High-dose vs low-dose proton pump inhibitors for upper gastrointestinal bleeding: a meta-analysis
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CRD summary
This generally well-conducted review concluded that the low-dose intravenous proton-pump inhibitors achieved the same efficacy as high-dose proton-pump inhibitors following endoscopic haemostasis in patients with upper gastrointestinal bleeding. The authors' conclusions reflect the evidence presented, but should be interpreted with a degree of caution given the limited quality and size of most of the included trials.

Authors' objectives
To assess the efficacy of high-dose versus low-dose proton-pump inhibitors for the treatment of upper gastrointestinal bleeding.

Searching
The following databases were searched up to September 2009 without language restriction: PubMed, EMBASE, the Cochrane Library and Web of Science. Search terms were reported. Reference lists of retrieved publications were screened.

Study selection
Randomised controlled trials (RCTs) that compared high-dose with low-dose proton-pump inhibitors following endoscopic haemostasis in patients with acute upper non-variceal gastrointestinal bleeding were eligible for inclusion. The high-dose proton pump inhibitors were defined as at least twice the low dose of any proton-pump inhibitors used during the 72 hours following endoscopic haemostasis. Trials where proton-pump inhibitor treatment was initiated prior to endoscopic haemostasis were excluded. Eligible trials had to report the outcomes of persistent bleeding, recurrent bleeding, need for surgery, or mortality.

The included trials evaluated omeprazole and pantoprazole, administered at different doses individually or in combination. Most proton-pump inhibitors were given as an intravenous bolus, but some patients were followed up with infusion. Included patients had gastric ulcers or duodenal ulcers (where reported). The mean age of most participants was over 60 years; most were men (where reported). Most included patients were at high risk (with peptic ulcer with spurting artery, ooze, non-bleeding visible vessel or clot); some patients had oesophageal ulcers (where reported). Most included trials were conducted in European; the remaining trials were conducted in Asia. Included trials were published from 1999 to 2008.

Two reviewers independently assessed studies for inclusion, with any disagreement resolved by discussion.

Assessment of study quality
The quality of trials was assessed using the criteria of sequence generation, allocation concealment, blinding, completeness of outcome data, and selective outcome reporting. The trials were classified as low risk of bias, unclear risk of bias, and high risk of bias.

Two reviewers independently performed validity assessment.

Data extraction
Data were extracted on event rates, to enable the calculation of odds ratios (ORs) with 95% confidence intervals (CIs).

Two reviewers independently performed data extraction, with any disagreement resolved by discussion.
Methods of synthesis
The trials were combined in meta-analyses. The pooled odds ratios with 95% confidence intervals were calculated. Statistical heterogeneity was assessed using the forest plot and $I^2$. The Mantel-Haenszel fixed-effect model was used when there was no significant heterogeneity; otherwise the DerSimonian and Laird random-effects model was employed.

Sensitivity analyses were performed by excluding trials that potentially biased the results. Subgroup analyses were performed on Asian versus European patients, the type of proton-pump inhibitors, endoscopic high-risk stigmata, and trial quality.

Publication bias was assessed using a funnel plot and the Egger's test.

Results of the review
Nine RCTs were included in the review (n=1,337 patients); three of these were abstracts. The sample size ranged from 24 to 474 patients. Four trials had a low risk of bias, two trials had an unclear risk of bias, and three trials had a high risk of bias.

There were no significant differences between high-dose and low-dose intravenous proton-pump inhibitors for re-bleeding (OR 1.09, 95% CI 0.78 to 1.53; nine RCTs), need for surgery (OR 1.52, 95% CI 0.64 to 3.61; six RCTs) and mortality (OR 1.02, 95% CI 0.48 to 2.20; six RCTs). No significant statistical heterogeneity was observed for these outcomes.

Subgroup analyses showed that there was no significant difference in re-bleeding rate between Asian and European patients. Sensitivity analyses did not materially alter the results. Results for other subgroup analyses were reported.

There was no evidence of publication bias.

Authors' conclusions
The low-dose intravenous proton-pump inhibitors achieved the same efficacy as high-dose proton pump inhibitors following endoscopic haemostasis in patients with upper gastrointestinal bleeding.

CRD commentary
The inclusion criteria of the review were clear. A number of relevant databases were searched for published and unpublished studies, reducing the potential for publication bias. Publication bias was further assessed, but using a funnel plot to assess the risk of publication bias in a small number of studies might be not appropriate. No language restriction was applied in the search, which minimised the risk of language bias. Sufficient attempts were made to minimise errors and biases in the review process.

Appropriate criteria were used to assess trial quality, but most included trials had a small size; only four trials were at low risk of bias. Statistical heterogeneity was assessed. Appropriate methods were used to pool the results.

The review was generally well conducted and the authors’ conclusions reflect the evidence presented. However, a degree of caution might be required in interpreting these conclusions given the limitations of the included trials.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further comparative trials are required to compare oral proton-pump inhibitors with intravenous proton-pump inhibitors following endoscopic haemostasis in western patient populations. Future trials should stratify the management of patients based on low-risk, intermediate-risk and high-risk endoscopic lesions.

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