

Preventing Recurrent Ulcer Bleeding in Patients on Antiplatelet Therapy: Comparison of 2 Approaches

Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;352:238–44.

Study Overview

Objective. To compare clopidogrel with aspirin plus esomeprazole for the prevention of recurrent ulcer bleeding in high-risk patients.

Design. Randomized double-blind trial with 2 active intervention groups.

Setting and participants. Adult users of low-dose (≤ 325 mg/day) aspirin who presented with upper gastrointestinal (GI) hemorrhage to a hospital in Hong Kong were eligible. Patients were required to have ulcer resolution on follow-up endoscopy performed 8 weeks prior to randomization. If present, *Helicobacter pylori* infection was eradicated. Concurrent users of nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, anticoagulants, or glucocorticoids were excluded, as were patients with prior gastric surgery, aspirin or clopidogrel allergy, erosive esophagitis, gastric-outlet obstruction, end-stage renal disease, cancer, or terminal illness.

Intervention. Patients were randomly assigned to clopidogrel 75 mg daily and twice-daily placebo or aspirin 80 mg daily plus esomeprazole 20 mg twice daily.

Main outcome measures. Recurrent ulcer bleeding, defined as hematemesis, melena, or 2-g/dL hemoglobin level drop and an ulcer or bleeding erosion seen on upper endoscopy. Lower GI bleeding was also assessed. Patients were followed for 1 year.

Main results. 320 patients (mean age, 72 years) participated. Recurrent ulcer bleeding occurred in 13 of 161 (8.6%) patients in the clopidogrel group and 1 of 159 (0.7%) in the aspirin plus esomeprazole group (absolute difference, 7.9% [95% confidence interval, 3.4–12.4]). Lower GI bleeding occurred in 4.6% of patients in each group.

Conclusion. In patients with aspirin-induced ulcer bleeding whose ulcers had healed, those treated with aspirin plus twice-daily esomeprazole had less recurrent ulcer bleeding

than patients treated with clopidogrel.

Commentary

For individuals who have had prior peptic ulcer disease while taking aspirin, resuming aspirin, even at a low dose, is associated with a high rate of recurrent ulcer complications [1]. Clopidogrel has been suggested as an alternative for patients with GI contraindications to aspirin who require antiplatelet treatment to prevent cardiovascular events [2,3]. There is some evidence that clopidogrel has less GI toxicity than aspirin. In a study of adults with atherosclerosis comparing clopidogrel with 325 mg of aspirin daily, GI hemorrhage was lower with clopidogrel. GI bleeding was reported by 2.0% of clopidogrel and 2.7% of aspirin users over a 1.9-year period [4]. However, rigorous comparisons of aspirin and clopidogrel in patients with high GI risk are lacking.

Chan et al have demonstrated that combining low-dose aspirin with high-dose proton pump inhibitors is safer than clopidogrel in high-risk patients. This study, therefore, represents an important advancement in our understanding of how to approach this common clinical problem. However, several unanswered questions still remain. Is twice daily proton pump inhibition required to offset the risk of using aspirin or would lower doses suffice? In a study by Lai et al [1], adding lansoprazole 30 mg once daily to low-dose aspirin therapy reduced the rate of recurrent ulcer bleeding in patients with treated *H. pylori* infection from 14.8% to 1.6%; however, this trial was small and as a result precise bleeding rates cannot be determined. Another remaining question is how much of the recurrent ulcer bleeding was caused by clopidogrel. Chan et al cite potential biological mechanisms by which clopidogrel could increase ulcer bleeding, but because their study did not have a true placebo group, we cannot determine how much of the recurrence was attributable to clopidogrel and how much would have occurred without antiplatelet therapy.

Applications for Clinical Practice

For patients requiring chronic antiplatelet therapy who have recovered from ulcer bleeding occurring on aspirin, clinicians should prescribe a proton pump inhibitor along with

low-dose aspirin. Substituting clopidogrel alone instead of aspirin and a proton pump inhibitor carries a much higher risk of recurrent GI hemorrhage.

—Review by Stephen D. Persell, MD, MPH

References

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