Meta-analysis: proton-pump inhibition in high-risk patients with acute peptic ulcer bleeding

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CRD summary
This review assessed the effects of proton-pump inhibitors (PPIs) in high-risk patients with acute bleeding peptic ulcers. The authors concluded that high-dose intravenous PPIs significantly reduce re-bleeding, surgery and mortality, and that oral and non high-dose PPIs also improve outcomes. The reliability of this conclusion is unclear given the incompletely reported study characteristics, review methods and quality results.

Authors' objectives
To assess the effects of contemporary pharmacological treatments in high-risk patients with acute bleeding peptic ulcers.

Searching
MEDLINE was searched from 1990 to April 2003 for studies reported in full in either English or French; the search terms were reported. Bibliographies of key articles, identified studies, reviews and meta-analyses were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion if they reported adequate information on the number of patients in each treatment group, interventions and outcomes.

Specific interventions included in the review
Studies of contemporary pharmacological treatments were eligible for inclusion. The review compared high-dose intravenous proton-pump inhibitors (PPIs; bolus plus constant infusion of at least 6 mg/hour), high-dose oral PPIs (at least twice the standard dosage) and non high-dose PPIs (using PPIs in doses other than those previously defined) with placebo and H2 receptor antagonists (H2RAs), with or without somatostatin (SST). Some studies also treated the patients endoscopically.

Participants included in the review
Studies of patients with bleeding peptic ulcers and high-risk stigmata for re-bleeding (Forrest Ia, Ib, IIA and IIB) were eligible for inclusion. Studies of patients with upper gastrointestinal tract bleeding from unspecified causes or non-peptic ulcer disease were excluded.

Outcomes assessed in the review
Studies that assessed re-bleeding, surgery and mortality were eligible for inclusion.

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

Assessment of study quality
The studies were assessed using the following criteria adapted from Cook et al. (1992): methods used to select the patients; baseline comparability of the treatment groups; methods of randomisation; blinding of the outcome assessment; description of endoscopic treatment; description of pharmacological treatments; re-bleeding defined; reporting of indications for surgery; and reporting of cause of death. Each component was given a score of 1 if the study met the quality criterion and 0 if it did not. Two reviewers independently assessed validity and resolved any disagreements with the aid of a third reviewer.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

For each study, outcome event rates for each treatment group and crude rate differences were calculated.

Methods of synthesis
How were the studies combined?
The studies were grouped by intervention and control, and pooled rate differences with 95% confidence intervals (CIs) were calculated using the random-effects model of DerSimonian and Laird. Variances used in the meta-analyses were given by the mixed-effects linear model used to explore differences between studies. One RCT was excluded from the meta-analyses of high-dose oral PPIs because it did not use initial endoscopic haemostasis.

How were differences between studies investigated?
Clinical heterogeneity was examined by considering differences between the studies with respect to mean age, percentage of patients in shock on admission, year of study and quality score. A mixed-effects weighted linear regression model was used to explore the influence on the results of mean age, year of publication, quality score and number of male patients. The weighting took account of multiple contributions from individual studies. The meta-analysis of mortality for high-dose intravenous PPI versus placebo was repeated after excluding one study with a low mortality rate in the placebo group. The meta-analysis for high-dose oral PPI was repeated after excluding one study in which only 13% of the patients had endoscopic treatment.

Results of the review
Eighteen RCTs (n=1,855) were included.

High-dose intravenous PPIs (4 RCTs, n=682).

Compared with placebo, high-dose PPI was associated with a significant decrease in re-bleeding (-14.6%, 95% CI: -16.2, -12.9) and surgery (-5.4%, 95% CI: -8.4, -2.4), but a non statistically significant reduction in mortality (-2.7%, 95% CI: -9.2, 3.8). Endoscopic treatment was used in 52% of the patients.

Compared with H2RA, high-dose PPI was associated with a significant decrease in re-bleeding (-20.6%, 95% CI: -24.7, -16.6), but there was no significant difference between treatments for surgery (-1.0%, 95% CI: -8.0, +6.1) or mortality (-2.4%, 95% CI: -17.7, +12.9). After excluding one RCT with a low mortality rate in the placebo group, the reduction in mortality with high-dose PPI was statistically significant (-5%, 95% CI: -7.7, -2.3).

High-dose oral PPIs (4 RCTs, n=448).

Compared with placebo, high-dose oral PPI was associated with a significant decrease in re-bleeding (-15.3%, 95% CI: -16.5, -14.0), but there was no significant difference between treatments for surgery (-3.3%, 95% CI: -6.3, +0.3) or mortality (-1.4%, 95% CI: -2.7, +0.2).

There was no statistically significant difference for re-bleeding, surgery or mortality between high-dose oral PPI and either H2RA or SST (the results were reported).

Non high-dose PPI treatment (10 RCTs, n=725).

Compared with placebo, non high-dose PPI was associated with a significant decrease in re-bleeding (-25.0%, 95% CI: -29.3, -20.7), surgery (-16.2%, 95% CI: -18.1, -14.2) and mortality (-3.5%, 95% CI: -4.6, -2.4).

Compared with H2RA or SST, there was a statistically significant decrease in re-bleeding (-14.4%, 95% CI: -21.2, -7.7), but there was no significant difference for surgery or mortality (the results were reported).
Authors' conclusions
High-dose intravenous PPIs significantly reduced re-bleeding, surgery and mortality, while studies suggested that high-dose oral PPIs reduced re-bleeding. Non high-dose PPIs also improved outcomes.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, outcomes and study design. The research question for interventions was broad and could have been explicitly defined given the actual focus of the review. Only one database was searched and this might have resulted in the omission of other relevant studies. By including publications in two languages the authors attempted to reduce language bias, but no attempts were made to minimise publication bias. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. The authors assessed validity using specified established criteria and attempted to minimise bias in their assessment. However, since the results were not reported, the quality of the included studies was unknown.

No information on the characteristics of the individual studies was presented, and the inclusion or exclusion of studies with patients who also received endoscopic treatment appeared inconsistent and was not reported clearly. The pooling of data in meta-analyses appeared appropriate and meta-analysis graphs were presented, thus allowing an examination of statistical heterogeneity. The meta-analysis took account of differences in prognostic factors between the studies. It is difficult to assess the reliability of the authors' conclusions given the limited search, incomplete description of review methods, and insufficient reporting of the validity assessment and characteristics of the individual studies.

One of the authors is a consultant for and a member of the speakers' bureau for AstraZeneca Canada and Altana Pharma Inc.

Implications of the review for practice and research
Practice: The authors stated that for patients with a bleeding peptic ulcer and high-risk stigmata, successful endoscopic treatment should be followed by either an oral or intravenous high-dose PPI. There is currently more evidence for intravenous PPIs.

Research: The authors stated that further research is required to define the optimal dose and mode of administration of PPIs for the treatment of patients with bleeding peptic ulcers.

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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.