

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

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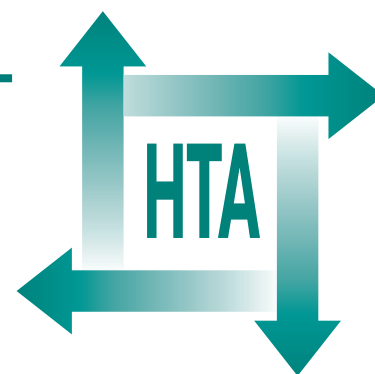
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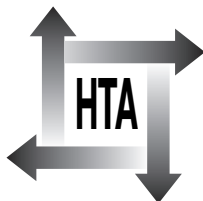


### Executive summary

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## 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<sub>2</sub>-receptor antagonist (H<sub>2</sub>RA), *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<sub>2</sub>RA, *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<sub>2</sub>RAs 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<sub>2</sub>RA. 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<sub>2</sub>RA (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<sub>2</sub>RAs (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<sub>2</sub>RAs 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<sub>2</sub>RAs 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<sub>2</sub>RA 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.

## Publication

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# NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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