Aspirin plus esomeprazole reduced recurrent ulcer bleeding more than clopidogrel in high-risk patients

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.

Clinical impact ratings: GIM/FP/GP ★★★★★★★ Hospitalists ★★★★★★★ Cardiology ★★★★★★★ Gastroenterology ★★★★★★☆

QUESTION

In patients with previous aspirin-induced ulcer bleeding, is clopidogrel noninferior to low-dose aspirin plus esomeprazole for preventing recurrent ulcer bleeding?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, outcome assessors, {data collectors, data analysis, and data safety and monitoring committee}†).*

Follow-up period: 12 months.

Setting: Prince of Wales Hospital, Hong Kong.

Patients: 320 patients (mean age 72 y, 66% men) who had a history of ulcer bleeding and endoscopically confirmed ulcer healing and had either negative test results for *Helicobacter pylori* or successful eradication of *H. pylori* and regular antiplatelet therapy during the trial. Exclusion criteria were concomitant use of nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, anticoagulant agents, or corticosteroids; history of gastric surgery (except patch repair); allergy to aspirin or clopidogrel; presence of erosive esophagitis, gastric-outlet obstruction, terminal illness, or cancer; or requirement for dialysis.

Intervention: Clopidogrel, 75 mg, plus placebo (n = 161), or aspirin, 80 mg, plus esomeprazole, 20 mg (n = 159), twice daily for 12 months.

Outcomes: Recurrent ulcer bleeding. Secondary outcomes were lower gastrointestinal bleeding and adverse effects.

Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

More patients in the clopidogrel group than in the aspirin-plus-esomeprazole group had recurrent ulcer bleeding (Table). The groups did not differ for lower gastrointestinal bleeding (Table). Adverse event rates for clopidogrel and aspirin plus esomeprazole for extragastrointestinal bleeding were 1.9% and 0%, respectively; for dyspepsia, 7.5% and 2.5%, respectively; for recurrent ischemic events, 5.6% and 6.9%, respectively; and 1.9% for both groups for allergy.

CONCLUSION

In patients with previous aspirin-induced ulcer bleeding, the addition of esomeprazole to aspirin was better than changing to clopidogrel for decreasing recurrent ulcer bleeding.

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*See Glossary.

†Information provided by author.

Clopidogrel vs aspirin plus esomeprazole for patients with previous aspirin-induced bleeding‡

Outcomes at 12 mo	Clopidogrel	Aspirin + esomeprazole	Difference (95% CI)
Cumulative incidence of recurrent ulcer bleeding	8.6%	0.7%	7.9% (3.4 to 12.4)
Cumulative incidence of lower gastrointestinal bleeding	4.6%	4.6%	No difference

‡CI defined in Glossary.

COMMENTARY

Use of antiplatelet agents (e.g., low-dose aspirin or clopidogrel) for prevention of cardiovascular events is widespread. Low-dose aspirin is ulcerogenic, so it cannot be used alone in patients at high risk for ulcer bleeding. Alternative approaches in such patients include adding a proton-pump inhibitor (PPI) to aspirin (1, 2) or using a nonaspirin agent (clopidogrel). The study by Chan and colleagues is the first to directly compare these 2 approaches in patients who have had 1 bleeding episode from an aspirin-associated ulcer. Somewhat surprisingly, the results of this study clearly show that the second option is not acceptable. Although clopidogrel had been believed to be nonulcerogenic, it was associated with a substantially higher incidence of recurrent ulcer bleeding than was low-dose aspirin plus a PPI (esomeprazole). Because the incidence of adverse events prevented by antiplatelet therapy was similar in the 2 groups, the recommendation to switch patients with a previous aspirin-associated bleeding ulcer to clopidogrel alone is not justified. In patients who truly cannot take aspirin, clopidogrel could be used with a concomitant PPI, although this has not yet been proven to be safe.

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References

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