

Similar Efficacy of Proton-Pump Inhibitors vs H₂-Receptor Antagonists in Reducing Risk of Upper Gastrointestinal Bleeding or Ulcers in High-Risk Users of Low-Dose Aspirin

Aspirin has emerged as one of the most important causes of upper gastrointestinal (GI) bleeding in developed countries over the past 2 decades¹, increase use of aspirin associate with increase in gastrointestinal bleeding and peptic ulcer disease.^{2,3,4}

Co-treatment of aspirin with a proton pump inhibitor (PPI) may reduce the risk of recurrent upper GI bleeding⁵, but because of potential drug interactions⁶ (such as interaction with clopidogrel may increase risk of serious cardiovascular outcome⁷), and safety concern among long term use, clinicians are looking for H₂-receptor antagonist (H₂RA) as alternative agents.⁸

An industry-independent, multicenter double-blind randomized trial, which is published in 2017, is conducted in 8 medical sites in Hong Kong and Japan, aimed to test the hypothesis that PPI is superior to H₂RA for upper GI protection in aspirin users with a high risk of bleeding. It was conducted in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. Patients were considered eligible for inclusion if they had endoscopically confirmed ulcer healing and negative results for *H.pylori* or successful eradication of *H.pylori* and anticipated regular use of aspirin (80 mg once daily) for the duration of the trial. The exclusion criteria were a history of gastric or duodenal surgery other than patch repair, severe erosive esophagitis (Los Angeles [LA] grade C or D), gastric outlet obstruction, terminal illness, or active malignancies. Patients were permitted to take antacids to relieve dyspepsia, iron supplement, non-study PPI/H₂RA, misoprostol, sucralfate, rebamipide, and other cytoprotective drugs were prohibited during the study.⁹

After sample size calculation, 270 Patients enrolled to study assigned randomly (by using of a computer-generated list of random numbers) of them 138 patients received 20 mg of rabeprazole once daily, and 132 received famotidine 40 mg once daily for 12 months. 87% of rabeprazole group and 85% of famotidine group took at least 70% of the assigned study drugs. The rates of discontinuation, excluding patients who reached study end points, were similar in the 2 groups: 9.3% in the rabeprazole group and

11.3% in the famotidine group. The subjects in the study were evaluated every 2 months; endoscopy was repeated if they developed symptoms of upper GI bleeding or had a reduction in hemoglobin level greater than 2 g/dL and after 12 months of follow-up evaluation. The adequacy of upper GI protection was assessed by end points of recurrent upper GI bleeding and a composite of recurrent upper GI bleeding or recurrent endoscopic ulcers at month 12.⁹

The results of this study were; among a total of 24 cases with suspected GI bleeding, the committee identified 5 cases of recurrent upper GI bleeding, 1 in the rabeprazole group and 4 in the famotidine group. None of them had GI bleeding related to *H. pylori* infection. The cumulative incidence of upper GI bleeding during the 12-month study was 0.7% (95% confidence interval [CI], 0.1%–5.1%) in the rabeprazole group and 3.1% (95% CI, 1.2%–8.1%) in the famotidine group (**P = 0.16**). The composite end point of recurrent bleeding or endoscopic ulcers was reached by 9 patients receiving rabeprazole (7.9%; 95% CI, 4.2%-14.7%) and 13 patients receiving famotidine (12.4%; 95% CI, 7.4%-20.4%) (**P = 0.26**).⁹

There are 4 of 24 cases met prespecified criteria for lower GI bleeding, 2 cases of rabeprazole and 2 cases of famotidine. The cumulative incidence was 1.5% in the rabeprazole group and 1.6% in the famotidine group (**P = 0.96**). Cardio-thrombotic events occurred in 2 patients (1.5%) receiving rabeprazole and in 5 (4%) receiving famotidine (**P = 0.23**).⁹

In conclusion findings contradict the (hypothesis) only existing randomized trial and results showed that there was no significant difference in recurrent upper GI bleeding between the 2 treatment groups suggesting that famotidine may be a reasonable alternative option for aspirin users who disfavor long-term PPI therapy. Further studies are needed to understand the long-term risk of developing GI complications in patients remained on lifelong aspirin, and whether periodic endoscopies at defined time points are warranted.

References:

1. J.J. Sung, E.J. Kuipers, H.B. El-Serag Systematic review: the global incidence and prevalence of peptic ulcer disease *Aliment Pharmacol Ther*, 29 (2009), pp. 938-946.
2. Lewis JD, Bilker WB, Brensinger C, Farrar JT, Strom BL. Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s: relationship to sales of nonsteroidal anti-inflammatory drugs and acid suppression medications. *Am J Gastroenterol*. 2002 Oct;97(10):2540-9.
3. Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut*. 2011 Oct;60(10):1327-35.
4. Taha AS, Angerson WJ, Prasad R, McCloskey C, Gilmour D, Morran CG. Clinical trial: the incidence and early mortality after peptic ulcer perforation, and the use of low-dose aspirin and nonsteroidal anti-inflammatory drugs. *Aliment Pharmacol Ther*. 2008 Oct 1;28(7):878-85.
5. Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med*. 2001 Mar 29;344(13):967-73.
6. Yucel E, Sancar M, Yucel A, Okuyan B. Adverse drug reactions due to drug-drug interactions with proton pump inhibitors: assessment of systematic reviews with AMSTAR method. *Expert Opin Drug Saf*. 2016;15(2):223-36.
7. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010 Nov 11;363(20):1909-17.
8. Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. *Lancet*. 2009 Jul 11;374(9684):119-25.
9. Chan FK, Kyaw M, Tanigawa T, Higuchi K, Fujimoto K, Cheong PK, et al. Similar Efficacy of Proton-Pump Inhibitors vs H2-Receptor Antagonists in Reducing Risk of Upper Gastrointestinal Bleeding or Ulcers in High-Risk Users of Low-Dose Aspirin. *Gastroenterology*. 2017 Jan;152(1):105-110.e1.

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