Critical Review Form
Therapy

Lau JY, Leung WK, Wu JC, Chan FK, Wong VW, Chiu PW, Lee VW, Lee KK, Cheung FK, Siu P, Ng EK, Sung JJ. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med. 2007 Apr 19;356(16):1631-40.

Objectives: **To evaluate the hypothesis that "that early intravenous infusion of a high-dose proton- pump inhibitor before endoscopy would have a therapeutic effect on bleeding ulcers, reduce the need for endoscopic therapy, and result in improved clinical outcomes." (p. 1632)**

Methods: **this double blind, placebo-controlled, randomized trial was conducted at the emergency department at the Prince of Wales Hospital in Hong Kong. Consecutive patients with overt signs of upper gastrointestinal (GI) bleeding were eligible. Patients with persistent shock (systolic blood pressure ≤ 90 mmHg or pulse ≥ 110 bpm despite attempted resuscitation) were excluded, as were patients who retired in 18, pregnant women, patients with an allergy to a proton pump inhibitor, and patients who were taking aspirin regularly for cardiovascular protection.**

Patients were randomly assigned to either an intravenous infusion of omeprazole (80 mg intravenous bolus followed by a continuous infusion of 8 mg per hour until endoscopy the following morning) or placebo. Identical-appearing vials of omeprazole and placebo were prepared and sealed in packages that were numbered according to a computer-generated list of random numbers in blocks of 20. After enrollment, the lowest numbered-package was opened.

Endoscopy was performed either the following morning or more urgently in patients with signs of ongoing bleeding as determined by the treating physicians. In each case the endoscopist evaluated the difficulty of the procedure on a 10-point visual analog scale. Rebleeding was considered to have occurred if there was vomiting of fresh blood, hypotensive shock with melana after stabilization, or a decrease in hemoglobin of more than 2 g/dL and decrease in the matter of more than 6% within 24 hours following a transfusion. Recurrent bleeding was confirmed on endoscopy if the ulcer was actively bleeding or if there was fresh blood in the stomach and a vessel at the ulcer base.

Patients were followed for 30 days through use of a regional computerized hospital-record system and through direct contact by a research nurse. The primary outcome was the need for endoscopic therapy during the first endoscopy. Secondary outcomes included signs of bleeding, need for urgent endoscopy, duration of hospital stay, need

for transfusion, need for emergency surgery, rates of rebleeding, and death from any cause within 30 days.

Between February 2004 and July 2005 a total of 638 patients were enrolled. 319 were randomly assigned to receive omeprazole and 319 to receive placebo. Seven patients were excluded from analysis, and two in the omeprazole group did not undergo endoscopy. The cause of bleeding found to be a peptic ulcer and 59.6% in the omeprazole and 59.9% in the placebo group.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. The study "vials were sealed in packages and numbered according to a computer-generated list of random numbers in blocks of 20, without stratification." (p. 1632)
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. The investigators used a computer-generated list of random numbers, and had the treating physician open the lowest-numbered package after each enrollment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All analyses were based on the intention-to-treat principle." (p. 1636)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, initial hemoglobin and hematocrit, initial blood pressure, coexisting disease, use of NSAIDs, use of warfarin, use of aspirin, and the incidence of peptic ulcer disease as the cause of bleeding.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. "All investigators were unaware of the group assignments." (p. 1632)

2.	Were clinicians aware of group allocation?	No. "All investigators were unaware of the group assignments." (p. 1632)
3.	Were outcome assessors aware of group allocation?	No. "All investigators were unaware of the group assignments." (p. 1632)
4.	Was follow-up complete?	No. Seven patients were excluded from analysis (5 omeprazole, 2 placebo). Three withdrew before drug administration and 4 because of a misdiagnosis of upper GI bleeding. An additional two patients in the omeprazole group did not undergo endoscopy, but were included in the final analysis.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Endoscopic treatment was required less frequently in the omeprazole group compared to the placebo group (19.1% versus 28.4%, P = 0.007; RR 0.67, 95% CI 0.51 to 0.90) • Among patients with peptic ulcer bleeding, endoscopic treatment was also required less frequently in the omeprazole compared to the placebo group (22.5% versus 36.8%, P = 0.002; RR 0.61, 95% CI 0.44 to 0.84). • Urgent endoscopy was required for seven patients in the omeprazole group and six patients in the placebo group (P = 0.79). • Hypotensive shock occurred in 18 patients in the omeprazole group and 24 patients in the placebo group (P = 0.35). • The mean number of blood product transfused was 1.54± 2.41 in the omeprazole group in 1.88± 3.44 in the placebo group (P = 0.12). • Emergency surgery was required in 1.6% of patients in the omeprazole group and 2.1% of patients in the placebo group (P = 2.1%). • Hospital length of stay was shorter in the omeprazole group (median 3 days, range 1 to 42) compared to the placebo group (median 3 days, range 1 to 54), P = 0.003. • Death occurred in 2.5% in the omeprazole group and 2.2% in the placebo group within 30 days (P = 0.78).
2.	How precise was the estimate of the treatment effect?	See above.

III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	No. This study was conducted in China, which has a significantly higher rate of H. pylori infection compared to the US. Given the differing etiologies of upper GI bleeding in Asian and North American populations, the results of this study may not apply in the US.
2.	Were all clinically important outcomes considered?	No. The authors considered many important outcomes, including mortality, recurrent bleeding, length of stay, and the need for blood transfusion. They did not consider cost, quality of life, or patient satisfaction.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. The study demonstrated no improvement in patient-important outcomes, specifically no improvement in mortality, rebleeding rates, or need for surgery. They did demonstrate a reduction in the need for endoscopic therapy, but the clinical importance of this is uncertain.

Limitations:

1. **Because of differences in the etiology of upper GI bleeding in Asia, and the significantly higher rate of H. pylori infection, it is difficult to apply the results of this study to a North American population (external validity).**

2. **Long-term aspirin users were excluded from this study, which may represent a significant portion of patients we see with upper GI bleeding.**

3. **While the authors demonstrated a reduction in the need for therapeutic maneuvers during endoscopy with the use of a PPI, they did not demonstrate any improvement in patient-important outcomes.**

Bottom Line:

This rigorous, blinded, randomized controlled trial of the use of intravenous omeprazole demonstrated a reduction in the need for therapy at the time of endoscopy, but no improvement in patient-important outcomes. Additionally, the study was conducted in Hong Kong, where a higher rate of H. pylori infection and differing etiologies of upper GI bleeding make it difficult to apply the results of this study to a North American population.