Antiplatelet and Anticoagulant Therapy in Patients With Gastrointestinal Bleeding

An 86-Year-Old Woman With Peptic Ulcer Disease

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Bleeding in the upper gastrointestinal tract is a common medical problem, with an incidence of 48 to 160 cases per 1000 adults per year and a mortality rate of 5% to 14%. The risk of gastrointestinal bleeding is increased with the use of antiplatelet medications including aspirin and clopidogrel, as well as warfarin or a combination of these medications. The recurrence rate for bleeding in patients who continue to take aspirin after an episode of peptic ulcer disease–related bleeding can reach up to 300 cases per 1000 person-years and varies by age, sex, and the use of nonsteroidal anti-inflammatory medications. Using the case of Ms S, an 86-year-old woman who presented to the emergency department with an episode of nonvariceal upper gastrointestinal tract bleeding, we address the management of patients who are receiving antiplatelet or anticoagulation therapy who present with gastrointestinal bleeding, including when to restart antiplatelet or anticoagulation therapy, interventions to reduce the risk of bleeding recurrence, and the potential for drug interactions between clopidogrel and proton pump inhibitors.

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An 86-year-old woman, Ms S, is physically active, engages in numerous social activities, and attends a class in political science. She presented to the emergency department after falling in her bathroom. Ms S had been feeling epigastric discomfort that was difficult to describe; it was episodic in nature and mild in intensity and there were no provocative or palliative factors. A few hours prior to her fall she had been feeling lightheaded with some weakness. When standing up, Ms S felt dizzy and fell to the ground but did not lose consciousness. She was transported to the hospital by ambulance.

In 2008, Ms S developed atrial fibrillation for which she was treated with warfarin. Her medical history includes a hysterectomy for endometrial cancer in 1986 followed by radiation therapy, a lumpectomy for breast cancer in 1998 with radiation therapy, hypertension, and benign positional vertigo. Her current medications included low-dose aspirin, 81 mg orally once daily; extended-release diltiazem, 120 mg orally once daily; valsartan, 80 mg orally once daily; vitamin D, 10 000 IU orally once daily; and warfarin, 7.5 mg orally once daily. Both of her parents had gastric ulcers.

In the emergency department, she was found to be diaphoretic, with a pulse of 103/min and regular and a blood pressure of 108/68 mm Hg. No orthostatic measurements were obtained on presentation. Her abdominal examination revealed no abnormalities but her rectal examination revealed melena. Her electrocardiogram revealed normal sinus rhythm with a heart rate of 102/min.

Ms S had 2 intravenous accesses established and she received crystalloids and was observed in a monitored setting. Her laboratory tests revealed a hemoglobin level of 7.6 g/dL (76 g/L) (compared with 13.7 g/dL [137 g/L] a month prior to her presentation), a white blood cell count of 9000/μL, and a platelet count of 151×10^3/μL. Her international normalized ratio (INR) was 3 and her urea level was 59 mg/dL (21 mmol/L); electrolyte, creatinine, and liver enzyme levels were otherwise normal.

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Table 1. Representative Measures of Risk Factors Associated With Upper Gastrointestinal Tract Events While Receiving Aspirin or Clopidogrel

Risk Factors	Effect (95% CI)[a]
While taking aspirin	
Aspirin dose among patients aged >60 y, OR	
75 mg	2.3 (1.2-4.4)
150 mg	3.2 (1.7-6.5)
300 mg	3.9 (2.5-6.3)
Age >70 y, OR	3.3 (1.3-8.7)
History of peptic ulcer disease, OR	15.2 (3.8-60.1)
Concomitant NSAIDs, RR	5.6 (4.4-7.0)
Concomitant COX-2 inhibitors, RR	5.8 (3.3 to 10.4)
Concomitant clopidogrel, RR	2.08 (1.34-3.21)
Concomitant high-dose corticosteroids, RR	4.43 (2.10-9.34)
Concomitant anticoagulants, OR	2.4 (1.4-4.1)
Concomitant clopidogrel and anticoagulants, HR	5.38 (3.48-8.32)
Helicobacter pylori infection, OR	4.7 (2.0-10.9)
While taking clopidogrel	
Concomitant aspirin or NSAIDs, OR	7.4 (3.5-15)
Concomitant anticoagulants, HR	3.46 (2.2-5.5)
Prior ulcer complication, OR	1.3 (1.1-1.5)

Abbreviations: COX-2, cyclooxygenase 2; HR, hazard ratio, NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; RR, relative risk.
[a]The measures of effect reported herein originate from numerous studies[10,14-20] with various designs and inclusion and exclusion criteria. Comparing risk factor estimates (ie, rows of the table) should be avoided.

She was transfused with 2 units of packed red blood cells, given 5 mg of vitamin K subcutaneously, and transfused with 1000 U of prothrombin complex concentrate (a mixture of clotting factors II, VII, IX, and X and proteins C and S). She was given 80 mg of pantoprazole intravenously as a bolus followed by an infusion of 8 mg/h while awaiting endoscopy.

After 12 hours, once Ms S was hemodynamically stable, she underwent an esophagogastroduodenoscopy (EGD) under conscious sedation. There was an anterior wall duodenal cap ulcer with a visible vessel at the base of the ulcer. The ulcer was injected with diluted epinephrine (1:10 000); a total of 8 mL of injectate was used, followed by thermal coaptive therapy. Her hemoglobin level increased to 100 g/L and her INR was 1.4.

She was hospitalized for 3 days and started an oral proton pump inhibitor (PPI) after completion of 72 hours of intravenous PPIs; her warfarin was restarted. She started eating 24 hours after the EGD and was discharged home after 4 days, receiving her usual medications but withholding the aspirin, with a scheduled 1-month follow-up.

MS S: HER VIEW

When I had the abdominal discomfort, I had attributed that to some food that I had eaten earlier and did not think much about it; even when I felt lightheaded, I thought that it was a form of my benign positional vertigo, but when I fell I got worried as this has never occurred to me, and I had not noticed the color of the stool prior to me being taken to the emergency department.

I am concerned by the fact that I had an episode of bleeding from an ulcer; could that be related to an inherited factor as both my parents had ulcers? Is there a possibility that this would recur? How long should I be on an acid suppressant? Is there any risk of an interaction between the heart medications and the acid medications? Is there any advantage to the use of dabigatran as an alternative to warfarin?

AT THE CROSSROADS: QUESTIONS FOR THE AUTHORS

How common is nonvariceal upper gastrointestinal (GI) bleeding and what are the risk factors? Should antiplatelet therapy be withheld during an episode of acute upper GI bleeding and, if so, when should it be reinstituted? In patients who have had bleeding and need to continue receiving antiplatelet therapy for coexisting cardiovascular and/or cerebrovascular disease, how should antiplatelet therapy be managed? Should anticoagulation be reinstated and, if so, when? Is there any advantage to the use of dabigatran as an alternative to warfarin? What are the potential interactions between PPIs and platelet inhibitors? Is Ms S's ulcer related to her parents' ulcers, and what is the likelihood that it will recur? How long should she take an acid suppressant? What do you recommend for Ms S?

DISCUSSION

For answering these questions, we performed a systematic literature search to identify articles with the highest level of evidence (eAppendix; available online at http://www.jama.com). We used the GRADE scoring system[1]:

(A) High quality: Further research is very unlikely to change confidence in the estimate of effect.

(B) Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

(C) Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

(D) Very low quality: Any estimate of effect is very uncertain.

Epidemiology and Risk Factors for Upper GI Bleeding

Bleeding in the upper GI tract is a common medical problem with significant health care, financial, and societal burdens. The incidence is 48 to 160 cases per 1000 adults per year,[2-6] with a mortality rate ranging from 5% to 14%[4,5,7-9]; most bleeding (80%-90%) is nonvariceal upper GI tract bleeding, and peptic ulcer disease (PUD) is an important cause of nonvariceal upper GI bleeding.[7,8]

Aspirin. In patients who are at low risk of GI complications, low-dose aspirin increases the risk of major nonvariceal upper GI bleeding by 1.5- to 3.2-fold, and the absolute rate is increased by 0.12% per year (95% CI, 0.07%-0.19%) with a number needed to harm of 833 patients (95% CI, 526-1429).[10] A meta-analysis of patients enrolled in ran-

domized trials found the rate of GI bleeding associated with aspirin use at doses less than 100 mg to be 1.1% (95% CI, 0.9%-1.3%), at doses of 100 to 325 mg to be 2.4% (95% CI, 2.2%-2.6%), and at doses greater than 325 mg to be 2.5% (95% CI, 1.8%-3.1%)[11] (A). Similar results were found in observational studies.[12,13]

Factors associated with an increased risk of bleeding while taking aspirin are prior PUD, age older than 70 years, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, clopidogrel, or anticoagulants[10,14-16] (TABLE 1). The risk of recurrent upper GI tract complications in patients receiving aspirin therapy varies by age, sex, and use of other NSAIDs and spans 0.8 to 300 cases per 1000 person-years.[10,14-16]

A cost-effectiveness analysis that modeled the effect of coadministration of aspirin and a PPI in patients taking low-dose aspirin for secondary prevention of cardiovascular events suggested that the combined administration results in fewer lifetime upper GI bleeding events (3.4% vs 7.2%) and fewer recurrent myocardial infarctions (26 fewer events per 10 000 patients), with an additional 38 days of life per patient compared with aspirin alone (C). This is attributed to a proposed increased adherence to aspirin (74% vs 71%) due to fewer dyspepsia symptoms.[21] However, this report did not specify criteria for the studies on which the cost-effectiveness analysis was based.

Clopidogrel. With use of clopidogrel alone, the odds ratio (OR) for developing upper GI bleeding is 1.3 (95% CI, 1.1-1.5)[15,16] and the incidence of upper GI bleeding with clopidogrel is less than that associated with aspirin: 0.5% vs 0.7%, respectively ($P<.05$)[22] (A). In contrast, among patients with a history of GI bleeding, 22% developed bleeding while taking clopidogrel[15,16] in the ensuing year. A meta-analysis identified the rate of GI bleeding while taking thienopyridines to be 1.6% (95% CI, 1.4%-1.8%)[11] (A).

The incremental risk of bleeding associated with use of clopidogrel is greatest in the first year,[23] and in a population-based case-control study, the rate ratio of GI bleeding during use of clopidogrel vs no treatment was 1.67 (95% CI, 1.27-2.20),[24] while in a similar Danish study it was 1.1 (95% CI, 0.6-2.1)[12] (B). The relative risk reductions associated with various doses of antiplatelet agents when given with PPIs and H_2 receptor antagonists are shown in TABLE 2.

Dual Antiplatelet Therapy (DAPT). A pooled analysis of published data found the incidence of major bleeding (requiring hospitalization) to be 1% with 325 mg/d or less of aspirin alone, 0.85% with clopidogrel alone, 1.7% with aspirin plus clopidogrel, and 2.5% with warfarin alone[26] (A). The associated rate ratios have been noted by some to be quite high: in a population-based case-control study, the adjusted OR for a serious GI bleed associated with DAPT was 7.4 (95% CI, 3.5-15) with a number needed to harm of 124[12] (B). The absolute increase in risk associated with use of DAPT is 1.3% (95% CI, 0.6%-1.9%) compared with clopidogrel alone.[27] The relative risk of severe bleeding with use of DAPT has been found to be a statistically nonsignificant 1.25 (95% CI, 0.97-1.61) compared with aspirin alone[28] (A).

Table 2. Adjusted Relative Risk Reduction of Upper Gastrointestinal Bleeding Associated With Use of Proton Pump Inhibitors and H_2 Receptor Antagonists[a]

	Relative Risk (95% CI)	
	Proton Pump Inhibitors	H_2 Receptor Antagonists
Nonaspirin NSAIDs	0.13 (0.04-0.19)	0.30 (0.17-0.53)
Aspirin, mg/d		
All dosages	0.30 (0.20-0.44)	0.40 (0.24-0.68)
100	0.32 (0.16-0.62)	0.33 (0.13-0.84)
200-300	0.32 (0.18-0.57)	0.44 (0.19-1.03)
>500	0.19 (0.08-0.47)	0.49 (0.16-1.51)
Clopidogrel/ticlopidine	0.19 (0.07-0.49)	0.83 (0.20-3.51)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
[a] These measures of effect are based on results from a case-control study by Lanas et al.[25]

Warfarin. Warfarin, a vitamin K antagonist, has the advantage of oral administration but a narrow therapeutic range and numerous drug and dietary interactions. Furthermore, in a systematic review and meta-regression that included patients receiving anticoagulation therapy managed in anticoagulation clinics (68.3%), community practices (24.4%), and clinical trials (7.3%), patients were found to achieve anticoagulation in a therapeutic range only 63.6% of the time (95% CI, 61.6%-65.6%), with patients managed in randomized controlled trials achieving a therapeutic range 66.4% of the time (95% CI, 59.4%-73.3%), in anticoagulation clinics 65.6% of the time (95% CI, 63.7%-67.7%), and in community practices 56.7% of the time (95% CI, 51.5%-62.0%)[29] (A).

The rate of major hemorrhage (defined as intracranial, retroperitoneal, intraocular, intramuscular with compartment syndrome, requiring an invasive procedure to stop bleeding, or active bleeding from any orifice associated with a systolic blood pressure <90 mm Hg, oliguria, or >2-g decrease in hemoglobin[30,31]) in randomized trials as well as in cohort studies for patients treated with warfarin for atrial fibrillation ranged from 1% to 7.4% per year[30,31] (A). A case-control study using the UK General Practice Research Database found that the adjusted rate ratio for GI bleeding for patients receiving warfarin was 1.98 (95% CI, 1.61-2.34); when warfarin was administered with aspirin, the adjusted rate ratio was 6.48 (95% CI, 4.25-9.87)[24] (B).

Triple Therapy. Warfarin combined with DAPT is used when DAPT is required for coronary stenting and anticoagulation is required for atrial fibrillation or mechanical heart valves. One study found the hazard ratio (HR) for bleeding to be 5.0 (95% CI, 1.4-17.8) compared with DAPT alone[32] (B). A national Danish registry-based study for patients with atrial fibrillation during a mean follow-up of 3.3 years (SD, 2.6 years) had an HR for GI bleeding of 5.38 (95% CI, 3.48-8.32) compared with warfarin monotherapy[17] (A).

Dabigatran. Dabigatran is a direct thrombin inhibitor that has been developed as a possible substitute for warfarin, and

although it has been associated with lower rates of stroke and systemic embolism compared with warfarin in patients with atrial fibrillation,[33,34] there have been reports of increased rates of myocardial infarction at the 150-mg twice-daily dosage (relative risk, 1.38; 95% CI, 1.00-1.91)[35] (B).

The benefit of dabigatran may be due to the reduced variability in the anticoagulation effect compared with warfarin. Although use of dabigatran might be more convenient for patients, it poses difficulty in assessment of nonadherence. In addition, in cases of bleeding, the effect of dabigatran cannot be acutely reversed. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, overall bleeding was no different between the dabigatran, 150-mg twice-daily, group compared with warfarin (relative risk, 0.93; 95% CI, 0.81-1.07). However, GI bleeding was higher in the dabigatran, 150-mg twice-daily, group compared with warfarin (OR, 1.50; 95% CI, 1.19-1.89), while the risk of GI bleeding was no different between the dabigatran, 110-mg twice-daily, group and the warfarin group (OR, 1.10; 95% CI, 0.86-1.41)[33] (B).

A cost-effectiveness analysis using a Markov decision model found the total cost of warfarin to be $143 193, of low-dose dabigatran to be $164 576, and of high-dose dabigatran to be $168 398, with an incremental cost-effectiveness ratio of $5229 per quality-adjusted life-year for dabigatran compared with warfarin. This is calculated based on the lifetime use of the medication in patients aged 65 years or older with nonvalvular AF and additional risk factors for stroke[36] (C).

Withholding Antiplatelet Therapy and Anticoagulation During Acute Upper GI Bleeding

A meta-analysis demonstrated that discontinuation of aspirin in patients with moderate to high risk of coronary artery disease events is associated with a 3-fold increase in major adverse cardiac events (OR, 3.14; 95%CI, 1.75-5.61) and more so in patients with coronary stents[37] (A). Another meta-analysis found that the time to adverse events varies, with acute coronary events occurring a mean of 8.5 (SD, 3.6) days, acute cerebrovascular events 14.3 (SD, 11.3) days, and acute peripheral arterial syndromes 25.8 (SD, 18.1) days after withholding aspirin.[38] However, events have been reported as early as 5 days afterward[38] (B).

In a randomized controlled trial[39] among patients presenting with acute bleeding due to PUD while taking aspirin, participants were randomized to early (after endoscopic therapy) vs late (after 8 weeks) reintroduction of aspirin. Although the results of the study were inconclusive with regard to the rates of recurrent PUD-related bleeding within 30 days in the early aspirin reintroduction group (difference, 4.9 percentage points; 95% CI, –3.6% to 13.4%), delayed aspirin resumption was associated with increased all-cause mortality (an absolute 12.9% vs 1.3%, a difference of 11.6%; 95% CI, 3.7%-19.5%). Patients in the early aspirin reintroduction group also had lower cardiovascular, cerebrovascular, and GI complications[39,40] (B).

It is currently recommended that antiplatelet therapy in the event of upper GI bleeding be restarted as soon as possible after discussion with the treating physician[4,41] when the risk of cardiovascular complications is thought to outweigh the risk of bleeding (B).

The data regarding the correction of coagulopathy and its subsequent reintroduction in the management of upper GI bleeding are scarce.[4] In a retrospective cohort study, 95% of patients who were receiving warfarin and developed an episode of nonvariceal upper GI bleeding had an INR at baseline between 1.3 and 2.7, and the INR was not predictive of recurrent nonvariceal upper GI bleeding[42] (B). In a case-control study, the correction of coagulopathy to 1.8 during hospitalization was associated with better outcomes[43](B). In a Canadian cohort study,[8] the presence of an INR greater than 1.5 was associated with increased mortality (B). In a cohort study in patients who underwent endoscopic therapy for upper GI bleeding, outcomes did not differ between patients receiving warfarin who had INR corrected to less than 2.5 and a control group who did not receive anticoagulants.[44]

Supratherapeutic coagulopathy should be corrected[44] (B), and restarting anticoagulation should be tailored to each individual patient. Anticoagulation should be reinitiated when the risks of withholding anticoagulation outweigh the risks of rebleeding (D); for example, in those with mechanical heart valves.

Management of Patients Requiring Continued Antiplatelet Therapy

Management of patients receiving antiplatelet agents for coexisting cardiovascular and/or cerebrovascular disease depends on the type of antiplatelet therapy and the history of GI bleeding.

Patients Taking Aspirin With No History of PUD. The use of famotidine, 20 mg twice daily, compared with placebo reduced the incidence of gastric ulcers (OR, 0.20; 95% CI, 0.09-0.47), duodenal ulcers (OR, 0.05; 95% CI, 0.01-0.4), and erosive esophagitis (OR, 0.2; 95% CI, 0.09-0.42).[45] The use of esomeprazole, 20 mg once daily, compared with placebo resulted in a reduction of erosive esophagitis (4.4% vs 18.3%; $P < .001$) as well as PUD (1.8% vs 6.2%; $P < .001$), respectively, over 26 weeks,[46] but patients in this study were not at high risk of bleeding; furthermore, end points were endoscopic as opposed to clinical outcomes[45] (B).

Patients With Prior PUD or Upper GI Bleeding While Taking Aspirin or Clopidogrel. In patients at moderate to high risk of bleeding, 7.7% receiving high-dose famotidine, 40 mg twice daily, experienced upper GI bleeding vs none of those receiving pantoprazole, 20 mg once daily.[47]

In a retrospective population-based cohort study, the use of a PPI compared with none in a population at high risk of GI complications decreased rehospitalization rates due to GI adverse events for patients taking aspirin (HR, 0.76; 95% CI, 0.64-0.91) while it did not affect rehospitalization rates

for patients receiving clopidogrel alone (HR, 1.08; 95% CI, 0.89-1.33)[48] (B).

A Cochrane systematic review[49] found that in patients receiving NSAIDs, standard doses of H_2 receptor antagonists reduced the incidence of endoscopic duodenal ulcers (risk ratio, 0.36; 95% CI, 0.18-0.74) but not gastric ulcers (risk ratio, 0.73; 95% CI, 0.50-1.08). Double-dose H_2 receptor antagonists decreased the incidence of both duodenal ulcers (risk ratio, 0.26; 95% CI, 0.11-0.65) and gastric ulcers (risk ratio, 0.44; 95% CI, 0.26-0.74). It should be noted that these relative risk reductions are for endoscopic end points and not clinically related symptoms or complications. In the same meta-analysis, PPIs reduced the incidence of both endoscopic duodenal ulcers (risk ratio, 0.20; 95% CI, 0.10-0.39) and gastric ulcers (risk ratio, 0.39; 95% CI, 0.31-0.50)[49] (A).

Although the use of misoprostol, a synthetic prostaglandin, reduces the recurrence of gastric ulcers in patients with a history of PUD who are taking low-dose aspirin, it is limited by its adverse effects, notably diarrhea at the dosages required for protection[49] (B).

In patients receiving aspirin (75-325 mg/d), *Helicobacter pylori* infection increases the risk of duodenal ulcers (OR, 18.5; 95% CI, 2.3-149.4)[18] (B). In *H pylori*–positive patients with a previous episode of upper GI bleeding, *H pylori* eradication was equivalent to the daily administration of a PPI[50] (rates of upper GI bleeding, 1.9% vs 0.9%, respectively; absolute difference, 1.0%; 95% CI for difference, –1.9% to 3.9%) (B). Another randomized controlled trial found that the combination of *H pylori* eradication with a PPI was superior to eradication therapy alone (HR, 9.6; 95% CI, 1.2-76.1), although this discrepant finding was perhaps due to inadequate eradication of *H pylori*[14] (B). Regardless, the wide confidence interval noted in the second trial may warrant further research on whether a PPI is necessary once *H pylori* is eradicated in this setting.

In *H pylori*–negative patients, use of aspirin with a PPI is associated with a reduction in rebleeding compared with clopidogrel therapy alone (OR, 0.06; 95% CI, 0.01-0.32), but mortality is unchanged (OR, 0.63; 95% CI, 0.24-1.64)[4] (B).

A case-control study found PPIs to be protective in patients taking clopidogrel (relative risk, 0.19; 95% CI, 0.07-0.49),[25] while another study was inconclusive (HR, 1.08; 95% CI, 0.89-1.33)[48] (C). A recent randomized trial of 165 patients demonstrated significantly fewer recurrent ulcers among long-term clopidogrel users with a history of PUD when administered a PPI compared with placebo[51] (B).

Patients Taking Aspirin and Clopidogrel. The COGENT trial demonstrated that concomitant PPIs decreased the risk of overt GI bleeding or GI bleeding of unknown origin (HR, 0.13; 95% CI, 0.03-0.56)[28] (B).

Possible Interaction Between PPIs and Clopidogrel

Response to antiplatelet therapy with clopidogrel varies because of numerous factors. Many alleles are involved in the enzymatic metabolism of clopidogrel, and allelic variation measured in current genetic testing has been estimated by some to account for only 12% of the total variation in platelet aggregation tests; one genetic polymorphism is the cytochrome P450 enzyme CYP2C19, required for the activation of this prodrug.[52] In individuals carrying a reduced-function allele, the active metabolite decreased and the risk of death due to cardiovascular causes, myocardial infarction, or stroke increased a relative 53% compared with noncarriers[53]; risk of stent thrombosis increased 3- to 3.6-fold.[53,54] More recent data have found no attributable significant differences in outcomes in the setting of co-PPI administration.[55] Indeed, PPIs are metabolized mainly by CYP2C19, and there has been concern that PPIs competitively inhibit the conversion of clopidogrel to its active compound at the level of CYP2C19 enzyme. Pharmacodynamic studies were equivocal and there was an unclear relationship to actual clinical outcomes.[56-58] A number of in vitro and ex vivo studies have been conducted, but these are limited by heterogeneity in antiplatelet activity study results, lack of standardized assays and accepted thresholds, and absence of a clearly established link between results and clinical outcomes.[59,60]

Two systematic reviews of mainly observational studies have found that studies that reported a positive association between PPI use while taking clopidogrel and major adverse cardiac outcomes were of low quality and at risk of biased results.[60,61] A common issue with these studies is that although there is biological plausibility, these studies cannot draw conclusions about causation because any association may be due to unmeasured or residual confounding.[60,62]

The recent COGENT trial[28] has shed light on this proposed interaction. This randomized controlled trial included patients receiving DAPT assigned to a PPI or placebo. The HR for cardiovascular events between the groups was 0.99 (95% CI, 0.68-1.44), suggesting that a clinically significant interaction between PPIs and clopidogrel is unlikely and that if there was one, it would be weak (B).

Despite the prior discussion, a US Food and Drug Administration (FDA) black box warning still persists regarding the coadministration of PPIs and clopidogrel, and the FDA has recommendations for clopidogrel dosing as well as choice of PPI.[63]

A similar concern has recently been raised about a proposed interaction between PPIs and aspirin resulting in decreased antiplatelet efficacy[64] (C). However, relevant data are drawn solely from observational information limited by possible unadjusted confounding. A randomized ex vivo platelet aggregation trial suggested no such interaction,[65] although such ex vivo data may not be clinically relevant.[66]

Latest Recommendations for Patients Receiving Antiplatelet Therapy

The American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association have issued a consensus document pertaining to

the reduction of GI risks associated with the use of antiplatelet therapy and NSAIDs,[19] which was recently updated with regard to the combined use of thienopyridines and PPIs[41] (TABLE 3). It states that for high-risk patients, gastroprotective medication should be administered, patients should be treated with combination antiplatelet therapy only for proper indications and when the benefits outweigh the risks, PPIs are the preferred agents, and patients should be tested for *H pylori* infection and it should be eradicated when present.

RECOMMENDATIONS FOR MS S

Because 60% of patients who experience rebleeding will do so with clinical symptoms of bleeding or a decrease in hemoglobin as the first symptom of recurrent PUD,[15,47] education and careful questioning must occur in follow-up.

A recent systematic review of factors that were associated with an increased mortality in patients experiencing recurrent complicated PUD identified the following as risk factors: advanced age, serious comorbidities, corticosteroid use, shock, low hemoglobin levels at initial presentation, low blood pressure, treatment delay, no history of PUD, ulcers that are Forrest class I to II at the time of endoscopy, and recurrence of complications.[67]

That both Ms S's parents had PUD raises the possibility of *H pylori* as a cause for her PUD, as this organism is commonly acquired in early childhood. Another unlikely possibility is multiple endocrine neoplasia, which is inherited in an autosomal dominant manner. Possible gene candidates relating to inflammation, angiogenesis, and the pharmacological effects of aspirin and NSAIDs have been proposed but remain largely speculative, with no direct clinical implications as to genetic counseling.[68-73] Ms S should be tested for the presence of *H pylori*. If the initial test result in the acute setting is negative, it should be repeated, given the high false-negative rate in the setting of acute bleeding[4] (TABLE 4), with 25% to 55% of patients with *H pylori* infection having false-negative results (A). In the acute setting of upper GI bleeding, the tests for detection of *H pylori* have a high positive predictive value (0.85-0.99) but a low negative predictive value (0.45-0.75). This might be related to the buffering effect of blood on the gastric pH because an alkaline environment is associated with false-negative results for tests that detect *H pylori*; a negative test result in the acute setting should thus indicate repeat testing[4] (A). If Ms S has a positive test result for *H pylori*, she should have eradication therapy followed by a confirmation test for eradication, either with endoscopy (histology

Table 3. Recommendations for Reduction of Gastrointestinal Risks Associated with Antiplatelet and NSAID Therapy[a]

Clinical Conditions	Recommendations
NSAIDs or COX-2 inhibitors and cardiac-dose aspirin	Gastroprotective therapy should be prescribed for at-risk patients.
Chronic-phase cardioprophylaxis	Aspirin dosages greater than 81 mg/d should not be prescribed. At-risk patients should receive gastroprotective therapy.
Combination antiplatelet therapy and anticoagulants	Should only be used with proper indication and when benefits outweigh risks. Should receive concomitant PPI. When aspirin (± clopidogrel) is combined with warfarin, an international normalized ratio of 2.0-2.5 is recommended.
High-risk patients with history of ulcer bleeding and taking aspirin	Substitution of aspirin with clopidogrel is not recommended. Clopidogrel is inferior to the combination of aspirin and a PPI.
Aspirin- or NSAID-associated gastroduodenal injury	When preventing or treating gastroduodenal injuries from these agents, PPIs are preferred agents to use.
History of ulcer disease	Test for and eradicate *Helicobacter pylori* prior to initiating long-term antiplatelet therapy.
Acute ulcer bleeding	Decision to discontinue antiplatelet therapy should be individualized and based on thrombotic risk weighed to risk of bleeding.
Endoscopy in patients receiving dual antiplatelet therapy	Endoscopy could be performed in patients receiving dual antiplatelet therapy.

Abbreviations: COX-2, cyclooxygenase 2; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.
[a] These recommendations are from the American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association, published in 2008 and updated in 2010, with regard to concomitant use of proton pump inhibitors and thienopyridine therapy and NSAID use.[19,41]

Table 4. Diagnostic Performance of *Helicobacter pylori* Tests in the Setting of Upper Gastrointestinal Bleeding[a]

	Performance (95% CI)			
Tests	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Serologic	0.88 (0.84-0.91)	0.70 (0.63-0.77)	0.88 (0.85-0.90)	0.70 (0.65-0.76)
Histologic	0.74 (0.71-0.77)	0.94 (0.90-0.96)	0.98 (0.97-0.99)	0.49 (0.47-0.50)
Urea breath test	0.93 (0.91-0.95)	0.88 (0.82-0.92)	0.97 (0.96-0.98)	0.73 (0.69-0.77)
Rapid urease test	0.68 (0.65-0.71)	0.94 (0.91-0.96)	0.97 (0.96-0.98)	0.49 (0.46-0.49)
Stool antigen	0.85 (0.85-0.89)	0.76 (0.68-0.82)	0.85 (0.82-0.88)	0.75 (0.69-0.80)
Culture	0.50 (0.46-0.55)	0.99 (0.96-1.00)	0.99 (0.97-1.00)	0.45 (0.43-0.45)

[a] These measures of effect are based on results from the international consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding by Barkun et al.[4]

or rapid urease test), urea breath test, or stool antigen test (A). In addition, given her current comorbidities, she does not require treatment with aspirin, and it should be discontinued. Because of Ms S's age, comorbidities, and presenting nonvariceal upper GI bleeding, we recommend that she continue a PPI indefinitely if aspirin is needed. The available data fail to demonstrate a clinically relevant interaction between PPIs and clopidogrel.

The mean annual incidence of stroke in atrial fibrillation is 4.5% (range, 3%-7%)[74]; this risk is similar whether atrial fibrillation is paroxysmal or permanent. (The multivariable-adjusted HR for ischemic stroke in paroxysmal atrial fibrillation compared with permanent atrial fibrillation is 1.07 [95% CI, 0.71-1.61] in individuals without a history of stroke.[75]) The risk of stroke may outweigh the overall risk of rebleeding once secondary prophylaxis has been initiated. The final decision with regard to anticoagulation thus needs informed consultation with Ms S and her treating physician and should take into consideration her risk of stroke (using the $CHADS_2$ score[76] or the CHA_2DS_2VASc score[77]) as well as her estimated risk of bleeding (eg, using the HAS-BLED score[78]). A patient with a risk profile similar to that of Ms S would have a risk of bleeding of 60 cases per 1000 person-years.[79] Based on Ms S's risk of stroke vs bleeding, we recommend continuing anticoagulation. A switch to dabigatran may represent a more efficacious option for the prevention of thrombotic complications of atrial fibrillation, but clear evidence of improved GI bleeding risk is lacking. Furthermore, it may complicate resuscitative efforts because its anticoagulation effect cannot be reversed; we would thus suggest that Ms S continue receiving warfarin.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Barkun reports receiving consultancy fees from Olympus Canada Inc and Cook Canada Inc. No other disclosures were reported.
Additional Contributions: We thank the patient for sharing her story and for providing permission to publish it.
Online-Only Material: The eAppendix is available at http://www.jama.com.

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