

Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding

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Abstract

Objectives To review randomised controlled trials of treatment with a proton pump inhibitor in patients with ulcer bleeding and to determine the impact on mortality, rebleeding, and surgical intervention.

Design Systematic review and meta-analysis.

Data sources Cochrane Collaboration's trials register, Medline, and Embase, handsearched abstracts, and pharmaceutical companies.

Review methods Included randomised controlled trials that compared proton pump inhibitor with placebo or H₂ receptor antagonist in endoscopically proved bleeding ulcer and reported at least one of mortality, rebleeding, or surgical intervention. Trials

were graded for methodological quality. Two assessors independently reviewed each trial, and disagreements were resolved by consensus.

Results We included 21 randomised controlled trials comprising 2915 patients. Proton pump inhibitor treatment had no significant effect on mortality (odds ratio 1.11, 95% confidence interval 0.79 to 1.57; number needed to treat (NNT) incalculable) but reduced rebleeding (0.46, 0.33 to 0.64; NNT 12) and surgery (0.59, 0.46 to 0.76; NNT 20). Results were similar when the meta-analysis was restricted to the 10 trials with the highest methodological quality: 0.96, 0.46 to 2.01, for mortality; 0.41, 0.25 to 0.68, NNT 10, for rebleeding; 0.62, 0.46 to 0.83, NNT 25, for surgery.

Conclusions Treatment with a proton pump inhibitor reduces the risk of rebleeding and the requirement for surgery after ulcer bleeding but has no benefit on overall mortality.

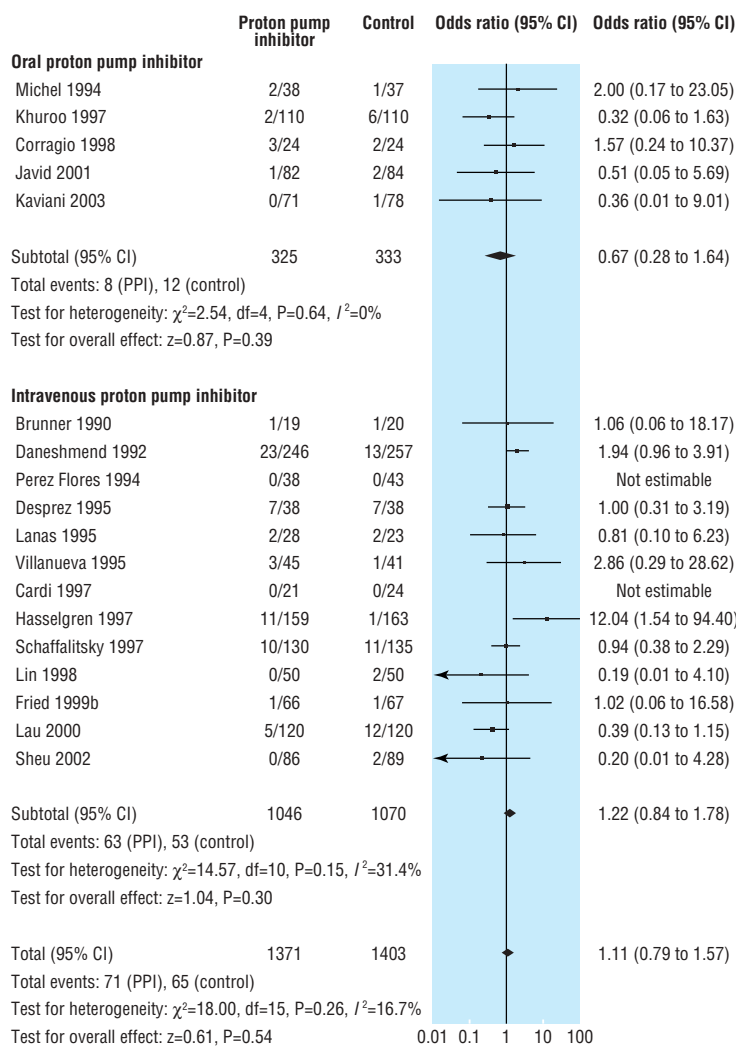


Fig 1 Odds ratios for individual trials and pooled data for mortality, according to route of administration of proton pump inhibitor (PPI)

Introduction

Peptic ulcers are the main cause of upper gastrointestinal bleeding,^{1,2} which is associated with considerable morbidity and mortality. The role of treatment with proton pump inhibitors for patients with active or recent ulcer bleeding is controversial. If given in an adequate dose by continuous intravenous infusion, proton pump inhibitors can maintain intragastric pH at 6 or above.^{3,4} At those levels of pH, peptic activity is minimised, platelet function is optimised, and fibrinolysis is inhibited; these effects should help to stabilise clot formation over an ulcer. Although proton pump inhibitors are already widely used for ulcer bleeding,^{5,6} intravenous therapy may have been overused and given inappropriately for patients at low risk.^{7,8} We systematically reviewed the published literature and analysed the results by meta-analysis to define the contribution of proton pump inhibitors to the management of ulcer bleeding.

Methods

We performed a literature search up to February 2003 of Medline, Embase, the Cochrane Central Register of Controlled Trials, and the specialised trials register of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group. We included randomised controlled trials that compared a proton pump inhibitor with placebo or an H₂ receptor antagonist for treating ulcer bleeding. Bleeding had to have been confirmed endoscopically. Our primary outcome measure was mortality within 30 days of randomisation. Secondary

References to the included trials,^{w1-w21} details of conference presentations, abstracts, and the Cochrane reference are on bmj.com

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Principal outcome measures in patients with ulcer bleeding according to treatment

Outcome at 30 days after randomisation	No of trials	No of patients		Heterogeneity (P value)	Pooled rates (%)		Odds ratio (95% CI)	Number needed to treat (95% CI)
		Proton pump inhibitor	Control		Proton pump inhibitor	Control		
Mortality	18	1371	1403	No (0.26)	5.2	4.6	1.11 (0.79 to 1.57)	Not calculable
Rebleeding	19	1408	1423	Yes (0.05)	10.6	18.7	0.46 (0.33 to 0.64)	12 (8 to 25)
Surgical intervention	17	1305	1336	No (0.42)	8.4	13.0	0.59 (0.46 to 0.76)	20 (14 to 50)

outcome measures included recurrent ulcer bleeding and surgery for ulcer bleeding within 30 days of randomisation.

Using predetermined sensitivity analyses, we examined the influence of the degree of study validity, the type of control treatment, the initial use of endoscopic haemostatic therapy, the site of ulcer, the presence of signs of recent haemorrhage at the initial endoscopy, restriction of the analysis to trials using intravenous (as opposed to oral) proton pump inhibitors, and restriction of the analysis to trials that had used a high intravenous dose. Our predetermined definition of "high dose" was the equivalent of omeprazole as an intravenous bolus of 80 mg followed by a continuous intravenous infusion of 8 mg/hour for 72 hours.

Results

We initially identified 172 articles and 21 trials met our predefined inclusion criteria; 18 were full peer reviewed publications^{w1-w18} and three were abstracts.^{w19-21} The funnel plots for the three outcomes of interest show slight asymmetry, suggesting the possibility of publication bias (see [bmj.com](#)). The table summarises the main results (see [bmj.com](#) for details of the included trials). Treatment with proton pump inhibitors was associated with reduced rebleeding and surgery but not with mortality. Figures 1, 2, and 3 show the forest plots for the three outcome measures.

In a planned subgroup analysis of the 10 trials with adequate concealment of allocation we obtained essentially similar results; the odds ratios (95% confidence intervals) for mortality, rebleeding, and surgery were 0.96 (0.46 to 2.01), 0.41 (0.25 to 0.68), and 0.62 (0.45 to 0.83), respectively. We could not calculate number needed to treat for mortality. The number needed to treat for rebleeding and surgery was 10 (6 to 25) and 25 (14 to 50), respectively. In another subgroup analysis of the 13 trials that routinely used endoscopic haemostatic therapy before randomisation, the pooled odds ratios for mortality, rebleeding, and surgery were 1.01 (0.64 to 1.61), 0.52 (0.39 to 0.70), and 0.53 (0.35 to 0.79).

Discussion

Proton pump inhibitors are widely used for patients with ulcer bleeding of varying severity,⁵⁻⁸ though they have not been specifically approved for that indication. Given the morbidity, mortality, and healthcare costs associated with bleeding peptic ulcer, it is important to establish definitively whether early treatment with proton pump inhibitors is associated with any meaningful clinical benefit. We deliberately focused on the use of proton pump inhibitors in patients with a proved diagnosis of ulcer bleeding and cannot, therefore, make any conclusions about their use for managing other causes of upper gastrointestinal tract bleeding. Although one

trial included patients with non-ulcer bleeding,^{w2} we excluded those patients from our analysis. The other trials we included were confined to patients with a proved diagnosis. While we cannot exclude the possibility of some publication bias (see [bmj.com](#)), our search was rigorous and we did not identify any other trials through contact with pharmaceutical companies.

Overall, we found no evidence that treatment with proton pump inhibitors reduces mortality after ulcer bleeding. There were, however, significant reductions in rates of rebleeding and surgery. Much of the mortality after an episode of ulcer bleeding may be unrelated to continued or recurrent bleeding but to comorbid

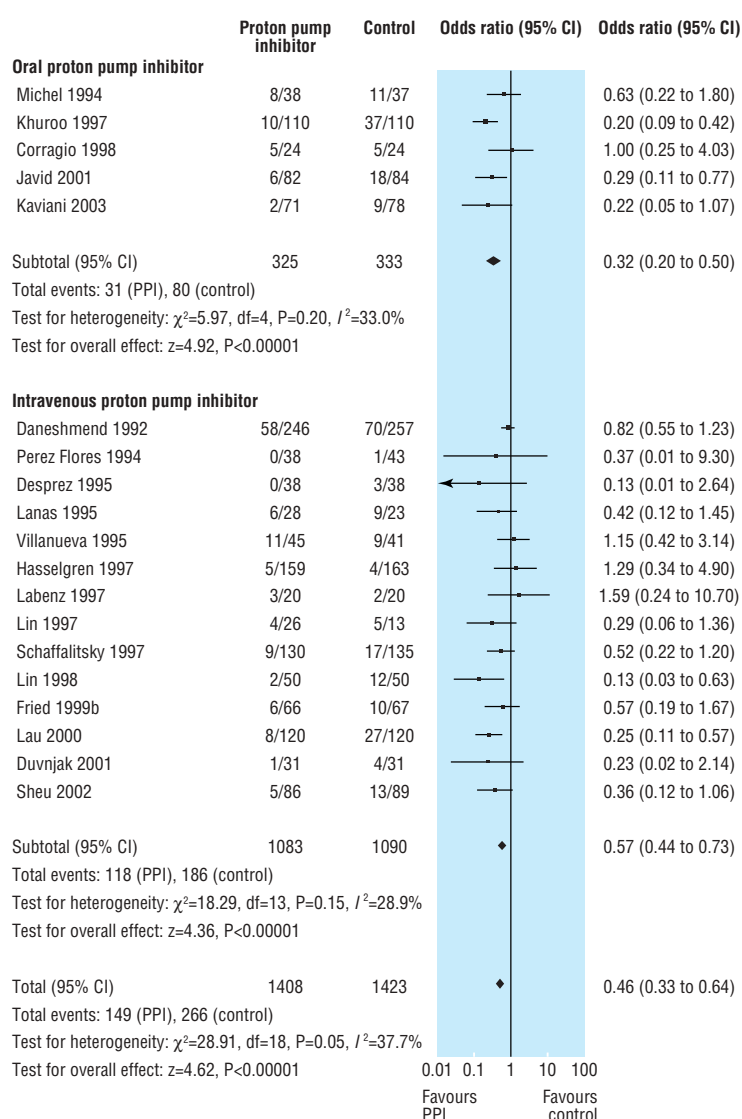


Fig 2 Odds ratios for individual trials and pooled data for rebleeding, according to route of administration of proton pump inhibitor (PPI)

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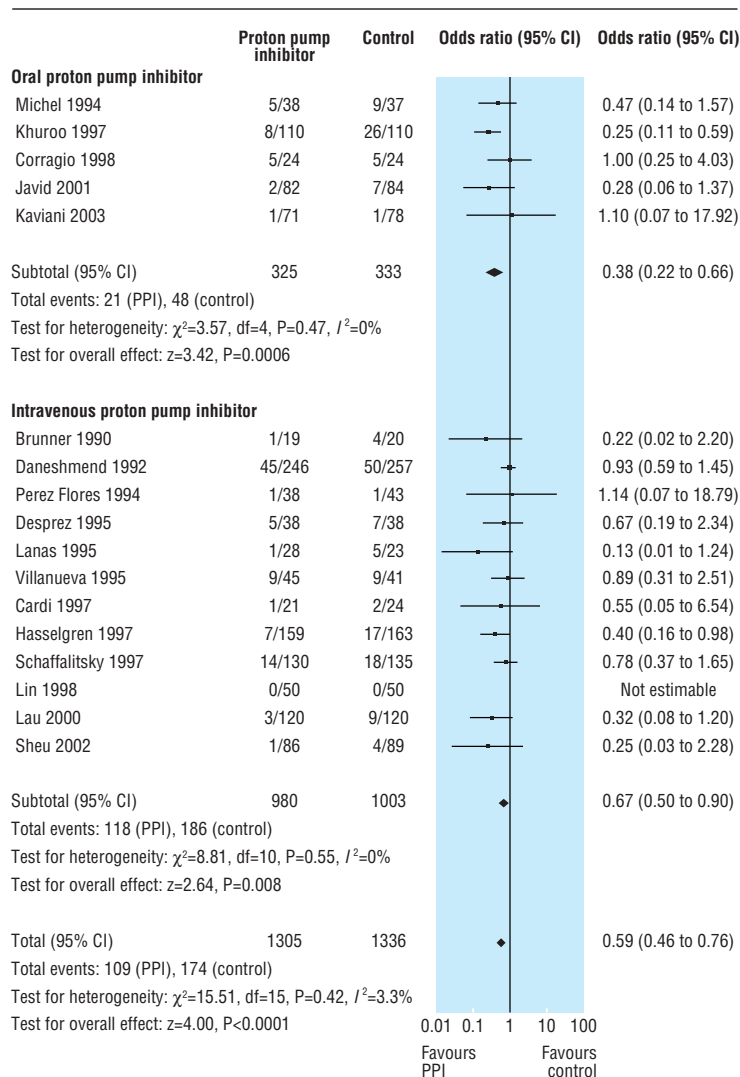


Fig 3 Odds ratios for individual trials and pooled data for rates of surgical intervention, according to route of administration of proton pump inhibitor (PPI)

disease.⁹ Alternatively, there may have been too few patients in our pooled analysis of mortality data to enable us to detect a difference. The data are also compatible with treatment causing a small excess of deaths, which we consider unlikely on clinical grounds. In most trials, we could not determine whether deaths were attributable to comorbid conditions.

What is already known on this topic

Proton pump inhibitors are effective for healing non-bleeding ulcers
 Their role in the management of patients with bleeding ulcers is unclear

What this study adds

This systematic review and meta-analysis found that proton pump inhibitor treatment reduces the risk of ulcer rebleeding but does not influence overall mortality from ulcer bleeding
 Requirement for surgery to manage ulcer bleeding is also likely to be reduced with early proton pump inhibitor treatment

Some trials compared proton pump inhibitor therapy with placebo and others with an H₂ receptor antagonist, though this is unlikely to have made any substantive difference in results. A meta-analysis by Collins and Langman,¹⁰ and its update by Levine and colleagues,¹¹ found no benefit of intravenous H₂ receptor antagonist over intravenous placebo in clinically important outcomes of bleeding duodenal ulcer and, at best, only small benefits in bleeding gastric ulcer.

This meta-analysis included randomised controlled trials of oral or intravenous proton pump inhibitor therapy; both methods of administration were associated with reduced rebleeding (see bmj.com). Oral treatment is widely available and has the obvious advantage of costing less than intravenous administration. In areas of the world where intravenous treatment is unavailable or particularly expensive, oral treatment would be appropriate. Furthermore, it would be less costly for any patient with recent ulcer bleeding who did not require endoscopic haemostatic therapy.

In summary, proton pump inhibitor treatment has not been shown to reduce mortality after ulcer bleeding. It is, however, a remarkably consistent observation that such treatment reduces rates of rebleeding and, in general, the need for surgical intervention. This may be associated with important cost savings, which should be further evaluated in formal cost effectiveness studies.

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Ethical approval: Not required.

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