

Celecoxib combined with esomeprazole prevented recurrent ulcer bleeding in patients with previous NSAID-induced ulcer bleeding

Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet*. 2007;369:1621-6.

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

QUESTION

In patients with previous nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer bleeding, is combination treatment with celecoxib and esomeprazole more effective than celecoxib alone for preventing recurrent ulcer bleeding?

METHODS

Design: Randomized controlled trial.

Allocation: Concealed.*

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

Follow-up period: Median 13 months (range 0.4 to 13 mo).

Setting: Prince of Wales Hospital, Hong Kong, China.

Patients: 273 patients (mean age 71 y, 52% women) who were taking nonselective NSAIDs for arthritis and presented to the hospital with upper gastrointestinal (GI) bleeding. All patients discontinued NSAIDs and took proton-pump inhibitors (PPIs) for 8 weeks. Patients were enrolled after their ulcers had healed by endoscopy if they tested negative for *Helicobacter pylori* infection and required regular use of NSAIDs during the trial. Exclusion criteria included concomitant use of low-dose aspirin (ASA), anticoagulants, or corticosteroids before index bleed-

ing; previous gastric or duodenal surgery except patch repair; allergy to celecoxib; or erosive esophagitis, gastric outlet obstruction, terminal illness, cancer, or renal failure (serum creatinine > 200 μmol/L). After the cardiovascular hazards of cyclooxygenase-2 inhibitors became known, patients were allowed to take prophylactic low-dose ASA during the study period.

Intervention: Celecoxib, 200 mg, plus esomeprazole, 20 mg ($n = 137$), or celecoxib alone ($n = 136$), twice daily for 12 months.

Outcomes: Recurrent ulcer bleeding (hematemesis or melena with ulcers or bleeding erosions confirmed by endoscopy, or decrease in hemoglobin ≥ 20 g/L with ulcers or erosions), global assessment of disease activity, arthritis pain, and adverse events.

Patient follow-up: 84% (intention-to-treat analysis).

MAIN RESULTS

At a median 13 months, the combination-treatment group had a lower cumulative inci-

dence of recurrent ulcer bleeding than did the celecoxib-alone group (Table). Groups did not differ for global assessment of disease activity, arthritis pain, or incidence of adverse events.

CONCLUSION

Combination treatment with celecoxib and esomeprazole was more effective than celecoxib alone for preventing recurrent ulcer bleeding in patients with previous nonsteroidal antiinflammatory drug-induced ulcer bleeding.

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*See Glossary.

†Information provided by author.

Celecoxib plus esomeprazole vs celecoxib alone in patients with previous NSAID-induced ulcer bleeding at median 13 months†

Outcome	Celecoxib + esomeprazole	Celecoxib alone	RRR (95% CI)	NNT (CI)
Recurrent ulcer bleeding	0%	8.8%	100% (69 to 100)	12 (7 to 20)

‡NSAID = nonsteroidal antiinflammatory drug; other abbreviations defined in Glossary. RRR, NNT, and CI calculated from data in article.

COMMENTARY

The highest incidence of GI complications associated with NSAID use occurs in patients who have had prior GI bleeding or prior complicated or uncomplicated ulcer; are > 75 years of age; and those taking concomitant clopidogrel, warfarin, steroids, or other NSAIDs. Combining ASA with a PPI reduces bleeding compared with placebo (1) or clopidogrel alone (0.7% vs 8.6%, $P = 0.001$) (2). However, neither combining diclofenac with omeprazole nor using celecoxib alone is sufficiently effective for preventing recurrent bleeding from NSAIDs (4.9% vs 6.4%, $P = 0.6$) (3).

The study by Chan and colleagues reinforces that switching to coxib monotherapy does not adequately prevent GI injury in high-risk patients, including those on concomitant ASA. However, the absence of recurrent bleeding in patients randomized to receive coxibs plus PPIs (even among the 15% of patients on ASA) makes this the optimal approach to prevent recurrent bleeding in patients who bleed while taking nonselective NSAIDs. Results from the subgroup taking ASA must be interpreted with caution because of small numbers.

PPI dosage is problematic. Taking PPIs once daily reduces ASA bleeds and uncomplicated NSAID ulcers but may not be sufficient to

prevent bleeding. Taking PPIs twice daily affects compliance and cost. In balancing cardiovascular and GI risks, data support taking PPIs plus celecoxib twice daily to prevent bleeding in persons at high risk, substituting celecoxib with naproxen if cardiovascular risk is unacceptable, and using PPIs once daily for patients taking ASA alone. Older patients at risk who need ASA or NSAIDs plus clopidogrel or warfarin should take PPIs twice daily.

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References

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