

Some Observations on PPI Therapy for Bleeding Ulcer

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Abstract: Proton pump inhibitor (PPI) therapy improves some outcomes after peptic ulcer bleeding. Recent meta-analyses have consistently found reduced rates of rebleeding and surgical intervention but there has been some discordance about effects on overall mortality. In general, more impressive results have been reported from trials conducted in Asia than elsewhere. PPI treatment for ulcer bleeding is not a substitute for appropriate endoscopic hemostatic treatment.

Proton pump inhibitors (PPIs) are not approved by the US Food and Drug Administration (FDA) for the management of acute upper gastrointestinal (GI) bleeding. However, they are widely used in this setting, regardless of whether or not diagnosis of a bleeding ulcer has been endoscopically confirmed. Multiple randomized controlled trials (RCTs) have compared PPI therapy with H₂-receptor antagonists (H₂RAs) or placebo in ulcer bleeding. In 2003, a multisociety consensus group evaluated all available evidence and recommended high-dose intravenous (IV) PPI therapy in patients with nonvariceal upper GI bleeding, who have undergone successful endoscopic hemostatic treatment (EHT).¹ More recently, several meta-analyses have attempted to combine the results of different RCTs.

Meta-analyses of Randomized Controlled Trials

Khuroo and associates² performed a meta-analysis of RCTs of PPI therapy given as part of the management of patients with any non-variceal source of upper GI bleeding. We have published a Cochrane Collaboration systematic review and meta-analysis of RCTs of PPI therapy for confirmed ulcer bleeding.^{3,4} Although there were differences in the design and scope of these two meta-analyses, their principal results were very similar: PPI treatment reduced the risk of rebleeding and the requirement for surgical intervention but had no demonstrable effect on all-cause mortality (Table 1). The benefits of PPI treatment were demonstrable when compared with either an H₂RA or placebo. There was benefit from both oral and IV PPI administration. However, the level of benefit attributable to

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Table 1. Summary Results From Two Published Meta-analyses of PPI Therapy for Nonvariceal Upper Gastrointestinal Bleeding or Bleeding Peptic Ulcer

	Pooled Odds Ratio (95% confidence interval)		
	All-Cause Mortality	Rebleeding	Surgical Intervention
Khuroo et al ²	1.02 (0.76–1.37)	0.48 (0.40–0.57)	0.61 (0.48–0.76)
Leontiadis et al ³	1.11 (0.79–1.57)	0.46 (0.33–0.64)	0.59 (0.46–0.76)

PPI therapy may not be widely understood by prescribers. Our best estimate of the numbers needed to treat (NNTs) to prevent a single episode of rebleeding and to obviate the need for surgical treatment of ulcer bleeding were 12 (95% confidence interval [CI], 8–25) and 20 (95% CI, 14–50), respectively.⁴ The NNT for prevention of one death was, by definition, incalculable because we did not find any significant effect from PPI treatment on overall mortality. In a planned subgroup analysis of the RCTs with the highest methodological quality, the results were very similar. Again, there was no significant benefit from PPI treatment in terms of all-cause mortality and the NNT values for prevention of rebleeding and surgical intervention were, respectively, 10 (95% CI, 6–25) and 25 (95% CI, 14–50).

Andriulli and colleagues⁵ reported a series of meta-analyses of RCTs of PPI treatment in peptic ulcer bleeding. They also found that PPI treatment, compared to treatment with an H2RA or placebo, reduced rebleeding but not all-cause mortality. They also provided valuable information on the proportion of patients with major endoscopic stigmata per trial.⁵

Bardou and coworkers⁶ reported slightly different conclusions. Their meta-analysis focused on RCTs of PPI treatment in patients with peptic ulcer bleeding exhibiting high-risk stigmata (ie, active bleeding, nonbleeding visible vessel [NBVV], or adherent clot) at index endoscopy.⁶ Eligible RCTs were divided into three groups: high-dose IV PPI treatment, high-dose oral PPI treatment, and non-high-dose PPI treatment. In each group, trials were pooled separately according to the control treatment used (placebo or H2RA). PPI treatment significantly reduced rebleeding in all analyses apart from that of high-dose IV PPI versus H2RA. The effect on surgery was less consistent. In addition, unlike the other meta-analyses, they found that mortality was significantly reduced with both non-high-dose PPIs and high-dose IV PPIs compared to placebo. However, we have some concerns about the inclusion of certain trials in their analysis of non-high-dose PPI treatment versus placebo,⁷ and it is important to note that the reduction in mortality was demonstrated only after the exclusion of the trial of Hasselgren and colleagues,⁸ which was found to be an outlier.

The Place of PPI Treatment With Respect to EHT

PPI treatment for ulcer bleeding is not a substitute for EHT; at best, it is an adjunct. Sung and colleagues⁹ in Hong Kong randomized patients with bleeding ulcer and high-risk endoscopic stigmata (NBVV or adherent clot) to IV omeprazole (Prilosec, AstraZeneca) treatment alone or to the combination of appropriate EHT and IV omeprazole. The patients who received combination treatment had a significantly lower rebleeding rate and a shorter duration of hospital stay. Although there was no statistically significant reduction in 30-day all-cause mortality, the trial was inadequately powered to detect such a difference.

The meta-analysis by Andriulli and associates⁵ included five RCTs that compared PPI treatment alone (IV or oral) with the combination of PPI treatment and EHT. Ninety-one percent of the patients included in this analysis had ulcers that were not actively bleeding at index endoscopy. Combination therapy significantly reduced rebleeding and surgical intervention rates, but there was no demonstrable effect on mortality.

Unlike PPI monotherapy, there is clear evidence that EHT given alone reduces mortality from ulcer bleeding, as well as rates of rebleeding and surgical intervention.¹⁰ Not all of the RCTs of PPI therapy for ulcer bleeding included in the meta-analyses administered EHT, even among patients with endoscopic high-risk stigmata.^{3,4} However, when we performed a preplanned subgroup analysis of those RCTs that did appropriately administer EHT, we again found statistically significant reductions in rebleeding and surgical intervention, but no demonstrable effect on all-cause mortality. When the PPI was administered IV in what we defined a priori as “high dose” (ie, the equivalent of omeprazole as a bolus of 80 mg followed by an infusion of 8 mg/hour for 72 hours), the NNTs for prevention of rebleeding and surgical intervention were, respectively, 11 (95% CI, 8–33) and 25 (95% CI, 17–100). There was no demonstrable effect on rates of surgical intervention when a lower IV dose—or oral PPI treatment—was administered, and the NNT for prevention of rebleeding was 14 (95% CI, 8–33).

Is There Really No Benefit on Mortality?

One of the more contentious issues concerning PPI therapy for bleeding ulcer is whether or not it decreases mortality rates. We found no improvement in all-cause mortality despite a reduction in rebleeding.^{3,4} Our interpretation of this finding is that much of the mortality following ulcer bleeding is not due to the effects of bleeding per se, but to associated comorbidity.^{3,4} Khuroo and colleagues attempted to subdivide the deaths following ulcer bleeding according to whether they were considered “ulcer deaths” or “non-ulcer deaths.”² They concluded that PPI treatment might reduce ulcer deaths but actually increase non-ulcer deaths. However, we feel that such a categorization is impracticable and cannot reliably be made based on the information available in the individual published RCTs.^{3,4,11} Khuroo and associates further concluded that there was evidence to suggest that IV—but not oral—PPI treatment for ulcer bleeding increased the odds for all-cause mortality and for non-ulcer deaths and suggested that there may be some unrecognized toxicity associated with IV PPI therapy.²

In our meta-analysis, the pooled odds ratio (OR) for 30-day all-cause mortality was 1.11 with a 95% CI 0.79–1.57.^{3,4} The extent of the CI indicates that PPI therapy is consistent with anything from a 21% reduction to a 57% increase in all-cause mortality. However, one outlier RCT, by Hasselgren and colleagues⁸ again had a major influence on this. That trial had an unexpectedly—and inexplicably—low mortality rate in the control arm and was terminated prematurely because of that observed difference. The trial was restricted to patients over 60 years old, which makes the unusually low mortality rate with placebo treatment even more difficult to rationalize. When we reanalyzed our results with the exclusion of the Hasselgren study, the pooled OR dropped to below unity, although it remained statistically nonsignificant (OR=0.95; 95% CI, 0.66–1.36).

Is Asia Different?

In the course of our review, our attention was drawn to differences in outcomes between RCTs conducted within and outside of Asia. In general, Asian RCTs were more likely to have reported improvement in mortality with PPI treatment than those conducted elsewhere. Furthermore, the observed reductions in rebleeding and surgical intervention appeared to be greater in the Asian RCTs. As we had found statistically significant heterogeneity for the endpoint of 30-day rebleeding in our full meta-analysis,^{3,4} we sought to explain this by examining the Asian and the non-Asian RCTs separately.¹² In the process, we included two more recent RCTs^{13,14} that had not been included in

our initial meta-analysis. When the Asian and non-Asian RCTs were pooled and analyzed separately, we found clear differences in outcomes.¹² Overall, there was a significant reduction in 30-day all-cause mortality demonstrable with PPI treatment for bleeding ulcer in the Asian RCTs (OR=0.35; 95% CI 0.16–0.74; NNT=33) but not in the non-Asian RCTs (OR=1.36; 95% CI, 0.94–1.96; NNT incalculable). Furthermore, the magnitude of the effects that PPI treatment had on rebleeding and surgical intervention rates were quantitatively greater in the Asian than the non-Asian RCTs.¹²

There are a number of possible reasons why PPI therapy for ulcer bleeding may be more efficacious in Asian than in non-Asian patients. First, the patients in the Asian RCTs had a mean age of 57 years whereas those in the non-Asian RCTs that provided that information had a mean age of 66 years. Therefore, the Asian subjects may have had fewer comorbidities, although a detailed analysis was not practicable from the information available in the individual publications. PPI treatment in Asian patients may produce a more profound reduction in acid secretion because of a lower parietal cell mass.¹⁵ *Helicobacter pylori* infection, which is highly prevalent in Asia, is also associated with an enhanced pharmacodynamic effect of PPIs.^{16,17} Furthermore, Asian patients are more likely to have genetically determined slow metabolism of PPIs.^{18,19} All these factors would tend to produce a greater antisecretory effect of PPI therapy in Asian than in non-Asian patients.

What's New Since the Meta-analyses?

As noted above, the results of two additional RCTs have become available since the completion of the meta-analyses. At the time of writing, both these RCTs were only available in abstract form.^{13,14} Barkun and coworkers¹³ performed a multinational RCT comparing IV pantoprazole (Protonix, Wyeth) and IV ranitidine for the management of patients with high-risk stigmata (active bleeding, venous oozing, NBVV) who had received appropriate EHT as part of their management. The pantoprazole dose used was 80 mg by IV bolus and 8 mg/hr by IV infusion for up to 72 hours. Despite the apparently appropriate dose of pantoprazole used, there was no demonstrable benefit over IV ranitidine in rates of rebleeding or all-cause mortality. Subgroup analyses, however, did show statistically significant reductions in rebleeding rates with pantoprazole among patients who had active arterial bleeding at initial endoscopy or had bleeding from gastric—as opposed to duodenal—ulcers.

Jensen and colleagues¹⁴ have reported the only RCT of IV PPI treatment conducted in the United States. In a design similar to the RCT of Barkun and colleagues,¹³

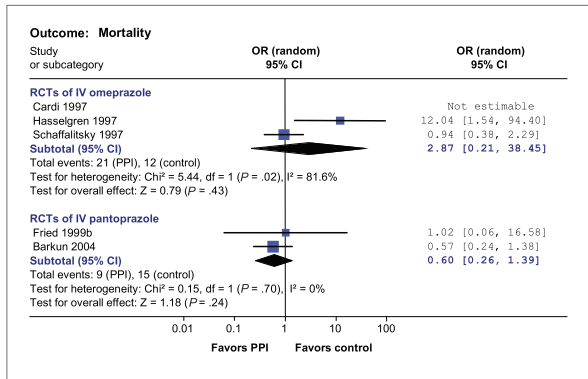


Figure 1. Forest plot of odds ratios (ORs) and 95% confidence intervals (CIs) for individual trials and pooled data concerning 30-day all-cause mortality for non-Asian randomized controlled trials (RCTs) of IV pantoprazole and IV omeprazole that gave the PPI as an initial bolus followed by a continuous infusion.

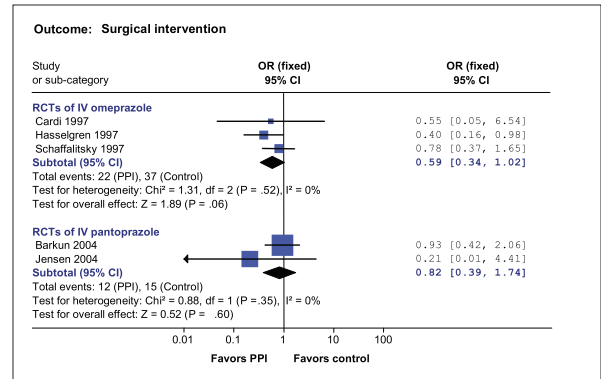


Figure 3. Forest plot of odds ratios (ORs) and 95% confidence intervals (CIs) for individual trials and pooled data concerning 30-day surgical intervention rates for non-Asian randomized controlled trials (RCTs) of IV pantoprazole and IV omeprazole that gave the PPI as an initial bolus followed by a continuous infusion.

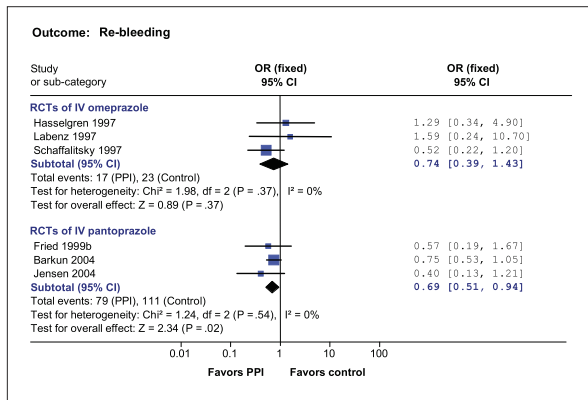


Figure 2. Forest plot of odds ratios (ORs) and 95% confidence intervals (CIs) for individual trials and pooled data concerning 30-day re-bleeding rate for non-Asian randomized controlled trials (RCTs) of IV pantoprazole and IV omeprazole that gave the PPI as an initial bolus followed by a continuous infusion.

they used the same dose of IV pantoprazole and applied appropriate EHT. This RCT was terminated prematurely because of problems with patient recruitment. Initially intended to have over 850 patients randomized to IV pantoprazole or IV ranitidine, analysis was subsequently confined to 149 patients. Although rebleeding rates after 3 and 30 days of randomization were numerically lower on IV pantoprazole than on IV ranitidine, the differences were not statistically significant. However, because of the small number of patients studied, there is a high likelihood of a type II statistical error—this RCT may have become underpowered to detect a true difference between the treatments.

In a recent update of our Cochrane Collaboration systematic review and meta-analysis,²⁰ we incorporated the results of these two more recent RCTs.^{13,14} In the updated analysis, the OR for 30-day all-cause mortality was 1.01 (95% CI, 0.74–1.40; NNT incalculable), which was similar to that reported in our initial analysis (Table 1). The OR for rebleeding was 0.49 (95% CI, 0.37–0.65; NNT=13), and that for surgery was 0.62 (95% CI, 0.48–0.79; NNT=33).

Does the Actual PPI Matter?

It is generally assumed that any beneficial therapeutic effect demonstrable with one PPI would be achievable with the others. Although this is a reasonable assumption, it is noteworthy that most RCTs have used omeprazole. Khuroo and associates² performed a sensitivity analysis of the 22 RCTs that had used omeprazole and found essentially no difference in outcomes when compared with the pooled results of all the RCTs using any PPI.

Intravenous omeprazole is not currently available in the United States although it is widely used in Europe and Asia. Currently, the only PPIs available in the United States as IV formulations are pantoprazole, lansoprazole (Prevacid, TAP), and esomeprazole (Nexium, AstraZeneca). We are aware of only one direct comparison between omeprazole and pantoprazole in the management of ulcer bleeding.²¹ This study was conducted in Italy and randomized 91 patients to IV bolus doses of omeprazole or pantoprazole after EHT for ulcer bleeding. It found no significant difference between the two treatments for rebleeding. Another study randomized 87 patients with ulcer bleeding to oral esomeprazole or IV omeprazole after EHT;²² there were no significant differences in outcomes

Table 2. Pooled Results Comparing Non-Asian RCTs of IV Pantoprazole and IV Omeprazole that Administered the PPI as an Initial Bolus Followed by a Continuous Infusion

	Pantoprazole (3 RCTs)		Omeprazole (4 RCTs)	
	OR (95% CI)	NNT	OR (95% CI)	NNT
Mortality	0.60 (0.26–1.39)	Not calculable	2.87 (0.21–38.45)*	Not calculable
Rebleeding	0.69 (0.51–0.94)	20 (14–100)	0.74 (0.39–1.43)	Not calculable
Surgical intervention	0.82 (0.39–1.74)	Not calculable	0.59 (0.34–1.02)	Not calculable

* Random effects model was used due to significant heterogeneity among the trials.

CI = confidence interval; OR = odds ratio; NNT = number needed to treat; RCTs = randomized controlled trials.

between the groups. Zhonglin and coworkers randomized patients to IV pantoprazole or IV omeprazole.²³ Control of intragastric pH was similar with the two PPIs but there was a suggestion of earlier arrest of bleeding with IV pantoprazole; however, the study was not blinded.

As noted above, there has been only one small US-based RCT of IV pantoprazole,¹⁴ but none of IV lansoprazole or esomeprazole. Currently, the available data on IV lansoprazole in upper GI bleeding are limited to one small Italian study,²⁴ which compared three regimens of IV bolus lansoprazole and IV bolus ranitidine in 46 patients with nonvariceal upper GI bleeding. Two of the regimens of lansoprazole were associated with a significant reduction in rebleeding compared to ranitidine.

We have identified only four RCTs of pantoprazole in ulcer bleeding.^{13,14,25,26} All four studies compared IV pantoprazole with IV ranitidine; all are currently only available in abstract form. None of these individual RCTs demonstrated a significant advantage of IV pantoprazole over IV ranitidine. All of the studies were conducted in Europe or North America, although one included some patients from South Africa.¹³ Three of the trials administered IV pantoprazole as an initial bolus followed by a continuous infusion.^{13,14,25} There have been four non-Asian RCTs of IV omeprazole that administered it as a bolus and continuous infusion.^{8,27–29} Two of these compared IV omeprazole with IV placebo^{8,29} and the other two compared it with IV ranitidine.^{27,28} Figures 1–3 and Table 2 show the pooled OR, 95% CI, and NNT for 30-day all-cause mortality, rebleeding, and surgical intervention for the three RCTs of IV pantoprazole and the four non-Asian RCTs of IV omeprazole that administered PPI as an initial bolus followed by a continuous infusion. As can be seen, neither omeprazole nor pantoprazole showed any evidence for reduced all-cause mortality and had broadly similar reductions in the risk of rebleeding. However, it is difficult to draw any definitive conclusions from this. We would predict that different PPIs would produce essen-

tially the same effects on outcomes of ulcer bleeding if administered in therapeutically equivalent doses.

What is the “Correct” Dose of IV PPI for Bleeding Ulcer?

Based on the published RCTs, it would appear that the equivalent of 80 mg of omeprazole by IV bolus injection followed by an 8 mg/h IV infusion should be recommended. This was also the recommendation by a multisociety consensus group in 2003.¹ When appropriately combined with EHT, this therapy was clearly efficacious in the trial by Lau and colleagues from Hong Kong.³⁰ However, as discussed above, any dose of IV PPI is likely to achieve higher intragastric pH levels in patients in Asia than in North America and Europe.

Might IV PPI therapy for ulcer bleeding be less efficacious here because we have been administering inadequate doses? With that in mind, Metz and associates³¹ have reported their results with IV infusions of lansoprazole and pantoprazole given over 24 hours in *H. pylori*-negative healthy volunteers. Various doses of IV lansoprazole were compared with IV pantoprazole (80 mg IV bolus plus 8 mg/hr IV infusion over 24 hours); results are summarized in Table 3. The ability of these doses to achieve and maintain an intragastric pH of 6 or above was substantially limited. The “80 + 8” dose regimen of pantoprazole only kept the pH above 6 for 27.9% of the 24-hour recording period. Because this was the dose used in the two most recent “negative” trials^{13,14} in Europe and North America, it is possible that the apparent lack of efficacy may be due to an inability to sufficiently elevate intragastric pH.

Summary and Conclusions

PPI therapy should be initiated in all patients with a confirmed endoscopic diagnosis of ulcer bleeding. However,

Table 3. Effects of IV Lansoprazole and IV Pantoprazole Given as a Bolus Followed by an Infusion Over 24 Hours in Healthy *H. pylori*-Negative Volunteers

	Time Intra-gastric pH >6, %	Mean Intra-gastric pH
Lansoprazole 90 mg bolus + 6 mg/h infusion for 24 h	38.1	5.4
Lansoprazole 120 mg bolus + 6 mg/h infusion for 24 h	34.6	5.3
Pantoprazole 80 mg bolus + 8 mg/h infusion for 24 h	27.9	5.0

Reproduced with permission from Metz et al.³¹

it is not a panacea and does not replace appropriate EHT for patients whose ulcers exhibit high-risk stigmata.

Patients requiring EHT for ulcer bleeding should initially receive PPI therapy as an IV bolus and infusion. Based on the results of RCTs, the infusion should last 72 hours. However, based solely on clinical judgment, an earlier switch to oral therapy may be appropriate in some patients whose conditions rapidly stabilize. In Asia, the recommended dose would be the equivalent of an 80 mg bolus and an 8 mg/hour infusion of omeprazole.^{12,30} However, no such precise recommendation can currently be made for North America and Europe, where the efficacy of IV PPI therapy is much less clear,¹²⁻¹⁴ perhaps because similar dosage regimens are ineffective in elevating pH adequately.³¹ Further studies may need to address the effectiveness of higher doses on intra-gastric pH; if higher doses can be shown to have a more profound and consistent effect on intra-gastric pH, they would then need to be tested in clinical trials in patients with ulcer bleeding. At the present time, therefore, our best recommendation is that the dose should be at least the equivalent of an 80 mg bolus and an 8 mg/hour infusion of omeprazole.

In the US, most patients admitted to a hospital with ulcer bleeding will have low-risk endoscopic stigmata such as a clean ulcer base or a flat pigmented spot in the ulcer base.³² For those patients, oral PPI therapy is appropriate and adequate and there is no need for IV PPI therapy. The early introduction of oral PPI therapy, generally among patients with low-risk stigmata, has beneficial effects on rebleeding and the need for surgical intervention,²⁰ and is substantially cheaper than continued IV therapy.

Finally, early PPI therapy remains only one aspect of the overall management of patients with ulcer bleeding. All such patients must be checked for *H. pylori* infection. For those who test positive, a clear treatment plan should be established before hospital discharge and a posttreatment test of eradication should be scheduled. Patients' use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) must also be reviewed. If possible, aspirin

and NSAID therapy should be withdrawn. Patients who require continuing aspirin and/or NSAID treatment after recovery from the bleeding episode should be maintained indefinitely on a PPI, even if *H. pylori* infection has been eradicated.

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