Gastrointestinal Bleeding in the Setting of Anticoagulation and Antiplatelet Therapy

Kassem Barada, MD, Heitham Abdul-Baki, MD,* Ihab I. El Hajj, MD,* Jana G. Hashash, MD,* and Peter H. Green, MD†*

Goal: To review the literature on the significance, risk factors, and management of occult and gross gastrointestinal (GI) bleeding in patients on antiplatelets and/or anticoagulants.

Study: Relevant original and review articles and their bibliographies were analyzed. Estimates of risks and therapeutic outcomes were obtained from randomized trials, whereas risk factor identification was gathered from cross-control and prospective cohort studies.

Results: Antiplatelets and anticoagulants do not diminish the positive predictive value of fecal occult blood testing to find GI pathology. They increase the risk of gross GI bleeding, and predictors of hemorrhage include history of GI bleeding or ulcer disease, higher intensity of anticoagulation, combination therapy, and presence of comorbid conditions. A bleeding site is identified in most patients with peptic ulcer being the most common. In case of significant bleeding, complete or partial reversal of anticoagulation is undertaken on the basis of the balance of risks between bleeding and thromboembolic events. Early endoscopy can reveal lesions requiring endoscopic hemostasis, which can be performed in the setting of low-intensity anticoagulation. In patients with history of peptic disease or bleeding from an acid-related lesion, proton-pump inhibitors and *Helicobacter pylori* eradication reduce the risk of upper GI bleeding even when antiplatelet therapy is continued.

Conclusions: Predictors of bleeding on antiplatelets and/or antithrombotics therapy have been identified, but formulation and validation of a GI bleeding index for stratification of risk in individual patients is suggested. Reversal of anticoagulation in bleeding patients is associated with a low risk of thromboembolic events and permits the performance of diagnostic and therapeutic endoscopy. Proton-pump inhibitors and *H. pylori* eradication reduce the risk of rebleeding in those with acid-related disease.

Key Words: gastrointestinal bleeding, anticoagulation, antiplatelet

(*J Clin Gastroenterol* 2009;43:5–12)

Gastrointestinal (GI) bleeding is a common and significant medical problem. Mortality from upper gastrointestinal (UGI) and lower gastrointestinal (LGI) bleeding rates at 3.5% to 13% and 1% to 5%, respectively.[1–3] In addition, GI bleeding has significant associated morbidity and cost.[4] Use of anticoagulants is a contributor to GI bleeding and may affect its management.[5,6] In addition, antiplatelets account for 14.5% of cases of UGI bleeding.[7] In a prospective study involving 18,820 hospital admissions, 376 were related to aspirin, clopidogrel, or warfarin, and the majority of those admissions were due to GI bleeding.[8] Furthermore, low-dose aspirin and antithrombotic drugs increase UGI and LGI bleeding-related morbidity.[9,10]

Antiplatelets and anticoagulants are commonly used for the treatment and prophylaxis of vascular diseases. A summary of their mechanism and duration of action and mode of reversal is shown in Table 1. Although knowledge about the risk of GI bleeding, its treatment and prevention in patients on anticoagulants and/or antiplatelets has expanded, many questions remain unanswered.

We performed a systemic review of the medical literature on GI bleeding in the setting of anticoagulation and/or antiplatelet therapy using PubMed database. Our search was based on the keywords "gastrointestinal bleeding" or "gastrointestinal hemorrhage" in combination with "aspirin," "clopidogrel," "heparin," "low molecular weight heparin," "warfarin," "antithrombotic," "anticoagulant," or "antiplatelet." The search covered publications between 1978 and February 2007. The search included original and review articles and their bibliographies. Estimates of risks and therapeutic outcomes were obtained from randomized trials, whereas risk factor identification was gathered from cross-control and prospective cohort studies.

OCCULT GI BLEEDING AND IRON-DEFICIENCY ANEMIA IN PATIENTS ON ANTICOAGULANT AND/OR ANTIPLATELET THERAPY

Fecal occult blood testing (FOBT) is used to screen for GI cancers and investigate iron-deficiency anemia.[12] Population studies found a rate of positive FOBT of 1.7% to 4.4%.[13,14] One study showed a higher rate reaching 16%.[15] The effect of anticoagulants and antiplatelets on occult GI blood loss has been investigated.[16–18] A study on 256 patients on warfarin or heparin found that 12% of the 175 patients who completed the study protocol had positive FOBT compared with 3% of controls.[17] Of 21 patients with positive tests, 16 underwent diagnostic evaluation revealing new findings in all but one. Four had colon cancer. There was no difference in the rate of lesions between the heparin and warfarin groups.

Bini et al[19] studied the positive predictive value of FOBT in persons taking warfarin. Lesions consistent with

Received for publication March 22, 2007; accepted May 16, 2007.
From the *Department of Internal Medicine, American University of Beirut, Lebanon; and †Division of Gastroenterology, Columbia University College of Physicians and Surgeons, New York, NY.
The authors declare no conflict of interest.
The authors confirm that there is no financial arrangement with any body or any institution or any company.
Reprints: Kassem Barada, MD, Gastroenterology Division, Internal Medicine Department, American University of Beirut Medical Center, PO Box 11-0236, Beirut 1107 2020, Lebanon (e-mail: kb02@aub.edu.lb).

TABLE 1. Commonly Used Antiplatelet and Anticoagulant Drugs[11]

	Mode of Action	Duration of Action*	Antidote	Monitoring Parameters
Aspirin	Acetylates platelet cyclo-oxygenase (COX)-1	Dose-independent Duration: 5-10 d Half-life: 15-20 min	No specific antidote Irreversible action	Signs of bleeding
Clopidogrel	Blocks adenosine 5′-disphosphate receptors	Dose-dependent Duration: 7 d	No specific antidote Irreversible action	Signs of bleeding
Warfarin	Inhibits Vitamin K	Dose-dependant Duration: 3-7 d Half-life: 36-42 h	Vitamin K	PT (INR), hematocrit
UFH	Potentiates action of antithrombin III	Dose-dependant Duration: 2-10 h Half-life: 30-150 min	Protamine	aPTT, platelets, hematocrit
LMWH	Potentiates action of antithrombin III	Dose-dependant Duration: up to 12 h Half-life: 3 to 4-fold that of UFH	Protamine (partial only)	Not necessary†

*After cessation of treatment.

†In cases of chronic renal failure monitor via anti-Xa.

aPTT indicates activated partial thromboplastin time; LMWH, low molecular weight heparin; PT, prothrombin time; UFH, unfractionated heparin.

occult bleeding were identified in 59.0% of patients on warfarin and 53.8% of controls ($P = 0.27$). More lesions were identified by colonoscopy in the warfarin group (36.2% vs. 25.7%, $P = 0.02$), but there was no difference in the frequency of UGI tract lesions. Hence, warfarin use did not seem to decrease the positive predictive value of FOBT.

Greenberg et al[16] conducted a prospective crossover study using Hemmocult II and HemoQuant tests on 100 participants taking aspirin (81 or 325 mg), warfarin, or none. Fecal blood loss was not increased by warfarin and was not related to the degree of anticoagulation. Aspirin caused a small dose-dependent increase in fecal blood loss that was not sufficient to interfere with FOBT.[16] Another study on 40 healthy volunteers given 30 to 325 mg of aspirin or placebo confirmed the results.[20]

Finally, in a study on 193 veterans who were referred for evaluation of positive FOBT, the chance of finding colonic pathology was not affected by the intake of low or high-dose aspirin; however, no UGI endoscopy was performed on patients with negative colonoscopy.[21] Overall, these studies suggest that aspirin use is not associated with false-positive FOBT.

The use of low-dose aspirin or warfarin or both in 267 patients with myocardial infarction who were followed up for 4 years did not lead to anemia or iron deficiency.[22] Furthermore, a study on 695 out-patients referred for evaluation of iron-deficiency anemia found no difference in the rate of GI malignancies between patients taking and those not taking aspirin or warfarin.[23]

In conclusion, the literature suggests that positive FOBT and iron-deficiency anemia may not be attributed to aspirin or warfarin intake, and that use of antiplatelets or anticoagulants does not diminish the positive predictive value of FOBT to find GI pathology. Consequently, the data does not support discontinuation of such drugs before doing FOBT, which is commonly practiced.[19] Finally, patients with positive FOBT or iron-deficiency anemia on antiplatelets/anticoagulants should have a full investigation for sources of blood loss.[16]

GROSS GI BLEEDING IN PATIENTS ON ANTIPLATELETS AND/OR ANTICOAGULANTS

Risk and Predictors

The risk of gross GI bleeding associated with use of antiplatelets and anticoagulants depends on the specific drug(s), the dose, the anticipated duration of administration, and the indication. Moreover, the patient's age, sex, comorbid conditions, and past medical history are important. Patient and drug-related factors thought to increase the risk of GI bleeding are listed in Table 2.

Aspirin

Aspirin use increases the risk of GI bleeding, but it is not clear if this is dose-dependent. The relative risk of major UGI bleeding increases from 1.8 with 100 mg to 7.6 with 500 mg of aspirin.[24] However, a meta-analysis of randomized controlled trials of low-dose aspirin showed that it increases the risk of GI bleeding about 2-fold, with no difference between "lower" (76 to 162.5 mg daily) and "higher" (> 162.5 to 325 mg daily) low-dose aspirin.[25]

TABLE 2. Risk Factors for GI Bleeding in Patients Using Antiplatelet and/or Anticoagulant Drugs

Patient-related Factors	Drug-related Factors
Old age[24–27]	Intensity of anticoagulation[25,28]
Female sex[26]	Combination therapy[29]*
History of GI bleeding[27,30]	Nonsteroidal anti-inflammatory drug use[31,32]
History of peptic ulcer disease[30]	Corticosteroid use[33]
H. pylori infection[34]	—
Chronic renal failure[25,27]	—
Congestive heart failure[35]	—
Diabetes mellitus[27,35]	—
Alcohol abuse[36,37]	—

*Combination of any 2 or more antiplatelet and/or anticoagulant drugs.

Whether old age is a risk factor for GI bleeding in patients on low-dose aspirin is unclear. The yearly risk of "UGI complication" in young patients with no history of UGI pathology is around 0.2%. It goes up to 12% in patients older than 80 with history of complicated ulcer.[26] In addition, a study using 100-mg aspirin/d in healthy individuals over 70 showed that the risk of bleeding is 3% per year. However, there was no control group younger than 70.[27] Moreover, Laine[28] suggests that low-dose aspirin doubles the risk of GI bleeding irrespective of age, and that baseline absolute risk in the elderly is high.

The impact of sex on the risk of GI bleeding on aspirin is unknown. In women, 100 mg every other day increased the risk of transfusion requiring GI bleeding 1.4-fold compared with placebo over 10 years.[29] In the Framingham study, women with atrial fibrillation given aspirin were as likely to have GI bleeding as men, although the number of patients was small.[30]

In a study on 991 patients on aspirin followed-up for 2 years, 21% of cases of UGI bleeding occurred within a month and 45% within 4 months of starting therapy.[31] However, acute aspirin administration doubles the risk of bleeding in patients undergoing coronary artery bypass surgery during the index hospitalization.[32]

A case-controlled study involving 368 patients taking low-dose aspirin found that history of GI bleeding or ulcer disease increased the risk of UGI bleeding 6.5 and 2.1-fold, respectively.[33] Furthermore, concomitant nonsteroidal anti-inflammatory drug or corticosteroid use probably increases the risk of GI bleeding in aspirin users.[34–38] Finally, in a large case-controlled study involving 1121 patients with bleeding peptic ulcer, the odds ratio for bleeding associated with heart failure and diabetes were 5.9 and 3.1, respectively.[39]

Clopidogrel

Compared with placebo, the risk of GI bleeding associated with clopidogrel use is not known. A lower risk of UGI bleeding associated with use of clopidogrel as compared with aspirin has been suggested.[25,40,41] However, clopidogrel use clearly increases the risk of GI bleeding in patients with history of dyspepsia, peptic ulcer, or GI bleed.[7,42]

Anticoagulants

In a study on stroke prevention in patients with atrial fibrillation, low-intensity anticoagulation with warfarin [International Normalized Ratio (INR) of 1.2 to 1.5] did not increase the risk of GI bleeding.[43] However, the risk increases dramatically with the intensity of anticoagulation particularly at $INR \geq 4.5$.[44,45] Old age is an independent risk factor for major bleeding on warfarin.[44,46] In elderly patients receiving warfarin for atrial fibrillation, independent predictors of bleeding (GI and non-GI) are old age, female sex, diabetes, and anemia.[46]

Intravenous heparin given for secondary stroke prevention had a greater morbidity-ratio estimate of GI bleeding than warfarin or aspirin.[47] Similarly, subcutaneous administration of heparin at 5000 to 12,500 U twice daily seems to be associated with a substantial risk of extracranial bleeding of 0.4% to 1.4% per 2 weeks.[48] The average daily frequency of fatal and major bleeding during heparin therapy were 0.05% and 0.8%, and bleeding affected the GI tract in 27% of cases.[49] The use of low molecular weight heparin is associated with a markedly lower risk of GI bleeding.[49,50] Predictors of bleeding on heparin include female sex, intensity of anticoagulation, old age, concomitant aspirin use, presence of comorbid conditions, and alcohol abuse.[44,49,50]

Combination Therapy

A recent large case-control study found that combining any 2 antiplatelet or anticoagulant medications substantially increases the risk of serious upper GI bleeding compared with monotherapy.[51] In the management of atherothrombosis with clopidogrel in high-risk patients (MATCH) and the clopidogrel in unstable angina to prevent recurrent events (CURE) studies, combining aspirin and clopidogrel substantially increased the risk of GI bleeding.[25,52,53] Moreover, in patients with mechanical valves, the addition of aspirin to warfarin doubled the risk of GI bleeding compared with the addition of placebo.[54] When the target INR is lowered, low-dose aspirin does not seem to alter the rate of GI bleeding when added to warfarin.[55]

Of interest are patients with acute coronary syndrome who receive a combination of antiplatelet, antithrombotic, and thrombolytic drugs. In 2 retrospective studies, the in-hospital risk of UGI bleeding was 0.6% and 0.7%[56] and this risk increased in the first year of follow-up.[57] Home but not in-hospital intake of antiplatelets was a predictor of in-hospital UGI bleeding.

For patients with acute coronary syndrome who require drug eluting stents (DES), dual antiplatelet therapy (aspirin and a thienopyridine) was initially recommended for a period of 3 to 12 months.[58–60] However, late stent thrombosis was later reported to occur years after DES implantation, and was thought to be related to cessation of clopidgrel.[61–64] This has prompted some investigators to suggest that patients with DES may require long term and possibly life long dual antiplatelet therapy, and that further studies are required to determine the optimal duration of such therapy.[62,63] The risk of GI bleeding within the first 30 days of dual antiplatelet therapy is 1.3%, and increases

dramatically to 12% in high-risk patients with previous GI bleeding.[65,66] Prolonging the duration of treatment or increasing the dose of antiplatelet drugs amplifies the risk of GI bleeding as shown by the CURE study.[67] In those who require long-term dual antiplatelet therapy, lowering the dose of aspirin (75 to 162 mg/d) may reduce the risk of bleeding complications.[68] In patients requiring triple therapy (dual antiplatelet medications and an anticoagulant drug), bleeding complications (GI and non-GI) ranged between 9.2% and 20% at 30 days of treatment.[69–71] Major bleeding events requiring blood transfusions or surgical intervention occurred in 1% to 15% of patients.[69–71] Lip and Karpha[69] reported that all major bleeding complications were GI, and were associated with age >75 years, overtherapeutic INR, and identifiable lesions in the GI tract.

In conclusion, it might be useful to divide patients taking antiplatelet and/or anticoagulant drugs into groups at low, intermediate, or high-risk for GI bleeding on the basis of the number of risk factors and their importance. Two such indices have been formulated and validated prospectively for the risk of major bleeding (GI and non-GI) in patients on warfarin therapy.[46,72]

Management

Clinical risk stratification of bleeding patients might help in recognizing those at risk for adverse outcome and need for urgent intervention and treatment.[73] Use of aspirin, clopidogrel, or warfarin was associated with longer duration of hospitalization and increased need for transfusion in UGI bleeders.[10] In patients with LGI bleeding, aspirin use was an independent predictor of severe hemorrhage.[9]

Site of GI Bleeding in Anticoagulated Patients

Most studies on etiology of GI bleeding in anticoagulated patients are retrospective, involve small number of patients, or originate from single centers. In those studies, a bleeding site was identified in more than 80% of patients with acute GI bleeding on anticoagulants,[74–76] and gastroduodenal ulcers and erosions accounted for more than 50% of lesions in those with UGI bleeding.[74,77–79] A prospective noncontrolled study of 18 episodes of bleeding in 17 patients using warfarin or heparin found that 44% of patients had duodenal ulcers.[80] This was confirmed by 2 controlled studies that found that peptic ulcer was the cause of UGI bleeding in 45% of patients.[74,79] Erosive esophagitis is also an important cause of GI bleeding in patients taking low-dose aspirin or antithrombotic agents.[78]

No studies addressed specifically the source of LGI bleeding in patients using aspirin, heparin, or warfarin. Of patients presenting with GI bleeding (unspecified as lower or upper), 25% to 33% were thought to have colonic pathology with polyps, diverticulae, and angiodysplasia being the most common.[75,76] Patients with supratherapeutic INR have mucosal abnormalities in the UGI and LGI tracts similar to those in patients with a therapeutic INR, except for a higher prevalence of gastritis.[75]

In 17% to 29% of patients with GI bleeding on antiplatelets or anticoagulants, no mucosal abnormality is found on endoscopic investigation.[74,78,79] The role of capsule endoscopy and/or enteroscopy in such patients is not known. A prospective nonrandomized study that examined small bowel pathology in patients with obscure GI bleeding using capsule endoscopy found that antiplatelets/anticoagulants use had no impact on the chance of finding mucosal pathology.[81]

Discontinuation of Anticoagulants and Reversal of Anticoagulation

In patients with clinically significant GI bleeding, continued administration of antiplatelets or anticoagulants is associated with an extremely high risk of continued or subsequent bleeding.[82,83] It is not clear, however, how long these drugs should be discontinued, whether reversal of anticoagulation should be partial or complete, and how best to achieve such a reversal. Usually, the decision is based on a balance between the risk of thromboembolism and that of continued or recurrent bleeding. Hence, it might be helpful to stratify patients with clinically significant GI bleeding into high-risk or low-risk for thromboembolism if anticoagulation is to be reversed partially or completely. According to The American Society of Gastrointestinal Endoscopy (ASGE) guidelines, high-risk patients are those with deep vein thrombosis or arterial embolism within the past 6 months, valvular heart disease with atrial fibrillation, mitral mechanical valve, any mechanical valve with a previous thromboembolic event, atrial fibrillation with a previous cardioembolic event or a risk factor for stroke, recurrent venous or arterial thromboembolism, or any hypercoagulable state with at least one thromboembolic event. Conversely, low-risk patients are those with isolated venous or arterial thromboembolic event older than 6 months, atrial fibrillation without valvular disease, aortic mechanical valve, or a bioprosthetic valve.[84]

Complete withdrawal of anticoagulation is associated with a low risk of thromboembolic events even in patients with prosthetic valves.[85] However, most studies involve a small number of patients and are not randomized. In one study on 28 patients with major bleeding, withholding warfarin for a mean of 15 days and reversal of anticoagulation was associated with no embolic complications.[86] In another study on 21 patients with prosthetic valves, withholding warfarin for a mean of 3 days was associated with only one thromboembolic event over a period of 8 months.[87] In patients with atrial fibrillation whose anticoagulation was withdrawn for endoscopic procedures, the risk of stroke was 1.06% per procedure.[88] Factors associated with increased risk were age above 80 years, history of stroke, hypertension, hyperlipidemia, and family history of vascular disease.[89]

Three controlled retrospective studies have addressed the management of GI bleeding in patients using antiplatelets and/or anticoagulants.[74,75,79] In all, partial reversal of anticoagulation to an INR of 1.5 to 2.5 using fresh frozen plasma and/or vitamin K was performed. Upper and lower GI diagnostic and therapeutic GI procedures were done a mean of 1 to 3.7 days after admission without complete reversal of anticoagulation. Mortality, hospital stay, and number of transfused units in patients using warfarin were similar to controls. A supratherapeutic INR on admission did not have a negative impact on major clinical outcomes.[75]

In patients using warfarin, early endoscopy might reveal lesions requiring endoscopic hemostasis and could lead to the diagnosis of previously unrecognized lesions.[79] In those with bleeding ulcers, endoscopic hemostasis after partial correction of the INR to 1.5 to 2.5 was not associated with increased risk of uncontrollable bleeding or emergency surgery. Overall mortality rate was low and was

similar to that in patients not receiving anticoagulants.[79] A retrospective controlled study by Wolf et al[6] suggests that performing therapeutic endoscopy in mildly to moderately anticoagulated patients with UGI bleeding is safe and is not associated with increased risk of rebleeding.

For nonbleeding or mildly bleeding patients with excessive anticoagulation (INR > 6), oral vitamin k_1 (1 to 5 mg) is effective in restoring the INR to the therapeutic range and is safe.[89,90]

For patients with life-threatening bleeding (GI and non-GI), emergency reversal of anticoagulation with recombinant factor VIIa (1.2 mg or 20 to 106 μg/kg) is effective in stopping or decreasing bleeding within 2 hours of administration.[91,92] In addition, Baglin et al[85] recommend administration of intravenous rather than oral vitamin K (5 to 10 mg) if reversal is to be sustained. Similarly, prothrombin complex concentrate (PCC) is effective for the immediate reversal of anticoagulation in patients with life-threatening hemorrhage.[93,94] Coadministration of vitamin K is essential for sustaining the reversal.[78,90] When oral vitamin K is used for warfarin reversal, the injectable formula of vitamin K is preferable to tablets because of its flexible dosing.[82] Thrombotic complications have been described after PCC administration, and anaphylactoid or fatal reactions to vitamin K may occur after administration of small doses intravenously.[93,95] In addition, reports on the use of PCC and recombinant factor VII specifically in GI bleeding have been limited to case reports or small numbers of patients. Therefore, the safety, efficacy, and optimal dose of recombinant factor VII, PCC, and vitamin K in patients with GI bleeding need to be determined in further studies.

No studies have compared complete and partial reversal of anticoagulation in patients with GI bleeding on basis of the risk for thromboembolic disease. We would like to suggest an approach that takes into account the risk of thromboembolic disease (Fig. 1).[96,97] The suggested algorithm needs validation in prospective studies.

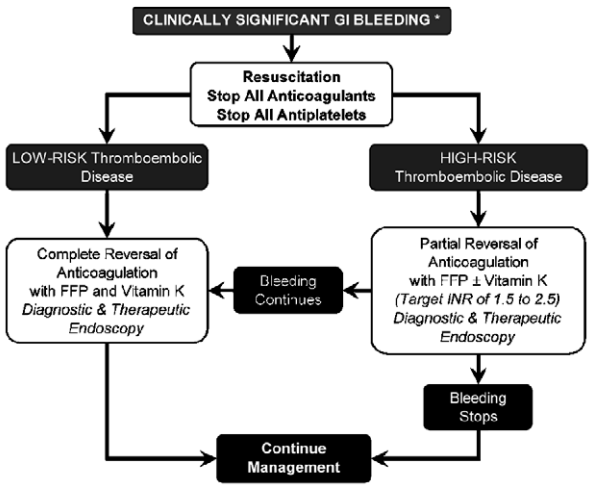

FIGURE 1. Suggested algorithm for management of acute GI bleeding in patients using antiplatelet and/or antithrombotic medications.[70,71,75,80,81]

PROPHYLAXIS

Gastroduodenal ulcers or erosions and erosive esophagitis account for 50% to 60% of lesions responsible for GI bleeding in patients on antiplatelets or anticoagulants.[75–80] Most studies on prophylaxis against GI bleeding have addressed the role of acid suppression and/or *Helicobacter pylori* eradication in patients known to have or are likely to have acid-related gastroduodenal injury.

Ranitidine reduces the risk of rebleeding in patients with ulcers.[98] Furthermore, proton-pump inhibitors (PPIs) reduce the risk of bleeding in patients who had a bleeding episode from an acid-related lesion despite continued intake of antiplatelets.[7,99]

In patients with UGI bleeding on aspirin, *H. pylori* infection is an independent risk factor.[100] Moreover, *H. pylori* eradication is equivalent to maintenance therapy with omeprazole in reducing the risk of recurrent bleeding on aspirin.[101]

In patients at low to moderate-risk of developing gastroduodenal injury, low-dose aspirin seems to be equivalent to clopidogrel,[102] but in those with documented aspirin-related ulcer bleeding, the risk of rebleeding is lower on aspirin plus a PPI than on clopidogrel alone.[103]

The literature, therefore, supports administration of a PPI and eradication of *H. pylori* infection in patients with history of upper GI ulceration or bleeding who need to take antiplatelets.[42,104,105] In elderly patients on aspirin, such therapy reduces the prevalence of ulcers, but its effect on bleeding risk is unclear.[106]

What to do in high-risk patients who have no history of peptic disease is unclear. Using the lowest effective dose of aspirin,[107] lowering the intensity of anticoagulation, and avoiding nonsteroidal anti-inflammatory drugs, corticosteroids, and combination therapy may reduce the risk of bleeding,[49,108] but need validation by randomized controlled studies. Kimmey[109] proposes that the indication for PPI in patients using aspirin increases as the number of risk factors for GI bleeding increases, which needs validation in prospective trials.

Most GI bleeding episodes on antiplatelets or anticoagulants occur within the first year of therapy. It is interesting to speculate if performing FOBT in asymptomatic high-risk patients might have a role in the management.[110] Investigation in those with positive tests might reveal peptic disease, *H. pylori* infection, or other treatable potential sources of bleeding.

REFERENCES

1. Strate LL. Lower GI bleeding: epidemiology and diagnosis. *Gastroenterol Clin North Am*. 2005;34:643–664.
2. Targownik LE, Nabalamba A. Trends in management and outcomes of acute nonvariceal upper gastrointestinal bleeding: 1993-2003. *Clin Gastroenterol Hepatol*. 2006;4:1459–1466.
3. van Leerdam ME, Vreeburg EM, Rauws EA, et al. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am J Gastroenterol*. 2003;98:1494–1499.
4. Dulai GS, Gralnek IM, Oei TT, et al. Utilization of health care resources for low-risk patients with acute, nonvariceal upper GI hemorrhage: an historical cohort study. *Gastrointest Endosc*. 2002;55:321–327.
5. Johnsen SP, Sorensen HT, Mellemkjoer L, et al. Hospitalisation for upper gastrointestinal bleeding associated with use of oral anticoagulants. *Thromb Haemost*. 2001;86:563–568.

6. Wolf AT, Wasan SK, Saltzman JR. Impact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage. *Am J Gastroenterol*. 2007;102:290–296.
7. Ibanez L, Vidal X, Vendrell L, et al. Upper gastrointestinal bleeding associated with antiplatelet drugs. *Aliment Pharmacol Ther*. 2006;23:235–242.
8. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329:15–19.
9. Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. *Arch Intern Med*. 2003; 163:838–843.
10. Taha AS, Angerson WJ, Knill-Jones RP, et al. Clinical outcome in upper gastrointestinal bleeding complicating low-dose aspirin and antithrombotic drugs. *Aliment Pharmacol Ther*. 2006;24:633–636.
11. Harder S, Klinkhardt U, Alvarez JM. Avoidance of bleeding during surgery in patients receiving anticoagulant and/or antiplatelet therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharmacokinet*. 2004;43:963–981.
12. Rockey DC. Occult gastrointestinal bleeding. *Gastroenterol Clin North Am*. 2005;34:699–718.
13. Boland CR. Malignant tumors of the colon. In: Yamada T, ed. *Textbook of Gastroenterology*. Vol 2. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:1940–1990.
14. Rockey DC. Occult gastrointestinal bleeding. *N Engl J Med*. 1999;341:38–46.
15. Levin B, Hess K, Johnson C. Screening for colorectal cancer. A comparison of 3 fecal occult blood tests. *Arch Intern Med*. 1997;157:970–976.
16. Greenberg PD, Cello JP, Rockey DC. Asymptomatic chronic gastrointestinal blood loss in patients taking aspirin or warfarin for cardiovascular disease. *Am J Med*. 1996;100: 598–604.
17. Jaffin BW, Bliss CM, LaMont JT. Significance of occult gastrointestinal bleeding during anticoagulation therapy. *Am J Med*. 1987;83:269–272.
18. Prichard PJ, Kitchingman GK, Walt RP, et al. Human gastric mucosal bleeding induced by low dose aspirin, but not warfarin. *BMJ*. 1989;298:493–496.
19. Bini EJ, Rajapaksa RC, Weinshel EH. Positive predictive value of fecal occult blood testing in persons taking warfarin. *Am J Gastroenterol*. 2005;100:1586–1592.
20. Greenberg PD, Cello JP, Rockey DC. Relationship of low-dose aspirin to GI injury and occult bleeding: a pilot study. *Gastrointest Endosc*. 1999;50:618–622.
21. Kahi CJ, Imperiale TF. Do aspirin and nonsteroidal anti-inflammatory drugs cause false-positive fecal occult blood test results? A prospective study in a cohort of veterans. *Am J Med*. 2004;117:837–841.
22. Hurlen M, Eikvar L, Seljeflot I, et al. Occult bleeding in three different antithrombotic regimes after myocardial infarction. A WARIS-II subgroup analysis. *Thromb Res*. 2006;118:433–438.
23. James MW, Chen CM, Goddard WP, et al. Risk factors for gastrointestinal malignancy in patients with iron-deficiency anaemia. *Eur J Gastroenterol Hepatol*. 2005;17:1197–1203.
24. Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin, and combinations. *Gut*. 2006;55:1731–1738.
25. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med*. 2006;119:624–638.
26. Patrono C, Garcia Rodriguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med*. 2005;353:2373–2383.
27. Silagy CA, McNeil JJ, Donnan GA, et al. Adverse effects of low-dose aspirin in a healthy elderly population. *Clin Pharmacol Ther*. 1993;54:84–89.
28. Laine L. Review article: gastrointestinal bleeding with low-dose aspirin-what's the risk? *Aliment Pharmacol Ther*. 2006; 24:897–908.
29. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352: 1293–1304.
30. Sam C, Massaro JM, D'Agostino RB Sr, et al. Warfarin and aspirin use and the predictors of major bleeding complications in atrial fibrillation (the Framingham Heart Study). *Am J Cardiol*. 2004;94:947–951.
31. Ng W, Wong WM, Chen WH, et al. Incidence and predictors of upper gastrointestinal bleeding in patients receiving low-dose aspirin for secondary prevention of cardiovascular events in patients with coronary artery disease. *World J Gastroenterol*. 2006;12:2923–2927.
32. Mangano DT. Aspirin and mortality from coronary bypass surgery. *N Engl J Med*. 2002;347:1309–1317.
33. Lanas A, Bajador E, Serrano P, et al. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med*. 2000; 343:834–839.
34. Battistella M, Mamdami MM, Juurlink DN, et al. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. *Arch Intern Med*. 2005;165:189–192.
35. Nielsen GL, Sorensen HT, Mellemkjoer L, et al. Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. *Am J Med*. 2001;111:541–545.
36. Kaufman DW, Kelly JP, Wiholm BE, et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. *Am J Gastroenterol*. 1999;94:3189–3196.
37. Landefeld CS, Cook EF, Flatley M, et al. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med*. 1987;82:703–713.
38. Sorensen HT, Mellemkjaer L, Blot WJ, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol*. 2000;95:2218–2224.
39. Weil J, Langman MJ, Wainwright P, et al. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. *Gut*. 2000;46:27–31.
40. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
41. Harker LA, Boissel JP, Pilgrim AJ, et al. Comparative safety and tolerability of clopidogrel and aspirin: results from CAPRIE. CAPRIE Steering Committee and Investigators. Clopidogrel versus aspirin in patients at risk of ischaemic events. *Drug Safety*. 1999;21:325–335.
42. Liberopoulos EN, Elisaf MS, Tselepis AD, et al. Upper gastrointestinal haemorrhage complicating antiplatelet treatment with aspirin and/or clopidogrel: where we are now? *Platelets*. 2006;17:1–6.
43. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*. 1992; 327:1406–1412.

44. Levine MN, Raskob G, Beyth RJ, et al. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:287S–310S.
45. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet*. 1996; 348:423–428.
46. Shireman TI, Mahnken JD, Howard PA, et al. Development of a contemporary bleeding risk model for elderly warfarin recipients. *Chest*. 2006;130:1390–1396.
47. Petty GW, Brown RD Jr, Whisnant JP, et al. Frequency of major complications of aspirin, warfarin, and intravenous heparin for secondary stroke prevention. A population-based study. *Ann Intern Med*. 1999;130:14–22.
48. Levine MN, Raskob G, Landefeld S, et al. Hemorrhagic complications of anticoagulant treatment. *Chest*. 2001;119: 108S–121S.
49. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. *Am J Med*. 1993;95:315–328.
50. Harenberg J, Huhle G, Piazolo L, et al. Long-term anticoagulation of outpatients with adverse events to oral anticoagulants using low-molecular-weight heparin. *Semin Thromb Hemost*. 1997;23:167–172.
51. Hallas J, Dall M, Andries A, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. *BMJ*. 2006;333:726.
52. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331–337.
53. Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation*. 2003;107:966–972.
54. Turpie AG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med*. 1993;329:524–529.
55. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med*. 2002;347: 969–974.
56. Barada K, Karrowni W, Abdallah M, et al. Upper gastrointestinal bleeding in patients with acute coronary syndromes: clinical predictors and role of proton pump inhibitors. *J Clin Gastroenterol*. 2007. In press.
57. Atar S, Cannon CP, Murphy SA, et al. Statins are associated with lower risk of gastrointestinal bleeding in patients with unstable coronary syndromes: analysis of the Orbofiban in Patients with Unstable coronary Syndromes-Thrombolysis In Myocardial Infarction 16 (OPUS-TIMI 16) trial. *Am Heart J*. 2006;151:976e1–6.
58. Popma JJ, Berger P, Ohman EM, et al. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:576S–599S.
59. Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J*. 2005;26:804–847.
60. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation*. 2006;113:156–175.
61. Artang R, Dieter RS. Analysis of 36 reported cases of late thrombosis in drug-eluting stents placed in coronary arteries. *Am J Cardiol*. 2007;99:1039–1043.
62. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007;297:159–168.
63. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med*. 2007;356:1009–1019.
64. Park DW, Park SW, Park KH, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. *Am J Cardiol*. 2006;98:352–356.
65. Ng FH, Wong SY, Chang CM, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. *Aliment Pharmacol Ther*. 2003;18:443–449.
66. Yusuf S, Zhao F, Mehta SR, et al. 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.
67. Peters RJ, Mehta SR, Fox KA, et al. 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.
68. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention-Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47:216–235.
69. Lip GY, Karpha M. Anticoagulant and antiplatelet therapy use in patients with atrial fibrillation undergoing percutaneous coronary intervention: the need for consensus and a management guideline. *Chest*. 2006;130:1823–1827.
70. Porter A, Konstantino Y, Iakobishvili Z, et al. Short-term triple therapy with aspirin, warfarin, and a thienopyridine among patients undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2006;68:56–61.
71. Rubboli A, Colletta M, Herzfeld J, et al. Periprocedural and medium-term antithrombotic strategies in patients with an indication for long-term anticoagulation undergoing coronary angiography and intervention. *Coron Artery Dis*. 2007;18: 193–199.
72. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*. 1998;105:91–99.
73. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet*. 2000;356:1318–1321.
74. Choudari CP, Rajgopal C, Palmer KR. Acute gastrointestinal haemorrhage in anticoagulated patients: diagnoses and response to endoscopic treatment. *Gut*. 1994;35:464–466.
75. Rubin TA, Murdoch M, Nelson DB. Acute GI bleeding in the setting of supratherapeutic international normalized ratio in patients taking warfarin: endoscopic diagnosis, clinical management, and outcomes. *Gastrointest Endosc*. 2003;58: 369–373.
76. Wilcox CM, Truss CD. Gastrointestinal bleeding in patients receiving long-term anticoagulant therapy. *Am J Med*. 1988; 84:683–690.
77. Tabibian N. Acute gastrointestinal bleeding in anticoagulated patients: a prospective evaluation. *Am J Gastroenterol*. 1989; 84:10–12.

78. Taha AS, Angerson WJ, Knill-Jones RP, et al. Upper gastrointestinal mucosal abnormalities and blood loss complicating low-dose aspirin and antithrombotic therapy. *Aliment Pharmacol Ther*. 2006;23:489–495.

79. Thomopoulos KC, Mimidis KP, Theocharis GJ, et al. Acute upper gastrointestinal bleeding in patients on long-term oral anticoagulation therapy: endoscopic findings, clinical management and outcome. *World J Gastroenterol*. 2005;11:1365–1368.

80. Choudari CP, Palmer KR. Acute gastrointestinal haemorrhage in patients treated with anticoagulant drugs. *Gut*. 1995;36: 483–484.

81. Qvigstad G, Hatlen-Rebhan P, Brenna E, et al. Capsule endoscopy in clinical routine in patients with suspected disease of the small intestine: a 2-year prospective study. *Scand J Gastroenterol*. 2006;41:614–618.

82. Baker RI, Coughlin PB, Gallus AS, et al. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *Med J Aust*. 2004;181:492–497.

83. White RH, McKittrick T, Takakuwa J, et al. Management and prognosis of life-threatening bleeding during warfarin therapy. National Consortium of Anticoagulation Clinics. *Arch Intern Med*. 1996;156:1197–1201.

84. Makar GA, Ginsberg GG. Therapy insight: approaching endoscopy in anticoagulated patients. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3:43–52.

85. Baglin TP, Keeling DM, Watson HG. Guidelines on oral anticoagulation (warfarin): third edition–2005 update. *Br J Haematol*. 2006;132:277–285.

86. Ananthasubramaniam K, Beattie JN, Rosman HS, et al. How safely and for how long can warfarin therapy be withheld in prosthetic heart valve patients hospitalized with a major hemorrhage? *Chest*. 2001;119:478–484.

87. Kuwada SK, Balm R, Gostout CJ. The risk of withdrawing chronic anticoagulation because of acute GI bleeding. *Am J Gastroenterol*. 1996;91:1116–1119.

88. Blacker DJ, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. *Neurology*. 2003;61:964–968.

89. Lubetsky A, Yonath H, Olchovsky D, et al. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. *Arch Intern Med*. 2003;163:2469–2473.

90. Sconce EA, Kamali F. Appraisal of current vitamin K dosing algorithms for the reversal of over-anticoagulation with warfarin: the need for a more tailored dosing regimen. *Eur J Haematol*. 2006;77:457–462.

91. Dager WE, King JH, Regalia RC, et al. Reversal of elevated international normalized ratios and bleeding with low-dose recombinant activated factor VII in patients receiving warfarin. *Pharmacotherapy*. 2006;26:1091–1098.

92. Ingerslev J, Vanek T, Culic S. Use of recombinant factor VIIa for emergency reversal of anticoagulation. *J Postgrad Med*. 2007;53:17–22.

93. Lankiewicz MW, Hays J, Friedman KD, et al. Urgent reversal of warfarin with prothrombin complex concentrate. *J Thromb Haemost*. 2006;4:967–970.

94. van Aart L, Eijkhout HW, Kamphuis JS, et al. Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: an open, prospective randomized controlled trial. *Thromb Res*. 2006;118:313–320.

95. Fiore LD, Scola MA, Cantillon CE, et al. Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis*. 2001;11: 175–183.

96. Cameron EA, Pratap JN, Sims TJ, et al. Three-year prospective validation of a pre-endoscopic risk stratification in patients with acute upper-gastrointestinal haemorrhage. *Eur J Gastroenterol Hepatol*. 2002;14:497–501.

97. Strate LL, Saltzman JR, Ookubo R, et al. Validation of a clinical prediction rule for severe acute lower intestinal bleeding. *Am J Gastroenterol*. 2005;100:1821–1827.

98. Jensen DM, Cheng S, Kovacs TO, et al. A controlled study of ranitidine for the prevention of recurrent hemorrhage from duodenal ulcer. *N Engl J Med*. 1994;330:382–386.

99. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med*. 2002;346:2033–2038.

100. Lanas A, Fuentes J, Benito R, et al. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Pharmacol Ther*. 2002;16: 779–786.

101. Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med*. 2001;344:967–973.

102. Ng FH, Wong BC, Wong SY, et al. Clopidogrel plus omeprazole compared with aspirin plus omeprazole for aspirin-induced symptomatic peptic ulcers/erosions with low to moderate bleeding/re-bleeding risk—a single-blind, randomized controlled study. *Aliment Pharmacol Ther*. 2004;19: 359–365.

103. 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.

104. Lanas A. Prevention of aspirin-induced gastroduodenal damage: *H. pylori* infection eradication versus proton pump inhibitors or both. *Dig Liver Dis*. 2004;36:655–657.

105. Lanas A, Rodrigo L, Marquez JL, et al. Low frequency of upper gastrointestinal complications in a cohort of high-risk patients taking low-dose aspirin or NSAIDs and omeprazole. *Scand J Gastroenterol*. 2003;38:693–700.

106. Pilotto A, Franceschi M, Longoa MG, et al. *Helicobacter pylori* infection and the prevention of peptic ulcer with proton pump inhibitors in elderly subjects taking low-dose aspirin. *Dig Liver Dis*. 2004;36:666–670.

107. Cryer B. Reducing the risks of gastrointestinal bleeding with antiplatelet therapies. *N Engl J Med*. 2005;352:287–289.

108. Younossi ZM, Strum WB, Schatz RA, et al. Effect of combined anticoagulation and low-dose aspirin treatment on upper gastrointestinal bleeding. *Dig Dis Sci*. 1997;42: 79–82.

109. Kimmey MB. Cardioprotective effects and gastrointestinal risks of aspirin: maintaining the delicate balance. *Am J Med*. 2004;117(suppl 5A):72S–78S.

110. Blackshear JL, Baker VS, Holland A, et al. Fecal hemoglobin excretion in elderly patients with atrial fibrillation: combined aspirin and low-dose warfarin vs conventional warfarin therapy. *Arch Intern Med*. 1996;156:658–660.

