Critical Review Form
Therapy

Hawkey GM, Cole AT, McIntyre AS, Long RG, Hawkey CJ. Drug treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points. Gut. 2001 Sep;49(3):372-9.

Objectives: **"to evaluate whether the endoscopic finding of blood in the stomach was sufficiently predictive of clinically important outcomes to be considered a surrogate end point," and "to investigate the effect of oral doses of lansoprazole, a proton pump inhibitor, and of tranexamic acid, an inhibitor of fibrinolysis, alone and in combination on this and other endoscopic findings." (p. 373)**

Methods: **This prospective randomized, double-blind, parallel group controlled trial was conducted at two hospitals in Nottingham, England over a 16-month period. Patients with presumed upper GI bleeding were eligible for entry. Exclusion criteria included bleeding to severe that it required emergency surgery, conditions that made active treatment inappropriate (e.g. terminal disease), pregnancy, active thromboembolic disease, coagulopathy, and the use of phenytoin or other drugs with known adverse drug reactions to the trial drug. Patients later determined clinically and endoscopically not to have had an upper GI bleed were excluded from the analysis.**

Patients were randomized in blocks of 4 to receive either lansoprazole (60 mg initial dose followed by 30 mg QID), tranexamic acid (2 g initial dose followed by 1 g QID), both drugs, or placebo. Patients were treated at the discretion of the medical team, and underwent endoscopy on the morning following admission or earlier if clinical need dictated. Endoscopists rated the amount of blood in the stomach on a 5-point scale (0-4), noted whether the blood was fresh or old, and noted all stigmata of bleeding.

The primary endpoints on endoscopy were whether there was blood in the stomach (using a dichotomized cut-off on the 5-point scale of 0-1 or 2-4), and other stigmata of upper GI bleeding. Secondary endpoints included whether the blood was fresh or old and the presence of active bleeding. Clinical endpoints included the amount of blood transfused, the incidence of rebleeding, need for surgery, or death.

A total of 414 patients were randomized, of whom 379 underwent endoscopy and 316 were found to have an upper GI bleed. Of these, an additional 39 were excluded due to inclusion > 72 hours after the onset of bleeding, 9 were excluded due to > 8 hours elapsing between the 1st dose of study medication and endoscopy, and 2 were excluded due to trial data not being entered. There were 290 patients eligible for assessment of endoscopic findings, of whom 228 were managed per protocol (55

placebo, 58 lansoprazole, 57 tranexamic acid, and 58 both). The mean age of all randomized patients was 58.4 years, 39.4% were female, and 35.0% were taking NSAIDs. Endoscopy was performed a median of 19 hours after admission, and 78 were found to have blood in the stomach.

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. Patients were randomized in blocks of 4 to either placebo, lansoprazole, tranexamic acid, or both lansoprazole and tranexamic acid.
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 describe the process or method of randomization. It is possible that the process would have allowed randomization to be subverted (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	No and yes. Specifically, for endoscopic outcomes patients "subsequently assessed on the basis of clinical and endoscopic findings not to have suffered upper gastrointestinal bleeding were excluded from drug efficacy analysis." (p. 373) For clinical outcomes, patients were analyzed according to an intention to treat analysis.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Not necessarily. Patients in all 4 groups were similar with respect to age, gender, history of peptic ulcer disease, and determination of being "high risk" of GI bleeding by the admitting team. The authors provide no data regarding medical comorbidities. Patients in the tranexamic acid and both drug groups were more likely to have a history of NSAID use. Patients in the tranexamic acid group were more likely to be diagnosed with a peptic ulcer as the cause of bleeding and less likely to be found to have esophageal varices.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	

<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>1.</td><td>Were patients aware of group allocation?</td><td>No. The authors note that the study was "double blind," though do not discuss the method of blinding.</td></tr>
<tr><td>2.</td><td>Were clinicians aware of group allocation?</td><td>No. The authors note that the study was "double blind," though do not discuss the method of blinding.</td></tr>
<tr><td>3.</td><td>Were outcome assessors aware of group allocation?</td><td>Likely no. The authors do not specifically mention blinding of outcome assessors.

"Each patient was visited on the ward daily by a clinical research assistant who obtained writ- ten confirmation of their verbal consent and recorded information about them, their management, and results." (p. 373)</td></tr>
<tr><td>4.</td><td>Was follow-up complete?</td><td>Yes. For the clinical outcomes, data was available for all patients. For endoscopic outcomes, 50 patients were deemed not eligible due to timing of treatment or endoscopy, or lack of trial data, and an additional 20 were patients were not "evaluable" due to missing doses of medication, undergoing endoscopy prior to treatment administration, having prohibited drugs, or being previously enrolled in the trial.</td></tr>
<tr><td>II.</td><td>What are the results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>• The authors note that finding more than a trace of blood was associated with an odds ratio for death of 3.6 (1.3–10.3) compared with finding none or a trace, though they do not provide raw data to support this.

• The risk of finding blood in the stomach at endoscopy (score of 0 or 1) was significantly reduced by both lansoprazole and tranexamic acid, with no synergy noted between them (Table 1). In the placebo group, 53.7% had blood at endoscopy.

Table 1. Risk of blood at endoscopy by group

<table>
<tr><td>Group</td><td>% with blood at endoscopy</td><td>OR (95% CI)</td></tr>
<tr><td>Lansoprazole</td><td>25.9%</td><td>0.22 (0.07-0.63)</td></tr>
<tr><td>Tranexamic acid</td><td>33.3%</td><td>0.27 (0.09-0.81)</td></tr>
<tr><td>Both</td><td>25.9%</td><td>0.26 (0.09-0.80)</td></tr>
</table>
• There were no differences in the incidence of stigmata of recent bleeding at endoscopy between the four groups.
• There was no significant difference in the risk of</td></tr>
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		rebleeding in the treatment groups (9.7% placebo, 9.8% lansoprazole, 8.7% tranexamic acid, and 9.4% both). • There was no statistically significant difference in the risk of death between the groups (4.9% placebo, 2.0% lansoprazole, 3.9% tranexamic acid, 4.7% both; p = 0.69†). † Calculated at: http://www.socscistatistics.com/tests/chisquare2/default2.aspx
2.	How precise was the estimate of the treatment effect?	See above. This was a relatively small study with wide confidence intervals. For the primary outcome (blood at endoscopy), none of the CI's crossed one.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Uncertain. The study was performed in the late 1990s in the United Kingdom. Changes in patient management may have occurred in the interim, and differences in comorbidities and management in the UK could conceivable affect the results. Additionally, most patients at our institution given a PPI prior to endoscopy receive the drug via the intravenous route, while patients in the study were given lansoparole orally.
2.	Were all clinically important outcomes considered?	No. The authors did not consider cost, length of stay, ICU length of stay, or long-term outcomes.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. For the clinically important outcomes (death, rebleeding) there was no difference between the 4 groups. For the endoscopic finding of blood at endoscopy, the use of lansoprazole and tranexamic did reduce the risk. The authors note a correlation between the finding of blood at endoscopy and mortality, and extrapolate their results to suggest that lansoprazole and tranexamic acid should reduce therefore reduce the risk of mortality. This extrapolation and supposition may be a bit optimistic, and firm conclusions can not be drawn from these results. The dangers of using surrogate outcomes that have not been well-validated must be considered.

Limitations:

1. **Details regarding the method of allocation concealment and the method of blinding were not provided (CONSORT guidelines).**

2. **The authors used surrogate outcomes (findings on endoscopy) rather than clinically important outcomes in their primary analysis. They then extrapolate**

two sets of results to draw conclusions regarding the effect of treatment on the clinically important outcome of mortality based on multiple separate analyses of the data.

3. **The primary surrogate outcome was the amount of blood observed at endoscopy, which is both subjective and not validated.**

4. **Lansoprazole was administered orally to patients in the study, whereas patients at our institution with a possible upper GI bleed are administered a PPI via the intravenous route (external validity).**

Bottom Line:

In this randomized controlled, double blind trial, neither lansoprazole or tranexamic acid, when given orally, had an effect on mortality or on rates of rebleeding. Both drugs did reduce the incidence of finding more than trace amounts of blood on endoscopy, which was also shown in this study to potentially be associated with lower mortality. Whether these results can be extrapolated to mean that lansoprazole and tranexamic acid reduce mortality to a degree that was too small to be detected in this study still remains to be seen.