Critical Review Form
Meta-analysis

Dorward S, Sreedharan A, Leontiadis GI, Howden CW, Moayyedi P, Forman D. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005415. Review. Update in: Cochrane Database Syst Rev. 2010;(7):CD005415.

Objectives: **"to assess the clinical effectiveness of PPI treatment initiated prior to endoscopy in acute upper gastrointestinal bleeding by systematic review and meta-analysis of randomised controlled trials." (p. 4)**

Methods: **A search of CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, and CINAHL was conducted up to September 2005, and then rerun in February 2006 in October 2008. Trials including participants admitted to the hospital with upper GI bleeding or who developed upper GI bleeding after admission for other reasons were eligible for inclusion. Only trials enrolling unselected patients with upper GI bleeding before the cause was ascertained by endoscopy, and in which the treatment group received either an oral or intravenous PPI, were included. The control group could receive either placebo, an H2 receptor antagonist, or no treatment. The primary outcome was all cause mortality within 30 days.**

To review authors independently checked trials and abstracts for inclusion. A third review author adjudicated in the event of discrepancies. Risk of bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions, and the articles were assessed for sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selected outcome reporting, and other potential sources of bias.

The initial search strategy identified 94 articles. 33 additional articles were identified during the update in October 2008. A total of six trials were included in the systematic review: five full peer-reviewed publications and one article published in the abstract form. All studies were randomized controlled trials with a parallel-group design. Four were conducted in Europe and two in Asia. These studies comprised a total of 2223 participants of whom 1114 were randomized to PPI and 1109 to control.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. The question of whether PPI treatment initiated prior to endoscopy in acute upper GI bleeding is important. Patients with upper GI bleeds are often critically ill and require multiple interventions. Any intervention that does not contribute to improved outcomes is superfluous and detracts from other care.
2.	Was the search for relevant studies detailed and exhaustive?	Yes. The authors searched all the relevant databases, as well as reference lists from trials selected by electronic searching, published abstracts from several important gastroenterology conferences, and several web-based resources such as clinicaltrials.gov.
3.	Were the primary studies of high methodological quality?	No. Only two trials adequately described the method of sequence generation, one trial had adequate concealment, and three trials were double-blinded. Most of the studies did not adequately describe potential sources of bias.
4.	Were the assessments of the included studies reproducible?	Yes. Risk of bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions, and the articles were assessed for sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selected outcome reporting, and other potential sources of bias.
II.	***What are the results?***	
1.	What are the overall results of the study?	• There is no statistically significant effect of PPI treatment on mortality: 4.9% for PPI treatment vs. 4.3% for control (OR 1.12, 95% CI 0.75 to 1.68; I^2 = 0%). • There was no statistically significant effect on rebleeding: 11% for PPI treatment vs. 13.1% for control (OR 0.81, 95% CI 0.62 to 1.06; I^2 = 0%). • There was no statistically significant differences in the need for surgery: 7.2% for PPI treatment vs. 7.9% for control (OR 0.90, 95% CI 0.65 to 1.25; I^2 = 0%). • There was no statistically significant effect on the need for blood transfusion: 53.2% for PPI treatment vs. 54.5% for control (OR 0.95, 95% CI 0.78 to 1.16; I^2 = 6.1%). • The use of a PPI did seem to reduce the incidence of stigmata of recent hemorrhage at index endoscopy, although there was a moderate amount of heterogeneity for this outcome: 37.2% for PPI treatment vs. 46.5% for control (OR 0.67, 95% CI 0.54 to 0.84; I^2 = 35%).

		• There was no significant difference in the incidence of blood observed in the stomach at index endoscopy, although there was a high degree of heterogeneity for this outcome: 20.6% for PPI treatment vs. 27.0% for control (OR 0.64, 95% CI 0.32 to 1.30; $I^2 = 62.9\%$). • There was no significant difference in the proportion of patients with active bleeding at index endoscopy: 11.3% for PPI treatment vs. 14.7% for control (OR 0.74, 95% CI 0.54 to 1.02; $I^2 = 0\%$). • There was a small reduction in the proportion of patients receiving endoscopic hemostatic treatment at index endoscopy: 8.6% for PPI treatment vs. 11.7% for control (OR 0.68, 95% CI 0.50 to 0.93; $I^2 = 0\%$).
2.	How precise are the results?	See above.
3.	Were the results similar from study to study?	The degree of heterogeneity was minimal for the majority of outcomes. For the outcome of stigmata of recent hemorrhage there was a moderate amount of heterogeneity, and for the outcome of blood in the stomach there was a high degree of heterogeneity.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	In this meta-analysis and systematic review, proton pump inhibitors did not seem to have any effect on patient informed outcomes. Specifically there was no reduction in mortality, rates of rebleeding, or need for surgery. While there was a reduction in the incidence of stigmata of recent hemorrhage at index endoscopy, there was no observed effect on the incidence of blood observed in the stomach.
2.	Were all patient important outcomes considered?	Yes. The authors included a wide array of outcomes, including many patient important outcomes as well as many outcomes observed at endoscopy.
3.	Are the benefits worth the costs and potential risks?	Uncertain. While there was no improvement in patient outcomes with the use of proton pump inhibitors in this meta-analysis, there also appears to be no great downside to their administration. In the event that administration of a proton pump inhibitor does not impede other important lifesaving measures, his administration may be worthwhile, with the understanding that it may not affect mortality, rebleeding rates, or need for surgery.

Limitations:

1. The authors included a wide array of studies, including those with IV and oral PPI administration, and those in whom the control treatments included placebo, mannitol, H2 receptor antagonists, and no treatment (heterogeneity).

2. The authors used primary fixed-effect models to pool data for the majority of the outcomes based on very little observed heterogeneity based on I^2 values. While there may have been little heterogeneity from a statistical standpoint, these studies differed greatly from clinical and methodological standpoints, and it may still have made more sense to use random-effects models (Fixed-effect vs. random-effects models).

3. The included studies were mostly of moderate to low quality, with variable use of blinding and allocation concealment.

Bottom Line:

In this meta-analysis and systematic review, proton pump inhibitors did not seem to have any effect on patient informed outcomes. Specifically there was no reduction in mortality, rates of rebleeding, or need for surgery. While there was a reduction in the incidence of stigmata of recent hemorrhage at index endoscopy, there was no observed effect on the incidence of blood observed in the stomach.