Meta-analysis of proton pump inhibitors in treatment of bleeding peptic ulcers  
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Authors' objectives
To evaluate the efficacy of proton-pump inhibitors (PPIs), compared with placebo and histamine-receptor antagonists (H2RAs), for reducing the incidence of rebleeding, surgery and death in acute gastrointestinal bleeding (GIB) associated with peptic ulcer disease.

Searching
MEDLINE, EMBASE and PREMEDLINE were searched systematically from 1966 to September 2000 for literature in the English language. The search terms included 'gastrointestinal', 'bleeding', 'hemorrhage', 'proton-pump inhibitor', 'omeprazole', 'pantoprazole', 'lansoprazole' and 'rebeprazole'. A manual search of the references from retrieved studies was also performed.

Study selection
Study designs of evaluations included in the review
Prospective, randomised, controlled clinical trials were considered for inclusion. The studies could be unblinded.

Specific interventions included in the review
Studies were included if they compared any PPI (omeprazole, pantoprazole, lansoprazole, rebeprazole) with any H2RA (cimetidine, ranitidine, famotidine, nizatidine) or placebo. Studies that were included in the meta analysis compared either ranitidine, cimetidine or placebo to various doses of omeprazole.

Participants included in the review
The included participants were adults (older than 18 years of age) with acute upper GIB peptic ulcers.

Outcomes assessed in the review
Studies were selected for review if they evaluated the incidence of rebleeding, need for surgery or incidence of death as an end point.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Methodological quality was not formally assessed. Each reference was read independently by all four authors to assess the adequacy of randomisation and description of withdrawals.

Data extraction
Data were extracted on: sample size; patient characteristics; the dose, timing, method of administration (intermittent bolus or continuous infusion), and route of administration of PPIs and control; use of endoscopic therapy; and incidence of rebleeding, surgery and death. Attempts were made to acquire additional information from investigators as required. Any discrepancies in the data extraction were resolved by group consensus through a review of the published trial.

Methods of synthesis
How were the studies combined?
The incidences of rebleeding, surgery and death were analysed separately for both the overall analysis and the
subgroup analyses. The trials were subgrouped by method of administration and the use of endoscopic therapy. The odds ratios (OR), along with 95% confidence intervals (CIs), and summary ORs were calculated using the method of DerSimonian and Laird (see Other Publications of Related Interest no.1) under a random-effects model. A statistically-significant result was assumed when the 95% CI of the OR did not include 1. The number-needed-to-treat to either benefit (NNTB) or harm (NNTH) one additional patient, along with the 95% CI, was calculated for the outcomes of rebleeding, surgery and death. Publication bias was investigated by visual inspection of funnel plots, where ORs were plotted against study sample size (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Heterogeneity was assessed using various methods. The graphical display of the trials' 95% CI of their OR and the summary OR was visually inspected. A vertical line drawn through the combined OR should intersect most of the horizontal lines of all individual studies in order for the trials to be considered homogeneous. Heterogeneity of the OR was formally tested using the Cochran Q chi-squared test (see Other Publications of Related Interest no.2). Statistical heterogeneity was assumed when the p-value was greater than 0.10. Heterogeneity was also evaluated visually using Galbraith plots (see Other Publications of Related Interest no.3). Where heterogeneity was detected, accepted methods for exploring statistical heterogeneity using clinical parameters were used (see Other Publications of Related Interest no.4).

Results of the review
Nine randomised controlled trials (n=1,829) were included in the meta-analysis.

The relative odds of rebleeding indicated a 50% reduction in the PPI-treated group (OR 0.50, 95% CI 0.33, 0.77, p=0.002; NNTB 9, 95% CI: 6, 13). The relative odds of surgery indicated a 53% reduction in the PPI-treated group (OR 0.47, 95% CI 0.29, 0.77, p=0.003; NNTB 17, 95% CI: 12, 35). The relative odds for mortality indicated a non significant 8% decrease in the odds of death in the PPI-treated group (OR 0.92, 95% CI 0.46, 1.83, p=0.81; NNTB 323, 95% CI: 47 to infinity, to NNTH 33).

The Cochrane Q test for heterogeneity of treatment effect was not significant for any of the outcomes. Visual inspection of the funnel plots for each outcome revealed no evidence of publication bias.

Authors’ conclusions
PPIs are superior to H2RAs and placebo in preventing rebleeding and the need for surgery in patients with GIB, although they do not appear to reduce mortality.

CRD commentary
This was a reasonably well-conducted and reported review. The inclusion criteria were appropriate to the review question, specifying relevant aspects such as the participants, interventions, study design and outcomes. The search for evidence covered three databases and the reference lists of retrieved articles. Data from the included trials were presented in adequate detail and the trials were summarised appropriately. However, the search was limited to the English language literature, which may have led to relevant studies being missed. It was also unclear how many of the reviewers were involved in the selection and data extraction of the studies. The authors indicated that their inclusion and exclusion criteria obviated the need for any formal assessment of methodological quality. However, it would have been useful to have examined the results of the included trials in the context of their individual attributes (e.g. blinding) and overall methodological quality.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors state that further research is required to determine whether PPI therapy alone is superior to endoscopic treatment and should be the focus of future, properly conducted, randomised, comparative clinical trials.
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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.