

# TOP Journal Club

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## Aspirin plus PPI safer than clopidogrel if there is history of GI bleeding

Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005; 352:238-244.

### Clinical Question

What is the best antithrombotic for patients with a history of upper gastrointestinal bleeding?

### Bottom Line

For patients with a history of bleeding peptic ulcer, the combination of aspirin and a proton pump inhibitor (PPI) twice a day was safer than clopidogrel in terms of bleeding side effects. Although esomeprazole (Nexium) was used in this study, generic omeprazole 20 mg give twice a day provides nearly the same degree of acid suppression at a much lower cost. This study calls into question the overall safety of clopidogrel (Plavix), which has been claimed to not significantly increase the risk of bleeding. (LOE=1b)

### Synopsis

Clopidogrel has been recommended by the American College of Cardiology as the preferred drug for patients who require an antithrombotic agent to prevent heart disease but who also have a history of bleeding peptic ulcer. This study compared clopidogrel with the combination of aspirin and esomeprazole in this setting. Patients with a source of upper gastrointestinal bleeding (52% gastric ulcer, 34% duodenal ulcer, 8% both, 6% other erosions) who had healing confirmed by endoscopy were randomized to clopidogrel 75 mg daily plus esomeprazole placebo twice daily or aspirin 80 mg daily plus esomeprazole 20 mg twice daily. Groups were fairly well balanced at the outset, allocation was concealed, and

analysis was by intention to treat.

Patients were treated for 12 months. The primary outcome (hematemesis, melena, or a decrease in hemoglobin of at least 2 g/dL accompanied by endoscopic evidence of ulcer or erosion) was seen in 8.6% of the clopidogrel group and 0.7% of the aspirin plus esomeprazole group (P=.001; number needed to treat=13).

Three patients in the clopidogrel group had severe bleeding complications not related to the gastrointestinal tract, including 2 intraventricular hemorrhages, 1 of which was fatal; there were no bleeding complications in the aspirin group. There were more deaths in the clopidogrel group (8 vs 4), but this difference was not statistically significant. There was no difference between groups in the likelihood of adverse cardiovascular events (9 vs 11).

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## Adding aspirin to clopidogrel after TIA and ischemic stroke: Benefits do not match risks

Antiplatelet therapy is effective for reducing the risk of recurrent stroke and other serious vascular events in patients with recent TIA and ischemic stroke. Effective antiplatelet agents include aspirin, ticlopidine, clopidogrel, dipyridamole, and the combination of aspirin and dipyridamole. The combination of aspirin and clopidogrel is more effective than aspirin in patients with acute coronary syndrome but is more hazardous than clopidogrel alone in patients with recent TIA and ischemic stroke. Further trials are needed to determine whether the combination of aspirin and clopidogrel may have a role immediately after TIA and ischemic stroke in patients with symptomatic large artery atherothromboembolism and continued for approximately 3 months before switching to less hazardous antiplatelet regimens.

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## Clonidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding

**Background** Concurrent therapy with a proton-pump inhibitor is a standard treatment for patients receiving aspirin who are at risk for ulcer. Current U.S. guidelines also recommend clonidogrel for patients who have major gastrointestinal intolerance of aspirin. We compared clonidogrel with aspirin plus esomeprazole for the prevention of recurrent bleeding from ulcers in high-risk patients.

**Methods** We studied patients who took aspirin to prevent vascular diseases and who presented with ulcer bleeding. After the ulcers had healed, we randomly assigned patients who were negative for *Helicobacter pylori* to receive either 75 mg of clonidogrel daily plus esomeprazole placebo twice daily or 80 mg of aspirin daily plus 20 mg of esomeprazole twice daily for 12 months. The end point was recurrent ulcer bleeding.

**Results** We enrolled 320 patients (161 patients assigned to receive clonidogrel and 159 to receive aspirin plus esomeprazole). Recurrent ulcer bleeding occurred in 13 patients receiving clonidogrel and 1 receiving aspirin plus esomeprazole. The cumulative incidence of recurrent bleeding during the 12-month period was 8.6 percent (95 percent confidence interval, 4.1 to 13.1 percent) among patients who received clonidogrel and 0.7 percent (95 percent confidence interval, 0 to 2.0 percent) among those who received aspirin plus esomeprazole (difference, 7.9 percentage points; 95 percent confidence interval for the difference, 3.4 to 12.4;  $P=0.001$ ).

**Conclusions** Among patients with a history of aspirin-induced ulcer bleeding whose ulcers had healed before they received the study treatment, aspirin plus esomeprazole was superior to clonidogrel in the prevention of recurrent ulcer bleeding. Our finding does not support the current recommendation that patients with

major gastrointestinal intolerance of aspirin be given clonidogrel.

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## Comparative inhibitory effects of cilostazol and ticlopidine on subacute stent thrombosis and platelet function in acute myocardial infarction patients with percutaneous coronary intervention.

We compared the effects of ticlopidine and cilostazol on the prevention of subacute stent thrombosis (SAT) in acute myocardial infarction (AMI) patients with stenting. We also analyzed the cause of the difference by measuring platelet aggregation activity. Consecutive patients who underwent successful stenting for AMI between March 2001 and March 2004 were analyzed. In addition to aspirin (100 mg/day), cilostazol (200 mg/day) was administered to 99 cases between March 2001 and May 2002 and ticlopidine (200 mg/day) was administered to 85 cases between June 2002 and February 2004. The incidence of SAT within four weeks after stenting was analyzed. Thirty-eight AMI patients were randomized and their platelet aggregation activity was measured using a laser-scattered aggregometer (18 cases in the cilostazol group and 20 cases in the ticlopidine group). SAT did not occur in the ticlopidine group while 5 cases (5.1%) of SAT occurred in the cilostazol group ( $P < 0.05$ ). The inhibitory activity of cilostazol for ADP-induced platelet aggregation was lower than that of ticlopidine ( $P < 0.05$ ). Cilostazol with aspirin after stenting in AMI patients showed more frequent SAT than ticlopidine with aspirin. One of the causes for this difference was speculated to be the weaker inhibitory activity of cilostazol for ADP-induced platelet aggregation.

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