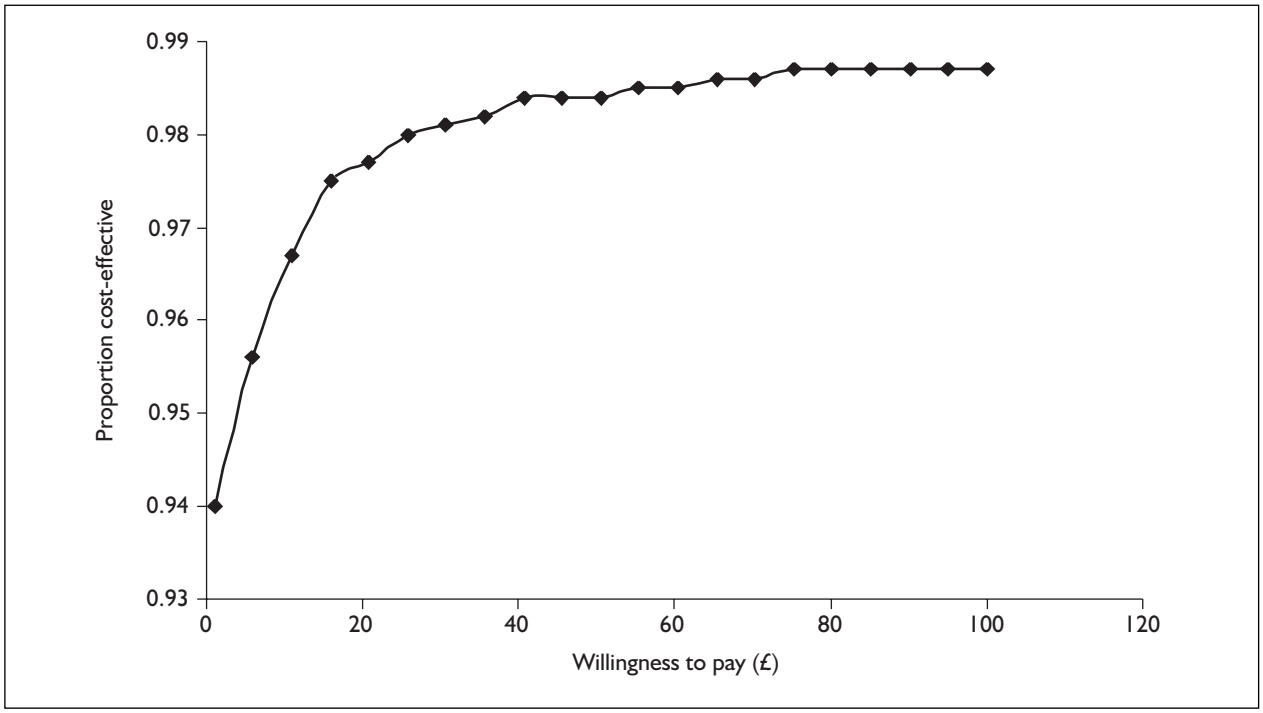

FIGURE 44 *CEAC:* H. pylori *eradication alone versus do nothing*

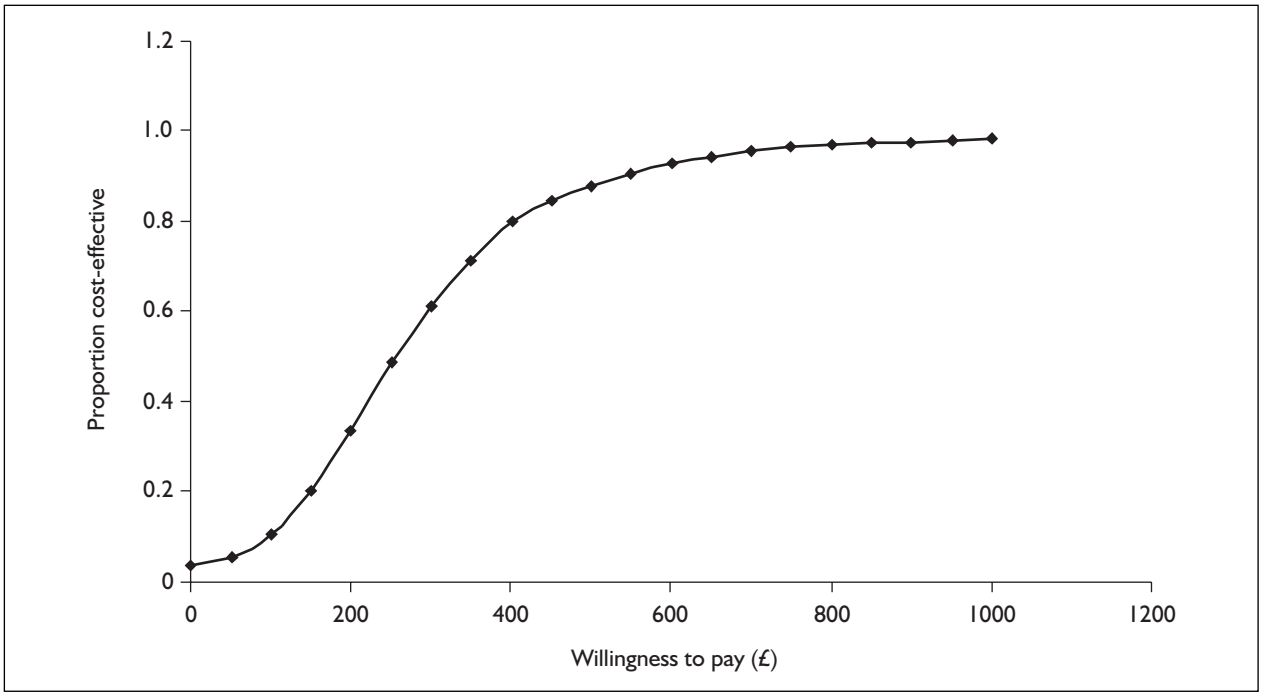

FIGURE 45 *CEAC:* H. pylori *eradication followed by misoprostol versus do nothing*

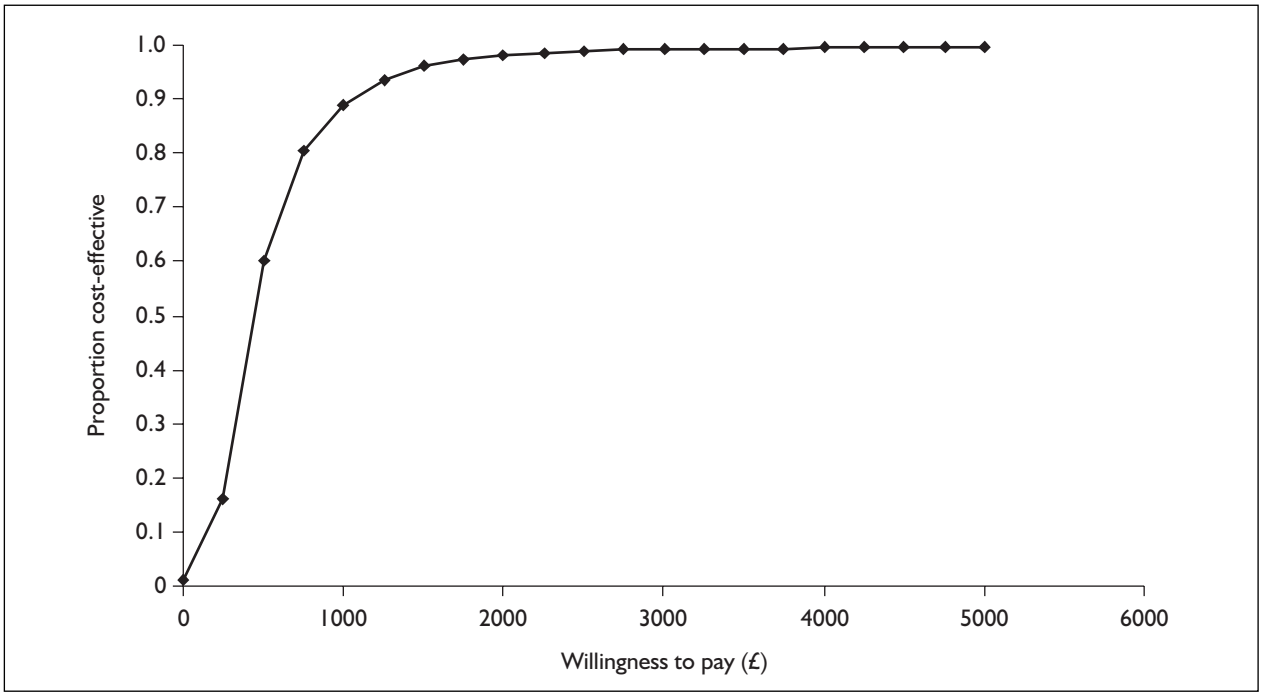

FIGURE 46 *CEAC:* H. pylori *alone versus* H. pylori *plus misoprostol*

H. pylori eradication was not dominated and had an ICER of £1200/QALY at 99 years.

Probability of misoprostol intolerance

The baseline was 11.7%; we tested a range of 5–20% and the results were essentially unchanged. To examine further the effect of higher intolerance reported with higher dose misoprostol (800 μg daily), we extended this to 50%; again the results were unchanged.

Cost of PPI

The baseline was 10.41 and the range tested was £0.01–10.41. At £5.00 per month, *H. pylori* followed

by PPI ceased to be dominated. Instead, it 'broke' the cost-effectiveness frontier with an ICER of £22,300 compared with *H. pylori* eradication. At £1.00 per month, PPI ceased to be dominated but remained less cost-effective than *H. pylori* eradication. Below £0.40 per month, PPI became the most cost-effective strategy. As PPIs are already 'cheap' at generic prices, none of these options is feasible.

Cost of misoprostol
The baseline was £10.14 and the range tested was £1.01–10.14; the results were unchanged. Misoprostol was under extended dominance across the range. *H. pylori* followed by misoprostol was not dominated at any point in the range.

Discount rates
Sensitivity analysis was also carried out using no discounting and also costs only discounted by 3%. No difference in relative cost-effectiveness was observed.

Conclusions

With regard to the six strategies considered for the prophylaxis against bleeding PUs amongst NSAID users, the two most cost-effective strategies were:

- *H. pylori* eradication
- *H. pylori* eradication followed by misoprostol if tolerated, otherwise switching to a PPI.

At a threshold of £100/QALY, the most cost-effective strategy was *H. pylori* eradication. At a threshold of £1000/QALY, the most cost-effective strategy was *H. pylori* followed by misoprostol if tolerated, otherwise switching to a PPI. Both strategies are sensitive to changes in age and *H. pylori* prevalence. *H. pylori* prevalence is expected to fall over time with a reduction in the cohort effect of older patients with *H. pylori* infection. However, the sensitivity analysis showed that eradication therapy remained cost-effective down to very low levels of *H. pylori* prevalence (5%).

Immigration from high-prevalence countries is changing the population profile of *H. pylori* infection in the UK and it may be considered advisable to maintain *H. pylori* eradication as the treatment of choice for all ages.

There are a number of major assumptions that have had to be made to construct this model:

1. There are no data on which to model the effect of stopping NSAIDs after a bleed. This is due to a lack of reliable RCT data in this area.
2. We have had to assume that the relative effects seen in RCTs of primary prevention apply also to secondary prevention after a bleed, but with a higher event rate. In general, the data from trials of secondary prevention of NSAID-induced and non-NSAID-induced ulcers are too sparse and contradictory to be of any use in modelling.
3. The clinical meta-analysis data largely apply to a reduction in endoscopic ulcers rather than bleeds, and we have assumed that the same relative effect will apply to actual bleeds.

This is further complicated by the fact that the one trial to examine the direct effect of *H. pylori* eradication versus PPI maintenance in the secondary prophylaxis of UGI bleeding, rather than endoscopic ulcers, found that fewer bleeds occurred in the PPI group (3/75 versus 13/75, RR bleed 4.3 (95% CI 1.3 to 13.8).[158] This is in direct contradiction of the predictions of this model. It may be that other factors, not captured in the model, act in favour of PPIs, or that patients in China are not representative of patients included in other studies. It may also be that both predictions are correct; eradication decreases minor endoscopy 'only' ulcers, but not significant bleeds from ulcers that do occur.

The question is therefore whether this model can be taken as a good guide for clinical practice or should be used just to guide further research. In view of the assumptions made and the lack of key data, it should be used as a guide only.

In particular, further research should focus on:

1. Large-scale studies of the effect of misoprostol, PPI and *H. pylori* eradication on the primary prevention of actual UGI bleeds rather than endoscopic ulcers alone. In view of the difficulty of controlling for residual confounding, these should be RCTs.
2. Similar studies in secondary prevention, but including the option of stopping NSAIDs altogether. There will be ethical issues here, as for many patients stopping NSAIDs will be the preferred option and only a small number of patients dependent on NSAID therapy will be suitable for randomisation.

Chapter 10
Conclusions

Proton pump inhibitors in the acute hospital management of patients with upper gastrointestinal haemorrhage

In summary, our systematic reviews have not provided evidence that PPI treatment reduces mortality following UGI bleeding, whether treatment is initiated prior to endoscopy or after endoscopic confirmation that the bleed originates from a PU.

There is a relative lack of evidence from randomised trials in which PPI therapy is used prior to endoscopy, even though this practice is currently widely used. Apart from the mortality outcome, we also found no evidence that PPI treatment initiated prior to endoscopy affected other clinically important outcomes, namely re-bleeding or the need for subsequent surgical intervention. There is some evidence that PPI treatment initiated prior to endoscopy reduces the proportion of patients with SRH at the index endoscopy; however, this observation is of uncertain clinical significance.

In the situation after endoscopic investigation and confirmation of a PU, the evidence is consistent that PPI therapy reduces re-bleeding rates. This appears to be evident whether only high-quality trials are examined in isolation, whether the PPI is administered orally or intravenously and whether or not endoscopic haemostatic treatment is first administered. In general, the evidence also indicates that need for surgical intervention is also reduced by PPI treatment. Despite the lack of evidence of an overall effect on mortality, PPI therapy significantly reduced mortality in trials within Asian populations and among patients with high-risk endoscopic stigmata (i.e. active bleeding or non-bleeding visible vessel) at index endoscopy.

The associated cost-effectiveness analysis we have conducted shows that the strategy of using oral PPI both before and after endoscopy, combined with endoscopic haemostatic therapy for those with major SRH is likely to be the most cost-effective. This strategy includes the use of PPI after endoscopy whether or not it was used immediately on admission. This strategy is compared with alternatives in which either no PPI or intravenous PPI are used and, under base-case assumptions, this strategy is clearly preferable on cost-effectiveness grounds, at any threshold over £25,000 per QALY, even if only short-term effects (over 28 days) are taken into account, and at any threshold over £200 per life-year gained if long-term effects are included (when life expectancy is also taken into account). Our model is the first to attempt to incorporate realistic timing into a model for acute treatment of bleeding ulcers.

Overall it may be concluded that the observed impact of PPI therapy on rates of re-bleeding and surgical intervention following a PU haemorrhage is likely to be of major clinical benefit and could be associated with important cost savings in some healthcare delivery models.

Future research recommendations

1. The issue of PPI administration prior to endoscopic diagnosis remains an important clinical question for which little evidence is available with either clinical or mortality outcomes. This needs to be explored further in large RCTs in which patients with acute UGI bleeding are randomised to PPI therapy before endoscopy. The comparator could be either post-endoscopic initiation of PPI treatment or pre-endoscopic initiation of a control treatment (placebo or H_2RA).
2. To address the issue of mortality requires a large, multicentre trial to be conducted in Europe and North America that would randomise patients to high-dose intravenous PPI or control treatment after any appropriate endoscopic intervention and address mortality as the primary end-point. Unfortunately, there are major obstacles to such a trial. Its size would necessarily be very large and recruitment is likely to prove extremely difficult, as evidenced by recent experiences in other trials in this area.
3. Randomised trials directly comparing different doses of PPIs and/or oral and intravenous administration of PPIs in patients with PU bleeding are also needed. These could be designed as non-inferiority trials, in order to reduce the number of patients required.

4. Future trials should stratify patients according to the anatomical location of the ulcer (i.e. gastric or duodenal) and report outcomes separately for each. The justification for this is that these conditions may have different aetiologies (i.e. DU is predominantly related to *H. pylori* infection whereas GU is predominantly due to aspirin or NSAID use). Furthermore, and as noted above, previous meta-analyses of H_2RAs in ulcer bleeding have suggested minor benefits in bleeding GU but no overall benefit in bleeding DU. It is at least conceivable that there may be differences in outcomes for PPIs.
5. Future trials would also benefit from reporting deaths according to whether or not these were directly attributable to the episode of bleeding, although we acknowledge that this will be difficult for some deaths. Death following an episode of ulcer bleeding may be directly related to the haemodynamic compromise produced by the haemorrhage or to unrelated causes. It would be helpful if we could differentiate between these two broad causes of death in published trials.
6. Most of the trials in these reviews used omeprazole as the PPI. Sensitivity analyses and meta-regression analysis did not provide any evidence of a differential effect among different PPIs. Moreover, we have no *a priori* reason to assume that the observed effects of PPI treatment are anything other than a class effect common to all PPIs by virtue of their powerful effect on intragastric acidity. There is, however, very limited evidence on head-to-head clinical outcome comparisons between different PPIs in PU bleeding, so such trials may still be considered relevant.

Proton pump inhibitors in the primary and secondary prevention of upper gastrointestinal haemorrhage

Our series of systematic reviews and meta-analyses have concluded the following.

In patients not using NSAIDs

There is evidence that recurrent bleeding was less frequent after *H. pylori* eradication therapy than after non-eradication ulcer healing antisecretory therapy (including PPIs), either with or without subsequent long-term maintenance antisecretory therapy. This advantage is expressed by an NNT with eradication therapy to prevent one episode of re-bleeding of seven when compared with ulcer healing treatment alone, and of 20 when compared with long-term maintenance antisecretory therapy (mainly because the risk of re-bleeding with maintenance antisecretory therapy was relatively low).

There is no evidence comparing antisecretory therapies with each other or with placebo, nor did we find any looking at this issue specifically in *H. pylori*-negative patients. For *H. pylori*-negative patients not on NSAIDs, a reasonable approach would be to confirm that they were really *H. pylori* negative and really not on NSAIDs. If Zollinger–Ellison syndrome and rare causes of PU (such as Crohn's disease) are excluded, then in the absence of anything better to offer, long-term PPI treatment seems reasonable.

In patients using NSAIDs

There is no evidence comparing PPI therapy with *H. pylori* eradication therapy for the primary prevention of UGI bleeding in *H. pylori*-positive patients using NSAIDs. We identified only one trial that compared *H. pylori* eradication therapy against PPI maintenance treatment for the secondary prevention of UGI bleeding in NSAID or low-dose aspirin users. Among *H. pylori*-positive patients with a history of UGI bleeding on low-dose aspirin, eradication of *H. pylori* was equivalent to treatment with PPI in preventing recurrent bleeding. On the other hand, PPI treatment was superior to eradication of *H. pylori* in preventing recurrent bleeding in patients on a non-aspirin NSAID, namely naproxen.

Meta-analyses of trials that studied PPI therapy in the secondary outcome (prevention of endoscopic PUs) provided evidence that, among NSAID users, for both primary and secondary prevention, PPI therapy was not statistically different to *H. pylori* eradication treatment. *H. pylori* eradication was, however, more effective than placebo for primary prevention of PU. There were no data comparing *H. pylori* eradication treatment with placebo for secondary prevention.

PPIs were also found to be superior to standard-dose H_2RAs in reducing endoscopic PUs among NSAID users. No study has compared PPIs with double-dose H_2RA. Standard doses of PPI and misoprostol and double doses of H_2RAs are effective in preventing NSAID-induced endoscopic GUs and DUs. PPIs are superior to misoprostol in preventing recurrence of NSAID-induced DUs and are comparable to misoprostol in preventing recurrence of NSAID-induced GUs. Full-dose

misoprostol reduces the occurrence of ulcer-related complications caused by NSAIDs. However, misoprostol is poorly tolerated and is associated with frequent adverse effects. Overall, the available data indicate that PPIs and H_2RAs are well tolerated. However, further data comparing these agents directly with misoprostol are required in order to compare clinical outcomes including ulcer-related complications.

With regard to the six strategies considered in the Markov model for prophylaxis against bleeding PUs in NSAID users, the two most cost-effective were *H. pylori* eradication and *H. pylori* eradication followed by misoprostol 200 μg twice daily. At a threshold of £100 per QALY, the most cost-effective strategy was *H. pylori* eradication. At a threshold of £1000 per QALY, the most cost-effective strategy was *H. pylori* eradication followed by misoprostol 200 μg twice daily. Both strategies were sensitive to changes in age and *H. pylori* prevalence. However, eradication therapy remained cost-effective down to very low levels of *H. pylori* prevalence (5%).

Summary

1. In patients not using NSAIDs, there is no evidence of prophylactic benefit from maintenance PPIs in *H. pylori*-positive patients who have had a UGI bleed, associated with a peptic ulcer, and who have been successfully treated with *H. pylori* eradication therapy. There is no available evidence in *H. pylori*-negative patients.
2. In patients commencing long-term aspirin or non-aspirin NSAID therapy, there is no direct evidence that PPI treatment will prevent subsequent primary UGI bleeds. Using a surrogate secondary outcome measure (development of endoscopic PUs), there is no statistical difference in clinical benefit between PPI treatment and *H. pylori* eradication (in positive patients), although eradication is favoured on cost-effectiveness criteria. There is no available evidence in *H. pylori*-negative patients.
3. In patients using long-term aspirin or non-aspirin NSAID therapy who have had a PU bleed, there is only direct evidence regarding re-bleeding from a single study comparing maintenance PPI with *H. pylori* eradication. In studies with a surrogate secondary outcome measure (development of endoscopic PUs), there is no statistical difference in clinical benefit between PPI treatment and *H. pylori* eradication (in positive patients), although eradication is favoured on cost-effectiveness criteria. There is no available evidence in *H. pylori*-negative patients.

Future research recommendations

1. Large-scale randomised trials in patients commencing long-term NSAID therapy of the effect of PPIs, misoprostol and *H. pylori* eradication on the primary prevention of actual UGI bleeds (rather than the development of endoscopic ulcers alone) are urgently required. The efficacy of combination therapy with PPI plus low-dose misoprostol could also be studied in the above-mentioned population.
2. Similar randomised trials in secondary prevention among NSAID users who have had a UGI bleed are also required, but these should include the option of stopping NSAIDs altogether. There may be compliance issues here since, for many patients, stopping NSAIDs will be the preferred option and only a small number of patients dependent on NSAID therapy will be suitable for randomisation.
3. In relation to *H. pylori* eradication in patients who have had a PU bleed, the findings of this review are relatively robust and unlikely to change with the results of further short- or medium-term follow-up trials. Although further short term trials of greater sample size would be useful, the main area of uncertainty is the assessment of the long-term beneficial results of *H. pylori* eradication and the role of other factors that could explain recurrence of bleeding despite *H. pylori* eradication (especially NSAID use and *H. pylori* re-infection).

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The four systematic reviews included in this report (Chapters 4, 5, 7 and 8) are all included in the Cochrane Database of Systematic Reviews.[25,48,58,257] The two reviews published prior to commencement of the report[48,58] have been updated and this report includes reference to the revised findings. The first authors of these two Cochrane reviews (AR and JG) are co-authors of this report and we thank the other authors involved with these reviews. One review[25] has been completed during the production of this report. All the authors are co-authors of this report. The final review[257] was specifically undertaken for this report and has been published as a Cochrane protocol.

Contribution of authors

Grigoris Leontiadis (Gastroenterologist and Systematic Reviewer) helped plan, conduct and write reviews 1 and 2 (Chapters 4 and 5) and the corresponding Cochrane reviews.[25,257] He also contributed to the overall writing of the report. Aravamuthan Sreedharan (Gastroenterologist and Systematic Reviewer) helped plan, conduct and write review 2 (Chapter 5) and the corresponding Cochrane review.[257] He also wrote Chapter 8 (reporting review 4) and organised and conducted the QoL evaluation (Appendix 5). He also contributed to the overall writing of the report. Stephanie Dorward (Research Assistant) was responsible for the project management of the study and its day-to-day administration. She provided assistance to review 2 (Chapter 5)[257] and to the supplementary review reported in Appendix 6. She also organised the QoL evaluation (Appendix 5). Pelham Barton (Health Economic Modeller) planned, conducted and wrote the first modelling and health economic evaluation (Chapter 6). Brendan Delaney (General Practitioner and Health Economic Modeller) helped design and plan the study, and planned, conducted and wrote the second modelling and health economic evaluation (Chapter 9) and the supplementary review reported in Appendix 6. Colin Howden (Gastroenterologist and Systematic Reviewer) helped plan, conduct and write reviews 1 and 2 (Chapters 4 and 5) and the corresponding Cochrane reviews.[25,257] He also contributed to the overall writing of the report. Mary Orhewere (Health Economic Modeller) contributed to the second modelling and health economic evaluation (Chapter 9). Javier Gisbert (Gastroenterologist and Systematic Reviewer) planned and conducted the Cochrane review[58] reported in Chapter 7. Virender Sharma (Gastroenterologist and Systematic Reviewer) helped plan, conduct and write review 1 (Chapter 4) and the corresponding Cochrane review.[25] Alaa Rostom (Gastroenterologist and Systematic Reviewer) planned and conducted the Cochrane review[48] reported in Chapter 8. Paul Moayyedi (Gastroenterologist, Systematic Reviewer and Health Economist) helped design and plan the study and contributed to the overall writing of the report. David Forman (Epidemiologist and Systematic Reviewer) helped design and plan the study and was responsible for its overall coordination. He also contributed to the overall writing of the report and the Cochrane review related to review 2[257] (Chapter 5).

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Appendix 1

MEDLINE search strategy for the research question 'What is the efficacy of PPI therapy in reducing mortality in patients with endoscopically documented acute bleeding from a peptic ulcer?'

randomized controlled trial.pt.
controlled clinical trial.pt.
randomized controlled trials.sh.
random allocation.sh.
double blind method.sh.
single-blind method.sh.
or/1-6
(animals not human).sh.
7 not 8
clinical trial.pt.
exp clinical trials/
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.
research design.sh.
or/10-17
18 not 8
19 not 9
comparative study.sh.
exp evaluation studies/
follow up studies.sh.
prospective studies.sh.
(control$ or prospectiv$ or volunteer$).ti,ab.
or/21-25
26 not 8
27 not (9 or 20)
9 or 20 or 28

exp stomach/
stomach.tw.
gastr$.tw.
exp duodenum/
duoden$.tw.
peptic$.tw.
exp esophagus/
esophag$.tw.
oesophag$.tw.
or/30-38
exp peptic ulcer/
exp peptic ulcer haemorrhage/
exp gastrointestinal haemorrhage/
(peptic adj5 ulcer$).tw.
(stomach adj5 ulcer$).tw.
(duoden$ adj5 ulcer$).tw.
(gastroduoden$ adj5 ulcer$).tw.
(bleed$ adj5 ulcer$).tw.
(rebleed$ adj5 ulcer$).tw.
(recurrent adj5 bleed$ adj5 ulcer$).tw.
(acute adj5 bleed$ adj5 ulcer$).tw.
(gastrointestinal adj5 bleed$).tw.
(gastrointestinal adj5 rebleed$).tw.
(gastrointestinal adj5 hemorrhag$).tw.
(gastrointestinal adj5 haemorrhag$).tw.
(ulcer adj5 hemorrhag$).tw.
(ulcer adj5 haemorrhag$).tw.
(haemorrhagic adj3 gastritis).tw.
(hemorrhagic adj3 gastritis).tw.
(haemorrhagic adj3 duodenitis).tw.
(hemorrhagic adj3 duodenitis).tw.
exp melena/
melena.tw.
melaena.tw.
exp hematemesis/
haematemesis.tw.
hematemesis.tw.
(coffee adj1 ground).tw.
or/40-67
exp omeprazole/
omeprazole.tw.
lansoprazole.tw.
pantoprazole.tw.
rabeprazole.tw.
esomeprazole.tw.
(proton adj5 pump adj5 inhibitor$).tw.
ppi$.tw.
or/69-76
39 and 68 and 77
78 and 29

Appendix 2

MEDLINE search strategy for the research question 'What is the efficacy of PPI therapy initiated prior to endoscopy in reducing mortality in unselected patients with acute upper gastrointestinal bleeding?'

exp stomach/
stomach.tw.
gastr$.tw.
exp duodenum/
duoden$.tw.
peptic$.tw.
exp esophagus/
esophag$.tw.
oesophag$.tw.
or/30-38
exp peptic ulcer/
exp peptic ulcer haemorrhage/
exp gastrointestinal haemorrhage/
(peptic adj5 ulcer$).tw.
(stomach adj5 ulcer$).tw.
(duoden$ adj5 ulcer$).tw.
(gastroduoden$ adj5 ulcer$).tw.
(bleed$ adj5 ulcer$).tw.
(rebleed$ adj5 ulcer$).tw.
(recurrent adj5 bleed$ adj5 ulcer$).tw.
(acute adj5 bleed$ adj5 ulcer$).tw.
(gastrointestinal adj5 bleed$).tw.
(gastrointestinal adj5 rebleed$).tw.
(gastrointestinal adj5 hemorrhag$).tw.
(gastrointestinal adj5 haemorrhag$).tw.
(ulcer adj5 hemorrhag$).tw.
(ulcer adj5 haemorrhag$).tw.
(haemorrhagic adj3 gastritis).tw.
(hemorrhagic adj3 gastritis).tw.
(haemorrhagic adj3 duodenitis).tw.
(hemorrhagic adj3 duodenitis).tw.
exp melena/
melena.tw.
melaena.tw.
exp hematemesis/
haematemesis.tw.
hematemesis.tw.
(coffee adj1 ground).tw.
or/40-67
exp omeprazole/
omeprazole.tw.
lansoprazole.tw.
pantoprazole.tw.
rabeprazole.tw.
esomeprazole.tw.
(proton adj5 pump adj5 inhibitor$).tw.
ppi$.tw.
or/69-76
39 and 68 and 77
78 and 29

Appendix 3

MEDLINE search strategy for the research question 'What is the efficacy of *H. pylori* eradication therapy in preventing recurrent bleeding from peptic ulcer in *H. pylori* positive patients compared with ulcer-healing antisecretory therapy with or without subsequent long-term prophylactic antisecretory therapy?'

randomized controlled trial.pt.
controlled clinical trial.pt.
randomized controlled trials.sh.
random allocation.sh.
double blind method.sh.
single-blind method.sh.
or/1-6
(animal not human).sh.
7 not 8
clinical trial.pt.
exp clinical trials/
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj25 blind$).mp. or mask$.ti,ab.
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.
research design.sh.
or/10-17
18 not 8
19 not 9
comparative study.sh.
exp evaluation studies/
follow up studies.sh.
prospective studies.sh.
(control$ or prospectiv$).mp. or volunteer$.ti,ab.
or/21-25
26 not 8
27 not (9 or 20)
9 or 20 or 28
exp peptic ulcer haemorrhage/
exp peptic ulcer perforation/
(bleed$ adj5 ulcer$).tw.
(rebleed$ adj5 ulcer$).tw.
(recurrent adj5 bleed$ adj5 ulcer$).tw.
(acute adj5 bleed$ adj5 ulcer$).tw.
(gastrointestinal adj5 bleed$).tw.
(gastrointestinal adj5 rebleed$).tw.
(gastrointestinal adj5 hemorrhag$).tw.
(gastrointestinal adj5 haemorrhag$).tw.
(ulcer adj5 hemorrhag$).tw.
(ulcer adj5 haemorrhag$).tw.
exp *helicobacter pylori*/
campylobacter pylori.tw.
(*helicobacter* adj3 pylori$).tw.
(h adj1 pylori$).tw.
or/42-45
or/30-41
46 and 47

Appendix 4

MEDLINE search strategy for the research question 'What is the efficacy of prophylactic PPI therapy in preventing recurrent peptic ulcer bleeds in patients taking NSAIDs compared with treatment?'

randomized controlled trial.pt.
controlled clinical trial.pt.
randomized controlled trials.sh.
random allocation.sh.
double blind method.sh.
single-blind method.sh.
or/1-6
(animals not human).sh.
7 not 8
clinical trial.pt.
exp clinical trials/
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.
research design.sh.
or/10-17
18 not 8
19 not 9
comparative study.sh.
exp evaluation studies/
follow up studies.sh.
prospective studies.sh.
(control$ or prospectiv$ or volunteer$).ti,ab.
or/21-25
26 not 8
27 not (9 or 20)
9 or 20 or 28
exp peptic ulcer/
exp peptic ulcer haemorrhage/
exp peptic ulcer perforation/
exp duodenal ulcer/
exp stomach ulcer/
(pep$ adj5 ulcer$).tw.
(stomach adj5 ulcer$).tw.
(duoden$ adj5 ulcer$).tw.
(gastr$ adj5 ulcer$).tw.
exp gastritis/
gastritis.tw.
gastropathy.tw.
(bleed$ adj5 ulcer$).tw.
(rebleed$ adj5 ulcer$).tw.
(recurrent adj5 bleed$ adj5 ulcer$).tw.
(acute adj5 bleed$ adj5 ulcer$).tw.
(gastrointestinal adj5 bleed$).tw.
(gastrointestinal adj5 rebleed$).tw.
(gastrointestinal adj5 hemorrhag$).tw.
(gastrointestinal adj5 haemorrhag$).tw.
(ulcer adj5 hemorrhag$).tw.
(ulcer adj5 haemorrhag$).tw.
(mucos$ adj5 injur$).tw.
exp pyloric stenosis/
(pyloric adj3 stenosis).tw.
(gastrointestinal adj3 perforat$).tw.
(gi adj3 perforat$).tw.
(ulcer$ adj3 perforat$).tw.
or/30-57
exp anti-ulcer agents/
exp omeprazole/
omeprazole.tw.
lansoprazole.tw.
pantoprazole.tw.
rabeprazole.tw.
esomeprazole.tw.
exp histamine H2 antagonists/
exp cimetidine/
cimetidine.tw.
exp ranitidine/
ranitidine.tw.
exp famotidine/
famotidine.tw.
exp nizatidine/
nizatidine.tw.
(histamine adj3 H2 adj3 antagonist$).tw.
(antiulcer adj5 agent$).tw.
(anti$ adj3 ulcer$ adj3 agent$).tw.
(H2 adj5 receptor adj5 antagonist$).tw.
(proton adj3 pump adj3 inhibitor$).tw.
exp misoprostol/
exp sucralfate/
misoprostol.tw.
sucralfate.tw.
or/59-83
Anti-inflammatory agents, non-steroidal/
nsaid$.tw.
nonsteroidal anti-inflammatory.tw.

non-steroidal anti-inflammatory.tw.
exp ibuprofen/
ibuprofen$.tw.
aceclofenac$.tw.
acemetacin$.tw.
dexketoprofen$.tw.
exp diclofenac/
diclofenac$.tw.
fenbufen$.tw.
fenoprofen$.tw.
flurbiprofen$.tw.
exp indometacin/
indometacin$.tw.
exp ketoprofen/
ketoprofen$.tw.
exp mefenamic acid/
(mefenamic adj3 acid$).tw.
nabumetone$.tw.
exp naproxen/
naproxen$.tw.
exp phenylbutazone/
phenylbutazone$.tw.
exp piroxicam/
piroxicam$.tw.
exp sulindac/
sulindac$.tw.
exp tolmetin/
tolmetin.tw.
exp antipyrine/
antipyrine.tw.
tenoxicam$.tw.
(tiaprofenic adj3 acid$).tw.
exp aspirin/
aspirin$.tw.
(acetylsalicylic adj3 acid$).tw.
aminopyrine.tw.
curcumin.tw.
clofazimine.tw.
or/85-125
58 and 84 and 126
127 and 29

Appendix 5

Quality of life data

Subjects

Prospective patients were chosen consecutively on the basis that they survived a UGI bleed. We planned to include 100 consecutive patients surviving a UGI bleed in Leeds General Infirmary or at The City Hospital, Birmingham. Recruitment from the Birmingham site of the project commenced at a later date than that in Leeds. Total patient recruitment was 57 between the two centres. Results have been pooled for both sites as the analysis for individual sites would not be significant due to the small numbers of patients recruited. Therefore, results are presented for the total of patients from both sites.

Inclusion criteria

- Patients over the age of 18 years presenting with UGI bleeding and have survived the episode.
- Patients with PU-related UGI bleed. In general, this was if the patient had endoscopy or surgery for UGI bleed that confirmed underlying ulcer disease.
- Patients with a UGI bleed were included if endoscopy proved that PU was the plausible explanation for the UGI bleed.

Exclusion criteria

- Patients with a normal endoscopy
- Patients with oesophageal variceal bleeding and also those with minor blood loss
- Patients who were critically ill and were unable to take part in the study

Interventions

The patients were surveyed using the EuroQoL questionnaire.[139] This was done at 7 days after bleeding or on discharge, whichever was earlier. A further questionnaire was administered at 4 weeks.

Results

All patients in both Birmingham and Leeds who were followed up at 4 weeks had the same and/or improved QoL score. No patients had a reduction in QoL measured by the EQ-5D score. In Leeds, 38/48 (79.1%) were followed up; in Birmingham, 7/9 (77.8%) were followed up. Overall, 35 (61.4%) patients were male.

Over the two sites, 45 patients were admitted with a UGI bleed and 10 developed bleeding while hospitalised for another reason. These data were missing for two patients.

End-points

End-points were length of stay in hospital, mortality, transfusion rates, requirement for surgery, repeat therapeutic endoscopy or other interventions.

The male:female ratio was 8:1 in Birmingham and 27:21 in Leeds.
The mean age (years) was 66.8 in Birmingham and 70 in Leeds. The overall combined mean age was 66.5; the median was 68.5.
From both sites, 38 patients had intravenous PPI, 12 had oral PPI, three had PPI administered by both routes and four had data missing.
With regard to mobility, two patients were reported as confined to bed, 37 had no mobility problems and 18 had some mobility problems.

The numbers of respondents were men 35 and women 22.

Tables 32–36 show the percentage (%) of patients reporting each level of problem on admission to hospital with an upper gastrointestinal bleed.

QoL scores

QoL scores are given in *Table 37*.

TABLE 32 *Mobility: percentage reporting each level of problem*

	Level[a]		
	1	2	3
Men	41	37	22
Women	24	48	28

[a] Level 1 = I have no problems in walking about;
Level 2 = I have some problems in walking about;
Level 3 = I am confined to bed.

TABLE 33 *Self-care: percentage reporting each level of problem*

	Level[a]		
	1	2	3
Men	59	19	22
Women	33	24	43

[a] Level 1 = I have no problems with self-care;
Level 2 = I have some problems with washing and dressing myself;
Level 3 = I am unable to wash or dress myself.

TABLE 34 *Usual activity: percentage reporting each level of problem*

	Level[a]		
	1	2	3
Men	26	37	37
Women	5	19	76

[a] Level 1 = I have no problems with performing my usual activities;
Level 2 = I have some problems with performing my usual activities;
Level 3 = I am unable to perform my usual activities.

TABLE 35 *Pain/discomfort: percentage reporting each level of problem*

	Level[a]		
	1	2	3
Men	59	37	4
Women	38	33	29

[a] Level 1 = I have no pain or discomfort;
Level 2 = I have moderate pain or discomfort;
Level 3 = I have extreme pain or discomfort.

TABLE 36 *Anxiety/depression: percentage reporting each level of problem*

	Level[a]		
	1	2	3
Men	70	26	4
Women	67	33	0

[a] Level 1 = I am not anxious or depressed;
Level 2 = I am moderately anxious or depressed;
Level 3 = I am extremely anxious or depressed.

TABLE 37 *QoL scores*

Patient No.	QOL score	Follow-up QoL score	PPI medication	Endoscopy
1	8.0	9.00		
2	8.0	8.00	I.v.	
3	5.0	7.00	I.v.	
4	6.5		I.v.	
5	7.0	10.00	I.v.	
6	9.0	10.00	I.v.	
7	5.0		Oral	
8	9.0	10.00	I.v.	
9	5.0	7.00	I.v.	
10	3.0		I.v.	
11	5.0	8.00	Oral	
12	2.5		Oral	
13	10.0	10.00	Oral	
14	7.5		I.v.	
15	5.0	7.00	I.v.	
16	5.0		I.v.	
17	7.5	8.00	I.v.	
18	1.0	9.00	I.v. and oral	
19	5.0	6.00	I.v.	
20	7.0	8.00	I.v.	
21	6.5	7.00	I.v.	
22	1.0	5.00	I.v.	
23	2.0	6.00	I.v.	
24	8.5	10.00	Oral	
25	5.0		I.v.	
26	5.0	6.00	I.v.	
27	7.0	8.00	I.v.	
28	10.0	10.00	None	
29	2.0	8.00	Oral	
30	5.0	6.00	I.v.	
31	7.5	8.00	I.v. and oral	
32	5.0	7.00	Oral	
33	5.0	8.00	I.v.	
34	3.0	6.00	I.v.	
35	5.0		Oral	
36	5.0	8.00	Oral	
37	3.0		I.v.	
38	9.5	10.00	Oral	
39	6.0	8.00	Oral	
40	7.0	8.00		
41	6.0	7.00	I.v.	
42	5.0			
43	3.0	8.00	I.v.	
44	5.0	8.00	I.v.	
45	6.0	7.00	Oral	
46	8.0	9.00	I.v. and oral	
47	10.0	10.00		
48	9.0	10.00	I.v.	
49	10.0	10.00		
50	5.0	6.00	I.v.	
51	5.0		I.v.	
52	9.0		I.v.	
53	5.0	5.00	I.v.	
54	7.0	8.00	I.v.	
55	9.0	10.00	I.v.	
56	5.0	6.00	I.v.	
57	5.0	8.00	I.v.	

Appendix 6

Supplementary systematic literature review: *H. pylori* eradication versus proton pump inhibitors to prevent upper gastrointestinal bleeds in NSAID users

Studies included

RCTs that compared *H. pylori* eradication treatment versus PPI treatment in patients receiving an NSAID were included if they met the following criteria:

- use of a concurrent control group
- patients taking NSAIDs
- patients with *H. pylori* infection
- concomitant therapy applied equally to both intervention arms
- endoscopic diagnosis of bleeding from peptic ulcer.

Types of participants

Participants were patients with *H. pylori* infection and receiving NSAID therapy.

Types of outcome measures

Intention-to-treat analysis was used. The primary outcome measure was bleeding from PU and the secondary outcome measure was PU at follow-up endoscopy.

In order to obtain suitable modelling parameters, RRs were calculated separately for primary and secondary prevention and according to whether PPI or placebo was the comparator and whether PPI was used after eradication or not. Primary prevention was defined as the prevention of a first UGI event in a patient taking an NSAID and secondary prevention as prevention of recurrent UGI events in patients having already had a first event.

Search strategy for identification of studies

Trials were identified by searching The Cochrane Library, MEDLINE (1966–February 2006) and EMBASE (1980–February 2006). We did not confine our search to English language publications. The search strategy (see below) was constructed by using a combination of subject headings and text words relating to the use of PPI, *H. pylori* eradication, NSAID and PU bleeding. The standard Cochrane search strategy filter identifying RCTs was applied to the search.

Data synthesis

Two reviewers (BD and SD) independently checked the trials and abstracts identified from the search for fulfilment of predefined inclusion criteria. The full text of all relevant studies was obtained.

Results

The search retrieved 1370 articles (378 from MEDLINE, 224 from the Cochrane Library, and 768 from EMBASE). Of these, only 18 met the inclusion criteria and the full-text articles were obtained. Seven of these RCTs were deemed relevant and data were extracted.[156,158,159,258–261] Characteristics of these studies are summarised in *Table 38*. The remaining non-relevant studies are listed in *Table 39* with reasons for non-inclusion.

Only one trial studied the primary outcome measure of our review, namely prevention of UGI bleeding.[158] This RCT compared *H. pylori* eradication therapy against PPI maintenance treatment for the secondary prevention of UGI bleeding in NSAID users and in low-dose aspirin users. The authors found that among *H. pylori*-positive patients with a history of UGI bleeding on low-dose aspirin, eradication of *H. pylori* was equivalent to treatment with omeprazole in preventing recurrent bleeding. On the other hand, omeprazole was superior to eradication of *H. pylori* in preventing recurrent bleeding in patients on non-aspirin NSAID, namely naproxen.

TABLE 38 *Characteristics of the seven extracted articles*

Study	Methods	Participants	Interventions	Outcomes	Notes
Chan, 1997[156]	RCT	100 NSAID-naive patients with *H. pylori* infection and musculoskeletal pain requiring NSAIDs	1-week eradication therapy (bismuth, tetracycline and metronidazole) versus no eradication. All patients received naproxen 750 mg daily	Endoscopic ulcers at 8 weeks	Primary prevention Eradication versus no eradication
Chan, 2001[158]	RCT	400 *H. pylori*-positive patients presenting with UGI bleeding from ulcers or erosions while taking aspirin or NSAIDs	Following PU healing with omeprazole, patients were restarted on either naproxen 500 mg twice daily (n = 150) or aspirin 80 mg daily (n = 250) and were randomised to 1-week eradication therapy (bismuth, tetracycline and metronidazole) versus 20 mg omeprazole daily for 6 months	Recurrent bleeding	Secondary prevention Eradication versus PPI
Chan, 2002[159]	RCT	100 *H. pylori*-positive patients, NSAID-naive, with dyspepsia or PU history, requiring NSAIDs	1-week eradication therapy (omeprazole, amoxicillin and clarithromycin) versus 1-week 20 mg omeprazole daily plus placebo. All patients were started on diclofenac 100 mg daily	Endoscopic ulcers at 6 months	Primary prevention Eradication versus PPI
Hawkey, 1998[258]	RCT	285 *H. pylori*-positive, chronic NSAID users with current or previous peptic ulceration, dyspepsia or both, who continued to use NSAIDs	1-week eradication therapy (omeprazole, amoxicillin and clarithromycin) versus 1-week 20 mg omeprazole daily plus placebo. Then, all patients received omeprazole 20 mg daily for at least 3 weeks	Ulcers at endoscopy at 1, 3 and 6 months	Secondary prevention Eradication versus placebo
Pilotto, 2000[260]	RCT	69 *H. pylori*-positive patients over 60 years old, needing NSAIDs, with dyspepsia but no ulcers. Probably NSAID-naive, but this is not clearly stated	1-week eradication therapy (pantoprazole, amoxicillin and clarithromycin) versus pantoprazole alone 40 mg daily for 1 month	Endoscopic ulcers at 1 month	Primary prevention Eradication versus PPI
Labenz, 2002[259]	RCT	660 *H. pylori*-positive, NSAID-naive patients with no past or current PU, requiring NSAIDs	Eradication (1 week of omeprazole, amoxicillin and clarithromycin), placebo or PPI in a factorial design	Endoscopic ulcers at 5 weeks	Primary prevention Eradication versus placebo versus PPI
Lai, 2003[261]	RCT	140 *H. pylori*-positive, chronic NSAID users, with no ulcers at baseline endoscopy	Eradication (2 weeks of metronidazole, clarithromycin and amoxicillin) versus placebo	Endoscopic ulcer at 12 weeks	Primary prevention Eradication versus placebo

TABLE 39 *Excluded studies*

Study	Reason for exclusion
Arkkila, 2003[141]	Study did not compare *H. pylori* eradication therapy with PPI
Giral, 2004[262]	Study did not compare *H. pylori* eradication therapy with PPI
Singh, 2005[263]	Study did not compare *H. pylori* eradication therapy with PPI
Bianchi Porro, 1996[264]	Study not an RCT
Papatheodoridis, 2004[265]	Study did not compare *H. pylori* eradication therapy with PPI
Yeomans, 1998[235]	Study did not compare *H. pylori* eradication therapy with PPI

TABLE 40 H. pylori *eradication on the prevention of NSAID-related UGI primary and secondary events: selected studies*

Comparison	Studies pooled	RR (95% CI)
Primary prevention		
Eradication vs placebo	Labenz,[259] Chan,[156] Chan,[159] Lai[261]	0.35 (0.20 to 0.61) for PU
Eradication vs PPI	Pilotto,[260] Labenz[259]	5.94 (0.73 to 48.6) for PU
Eradication then PPI vs placebo	Labenz[259]	0.19 (0.04 to 0.89) for PU
Eradication then PPI vs PPI	Labenz[259]	4.48 (0.21 to 92.6) for PU
Secondary prevention		
Eradication vs placebo	Hawkey[258]	1.07 (0.6 to 1.9) for PU recurrence
Eradication vs PPI	Chan[158]	4.33 (1.29 to 14.59) for UGI re-bleed patients on naproxen 2.00 (0.18 to 21.78) for UGI re-bleed patients on aspirin
Eradication then PPI vs placebo	No data	–

We did not identify any trials comparing *H. pylori* eradication therapy with PPI therapy for the primary prevention of UGI bleeding in NSAID users.

The remaining six of the included trials studied the secondary outcome measure of our review, namely prevention of endoscopic PUs, primary or secondary. Of note, Vergara and colleagues[266] included the same six studies in their recent systematic review and meta-analysis on the role of *H. pylori* eradication in the prevention of PUs in NSAID users. These authors had performed a literature search up to December 2004; apparently no further relevant studies had been published up until the date of our literature search (February 2006). The meta-analysis by Vergara and colleagues showed that *H. pylori* eradication treatment compared with no treatment reduced the incidence of PU in NSAID users who had not been on NSAIDs previously. *H. pylori* eradication did not have a significant effect on the incidence of PUs (compared with no treatment) among NSAID users who had been receiving NSAIDs on a chronic basis previously. However, eradication treatment was less effective than treatment with a maintenance PPI for preventing NSAID-associated ulcers.

We followed a different method for categorising the strategies examined by these studies, as stated in the methods section above and shown in *Table 40*. We found that regarding primary prevention of PUs among NSAID users, *H. pylori* eradication treatment was more effective than placebo, but not statistically different from PPI treatment. Regarding secondary prevention of PUs among NSAID users, *H. pylori* eradication treatment was not statistically different from PPI treatment; we found no data for the comparison of *H. pylori* eradication treatment with placebo.

Forest plots

Forest plots are shown in *Figures 47* and *48* as RR meta-analysis plots (fixed effects).

Search strategy

randomized controlled trial.pt.
controlled clinical trial.pt.
randomized controlled trials.sh.
random allocation.sh.
double blind method.sh.
single-blind method.sh.
or/1-6
(animals not human).sh.
7 not 8
clinical trial.pt.
exp clinical trials/
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.
research design.sh.
or/10-17
18 not 8
19 not 9
comparative study.sh.
exp evaluation studies/
follow up studies.sh.
prospective studies.sh.
(control$ or prospectiv$ or volunteer$).ti,ab.
or/21-25
26 not 8
27 not (9 or 20)
9 or 20 or 28
exp peptic ulcer haemorrhage/
exp peptic ulcer perforation/
(bleed$ adj5 ulcer$).tw.

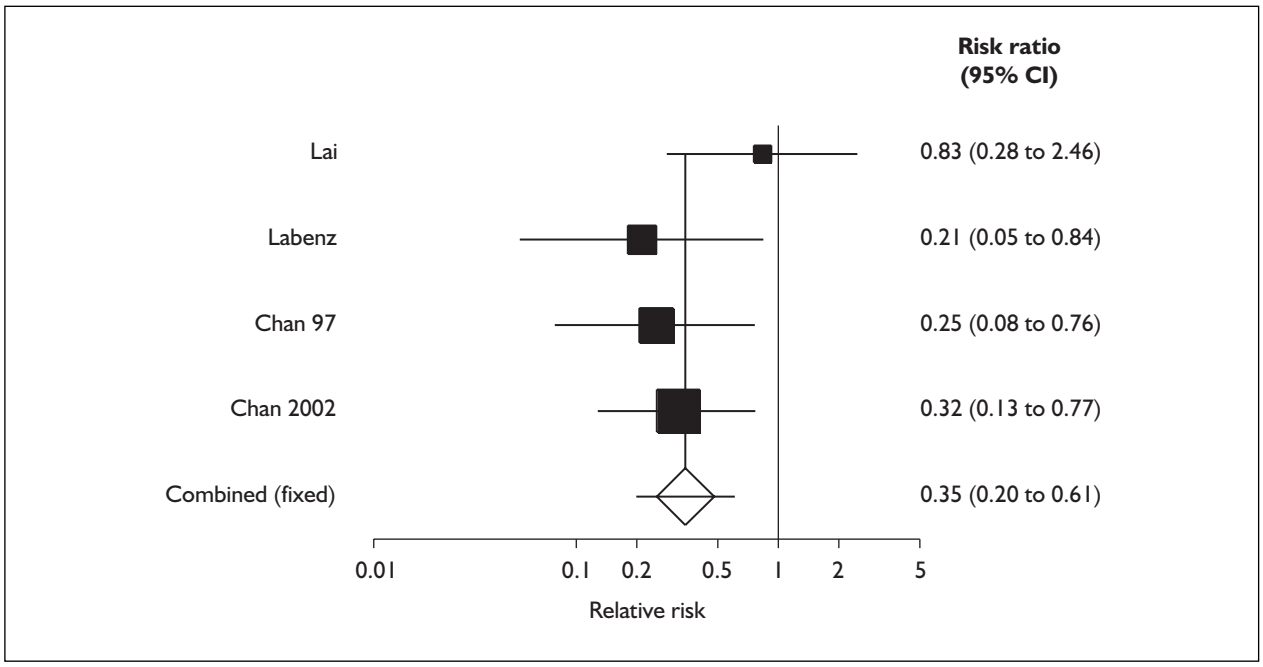

FIGURE 47 *Primary prevention:* H. pylori *eradication versus placebo*

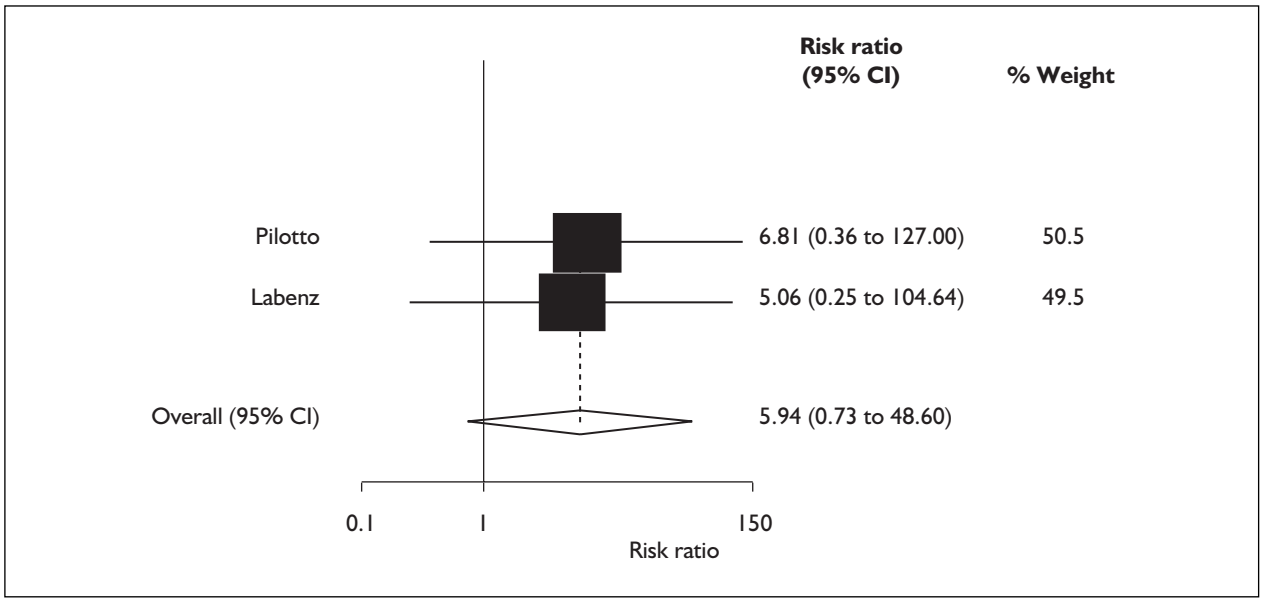

FIGURE 48 *Primary prevention:* H. pylori *eradication versus PPI*

(rebleed$ adj5 ulcer$).tw.
(recurrent adj5 bleed$ adj5 ulcer$).tw.
(acute adj5 bleed$ adj5 ulcer$).tw.
(gastrointestinal adj5 bleed$).tw.
(gastrointestinal adj5 rebleed$).tw.
(gastrointestinal adj5 hemorrhag$).tw.
(gastrointestinal adj5 haemorrhag$).tw.
(GI adj5 bleed$).tw.
exp peptic ulcer/
exp duodenal ulcer/
exp stomach ulcer/
(pep$ adj5 ulcer$).tw.
(duoden$ adj5 ulcer$).tw.
(stomach adj5 ulcer$).tw.
(gastric adj5 ulcer$).tw.
(stomach adj5 lesion$).tw.
(gastric adj5 lesion$).tw.
(stomach adj5 erosi$).tw.
(gastric adj5 erosi$).tw.
(mucosa$ adj5 injur$).tw.
or/30-52
exp helicobacter pylori/

(H adj3 pylori).tw.
(campylobacter adj3 pylori).tw.
(pylori adj5 erad$).tw.
(pylori adj5 therap$).tw.
(pylori adj5 positive).tw.
exp proton pumps/
(proton adj3 pump adj3 inhibitor$).tw.
ppi.tw.
exp omeprazole/
omeprazole.tw.
lansoprazole.tw.
pantoprazole.tw.
rabeprazole.tw.
esomeprazole.tw.
exp histamine h2 antagonists/
cimetidine.tw.
exp cimetidine/
famotidine.tw.
exp famotidine/
nizatidine.tw.
exp nizatidine/
ranitidine.tw.
exp ranitidine/
exp amoxicillin/
amoxycillin.tw.
amoxicillin.tw.
exp macrolides/
exp clarithromycin/
exp erythromycin/
exp azithromycin/
exp tetracycline/
bismuth citrate.tw.
bismuth subcitrate.tw.
colloidal bismuth.tw.
exp nitroimidazoles/
nitroimidazole.tw.
exp metronidazole/
metronidazole.tw.
exp tinidazole/
tinidazole.tw.
or/54-94
exp proton pumps/
(proton adj3 pump adj3 inhibitor$).tw.
PPI$.tw.
exp omeprazole/
omeprazole.tw.
lansoprazole.tw.
pantoprazole.tw.
rabeprazole.tw.
esomeprazole.tw.
exp bismuth/
exp antacids/
exp alginates/
Aluminum hydroxide/
exp magnesium hydroxide/
exp magnesium oxide/
exp calcium carbonate/
(magnesium adj5 carbonate).tw.
exp magnesium hydroxide/
exp magnesium oxide/
Magnesium silicates/
exp carbenoxolone/
exp misoprostol/
exp sucralfate/
exp muscarinic antagonists/
exp dicyclomine/
exp pirenzepine/
exp propantheline/
algicon.tw.
alginates.tw.
(alumin?um adj5 hydroxide).tw.
(calcium adj5 carbonate).tw.
gaviscon.tw.
hydrotalcite.tw.
maalox.tw.
(magnesium adj5 hydroxide).tw.
(magnesium adj5 oxide).tw.
(magnesium adj5 trisilicate).tw.
(sodium adj5 bicarbonate).tw.
(sodium adj5 carbonate).tw.
(mucosal adj5 protecting adj5 agent$).tw.
carbenoxolone.tw.
misoprostol.tw.
sucralfate.tw.
antimuscarinic$.tw.
(muscarinic adj5 receptor adj5 antagonist$).tw.
dicyclomine.tw.
pirenzepine.tw.
propantheline.tw.
placebo.tw.
or/96-144
Anti-inflammatory agents, non-steroidal/
nsaid$.tw.
nonsteroidal anti-inflammatory.tw.
non-steroidal anti-inflammatory.tw.
exp ibuprofen/
ibuprofen$.tw.
aceclofenac$.tw.
acemetacin$.tw.
dexketoprofen$.tw.
exp diclofenac/
diclofenac$.tw.
fenbufen$.tw.
fenoprofen$.tw.
flurbiprofen$.tw.
exp indometacin/
indometacin$.tw.
exp ketoprofen/
ketoprofen$.tw.
exp mefenamic acid/
(mefenamic adj3 acid$).tw.
nabumetone$.tw.
exp naproxen/
naproxen$.tw.

exp phenylbutazone/
phenylbutazone$.tw.
exp piroxicam/
piroxicam$.tw.
exp sulindac/
sulindac$.tw.
exp tolmetin/
tolmetin.tw.
exp antipyrine/
antipyrine.tw.
tenoxicam$.tw.
(tiaprofenic adj3 acid$).tw.
exp aspirin/
aspirin$.tw.
(acetylsalicylic adj3 acid$).tw.
or/146-183
53 and 95 and 145 and 184
185 and 29

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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