Critical Review Form
Therapy

Daneshmend TK, Hawkey CJ, Langman MJ, Logan RF, Long RG, Walt RP. Omeprazole versus placebo for acute upper gastrointestinal bleeding: randomised double blind controlled trial. BMJ. 1992 Jan 18;304(6820):143-7.

Objectives: **"To investigate the possible therapeutic role of omeprazole, a powerful proton pump inhibitor, in unselected patients presenting with upper gastrointestinal bleeding." (p. 143)**

Methods: **This randomized, double blind, placebo-controlled study was conducted at two hospitals in Nottingham, England between May 1986 and November 1989. Adult patients aged 18 years or older with upper gastrointestinal (GI) bleeding or a history of melena or hematemesis within 24 hours preceding admission were eligible for enrollment. Exclusion criteria included pregnancy, severe physical illness that precluded treatment according to the protocol (e.g. terminal illness or advanced malignancy), need for immediate surgery, "trivial bleeding," admission to the hospital for other reasons besides GI bleeding, inability to initiate treatment within 12 hours of admission, and the potential for adverse drug interactions.**

Patients were randomized to receive either omeprazole (80 mg IV initially followed 40 mg IV every 8 hours for three doses, then 40 mg PO every 12 hours for 3 days) or placebo (which consisted of IV mannitol). Endoscopists were asked to note the presence of absence of signs suggestive of rebleeding. All medical care was at the discretion of the admitting medical team.

Outcomes included death, rebleeding, operation rates, and transfusion requirements. Rebleeding was defined as "overt hematemesis; passage of fresh blood from the rectum; a fall in hemoglobin concentration of more than 20 g/l within any 24 hour period after the first 24 hours; shock in the presence of continuing melaena; or the presence of fresh blood in the stomach or duodenum, or both, at repeat endoscopy when further bleeding was suspected." (p. 143)

A total of 1154 patients were randomized. Four patients were excluded due to not being given the appropriate study treatment, and 3 more patients were excluded because the treatment given could not be identified. This left 1147 patients, of whom

578 were given omeprazole and 569 were given placebo. An additional per protocol analysis was performed after excluding 98 patients with protocol violations, with 529 patients in the placebo group and 520 in the omeprazole 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 treatments were randomized in blocks of ten.
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?	Uncertain. The authors do not provide any details regarding the method of randomization or the method of allocation. It is conceivable that randomization could have been subverted (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	No. According to the authors, "All study variables were analysed according to intention to treat." (p. 144) However, 4 patients were excluded due to not being given the appropriate study treatment, and 3 more patients were excluded because the treatment given could not be identified.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to gender, age, vital signs, initial hemoglobin level, prior history of ulcer/GI bleeding/gastric surgery, final diagnosis, and ulcer locations. The incidence of NSAID use and anticoagulation was not reported. Medical comorbidities were also not reported.
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. The study was "double blinded" and placebo controlled.
2.	Were clinicians aware of group allocation?	No. The study was "double blinded" and placebo controlled.
3.	Were outcome assessors aware of group allocation?	No. The study was "double blinded" and placebo controlled.
4.	Was follow-up complete?	Yes. Aside from those patients exclude for not receiving the appropriate treatment or in whom the treatment received was unclear, outcome data was available for all randomized patients.
II.	**What are the results (answer the**	

	questions posed below)?	
1.	How large was the treatment effect?	• There was no significant difference in mortality between the treatment and placebo groups (6.9% vs. 5.3%; RR 1.31, 95% CI 0.83-2.08†). • Rebleeding was less common in the treatment group compared to the placebo group, but this difference did not achieve statistical significance (15% vs. 18%; RR 0.84, 95% CI 0.64-1.09†). • There was no significant difference in the number of patients requiring transfusion between the treatment and placebo groups (52% vs. 53%; RR 0.97, 95% CI 0.87-1.09†). • There was no difference in the median time to discharge between the groups (5 days in the treatment group vs. 6 days in the placebo group). • Patients in the treatment group were less likely to have signs of bleeding on endoscopy than those in the placebo group (33% vs. 45%, p < 0.0001; RR 0.73, 95% CI 0.63-0.86†). • The results of the per protocol analysis were similar to those in the intention to treat analysis. † Calculated using http://www.neoweb.org.uk/Additions/compare.htm
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. There patients treated in the United Kingdom during the last 1980s (over 25 years ago). Changes in patient management and in particular therapies for acute upper GI bleed have likely changed in that time period, make it difficult to apply the results to our patient population (external

		validity). Also, while not specifically mentioned in the article, they appeared to enroll patients after hospital admission, rather than directly in the emergency department.
2.	Were all clinically important outcomes considered?	No. The authors considered the most important outcomes, including death, rebleeding rates, and need for surgery. Cost, quality of life, and patient satisfaction were not considered.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. This paper demonstrated no improvement in patient-important outcomes with the use of a proton pump inhibitor prior to endoscopy. While there was a decrease in signs of bleeding on endoscopy, this outcome has been validated as a surrogate for more important patient-centered outcomes, and requires further investigation.

Limitations:

1. **The authors do not provide any details regarding the method of randomization or the method of allocation. It is conceivable that randomization could have been subverted (allocation concealment).**

2. **The authors do not report the incidence of NSAID use or anticoagulant use for the two groups, nor do they provide details regarding medical comorbidities.**

3. **It is unlikely that we can apply the results of this study to our patients, given that it was conducted over 25 years ago in the United Kingdom on patients already admitted to the hospital (external validity).**

Bottom Line:

This large, well-done, randomized controlled, blinded study evaluated the use of IV omeprazole prior to endoscopy. There was no reduction in death, rebleeding rates, or need for surgery with the use of omeprazole. While the authors did demonstrate a reduction in the incidence of signs of bleeding on endoscopy, they correctly note that "there is no evidence yet that a reduction in endoscopic stigmata is of clinical benefit."