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Antithrombotic Agents

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Ask the Expert features questions submitted by members with answers provided by ASGE physician experts.

1. **Q. In general, how soon should anticoagulants or antiplatelet medications be stopped prior to a procedure? Is there a simple algorithm that can be followed for each class of drug?**

   A. There are a number of important, basic considerations prior to the interruption of antithrombotic agents. First, you must know if your planned procedure is high or low risk for procedural bleeding (Table 1). For most low-risk procedures, it is unnecessary to interrupt anticoagulants or antiplatelet agents, including aspirin. For high-risk procedures, the timing of drug discontinuation depends on the agent, its half-life and the anticipated residual antithrombotic effect.

   If you plan to perform a high-risk procedure and the patient is on warfarin, hold the drug for five days prior to the procedure. The timing of the last dose of a direct oral anticoagulant agent (DOAC) depends on the patient's creatinine clearance, because these agents have a significant component of renal excretion. With renal dysfunction, anticipate residual anticoagulant effect associated with impaired drug excretion, and time the drug discontinuation accordingly (Table 2).

Table 1: Procedure Risk for Bleeding

Low-risk Procedure	High-risk Procedure
Diagnostic EGD, colonoscopy or flexible sigmoidoscopy with mucosal biopsies	Variceal band ligation
Diagnostic push enteroscopy or balloon-assisted enteroscopy	Polypectomy ≥1 cm
Capsule endoscopy	Biliary or pancreatic sphincterotomy, EUS with FNA
ERCP with stent placement or papillary balloon dilation without sphincterotomy	Endoscopic hemostasis (including APC, bipolar cautery, and laser ablation)
Nonthermal polypectomy <1 cm	Mucosal resection
Mechanical clipping or injection therapy	Pneumatic or bougie dilation

Footnote to Table 1:
APC: argon plasma coagulation
EGD: esophagogastroduodenoscopy
ERCP: endoscopic retrograde cholangiopancreatography
EUS: endoscopic ultrasonography
FNA: fine-needle aspiration

All procedures (including high-risk procedures) can be safely performed without discontinuation of cardiac aspirin (81mg/day), and discontinuation is not recommended. Thienopyridine agents including clopidogrel, prasugrel, ticagrelor and ticlid, inhibit the P2Y12 receptor on the platelet and thereby inhibit platelet aggregation. Inhibition is irreversible for clopidogrel and prasugrel and reversible for ticagrelor; with the antiplatelet effect lasting 3–10 days. In general, clopidogrel and prasugrel should be discontinued 5–7 days prior and ticagrelor discontinued 3–5 days prior to a high-risk procedure, whereas ticlopidine needs to be discontinued 10–14 days prior to a high-risk procedure to ensure adequate platelet function. If these thienopyridine agents are part of dual antiplatelet therapy with low-dose aspirin, the aspirin should be continued in the peri-endoscopic period.

Table 2: Direct Oral Anticoagulant Agents

Factor Xa Inhibitor						Direct Thrombin Inhibitor	
Rivaroxaban (Xarelto)		**Apixaban (Eliquis)**		**Edoxaban (Savaysa)**		**Dabigatran (Pradaxa)**	
Creatinine clearance (ml/min)	Time of discontinuation (days)	Creatinine clearance (ml/min)	Time of discontinuation (days)	Creatinine clearance (ml/min)	Time of discontinuation (days)	Creatinine clearance (ml/min)	Time of discontinuation (days)
>90	≥1					>80	1-3
60-90	2	>60	1-2	>60	≥1	50-80	1-3
30-59	3	30-59	3	30-60	≥1	30-49	1.5-4
15-29	4	15-29	4	15-30	≥1	≤29	2-6

2. Q. If an endoscopic procedure requires a biopsy or polypectomy, how soon should anticoagulation or antiplatelet therapy be resumed following the procedure? Does the timing for restarting the agents change if the patient is on dual antiplatelet therapy (DAPT)?

Endoscopy with biopsy is considered a low-risk procedure with no need to discontinue antithrombotic agents prior to the procedure. For higher-risk procedures requiring that the antithrombotic agent be held, the drugs should be resumed immediately after immediate procedural hemostasis is achieved. Examples of immediate post-polypectomy hemostasis include a dry polypectomy site, a site after cautery or mechanical hemostasis with resolution of oozing. In most cases, antithrombotic agents can be resumed on the same day as the procedure for medications taken twice daily or the next day for those taken once daily. The approach does not differ with DAPT — aspirin should not be stopped, and the thienopyridine should be resumed as soon as hemostasis is achieved.

3. **Q. When patients on anticoagulation therapy are referred by their primary care providers (PCPs) for an endoscopic procedure, do you recommend that the PCP manages the protocol to stop and resume their anticoagulation therapy in relation to procedure, or do you, as the endoscopist, make the determination? If the PCP should decide, what is the best way to communicate this to the PCP?**

   A. The approach to peri-procedural antithrombotic drug management will vary based on your practice setting. In any large or medium-sized GI group practice, it is reasonable to have an allied health member or endoscopy nurse screen open access cases at the time of scheduling and provide appropriate advice for peri-procedural drug management. If you plan to defer this management to your referring PCPs, ensure that they understand the most up-to-date best practice recommendations for drug management to assure patient safety in the peri-endoscopic period.

4. **Q. For sphincterotomy, when is hemostasis achieved after the procedure? When is it safe to restart antiplatelet or antithrombotic medications?**

   A. When guidelines recommend resumption of antithrombotic agents "when hemostasis is achieved," they are referring to immediate procedural hemostasis. Only the endoscopist can judge the status of his or her intervention and whether procedural bleeding was clinically significant or not. If a sphincterotomy was performed with appropriate current settings and is dry by the end of the procedure, you have immediate hemostasis. If some post-sphincterotomy bleeding occurred, required a therapeutic maneuver (cautery, etc.) and hemostasis was achieved by the end of the procedure, you have hemostasis. Once hemostasis is achieved, antithrombotic medications must be restarted. Prolonged, temporary interruption of antithrombotic agents increases the risk of thromboembolic consequences for a patient with cardiovascular disease.

5. **Q. If a patient who is taking warfarin and has a cardiac valve and embolic history presents with a GI bleed, when should warfarin be stopped prior to a procedure and when should the patient resume taking it after the procedure?**

   A. In the acute GI-bleeding setting, the principles for reversal and resumption of anticoagulation are as follows: First, assess the thromboembolic risk of the patient prior to discontinuing warfarin. If the patient has a mechanical heart valve in the mitral position, an aortic caged-ball or tilting disk prosthesis, or if he or she has a mechanical heart valve in any position AND a history of stroke or transient ischemic attack (TIA) in the previous six months, then he or she is at high risk of thromboembolism. For these aforementioned high-risk patients with mechanical valves, discontinue the warfarin and initiate a heparin bridge. Proceed with endoscopy and hemostasis when the international normalized ratio (INR) is $\leq$2.5. There is no need to normalize the INR prior to endoscopy because doing so only increases the time to endoscopy without improving the post-procedural re-bleeding rate.

   Once endoscopic hemostasis has been achieved, restart the warfarin; same day resumption of warfarin is achievable in most patients. The optimal time for restarting warfarin is in the first four to seven days following initial discontinuation of the drug. In patients with a mechanical heart valve, bridge therapy must be continued until warfarin levels are therapeutic.

6. **Q. A patient with a recently placed coronary stent or stents who is on both clopidogrel and warfarin presents with a GI bleed. A duodenal ulcer with overlying clot is found on endoscopy. What are the short-term recommendations regarding the patient's anticoagulation or antiplatelet therapy? What are the long-term recommendations?**

A. In this patient, discontinuation of clopidogrel and warfarin at presentation is the appropriate first step in antithrombotic reversal. The cessation of antiplatelet therapy is not recommended within 90 days of an acute coronary syndrome or within 30 days of placement of a drug-eluting or bare-metal stent due to a very high risk of thromboembolic events, including stent occlusion with death. The patient, in this case, has been on clopidogrel so his or her circulating platelets will be ineffective for five to seven days, and this antithrombotic effect is further amplified by the patient's concomitant warfarin use.

If the INR is ≤2.5, it is safe to proceed immediately to endoscopic intervention following appropriate resuscitation. If the patient's INR is supratherapeutic, warfarin needs to be reversed with 4-factor prothrombin complex (PCC). PCC is preferred over fresh frozen plasma (FFP), because the volume of FFP required to appropriately reverse the anticoagulant effect is often much higher than the patient's cardiac hemodynamics can support. Once endoscopic hemostasis is achieved, antithrombotic therapy must be resumed; this can be achieved in most patients on the same day.

If the patient is on a DOAC, as opposed to warfarin, similar principles apply as follows: 1) reverse the antithrombotic effect, 2) perform endoscopic hemostasis promptly and 3) restart the antithrombotic once hemostasis is achieved. An important concern about the temporary interruption of a DOAC is the risk of arterial or venous thromboembolism due to the short half-life of the drug.

When DOAC is held, the DOAC plasma concentration declines rapidly. Fifty-percent of the anticoagulant effect remains after one half-life has elapsed (i.e., within 12 to 15 hours). The risk of a decreased anticoagulant effect is greatest among persons with a moderate to high thromboembolic risk (5 percent to >10 percent). These include patients with atrial fibrillation and a recent (<6 months prior) stroke or transient ischemic event or with a CHA2DS2-VASc score >3.

To anticipate the residual anticoagulant effect after temporary interruption of the drug, you must know the patient's creatinine clearance (CrCl). If the patient has a normal CrCl (>80 mL/min), you need to consider the rapid dissipation of the anticoagulant effect. For example, if the patient's last DOAC dose was on the evening prior to his presentation and he or she received aggressive resuscitation to promote renal excretion of the DOAC, by the time you complete your endoscopy (>12 hours after the last DOAC dose), <50 percent of the anticoagulant effect of the DOAC will be present. Therefore, a delay in resuming the DOAC following endoscopic hemostasis will leave this patient at risk of thromboembolism. In all patients, prompt re-initiation of the anticoagulant immediately after endoscopic hemostasis is achieved is desirable. Often, the DOAC can be restarted with the patient's next expected scheduled dose.

7. Q. What are your criteria for proton pump inhibitor (PPI) prophylaxis for patients who are on long-term anticoagulant or antiplatelet therapy?

A. Current multidisciplinary best practice recommendations endorse PPI use for the gastroprotection of patients at highest risk of upper GI bleeding — those with a prior history of upper GI bleeding and peptic ulcer disease, the elderly, highly co-morbid and those patients concomitantly prescribed aspirin, thienopyridine antiplatelet agents, other nonsteroidal anti-inflammatory drugs (NSAIDs) and/or anticoagulants. Chronic aspirin or DAPT in patients with a prior history of upper GI bleeding or those >65 years of age merit PPI gastroprotection to decrease the risk of antiplatelet-related upper GI bleeding. In patients prescribed chronic aspirin therapy, PPI use has been shown to effectively decrease recurrent GI bleeding even in the setting of failure of *Helicobacter pylori* eradication and concomitant use of non-aspirin NSAIDs. There is no evidence to support a reduction in thromboembolic protection among patients prescribed a PPI and a thienopyridine antiplatelet agent.

In warfarin users, the incidence of GI bleeding increases as mean INR values increase, with an INR of at least ~3.0 indicative of those at highest risk. Among patients prescribed DOACs, the risk of GI bleeding varies by specific agent and patient age, with the very elderly (>75 years) at greatest risk. A recent study of dabigatran users revealed a ~50 percent risk reduction in upper GI bleeding among persons with a prior history of peptic ulcer prescribed PPI gastroprotection. Data regarding the benefit of PPI prophylaxis for patients prescribed anticoagulants without the use of cardiac aspirin, a prior history of upper GI bleeding or older age are less definitive. There is no evidence that PPIs interact with DOACs to diminish the antithrombotic effect.

Do you always need to prophylax with a PPI? Comparison of the effectiveness of a PPI with a histamine-blocker for gastroprotection in patients prescribed antithrombotic agents has demonstrated that both can be useful. However, a PPI is slightly more effective (~50 percent reduction) than a histamine-receptor blocker (~40 percent reduction) in the prevention of upper GI bleeding. Future comparative studies are needed to better inform clinical decision-making regarding the choice of prophylaxis in cardiac patients on chronic antithrombotic therapy.

8. Q. For an average-risk patient undergoing screening colonoscopy and on anticoagulation or antiplatelet therapy, should the patient return for a repeat colonoscopy with polypectomy if a polyp is found on the screening exam?

A. Even in a person at average risk of colon cancer, you should plan for the possibility of multiple polypectomies and/or other high-risk endoscopic interventions. In a patient with non-valvular atrial fibrillation and a low-to-moderate CHA2DS2-VASc score (i.e., <4), administration of the anticoagulant can be interrupted briefly without conferring additional thromboembolic risk. Similarly, for most patients on DAPT, temporary interruption of the thienopyridine (five to seven days prior to colonoscopy), with continuation of low-dose aspirin, is relatively safe. For all antithrombotic drugs (thienopyridines and anticoagulants), prompt resumption of the agent after endoscopic hemostasis has been assured is required to minimize thromboembolic adverse events.

I have found that most patients are unwilling to return for a second therapeutic procedure if polyps were left behind during a screening exam. Their preference is often dictated by an unwillingness to take the laxative preparation twice, inability to arrange for a driver for the second exam or financial concerns regarding commercial insurer or government payer coverage for a second therapeutic exam. You can perform polypectomy while continuing antithrombotic therapy, but do so acknowledging the increased risk of delayed post-polypectomy bleeding. This can be discussed with the patient before the exam (see question #9), and if agreement is reached, you can perform the procedure with the expectation of complete polyp removal while the patient remains on antithrombotic therapy. From a healthcare delivery standpoint, I do not believe that planning a two-step colon cancer screening procedure for an average-risk person is desirable.

9. Q. Are there instances when a polyp can be removed or endoscopic therapy performed while the patient remains on clopidogrel or other antiplatelet therapy?

A. In some patients, the risk-benefit ratio of temporary discontinuation of antithrombotic therapy is unfavorable. These patients include those in whom a drug-eluting or bare-metal stent has been placed within the previous 30 days; those who have suffered an acute coronary syndrome event within the previous 90 days; or those who have a history of prior coronary stent occlusion following temporary interruption of their antiplatelet agent. For these high-risk patients, it is important to individualize peri-endoscopic antithrombotic management. Deferring a non-urgent therapeutic endoscopic procedure until the patient has had the required minimum period of dual antiplatelet therapy is often the best choice. If clinical circumstances do not permit postponement of the procedure, you should discuss the relative risk of thromboembolism and post-procedural bleeding with the patient and his or her cardiologist prior to discontinuing the thienopyridine agent (clopidogrel, prasugrel, ticagrelor, ticlopidine). If you do discontinue the thienopyridine agent, it is critically important that the low-dose aspirin be continued throughout the peri-endoscopic period; in other words, you should never discontinue both the aspirin and the thienopyridine agent at the same time. Discontinuation of aspirin is associated with an increase in cardiovascular morbidity.

Polypectomy can be performed on DAPT and is associated with no increase in immediate post-polypectomy bleeding but can be associated with up to an 11 percent increase in delayed post-polypectomy bleeding. This risk is not significantly altered with the use of prophylactic mechanical hemostasis to close a post-polypectomy defect. In my practice, I discuss these issues before a procedure to ensure that the patient knows the symptoms of a post-polypectomy bleed and promptly notifies our office or on-call service. In this way, we can expeditiously address any post-polypectomy bleeding that might occur.

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References and Resources are provided on the next page.

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Additional Resources

ASGE Standards of Practice Committee Guideline: **"The management of antithrombotic agents for patients undergoing GI endoscopy,"** published in *GIE: Gastrointestinal Endoscopy*, January 2016

