Case presentation: A 59-year-old man with a history of hypertension, dyslipidemia, and smoking was hospitalized with acute coronary syndrome requiring emergency percutaneous coronary intervention with 4 drug-eluting stents. His discharge medications included dual antiplatelet therapy with aspirin 325 mg/d and clopidogrel 75 mg/d. Three weeks after discharge, he returned to the Emergency Department with bloody stools and a hematocrit of 23% (previously 36%) and required 3 units of packed red blood cells. Endoscopy showed a bleeding duodenal ulcer with adherent clot (Figure).

Background
We prescribe dual antiplatelet therapy with aspirin and clopidogrel to prevent and treat cardiovascular, cerebrovascular, and peripheral arterial disease. According to American Heart Association statistics, 700,000 patients had stroke, 13 million had coronary artery disease, and 8 to 12 million suffered from peripheral arterial disease in 2002. Each year, 1.2 million patients in the United States receive dual antiplatelet therapy for various vascular conditions such as coronary artery disease, transient ischemic attack, thrombotic stroke, and peripheral vascular disease probably exceeds several million.

The use of aspirin compared with placebo reduces the risk of myocardial infarction, stroke, or death from vascular causes by ~25%. In the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, administration of clopidogrel decreased the relative risk of vascular events by 8.7% compared with aspirin. The addition of clopidogrel to aspirin in patients with acute coronary syndrome reduces the risk of reinfarction, stroke, and death by 20% compared with aspirin alone.

The net benefit from using dual antiplatelet therapy in high-risk vascular disease patients comes at the cost of increased gastrointestinal (GI) complications. Major complications include gastroduodenal ulcerations that can lead to GI hemorrhage, perforation, and death. Minor complications include dyspepsia, pill esophagitis, subepithelial hemorrhages, erosions, and ulcerations in the stomach and duodenum. Patients at especially high risk for GI complications while on antiplatelet therapy are the elderly; those with a history of gastroduodenal ulcers, gastroesophageal reflux disease, esophagitis, untreated Helicobacter pylori infection, intestinal polyps, or cancer; and those using concomitant anticoagulants, steroids, or nonsteroidal anti-inflammatory drugs.

Risk of GI Complications With Aspirin
The suppression of gastroduodenal mucosal prostaglandin synthesis is one of the important mechanisms of mucosal damage by aspirin. Serious GI ulcer complications are 2- to 4-fold more common in patients who take 75 to 300 mg/d of aspirin compared with controls. Aspirin doses as low as 10 mg/d can significantly decrease the gastric mucosal prostaglandin level and cause gastric erosions. During a 4-year period in the United Kingdom Transient Ischemic Attack study, GI complications in patients taking aspirin ranged from mild dyspepsia (31%) to life-threatening bleeding and perforation (3%).

While examining the relationship between aspirin intake and hospitalization with peptic ulcer bleeding, Weil et al found that all doses of aspirin are associated with an increased risk of GI bleeding. The risk of GI bleeding was dose related: odds ratio 2.3 for 75 mg/d, 3.2 for 150 mg/d, and 3.9 for 300 mg/d. The risk of upper GI bleeding for plain, enteric-coated, or buff-
ered aspirin did not differ. Long-term aspirin therapy, even at a low dose (50 to 162.5 mg/d), may cause overt GI bleeding.

Risk of GI Complications With Clopidogrel

It is unclear how clopidogrel causes GI erosions or ulcerations. Clopidogrel has no effect on the cyclooxygenase pathway and therefore acts independently of aspirin. In a retrospective analysis, the frequency of GI bleeding in a high-risk population with prior peptic ulcer disease was 12%.

Risk of GI Complications With Dual Antiplatelet Therapy

The risk of overt GI bleeding with dual antiplatelet therapy can be as high as 1.3% within the first 30 days of therapy. In the Clopidogrel for Unstable Angina to Prevent Recurrent Events (CURE) study, Peters et al showed that the risk of bleeding increases with an increasing dose of aspirin with or without clopidogrel. The dose of clopidogrel remained fixed at 75 mg/d. At the highest dose of aspirin (≥200 mg) given with placebo, bleeding was higher (3.7%) than the risk of GI bleeding with the combination of clopidogrel and aspirin in the lowest-dose (≤100 mg) group (3.0%).

Efficacy of Dual Antiplatelet Therapy

Drug-eluting stents have become the standard of care for percutaneous coronary intervention to reduce the risk of in-stent restenosis. However, in-stent thrombosis, a catastrophic and potentially fatal complication, may occur more often with drug-eluting than bare metal stents. The strongest predictor of stent thrombosis is discontinuation of antiplatelet therapy, exceeding other independent predictors such as renal failure, bifurcation lesions, diabetes, and low ejection fraction. Hence, after percutaneous coronary intervention with drug-eluting stents, aspirin is prescribed lifelong and clopidogrel is prescribed for at least 3 months. However, McFadden et al reported 4 cases of late stent thrombosis occurring as late as 442 days after implantation of drug-eluting stents and resulting in myocardial infarction when antiplatelet therapy was discontinued. Late thrombosis seen with drug-eluting stents is attributed to delayed vascular healing and delayed re-endothelialization, rendering the stent prothrombotic. Some cardiologists continue patients on antiplatelet therapy indefinitely if no adverse bleeding events are encountered.

Aspirin and clopidogrel “resistance” has been increasingly identified with the availability of point-of-care platelet aggregation tests. Many patients on aspirin and clopidogrel therapy do not achieve the desired level of platelet inhibition. One way to overcome aspirin and clopidogrel resistance is to use higher loading and maintenance doses.

The inhibition of platelet aggregation by clopidogrel is dose dependent. A higher loading dose of clopidogrel is now being used more often than the conventional 300-mg dose because of more rapid and higher levels of platelet inhibition. Patti et al reported that a 600-mg loading dose was safe and more effective in reducing periprocedural infarction than a 300-mg loading dose.

Monitoring and Diagnosis of GI Complications

Several methods can be used to monitor and diagnose occult and overt GI complications of dual antiplatelet therapy. The tests range from least specific (fecal occult blood test) to the gold standard of traditional endoscopy. Patients can also be monitored for clinical symptoms such as dyspepsia or bloating by using a symptom diary or a validated scoring system similar to the Gastrointestinal Symptoms Rating Scale questionnaire (Table).

A noninvasive imaging test that does not require sedation to diagnose occult GI complications is the PillCam ESO capsule endoscopy (Given Imaging, Haifa, Israel).
Gastrointestinal Symptom Rating Scale: A Validated Rating Scale of GI Symptoms in Patients With Peptic Ulcer Disease

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain syndrome</td>
<td>Patients are asked to rate subjective symptoms associated with each syndrome from 0 to 3 on the basis of severity, frequency, duration, and need for antacids for relief of symptoms. The sum of the scores for all items for abdominal pain syndrome and dyspeptic syndrome is the GSRS total score for peptic ulcer disease. The higher the overall score, the more severe are the symptoms.</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td></td>
</tr>
<tr>
<td>Colicky pain</td>
<td></td>
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<tr>
<td>Dull pain</td>
<td></td>
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<tr>
<td>Undefined pain</td>
<td></td>
</tr>
<tr>
<td>Dyspeptic syndrome</td>
<td></td>
</tr>
<tr>
<td>Epigastric pain</td>
<td></td>
</tr>
<tr>
<td>Heartburn</td>
<td></td>
</tr>
<tr>
<td>Acid regurgitation</td>
<td></td>
</tr>
<tr>
<td>Sucking sensation in the epigastrium</td>
<td></td>
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<tr>
<td>Nausea and vomiting</td>
<td></td>
</tr>
</tbody>
</table>

GSRS indicates Gastrointestinal Symptom Rating Scale.

*D0 = No symptoms; 1 = occasional episode for short duration; 2 = frequent and prolonged episodes; 3 = severe continuous episodes. The minimum score is 0, and a maximum score is 27 for peptic ulcer disease.

Is GI Prophylaxis Needed for Dual Antiplatelet Therapy?

Patients on dual antiplatelet therapy can develop both upper and lower GI bleeding. GI hemorrhage is associated with an increased mortality rate, a greater need for surgery, blood transfusions, a prolonged length of hospital stay, and increased overall healthcare costs. Although upper GI bleeding can be prevented with appropriate prophylaxis, there is no effective prophylaxis for lower GI bleeding.

Prophylactic acid-suppressive therapy is beneficial in the prevention of upper GI complications. Two major classes of protective agents are (1) H₂ antagonists and (2) proton pump inhibitors (PPIs).

H₂ antagonists reversibly block H₂ receptors on the basolateral membrane of gastric parietal cells.¹⁷ Until the early 1990s, H₂ antagonists were the mainstay of pharmacotherapy for the prevention and management of upper GI bleeding. Between 1984 and 2000, 32 randomized controlled trials compared H₂ antagonists with placebo.¹⁸ Agents evaluated in these studies included cimetidine, ranitidine, and famotidine. Many were limited by a small sample size and unsatisfactory study design.

Factors limiting the utility of H₂ antagonists include the development of tachyphylaxis, the need for dosage adjustment in renal insufficiency, and side effects such as thrombocytopenia and mental status abnormalities.

The introduction of PPIs has led to a safer and more effective strategy in the prevention and management of GI ulceration.¹⁷ PPIs irreversibly inhibit hydrogen ion pumps in gastric parietal cells. PPIs block the final step of acid production, negate stimulation of gastric secretion, and lead to prolonged acid suppression.

Yeomans et al¹⁹ showed that omeprazole, a PPI, is more effective than H₂ receptor antagonists in suppressing gastric acid, preventing ulcers, and healing ulcers that are related to chronic use of nonsteroidal anti-inflammatory drugs such as aspirin.

Chan et al²⁰ randomized 320 patients with vascular disease who had previous GI bleeding while taking aspirin to clopidogrel alone versus aspirin plus esomeprazole. The cumulative incidence of recurrent ulcer bleeding over a 12-month period in this study was 8.6% in patients who received clopidogrel and 0.7% in patients who received aspirin and esomeprazole.

Is it justifiable to start all patients requiring dual antiplatelet therapy on prophylactic acid-suppressive therapy? The risk of an adverse GI event in antiplatelet users depends on the patient’s baseline risk, added risk associated with the dose and duration of aspirin and clopidogrel therapy, and protection conferred by cotherapy with acid-suppressive agents. Physicians who prescribe antiplatelet therapy should be aware of an individual patient’s risk of GI complications. During every office visit, physicians should ask about new or worsening GI symptoms. Initiating prophylactic acid-suppressive therapy may be reasonable in high-risk patients for the duration of antiplatelet therapy; however, clinical trials are urgently needed to confirm or refute this hypothesis.

Patients who undergo PCI for acute coronary syndrome are usually discharged on 5 classes of medications: aspirin, clopidogrel, a β-blocker, an angiotensin-converting enzyme inhibitor, and a statin. These medications reduced the morbidity and mortality rates in large-scale randomized controlled trials. Before subjecting PCI patients to a routine prophylactic acid-suppressive therapy as the sixth standard medication, we need large-scale trials to assess cost-effectiveness and to determine whether the benefit outweighs the risks of polypharmacy.

Case

Our patient represents a frequent clinical scenario that physicians often encounter in their practice. Given his multiple risk factors and the recent implantation of 4 drug-eluting stents, he should receive indefinite antiplatelet therapy. Although antiplatelet

agents were stopped for 1 day during the upper GI bleeding, they were resumed immediately when active bleeding stopped. He was discharged home on a PPI along with antiplatelet therapy.

References

Gastrointestinal Complications of Dual Antiplatelet Therapy
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