

# Should Proton Pump Inhibitors Be Used for Acute Peptic Ulcer Bleeding?

## EBEM Commentators

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## SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding (Cochrane Review). Chichester, UK: Cochrane Library; 2006;issue 1.

The *Annals'* EBEM editors prepared the abstract of this Cochrane systematic review, as well as the Evidence-Based Medicine Teaching Points.

## OBJECTIVE

To determine the efficacy of proton pump inhibitors when compared to placebo or histamine type 2 ( $H_2$ -receptor antagonists;  $H_2RA$ ) in the management of acute bleeding from peptic ulcers.

## DATA SOURCES

The authors searched CENTRAL, the Cochrane Library (Issue 4, 2004), MEDLINE (1966 to November 2004), and EMBASE (1980 to November 2004), proceedings of recent major meetings through November 2004, and the reference lists of included articles. The authors contacted pharmaceutical companies and experts in the field for additional published or unpublished data. This review is considered updated to November 2005.

## STUDY SELECTION

Trials were included if they were randomized control trials of oral or intravenous proton pump inhibitors compared with either placebo or  $H_2RA$  given for acute bleeding from peptic ulcer and if they met the following criteria: use of a concurrent control group, concomitant therapy applied to both intervention arms, diagnosis made endoscopically, ability to

isolate data for patients with bleeding peptic ulcers, and at least 1 of the following outcomes reported: death, rebleeding, surgical intervention, and further endoscopic treatment.

## DATA EXTRACTION AND ANALYSIS

Two reviewers checked trials and abstracts identified from the search for fulfillment of the inclusion criteria. Disagreements were resolved by consensus, with no  $\kappa$  values reported about intraobserver agreement. For the included studies, 2 reviewers graded the methodologic quality according to allocation concealment. Other assessments of study quality included blinding, baseline comparability of treatment groups, and description of withdrawals and dropouts.

Odds ratios (ORs) were reported for dichotomous outcomes. Data among trials were considered heterogeneous when  $P < .10$ . The numbers-needed-to-treat (NNTs) and their 95% confidence intervals (CIs) were calculated by us (B.E., J.E.R.) with the summary data in the graphs and an online NNT calculator (available at <http://www.nntonline.net>). When the result was not statistically significant, the OR is reported. Whenever the OR result was significant, the NNT is reported.

## MAIN RESULTS

Twenty-four trials with a total of 4,372 participants were included. Of these, 12, 11, and 1 had allocation concealment that was adequate, uncertain, and inadequate, respectively. Ten trials were double blinded and 7 were unblinded; insufficient information was provided to determine the blinding status in the remaining 7. Most trials were adequately balanced regarding baseline characteristics of treatment groups, although not all trials provided these data. Only 6 trials reported detailed descriptions of withdrawals and dropouts. Trials did not consistently report comorbidity of participants, which may have affected analysis of mortality data. Funnel plots and Egger's linear regression tests revealed no statistically significant publication bias for mortality or rebleeding. There was, however, publication bias for surgical intervention, but how big an effect this would have on the results was not further delineated.

Overall, proton pump inhibitor treatment did not reduce mortality (OR 1.01; 95% CI 0.70 to 1.40) but reduced rebleeding (NNT 11; 95% CI 9 to 17), surgical (NNT 19; 95% CI 14 to 33), and endoscopic interventions (NNT 9; 95% CI 8 to 13) and adverse outcomes (rebleeding, repeated endoscopic treatment, surgery or death, NNT 11; 95% CI 8 to 38). Statistical heterogeneity was found among trials for rebleeding ( $P=.04$ ) but not for mortality ( $P=.24$ ), surgery ( $P=.45$ ), endoscopic interventions ( $P=.25$ ), or adverse outcomes ( $P=.16$ ).

Effects on mortality and rebleeding rates were independent of the study quality, route of proton pump inhibitor administration, type of control treatment (H<sub>2</sub>RA versus placebo), and decision to attempt initial endoscopic hemostasis. The route of proton pump inhibitor administration and application of initial endoscopic hemostasis did not affect the surgical intervention rates; however, the choice of control treatments did. In particular, proton pump inhibitors significantly reduced surgical intervention rates compared with placebo (NNT 24; 95% CI 17 to 74) but not when compared with H<sub>2</sub>RA (OR 0.73; 95% CI 0.47 to 1.13).

There were some differences between the 8 studies conducted in Asia and 16 conducted elsewhere (14 of which were only in Europe). For the Asian trials involving 1,153 patients, proton pump inhibitors reduced mortality (NNT 71; 95% CI 55 to 178), and this result was robust to the exclusion of any single trial. For the 16 trials elsewhere involving 3,219 patients, proton pump inhibitors had no effect on mortality (OR 1.36; 95% CI 0.94 to 1.96). Finally, proton pump inhibitors were more effective in preventing rebleeding in the Asian trials (NNT 6; 95% CI 6 to 7) than in the trials elsewhere (NNT 83; 95% CI 55 to 211), and there was no heterogeneity in rates of rebleeding within each group ( $P=.95$  for Asian trials, 0.85 for trials elsewhere).

## CONCLUSIONS

Proton pump inhibitor treatment in peptic ulcer bleeding reduces rebleeding and surgical and further endoscopic intervention rates in studies comparing treatment with placebo or H<sub>2</sub>RA; however, there is no evidence of an overall effect on mortality.

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## COMMENTARY: CLINICAL IMPLICATION

Upper gastrointestinal bleeding as a result of peptic ulcer is a common medical condition associated with substantial morbidity, mortality, and health care cost. In the United States, 150,000 patients are hospitalized each year for bleeding ulcers, with an average hospital cost per admission of \$5,000; the total

yearly cost for such hospitalizations is \$750 million.<sup>1</sup> Clearly, this is an important illness, and its presentation to the emergency department (ED) is a common occurrence.

Upper gastrointestinal bleeding commonly presents with hematemesis or melena, although hematochezia can occur when bleeding is massive. The initial evaluation of the ED patient includes assessing hemodynamic stability and consideration of fluid resuscitation. Endoscopy is the procedure of choice for diagnosing and treating active upper gastrointestinal bleeding and preventing rebleeding.<sup>2</sup> Endoscopy allows gastroduodenal ulcers to be risk stratified by the presence or absence of stigmata of ulcer hemorrhage. Further treatment may include diagnosis and treatment of comorbid conditions, prompt administration of acid-suppressing drugs, blood transfusion, or surgery.<sup>3</sup>

Proton pump inhibitors likely affect peptic ulcer bleeding by inhibiting gastric acid production. Proton pump inhibitors are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus. In this acidic environment, the proton pump inhibitor becomes protonated, producing the sulphenamide form of the drug that binds covalently to the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme, irreversibly inhibiting acid secretion by the proton pump.<sup>4</sup>

This high-quality Cochrane meta-analysis concludes that patients given proton pump inhibitors have less rebleeding and surgical interventions. These results are consistent whether only high-quality trials are examined in isolation, whether the proton pump inhibitor is given orally or intravenously, and whether or not endoscopic treatment is administered first.

Although early proton pump inhibitor treatment significantly influences some treatment outcomes after peptic ulcer bleeding, it does not appear to reduce mortality. When all Asian studies were evaluated separately, however, proton pump inhibitor treatment reduced mortality, rebleeding, and surgery, and these results remained significant regardless of the trials removed. For the studies done elsewhere, there are only marginal reductions in the rates of rebleeding and surgical interventions.

## TAKE HOME MESSAGE

The observed impact of proton pump inhibitor therapy on rates of rebleeding and surgical interventions are likely to be of major clinical benefit and may decrease health care costs. Although mortality appears unaffected, sufficient benefit in reducing rebleeding and the requirement for endoscopic and surgical interventions exists to warrant use of these agents in the ED.

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**EBEM TEACHING POINT**

Heterogeneity should be reported and evaluated in systematic reviews that present meta-analyses. Heterogeneity occurs when the results of trials differ more than one would expect from chance alone. It can be suspected using visual inspection of graphic displays in which forest plots demonstrate nonoverlapping 95% CI bars. Alternatively, the  $\chi^2$  test can be used to calculate *P* values comparing results among trials; when *P* < .10, heterogeneity is considered to be present. Finally, an *I*<sup>2</sup> statistic may be produced to quantify the heterogeneity. What value does finding heterogeneity have? Apart from chance alone, heterogeneity suggests that trials differ in design or study elements (eg, populations, interventions, comparisons, or outcomes). One approach to exploring the factors associated with heterogeneity is to perform subgroup analyses, looking for subgroups in which the results are homogeneous within each subgroup. However, if subgroups are not chosen a priori (ie, before the meta-analysis is performed), definitive conclusions cannot be reached. Even when the subgroups are chosen in advance and their numbers are limited, heterogeneity evaluation simply provides hypotheses that may be confirmed by further testing. Finally, although post hoc subgroups analysis sometimes gives spurious results, this is less likely if the way the total population is divided into subgroups is biologically plausible, if the differences between subgroups are large, and if the differences are confirmed in trials involving both populations in the same study.<sup>5</sup>

In this meta-analysis, the authors found heterogeneity in the results for rebleeding. When studies in Asia and elsewhere were examined separately by post hoc analysis, the results were homogeneous in each separate group, and proton pump inhibitors more effectively prevented rebleeding among Asians than patients elsewhere. Some possible explanations for this

include younger age of Asian patients in the studies, less comorbidity, and increased inhibition of gastric acid secretion in Asian patients because of decreased parietal cell mass.<sup>6</sup> In addition, proton pump inhibitors may work more effectively because Asians tend to have a higher prevalence of *Helicobacter pylori* infection<sup>7</sup> and because Asians are known to more slowly metabolize proton pump inhibitors than other genetic groups.<sup>8</sup> Thus, consideration of heterogeneity led to suggesting differences in the effectiveness of proton pump inhibitors in different populations, which may help clinicians decide whether to use proton pump inhibitors or not in their own patient populations.

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