Gastrointestinal Complications of Dual Antiplatelet Therapy

Neelima G. Vallurupalli and Samuel Z. Goldhaber

Circulation 2006;113;e655-e658
DOI: 10.1161/CIRCULATIONAHA.105.590612
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Gastrointestinal Complications of Dual Antiplatelet Therapy

Neelima G. Vallurupalli, MD; Samuel Z. Goldhaber, MD

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 U 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 with aspirin and clopidogrel after percutaneous coronary intervention with drug-eluting stents. The number of patients in the United States who 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%.[1] 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.[2] 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.[3]

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.

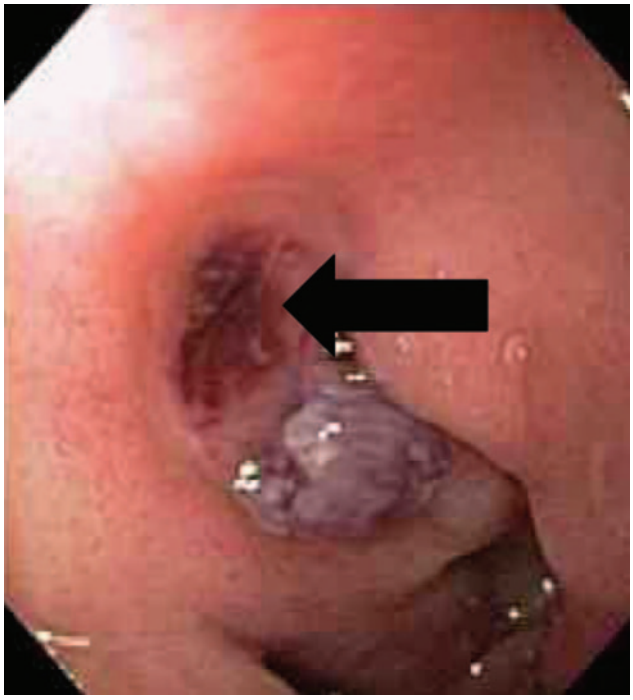
Risk of GI Complications With Aspirin

The suppression of gastroduodenal mucosal prostaglandin synthesis is one of the important mechanisms of mucosal damage by aspirin.[4] 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.[5,6] Aspirin doses as low as 10 mg/d can significantly decrease the gastric mucosal prostaglandin level and cause gastric erosions.[7] 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%).[8]

While examining the relationship between aspirin intake and hospitalization with peptic ulcer bleeding, Weil et al[5] 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-

From the Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.
Correspondence to Samuel Z. Goldhaber, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail sgoldhaber@partners.org
(*Circulation.* 2006;113:e655-e658.)

Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.105.590612



Endoscopic image of bleeding duodenal ulcer with clot on top. This image was taken in a patient with a history similar to that of our patient. Arrow points to the base of duodenal ulcer with active bleeding. Picture contributed by Sarathchandra Reddy, MD, and Edwin Chun Ouyang, MD, PhD, Division of Gastroenterology, Brigham and Women's Hospital, Boston, Mass.

ered aspirin did not differ.[9] Long-term aspirin therapy, even at a low dose (50 to 162.5 mg/d), may cause overt GI bleeding.[10]

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%.[11]

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.[3] In the Clopidogrel for Unstable Angina to Prevent Recurrent Events (CURE) study, Peters et al[12] showed that the risk of bleeding increases with 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.[13] Hence, after percutaneous coronary intervention with drug-eluting stents, aspirin is prescribed lifelong and clopidogrel is prescribed for at least 3 months.[14] However, McFadden et al[15] 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[16] 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 Imag-

Gastrointestinal Symptom Rating Scale: A Validated Rating Scale of GI Symptoms in Patients With Peptic Ulcer Disease

Abdominal pain syndrome Epigastric pain Colicky pain Dull pain Undefined pain	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.
Dyspeptic syndrome Epigastric pain Heartburn Acid regurgitation Sucking sensation in the epigastrium Nausea and vomiting	

GSRS indicates Gastrointestinal Symptom Rating Scale.

*0=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.

ing, Inc, Norcross, Ga). The disposable, ingestible PillCam ESO endoscope is an 11×26-mm capsule. It acquires video images from both ends of the device during passage through the esophagus. The capsule transmits the acquired images via a digital radiofrequency communication channel to an external data recorder unit. On completion of the examination, the accumulated data are processed with image reconstruction and are interpreted by a GI specialist. The PillCam is excreted in the feces and does not need to be retrieved.

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) H_2 antagonists and (2) proton pump inhibitors (PPIs).

H_2 antagonists reversibly block H_2 receptors on the basolateral membrane of gastric parietal cells.[17] Until the early 1990s, H_2 antagonists were the mainstay of pharmacotherapy for the prevention and management of upper GI bleeding. Between 1984 and 2000, 32 randomized controlled trials compared H_2 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 H_2 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 al[19] showed that omeprazole, a PPI, is more effective than H_2 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 al[20] 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

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81–106.
2. CAPRIE Steering Committee. A randomized, blinded, trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). *Lancet*. 1996; 348:1329–1339.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.
4. Cohen MM, MacDonald WC. Mechanism of aspirin injury to human gastroduodenal mucosa. *Prostaglandins Leukot Med*. 1982; 9:241–255.
5. Weil J, Colin-Jones D, Langman M, Lawson D, Logan R, Murphy M, Rawlins M, Vessey M, Wainwright P. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ*. 1995;310: 827–830.
6. Sorensen HT, Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, Olsen JH. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol*. 2000;95: 2218–2224.
7. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology*. 1999;117:17–25.
8. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom Transient Ischaemic Attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54: 1044–1054.
9. Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet*. 1996;348:1413–1416.
10. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ*. 2000;321:1183–1187.
11. Ng FH, Wong SY, Chang CM, Chen WH, Kng C, Lanas AI, Wong BC. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. *Aliment Pharmacol Ther*. 2003;18:443–449.
12. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study. *Circulation*. 2003;108:1682–1687.
13. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126–2130.
14. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110:e82–e292.
15. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364:1519–1521.
16. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation*. 2005;111:2099–2106.
17. Rivkin K, Lyakhovetskiy A. Treatment of nonvariceal upper gastrointestinal bleeding. *Am J Health Syst Pharm*. 2005;62:1159–1170.
18. Levine JE, Leontiadis GI, Sharma VK, Howden CW. Meta-analysis: the efficacy of intravenous H2-receptor antagonists in bleeding peptic ulcer. *Aliment Pharmacol Ther*. 2002;16:1137–1142.
19. Yeomans ND, Tulassay Z, Juhasz L, Racz I, Howard JM, van Rensburg CJ, Swannell AJ, Hawkey CJ. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs: Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) Study Group. *N Engl J Med*. 1998;338:719–726.
20. Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, Hui AJ, Wu JC, Leung WK, Lee VW, Lee KK, Lee YT, Lau JY, To KF, Chan HL, Chung SC, Sung JJ. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med*. 2005;352:238–244.