New Anticoagulant and Antiplatelet Agents: A Primer for the Gastroenterologist

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A large number of patients worldwide receive anticoagulant and antiplatelet agents, collectively known as antithrombotic agents. Several new anticoagulants and antiplatelet agents recently were approved for use. Gastroenterologists may be unfamiliar with the mechanism of action, indications for use, and pharmacokinetics of these newer drugs. In patients undergoing elective and urgent endoscopic procedures, clinicians must be familiar with these medications to optimize outcomes. When the decision is made to continue the newer antithrombotic agents for elective procedures, the clinician must understand the risk that these agents may impart on procedural-induced bleeding. Finally, it is important to understand how to manage these agents in the presence of acute gastrointestinal bleeding. In this article the use of newer antithrombotic agents is reviewed.

Keywords: Anticoagulants/Administration and Dosage; Atrial Fibrillation; Drug Administration Schedule; Drug Monitoring; Thrombosis/Drug Therapy; Endoscopy; Gastrointestinal.

Podcast interview: www.gastro.org/cghpodcast. Also available on iTunes.

Development of New Anticoagulants

The vitamin K antagonist, dicoumarol, was first isolated at the Wisconsin Alumni Research Foundation and therefore subsequently was named warfarin. Warfarin was essentially the only oral anticoagulant used in the United States for more than 50 years. It is Food and Drug Administration (FDA) approved for prophylaxis and treatment of venous thrombosis and its extension, PE, and for prophylaxis and treatment of thromboembolic complications associated with AF and/or mechanical heart valve placement, and for secondary prevention of thrombotic events after myocardial infarction (MI). Unfortunately, warfarin has a narrow therapeutic window and safety margin, a slow onset and offset, requires frequent and careful laboratory monitoring, and its anticoagulation effects are altered by diet and many medications. Such limitations have led to the development of newer anticoagulants. On the other hand, warfarin has a proven track to understand how to manage these agents in the setting of urgent/emergent endoscopic procedures and in the presence of acute gastrointestinal (GI) bleeding.

Several societies have published guidelines that define which endoscopic procedures are low risk and high risk for bleeding and the management of traditional antithrombotic agents in the periprocedural period. Patients at high, moderate, and low risk for thromboembolic events when antithrombotic agents have been discontinued also have been defined, and recommendations made as to which patients should receive periprocedural bridging anticoagulation. In this review, details of these guidelines are not discussed; instead, we focus on the antithrombotic agents themselves.

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record, is familiar to nearly all clinicians, and can be reversed easily and rapidly. Historically, this has been achieved with vitamin K and plasma. For severe warfarin-related bleeding, 4-factor prothrombin complex concentrates (PCCs) are now recommended as first-line agents, especially in patients with cardiac failure in whom administration of fresh-frozen plasma may be associated with volume overload. PCCs may be useful in the treatment of uncontrollable bleeding in the setting of newer anticoagulants. Thus, before discussing the new anticoagulants agents, it is worthwhile to discuss reversal agents.

Reversal Agents for Novel Anticoagulants

Traditional anticoagulant reversal agents include fresh-frozen plasma and vitamin K (for VKAs), and protamine sulfate (for unfractionated and low molecular weight heparin). These agents have no role in reversal of novel oral anticoagulants.

It is strongly recommended that a specialist with specific knowledge of the novel antithrombotic agents be involved when decision making requires reversal of the newer anticoagulants. It also must be emphasized that there are no proven reversal agents for new oral anticoagulants and the data for reversal are quite limited. In addition, when attempts are made to reverse the effects of novel anticoagulants, there is the potential for increasing the thrombotic risk.

Recombinant Factor VIIa

Factor VII (FVII) initiates coagulation in conjunction with tissue factor through the activation of factor X and subsequently prothrombin (Figure 1). Recombinant factor VIIa is FDA-approved (NovoSeven; Novo Nordisk Inc, Plainsboro, NJ) for the treatment of hemophilia. It has been used off-label, either alone or in conjunction with other agents for the reversal of novel anticoagulants as described with each agent. Use of this agent should be restricted to patients with major GI bleeding that otherwise cannot be controlled with supportive care and endoscopic measures.

Prothrombin Complex Concentrates

PCCs contain clotting factors prepared from pooled and concentrated human plasma. Three of the FDA-approved PCCs are indicated for the treatment of hemophilia, and one for reversal of warfarin-induced major bleeding. It is important to note that not all PCCs are the same and are distinguished by factor content (3-factor or 4-factor PCCs). Nonactivated 3-factor PCCs available in the United States are Bebulin VH (Baxter Healthcare Corporation, Princeton, NJ) and Profilnine SD (Grifols Biologicals Inc, Los Angeles, CA). These agents contain factors II, IX, and X. Nonactivated 4-factor PCCs contain factors II, VII, IX, and X, and proteins C and S and antithrombin, and only one such agent recently became
available in the United States. This agent, Kcentra, is FDA approved for urgent reversal of warfarin-induced bleeding. Compared to fresh frozen plasma, this agent carries less than half the risk for volume overload in patients with heart failure. There is a small increased risk of thrombosis associated with its use. One activated 4-factor PCC, Factor VIII inhibitor bypass activity (FEIBA NF; Baxter Healthcare Corporation, Westlake Village, CA) is available in the United States. Theoretically, the addition of recombinant FVIIa (rFVIIa) to a 3-factor PCC is equal to a 4-factor PCC, although this has not been substantiated in clinical practice.

### New Anticoagulants

New anticoagulants are available that can be administered orally, subcutaneously, or intravenously and act by directly inhibiting factor Xa (direct factor X inhibitors [DXIs]) or thrombin (direct thrombin inhibitors [DTIs]) (Figure 1 and Table 1). If the decision is made to discontinue any of these agents before endoscopic procedures to limit the risk of bleeding, 3 plasma drug half-lives is the minimum amount of time (drug concentration, approximately 10%) to wait before performing the procedure; 5 drug half-lives are safer. There are, however, no data that have determined outcomes of endoscopic procedures specifically based on time intervals of drug discontinuation. Table 2 provides the half-lives of the 3 oral anticoagulants based on the estimated rate of creatinine clearance (CrCl).

### Oral Agents

Clinicians need to be most familiar with the new oral anticoagulants because these increasingly are being prescribed and encountered in gastroenterology practices. Oral agents include dabigatran, rivaroxaban, and the recently approved apixaban. These 3 agents have been found to be at least as effective as warfarin for the prevention of thromboembolic complications of AF and the treatment of venous thromboembolism with favorable safety profiles.

Although an advantage of novel anticoagulants over warfarin is the lack of a need for monitoring, there is also a lack of routinely available monitoring assays for these agents. Standard hemostatic test results often are abnormal in patients taking new oral anticoagulants. Routine hemostatic tests can be useful for determining the absence of residual drug effect when normal, but

### Table 1. Overview of New Oral Anticoagulant Agents

<table>
<thead>
<tr>
<th>Agent (trade name)</th>
<th>Mechanism of action</th>
<th>Onset of action, h</th>
<th>Half-life based on CrCl, mL/min</th>
<th>Management of uncontrolled bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>DTI</td>
<td>1–3</td>
<td>&gt;80 d, 14 h; 50–79 d, 17 h; 30–49 d, 19 h; &lt;30 d, 28 h</td>
<td>Hemodialysis, charcoal hemoperfusion; consider FEIBA or recombinant activated Factor VIIa only in extreme emergencies, given the risk of thrombosis</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Direct Factor Xa inhibitor</td>
<td>1–3</td>
<td>&gt;80 d, 8 h; 50–79 d, 9 h; 30–49 d, 9 h; &lt;30 d, 9.5 h</td>
<td>Consider PCCs, particularly 4-factor (Kcentra) in cases of severe bleeding unresponsive to more conservative measures</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>Direct Factor Xa inhibitor</td>
<td>1–3</td>
<td>&gt;50 d, 15 h; &lt;30–49 d, 18 h</td>
<td>Charcoal hemoperfusion; consider PCCs, particularly 4-factor (Kcentra) in cases of severe bleeding unresponsive to more conservative measures</td>
</tr>
</tbody>
</table>

### Table 2. Effects of New Oral Anticoagulants on Routine Hemostatic Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>aPTT</th>
<th>PT</th>
<th>TT</th>
<th>ECT</th>
<th>Anti-FXa activity assays</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Moderately sensitive; reflects relative intensity of effect</td>
<td>Insensitive</td>
<td>Highly sensitive</td>
<td>Sensitive; good linear relationship; not uniformly available</td>
<td>Not useful</td>
<td>Normal aPTT and TT likely exclude substantial drug effect</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Reasonably sensitive</td>
<td>Insensitive and reagent-dependent</td>
<td>No effect</td>
<td>No effect</td>
<td>Probably accurate</td>
<td>A normal PT or anti-Xa level likely exclude clinically relevant circulating drug</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Reasonably sensitive</td>
<td>Insensitive and reagent-dependent</td>
<td>No effect</td>
<td>Unlikely to have effect</td>
<td>Probably accurate</td>
<td>A normal anti-Xa level exclude clinically relevant circulating drug</td>
</tr>
</tbody>
</table>

ECT, ecarin clotting time.
abnormal clotting tests do not necessarily reflect the degree of anticoagulation. Moreover, commercial reagents for routine laboratory tests vary in responsiveness to the new agents. Laboratory assay monitoring has not shown improved safety or efficacy of the clinical use of these novel agents. It must be emphasized that the international normalized ratio is only standardized for VKAs and is of no value for monitoring therapy with new oral anticoagu-
lants. Table 2 shows the effects of each oral anticoagulant drug on clotting tests.

**Dabigatran (Pradaxa; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT).** Dabigatran, a DTI, was the first new oral anticoagulant to be approved in nearly 50 years in the United States. It is FDA-approved for the prophylaxis of thromboembolic complications in nonvalvular AF. In the landmark Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial, dabigatran and warfarin were compared in patients with nonvalvular AF. Although dabigatran reduced embolic complications, its use were compared in patients with nonvalvular AF. Although dabigatran reduced embolic complications, its use conferred a significant increased risk in all causes of GI bleeding. However, a recent analysis of postmarketing data suggested that GI bleeding rates associated with dabigatran use do not appear to be higher than those associated with warfarin. Nonetheless, dabigatran is assumed to increase the risk of postprocedural bleeding significantly after high-risk endoscopic procedures. This increase in GI bleeding is believed to be caused by active drug present in the GI tract, which may promote bleeding through a topical effect.

In the RE-LY trial, dabigatran-treated patients experienced more frequent upper GI symptoms, apart from bleeding, compared with warfarin-treated controls. However, the symptoms were usually mild to moderate, appeared within 3 months of initiation of treatment, and added to the significantly greater frequency of dabigatran discontinuation compared to warfarin. Upper GI symptoms were associated with an increased risk of GI bleeding (including life-threatening bleeding), although the risk is comparable in patients with these symptoms who are treated with warfarin.

Although specific laboratory monitoring is neither widely available nor indicated for dabigatran, it affects routine hemostatic tests (Table 2). The prothrombin time (PT) is relatively insensitive to dabigatran but the drug prolongs the activated partial thromboplastin time (aPTT), thrombin time (TT), and ecarin clotting time, a specific assay for thrombin generation. The TT is most sensitive for dabigatran effect and the PT is least sensitive. The aPTT is most readily available and easily obtained. A normal aPTT and TT excludes the presence of clinically important levels of circulating dabigatran. Furthermore, dabigatran may adversely impact other thrombophilia testing, including lupus anticoagulant evaluation.

Dabigatran has a half-life of 12 to 17 hours in patients with normal renal function and most experts recommend the drug be withheld 1 to 2 days before endoscopic procedures with high bleeding risk in the setting of normal renal function. Because the drug is excreted primarily via the kidneys, recommendations are for the agent to be withheld for longer periods in patients with moderate to severe renal impairment based on the estimated CrCl rate. With a CrCl of 30 to 49 mL/min, the drug should be withheld for at least 3 days and in those with a CrCl less than 30 mL/min (for which the half-life is >24 h), the drug should be withheld for at least 5 days (Table 1).

At our institution a more conservative approach is taken with the timing of withdrawal before high-risk procedures. We have recommended withholding dabigatran for 5 days before an invasive high-risk bleeding procedure in patients with a CrCl greater than 50 mL/min and for 7 days for those with chronic kidney disease.

The action of dabigatran is not reversible and elective high-risk bleeding procedures should be avoided if possible in patients receiving the drug. It is not known whether the drug can be continued safely for removal of large polyps when prophylactic measures to prevent bleeding are undertaken such as placement of endoloops with or without endoclips (for pedunculated polyps), or placement of endoclips alone (for sessile polyps) as described in the setting of conventional antithrombotic agents. Use of cold snare polypectomy could be considered for polyps less than 1 cm because the risk for delayed bleeding with this technique is extremely low.

In the setting of active GI bleeding (postprocedural or otherwise), withholding the drug and supportive care including appropriate transfusion of packed red blood cells and endoscopic therapy for hemostasis is the treatment of choice. If endoscopic measures fail, interventional radiologic procedures for embolization, when appropriate, are indicated.

In patients undergoing elective endoscopic retrograde cholangiopancreatography (ERCP) in whom prior sphincterotomy was performed, the risk of bleeding is not likely increased (assuming the sphincterotomy is not extended using electrocautery) and antithrombotic agents can be continued in this setting. For patients requiring emergency ERCP we recommend avoidance of a sphincterotomy if possible. Because the main indications for emergent/urgent ERCP are relief of cholangitis and treatment of bile leaks, we recommend biliary stent placement without endoscopic sphincterotomy, or balloon sphincteroplasty (for stones), although the latter carries a higher risk of post-ERCP pancreatitis. At a later date, elective sphincterotomy can be performed, if necessary, after temporary cessation of dabigatran. If sphincterotomy is required during emergent ERCP (eg, precut or access sphincterotomy), then measures to prevent bleeding such as placement of endoclips or cautering the sphincterotomy site could be considered. Alternatively, bleeding can be managed expectantly.

There is no specific antidote for the dabigatran’s anticoagulant effect. Fresh-frozen plasma and PCCs do not reverse the effects of dabigatran. FEIBA, rFVIIa, and hemodialysis have been used in animals, normal volunteers, and, anecdotally, in patients, and thus can be considered when supportive and endoscopic/percutaneous
management fail to control ongoing severe bleeding. Both of these agents should be used judiciously and only when absolutely necessary given the prothrombotic risk. Hemodialysis is effective in removing the drug, particularly in patients with renal impairment.19,22 Charcoal hemoperfusion also may be effective (Table 1).18

**Rivaroxaban (Xarelto; Janssen Pharmaceuticals, Inc, Titusville, NJ).** Rivaroxaban, an oral DXI, is FDA-approved for stroke prophylaxis in patients with nonvalvular AF and the prophylaxis of DVT and pulmonary embolus after hip and knee replacement surgery.32 It recently was FDA-approved for the acute treatment of DVT and PE. Clinicians should be aware that the drug is avoided in the setting of advanced cirrhosis, especially advanced hepatic disease with coagulopathy (Child–Pugh class B or C) and severe renal insufficiency.23

Similar to dabigatran, specific laboratory monitoring is neither widely available nor indicated for rivaroxaban. Rivaroxaban may impact normal hemostatic tests (Table 2). However, a normal PT suggests a lack of clinically relevant anticoagulation effect.32 Anti–factor Xa chromogenic assay levels correlate well with plasma drug concentrations, but are not uniformly available, especially in emergent situations.32

In patients with normal renal function, the half-life of rivaroxaban is 5 to 9 hours in young patients and 11 to 13 hours in elderly patients32 and the drug should be withheld for 1 to 2 days before high-risk endoscopic bleeding procedures (Table 1). Similar to dabigatran, the timing of cessation before endoscopic high-risk bleeding procedures is increased in the presence of severe renal insufficiency. Recommendations are to withhold the drug for 2 days in patients with a CrCl of 60 to 90 mL/min and for 3 days for a CrCl of 30 to 59 mL/min (Table 1). Similar to dabigatran, our institutional guidelines are more conservative than these recommendations. In patients with a CrCl greater than 50 mL/min, we would recommend discontinuation for 3 days before the anticipated procedural date. For patients with stage 3 chronic kidney disease (CrCl of 30–59 mL/min), we would recommend stopping for 5 days, and for patients with a CrCl of 30 to 59 mL/min, we would recommend stopping for 7 days. For stage 4 disease (CrCl 15–29 mL/min), we would suggest stopping for 7 days to allow adequate time for complete drug metabolism. Patients with stage V chronic kidney disease should not be taking this medication. If the CrCl is <15 mL/min, then elective procedures should be postponed until complete drug metabolism can be insured.

In the setting of emergent endoscopic procedures and active GI bleeding the same general concepts apply as for dabigatran with supportive care and endoscopic therapy. In the setting of life-threatening bleeding, PCCs (FEIBA, 4-factor PCC) may be of benefit,18,34 although cannot be guaranteed. Dialysis is not effective, although charcoal hemoperfusion may be effective (Table 1).18

**Apixaban (Elquis; Bristol-Myers Squibb Company, Princeton, NJ).** Apixaban, another DXI, is FDA-approved for the prophylaxis of stroke in the setting of nonvalvular AF. Early studies suggested there is a lower, although nonsignificant, rate of GI bleeding compared with warfarin in patients treated for prophylaxis of complications from AF.35 In a recent meta-analysis, apixaban appeared to carry a lower rate of both major bleeding and GI bleeding compared with dabigatran. There are no randomized trial data with head to head comparison of these agents currently available or on the near horizon.36

Apixaban has a half-life of 8 to 15 hours and is less dependent on renal clearance compared with other agents (Table 1).22 Because the drug’s mechanism of action is the same as rivaroxaban, it is anticipated to have similar effects on normal hemostatic parameters and factor Xa chromogenic assays, and reversal (Tables 1 and 2).

Management of patients requiring emergent endoscopic procedures and those with active GI bleeding should likely be approached in a manner similar to rivaroxaban.

**Subcutaneous Agents**

**Fondaparinux (Arixtra; GlaxoSmithKline, Research Triangle Park, NC).** Fondaparinux is a subcutaneously administered Factor Xa inhibitor that is FDA-approved for prophylaxis of DVT and PE in patients undergoing hip fracture, hip replacement, knee replacement, or abdominal surgery. It also is approved for the treatment of acute DVT and PE when administered with warfarin. Fondaparinux nearly completely is cleared by the kidney with a half-life of 17 hours in young patients and 21 hours in elderly patients.37,38 Fondaparinux should be discontinued for 36 to 48 hours before an endoscopic procedure with a high risk of bleeding.39 Longer times are required when the estimated CrCl is less than 60 mL/min.40

Fondaparinux has no effect on the PT and a minimal effect on the aPTT.19 Fondaparinux-specific anti-Xa assays can determine anticoagulant activity, although are not universally available.

As with other novel agents there are no specific reversal agents. Nonspecific agents that may be used in the setting of major bleeding may include nonactivated PCCs and recombinant factor VIIa.6

**Desirudin (Iprivask; GlaxoSmithKline).** Desirudin is a subcutaneously administered DTI that is FDA-approved for prophylaxis of DVT and PE in patients undergoing elective hip replacement. It has a short half-life and should be discontinued for 2 hours before high-risk procedures.

The aPTT dose-response to desirudin is not linear and plateaus at higher doses.38 However, a normal aPTT and TT exclude clinically relevant residual drug effect. The ecarin clotting time shows a more linear dose response and, if normal, also excludes a clinically relevant residual anticoagulant effect.38 This assay is not widely available.
There are no reversal agents for this drug, although rFVIIa may be effective.48

**Intravenous Agents**

Two available intravenous DTI agents are mentioned only in passing because they are encountered uncommonly in gastroenterological practices. Both agents have short half-lives.

Bivalirudin (Angiomax; The Medicines Company, Parsippany, NJ) is FDA-approved for patients undergoing percutaneous coronary interventions (PCI) as an alternative to heparin. When used for PCI, bivalirudin use may also include antiplatelet therapy with aspirin and a thienopyridine. Argatroban (GlaxoSmithKline) is FDA-approved for use in patients with heparin-induced thrombocytopenia.

With these agents, all thrombin-dependent coagulation assays are affected, including the PT/international normalized ratio, aPTT, TT, and ecarin clotting time in a dose-dependent fashion.

**Resumption of Anticoagulants**

The ideal timing of resumption of newer antithrombotic agents after high-risk endoscopic procedures and endoscopic hemostasis of GI bleeding is not known. As with many decisions related to anticoagulation, the risk of bleeding must be balanced against the risk of thromboembolic events. The mechanisms of immediate (intraprocedural) and early bleeding (within 24 hours) differ from those causing delayed bleeding. The former are associated with severing of blood vessels, while the latter are associated with the result of tissue injury, vessel erosion, and delayed sloughing of the hemostatic eschar. Thus, in those patients in whom there is a low risk of delayed bleeding, one may consider re-initiation of anticoagulants early after the procedure (within 12–24 h).49 We recommend delaying re-initiation of oral anticoagulants for at least 48 hours after high-risk procedures because full anticoagulation occurs shortly after administration. For patients in whom biliary sphincterotomy is performed, resumption of these agents should be delayed for at least 72 hours because re-initiation of traditional anticoagulants within this period is associated with an increased risk of delayed bleeding.50 For patients who are at high risk of delayed bleeding (eg, after endoscopic mucosal resection of large sessile polyps and endoscopic submucosal dissection) and who are at low risk for antithrombotic events, it would be reasonable to hold anticoagulation for 7 days.

In a recent trial of patients receiving warfarin in the setting of active GI bleeding, resumption of anticoagulation at a mean of 4 days after hemostasis was achieved was associated with a 3-fold lower risk of death, a more than 10-fold reduction in thrombotic events, and an increased risk of recurrent GI bleeding (nonsignificant) compared with patients whose warfarin was withheld.45 There were no fatalities in patients who had recurrent bleeding when therapy was resumed. Whether these data can be used to guide patients on newer anticoagulants is not known.

**Antiplatelet Agents**

The time-honored antiplatelet agent is aspirin. In patients with coronary stents, aspirin is used in combination with another agent, commonly referred to as dual-antiplatelet therapy, to prevent stent thrombosis. It is important to note that premature discontinuation of these agents in anticipation of endoscopic procedures may lead to stent thrombosis44,45 and precipitation of MI with a mortality rate of 50% or higher. The greatest risk of stent thrombosis of bare-metal stents is within 6 weeks after placement, and for drug-eluting stents is 3 to 6 months after placement.46 Some patients with coronary stents require dual-antiplatelet therapy indefinitely. For management of antiplatelet agents in patients with coronary stents during the peri-endoscopic period it is strongly advised that the ordering gastroenterologist and/or endoscopist performing the procedure coordinate decision making of antiplatelet therapy with the patient’s cardiologist or primary provider. We believe such coordination potentially will minimize the risk of premature antiplatelet discontinuation and subsequent stent thrombosis. Moreover, this approach may reduce the risk of bleeding if practitioners continue these agents unnecessarily as a result of fear of stent thrombosis.

**Newer Antiplatelet Agents**

**Oral Agents**

FDA-approved, orally administered, adenosine diphosphate–receptor/P2Y12 inhibitors include clopidogrel, prasugrel, and ticagrelor (Table 3). All 3 agents are used acutely and/or long term, primarily for the treatment of coronary artery disease in patients with and without coronary stents or other percutaneous interventions.

**Clopidogrel (Plavix; Bristol-Myers Squibb/Sanoﬁ Pharmaceuticals Partnership, Bridgewater, NJ).** Clopidogrel is FDA-approved for the treatment of recent acute coronary syndromes (unstable angina, MI, non-ST elevation MI or ST elevation MI), recent stroke, or established peripheral arterial disease. Clopidogrel is a pro-drug that requires hepatic metabolism for activation through the CYP2C19 pathway. Clopidogrel is absorbed rapidly, with 25% to 30% platelet inhibition achieved as early as 2 days, and 50% to 60% platelet inhibition achieved by 1 week after initiation when usual maintenance doses (75 mg/d) are administered. Clopidogrel loading (300–600 mg) can achieve platelet inhibition within 2 to 4 hours when the higher dose is administered.10 The hemostatic implications of clopidogrel loading include the possibility of rapid...
initiation of antiplatelet therapy if the endoscopic procedure performed had a lower risk of bleeding than anticipated pre-procedurally (eg, anticipated sphincterotomy or polypectomy was not performed). Early and rapid re-institution of antiplatelet therapy may increase the risk of delayed bleeding (eg, postpolypectomy, post-sphincterotomy) as has been described for warfarin.42

Clopidogrel increases the risk of postprocedural bleeding in patients undergoing high-risk endoscopic procedures, especially when used in combination with aspirin.8 When the decision is made to withhold Clopidogrel for a procedure with a high risk of bleeding, it should be withheld for at least 5 days. The drug irreversibly inhibits platelets for their lifespan (10–11 days). For each day after interruption, approximately 10% to 14% of platelet population is regenerated.8 Thus, some platelet function is restored even after 1 day of drug discontinuation as new platelets enter the circulation.

An important drug interaction with clopidogrel is the use of proton pump inhibitors. Administration of any of the proton pump inhibitors can attenuate clopidogrel activation by inhibiting hepatic cytochrome CYP2C19. The clinical implications of this inhibition are unclear,47 although a recent meta-analysis suggested proton pump inhibitor administration did not increase the incidence of major adverse cardiovascular events, although it significantly reduced the risk of adverse GI events in patients receiving clopidogrel.48

**Prasugrel (Effient; Eli Lilly and Company, Indianapolis, IN).** Prasugrel is FDA-approved for the reduction of cardiovascular events and stent thrombosis in patients with acute coronary syndrome and both non-ST-elevation MI and ST-elevation MI, managed with percutaneous coronary intervention. Like clopidogrel, this drug requires hepatic metabolism for activation, however the pathway for activation is CYP3A4 and CYP2B6. Therefore, PPI therapy does not impair activation. Prasugrel has a rapid onset of action and is 10 to 100 times more potent than clopidogrel in inhibiting platelet aggregation.49 A 60-mg loading dose can produce greater platelet inhibition than a 600-mg clopidogrel loading dose.47 It is also a nonreversible platelet inhibitor and should be withheld for 7 days before an elective high-risk procedure.

**Ticagrelor (Brilinta; AstraZeneca, Wilmington, DE).** Ticagrelor is a nonthienopyridine ADP P2Y12 platelet inhibitor that is FDA-approved for a reduction in the rate of thrombotic cardiovascular events in patients with acute coronary syndrome with or without coronary stents. Like prasugrel, ticagrelor is metabolized by the CYP3A4 cytochrome, however both the parent drug and metabolite provide platelet inhibition. Ticagrelor has a more rapid onset and offset of platelet inhibition than clopidogrel and prasugrel,47 with peak inhibition 2 to 4 hours after administration.49 The antiplatelet effects decline rapidly over a 72-hour period after cessation, and platelet activity is near normal at 5 days.47

Monitoring of antiplatelet function or platelet aggregometry may allow for determination of residual drug effects but these studies have been performed primarily in patients undergoing cardiac surgery or percutaneous coronary interventions and have not predicted clinical outcomes.8,49 Their use before endoscopic procedures has not been studied.

The safety of high-risk emergent endoscopic procedures while on single-agent antiplatelet therapy is unknown, particularly because patients usually are receiving both aspirin and another antiplatelet agent. The same precautions should be applied as for anticoagulants.

Treatment of GI bleeding either postprocedurally or otherwise is similar to that in patients taking anticoagulants. Reversal of the action of these antiplatelet agents traditionally includes administration of platelets. Platelet transfusion alone, however, may not be completely effective in restoring hemostasis.

**Intravenous Agents**

Glycoprotein IIb/IIIa inhibitors are potent antagonists of platelet aggregation. These drugs uncommonly are encountered by gastroenterologists because they are used acutely during percutaneous coronary interventions. They achieve rapid, reversible platelet inhibition and have short half-lives (minutes to hours), and include abciximab (Reopro; Eli Lilly and Company), tirofiban (Aggrastat; Baxter Healthcare Corporation, Princeton, NJ), and Eptifibatide (Integrilin; Schering Corporation, Kenilworth, NJ).

### Table 3. Overview of Newer Oral Antiplatelet Agents

<table>
<thead>
<tr>
<th>Agent (trade name)</th>
<th>Mechanism of action</th>
<th>Recommended interval between last dose and high-risk endoscopic procedure, d</th>
<th>Laboratory monitoring</th>
<th>Emergency reversal agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>ADP P2Y12-receptor antagonist</td>
<td>5</td>
<td>None (consider platelet function testing)</td>
<td>Consider platelet transfusion</td>
</tr>
<tr>
<td>Prasugrel (Effient)</td>
<td>ADP P2Y12 receptor antagonist</td>
<td>7</td>
<td>None (consider platelet function testing)</td>
<td>Consider platelet transfusion</td>
</tr>
<tr>
<td>Ticagrelor (Brilinta)</td>
<td>ADP P2Y12 receptor antagonist</td>
<td>5</td>
<td>None (consider platelet function testing)</td>
<td>Consider platelet transfusion</td>
</tr>
</tbody>
</table>

ADP, adenosine diphosphate.
Resumption of Oral Antiplatelet Agents

After an endoscopic procedure, the risk of bleeding must be weighed carefully against the risk of thrombosis. Deciding when to re-initiate therapy therefore can be quite complicated. We advocate a close collaboration between the endoscopist and the clinician prescribing these agents to strike a balance between the risks of bleeding and clotting. As mentioned, clopidogrel initiated at maintenance doses has a delayed onset of action and can be re-initiated within 48 hours after high-risk endoscopic procedures. Cautious re-initiation of prasugrel and ticagrelor should be considered because they have a more rapid onset of action, are potent antiplatelet inhibitors, and their action cannot be reversed reliably.

Conclusions

There are now a variety of new anticoagulants and antiplatelet agents. Knowledge of these antithrombotic agents is essential for optimizing endoscopic outcomes after high-risk procedures and GI bleeding. When a decision has been made to discontinue the agents temporarily before endoscopy, knowledge of the pharmacodynamics allows the timing of cessation and re-initiation to be determined to minimize bleeding risk. New antithrombotic agents are on the horizon and a deeper understanding of the mechanism of action of these drugs by the gastroenterologist is needed as more of these drugs are approved.

References


1. After a high-risk endoscopic procedure, new oral anticoagulants can be resumed at:
   a. same day as the procedure
   b. day after for cold snare polypectomy of small polyps
   c. 72 hours for sphincterotomy
   d. 7 days for EMR

2. A patient with severe heart failure (EF 15%), on chronic anticoagulation with warfarin is admitted with severe life-threatening GI bleed. INR is 8.5. The best course of action is
   a. immediate upper endoscopy under anesthesia
   b. vitamin K subcutaneously daily for 3 days
   c. 4-6 units of fresh frozen plasma to improve INR
   d. therapy with non-activated 4-factor prothrombin complex concentrate

True or False

3. Of the three new oral anti-thrombotic agents, rivaroxaban has the shortest half life

4. The new oral anticoagulants (dabigatran, rivaroxaban and apixaban) usually prolong PTT but do not change PT or INR.

5. Ticagrelor’s antiplatelet action declines rapidly after stopping therapy, with near-normal platelet function 5 days after stopping.

6. Dabigatran may be associated with increased risk of GI bleeding post procedure, in part because active drug present in the GI tract may promote bleeding through a topical effect

7. A patient with post-polypectomy bleeding while on dabigatran should be given fresh frozen plasma transfusions.

8. Prasugrel is more potent than clopidogrel and should be withheld for 7 days before high risk procedures

9. When re-starting anti-platelet agents post high risk procedure, clopidogrel at standard dose has a slower onset of action than prasugrel and ticagrelor and can be started earlier.