Communication from the ASGE Standards of Practice Committee

GUIDELINE

The management of antithrombotic agents for patients undergoing GI endoscopy

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature was performed using PubMed and the Cochrane Database, with dates of search from August 1966 to December 2014. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When limited or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).[1]

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines.

Antithrombotic therapy is used to reduce the risk of thromboembolic events in patients with conditions such as atrial fibrillation (AF), acute coronary syndrome (ACS), deep vein thrombosis (DVT), hypercoagulable states, and endoprostheses. Antithrombotics include medications classified as anticoagulants or antiplatelet agents (APAs). Anticoagulants prevent the clotting of blood by interfering with the native clotting cascade and include the following 4 drug classes: vitamin K antagonists (eg, warfarin), heparin derivatives (eg, unfractionated [UFH] and low molecular weight [LMWH], fondaparinux [Arixtra, GlaxoSmithKline, Research Triangle Park, NC, USA]), direct factor Xa inhibitors (eg, rivaroxaban [Xarelto, Janssen Pharmaceuticals, Inc, Raritan, NJ, USA], apixaban [Eliquis, Bristol-Myers Squibb Company, Princeton, NJ, USA], edoxaban [Savaysa, Daiichi Sankyo Co, LTD, Tokyo, Japan]), and direct thrombin inhibitors (eg, dabigatran [Pradaxa, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Conn, USA], hirudins, argatraban [Acova, Abbott Laboratories, North Chicago, Ill, USA]). APAs decrease platelet aggregation, thus preventing thrombus formation. APAs include the thienopyridines (eg, clopidogrel, [Plavix, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, NJ, USA], prasugrel [Effient, Eli Lilly and Company, Indianapolis, Ind, USA], ticlopidine [Ticlid, Roche Pharmaceuticals, Nutley, NJ, USA], and ticagrelor [Brilinta, AstraZeneca, Wilmington, Del, USA]), the protease-activated receptor-1 (PAR-1) inhibitor vorapaxar (Zontivity, Merck Sharp & Dohme Corp, Whitehouse Station, NJ, USA), glycoprotein IIb/IIIa receptor inhibitors (GPIIb/IIIa inhibitors) (eg, abciximab [ReoPro, Eli Lilly and Company, Indianapolis, Ind, USA], eptifibatide [Integrilin, Merck Sharp & Dohme Corp, Whitehouse Station, NJ, USA], and tirofiban [Aggrastat, Medicure Pharma, Inc, Somerset, NJ, USA]),

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TABLE 1. System for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕O
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕OO
Very low quality	Any estimate of effect is very uncertain.	⊕OOO

Adapted from Guyatt et al.[1]

TABLE 2. Antithrombotic drugs: duration of action and approach to reversal when indicated

			Approach to reversal based on procedural urgency	
Drug class	**Specific agent(s)**	**Duration of action**	**Elective**	**Urgent**
APAs	Aspirin	7-10 days	NA	Hold, can give platelets
	NSAIDs	Varies	NA	Hold
	Dipyridamole (Persantine)	2-3 days	Hold	Hold
	Cilostazol (Pletal, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan)	2 days	Hold	Hold
	Thienopyridines: clopidrogrel (Plavix) prasugrel (Effient) ticlodipine (Ticlid) ticagrelor (Brilinta)	5-7 days: clopidogrel, 3-5 days: ticagrelor 5-7 days: prasugrel 10-14 days[98]: ticlopidine	Hold	Hold
	GPIIb/IIIa inhibitors: tirofiban (Aggrastat) abciximab (ReoPro) eptifibatide (Integrilin)	tirofiban: 1-2 seconds abciximab: 24 hours eptifibitide: 4 hours	NA	Hold HD: tirofiban
	PAR-1 inhibitor: vorapaxar (Zontivity)	5-13 days	Hold	Hold
Anticoagulants	Warfarin (Coumadin)	5 days	Hold	Vitamin K, PCC
	UFH	IV 2-6 hours SQ 12-24 hours	Hold	Protamine sulfate* (partial)
	LMWH: enoxaparin (Lovenox) dalteparin (Fragmin, Pfizer Inc, New York, NY, USA)	24 hours	Hold	Protamine sulfate, consider rVIIa
	Fondaparinux (Arixtra)	36-48 hours		Protamine sulfate, consider rVIIa
	Direct factor Xa Inhibitor: rivaroxaban (Xarelto) apixaban (Eliquis) edoxaban (Savaysa)	See Tables 7 and 8	Hold	Charcoal (if last intake within 2-3 hours); nonactivated PCC or activated PCC
	Direct thrombin inhibitor, oral: dabigatran (Pradaxa) IV: Desirudin (Iprivask, Aventis Pharmaceuticals Inc., Bridgewater, NJ, USA)	See Table 9	Hold	Charcoal (if last intake within 2-3 hours); nonactivated PCC or activated PCC; HD

NSAIDs, Nonsteroidal anti-inflammatory drugs; *NA,* not applicable; *HD,* hemodialysis; *PCC,* prothrombin complex concentrate; *rVIIa,* recombinant factor VIIa.
*Caution: Can cause severe hypotension and anaphylaxis.

aspirin (acetylsalicylic acid [ASA]), and nonsteroidal anti-inflammatory drugs. The duration of action and reversal routes for the antithrombotic drug classes are described in Table 2.

Adverse events of antithrombotic therapy include GI bleeding,[2,3] and their use increases the risk of hemorrhage after some endoscopic interventions.[4-6] For patients taking these medications who require endoscopy, one should consider the following important factors: (1) the urgency of the procedure, (2) the bleeding risk of the procedure, (3) the effect of the antithrombotic drug(s) on the bleeding risk, and (4) the risk of a thromboembolic event related to periprocedural interruption of antithrombotic agents.[7]

PROCEDURE RISKS

Common endoscopic procedures vary in their potential to induce bleeding, and these have been outlined in other

TABLE 3. Procedure risk for bleeding (overall)

Higher-risk procedures	Low-risk procedures
Polypectomy	Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy) including mucosal biopsy
Biliary or pancreatic sphincterotomy	ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy
Treatment of varices	
PEG placement*	Push enteroscopy and diagnostic balloon-assisted enteroscopy
Therapeutic balloon-assisted enteroscopy	Capsule endoscopy
EUS with FNA†	Enteral stent deployment (Controversial)
Endoscopic hemostasis	EUS without FNA
Tumor ablation	Argon plasma coagulation
Cystgastrostomy	Barrett's ablation
Ampullary resection	
EMR	
Endoscopic submucosal dissection	
Pneumatic or bougie dilation	
PEJ	

PEJ, Percutaneous endoscopic jejunostomy.
*PEG on aspirin or clopidogrel therapy is low risk. Does not apply to DAPT.
†EUS-FNA of solid masses on ASA/NSAIDs is low risk.

ASGE guidelines (Table 3).[8] Studies on postprocedural bleeding risks have been conducted in patients who are not on complex antithrombotic regimens and thus may not accurately reflect the bleeding risk of patients using newer antithrombotic therapies. Traditionally, low-risk procedures have included diagnostic EGD, colonoscopy, ERCP without sphincterotomy, biliary stent placement, and push or balloon-assisted enteroscopy. Mucosal biopsy sampling performed as part of these procedures confers a low risk of GI bleeding. Similarly, EUS without FNA, capsule endoscopy, and argon plasma coagulation[8] are low risk. Nonachalasia esophageal dilation has been associated with a low risk of bleeding in large series[9,10,11]; however, the safety of dilation while on anticoagulants is unknown, and the potential for an inaccessible site of bleeding argues for caution in this setting. High-risk endoscopic procedures are associated with a potential for bleeding that requires an intervention, such as hospitalization, transfusion, endoscopic treatment, or surgery.[12] These high-risk procedures include polypectomy,[13,14] therapeutic balloon-assisted enteroscopy (other than argon plasma coagulation),[15,16] endoscopic sphincterotomy,[17] EUS with FNA, percutaneous endoscopic gastrostomy,[18-20] percutaneous endoscopic jejunostomy,[21] tumor ablation (esophagus, stomach, colon, and rectum),[22] endoscopic submucosal dissection,[23] EMR,[24] pneumatic balloon dilation for achalasia,[25] treatment of varices,[26] ampullary resection, per-oral endoscopic myotomy,[27] cystoenterostomy,[28] and endoscopic therapy of Zenker's diverticulum.[29] The risk of bleeding after polypectomy ranges from .3% to 10% and depends on a number of factors, including the polyp size, location, morphology (nonpolypoid, sessile, pedunculated), resection technique (cold or hot forceps, cold snare, or snare cautery), and type of cautery used.

TABLE 4. CHA_2DS_2-VASc scoring system

CHA_2DS_2-VASc score or assessment	Risk of stroke (CVA)	% Risk of annual CVA
0	Low	0
1	Moderate	1.3
2	High	2.2
3	High	3.2
4	High	4.0
5	High	6.7
6	High	9.8
7	High	9.6
8	High	6.7
9	High	15.2

CHA_2DS_2-VASc, Congestive heart failure [1 point], Hypertension [1 point], Age $\geq$ 75 years [2 points], Diabetes mellitus [1 point], Stroke [2 points], Vascular disease [1 point], Age 65-74 years [1 point], Sex category, ie, female sex [1 point].
CVA, cerebrovascular accident.

There is controversy with regard to whether enteral stent placement is high or low risk. One retrospective review of 85 patients with esophageal stents described a bleeding risk as high as 5.3%.[30] However, subsequent prospective multicenter studies as well as systematic reviews have described bleeding rates in the range of .5% to 1% in a variety of GI locations.[31,32]

CONDITION RISKS

The probability of a thromboembolic event related to the temporary interruption of antithrombotic therapy for an endoscopic procedure depends on the indication for

TABLE 5. Risk for thromboembolic event in patients with mechanical heart valve(s) or VTE on anticoagulation[37]

	Clinical indication for warfarin therapy	
Annual risk	**Mechanical heart valve**	**VTE**
High	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 months) CVA or TIA	• Recent (within 3 months) VTE • Severe thrombophilia (deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Medium	• Bileaflet aortic valve prosthesis and one or more of the following risk factors: AF, prior CVA or TIA, hypertension, diabetes, congestive heart failure, age $\geq$ 75 years	• VTE within the past 3-12 months • Nonsevere thrombophilia (heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 months or palliative)
Low	• Bileaflet aortic valve prosthesis without AF and no other risk factors for CVA	• VTE > 12 months previous and no other risk factors

VTE, venous thromboembolism; *CVA*, cerebrovascular accident; *TIA*, Transient ischemic attack; *AF*, atrial fibrillation.

antithrombotic therapy and individual patient characteristics. For example, in patients with nonvalvular AF, important determinants of risk for a cerebrovascular accident (CVA) are included in the CHA_2DS_2-VASc index (Table 4).[33] This score ranges from 0 to 9 and considers thromboembolic risk factors of congestive heart failure (1 point), hypertension (1 point), age $\geq$ 75 years (2 points), diabetes (1 point), stroke (2 points), vascular disease (prior myocardial infarction [MI], peripheral artery disease, or aortic plaque) (1 point), age 65 to 74 years (1 point), and sex category (female) (1 point). The higher the score, the greater the thromboembolic risk, and patients with a score of $\geq$2 are considered to be at high risk of thromboembolism (>2.2%/year). These patients are frequently prescribed an anticoagulant to mitigate thromboembolic risk.

High thrombosis risk scenarios for patients on APA therapy include placement of drug-eluting coronary stents $\leq$ 12 months previously or bare metal coronary stents $\leq$ 1 month previously. For patients with ACS, a bare metal coronary stent placed $\leq$12 months previously is considered a high-risk setting.[4] Endoscopists should be aware of specific clinical risk factors that will predispose a patient to higher rates of stent occlusion beyond 1 year after stent insertion and approach modification of antiplatelet regimens cautiously in these cases. These patients include those with a prior history of stent occlusion, because 1 in 5 patients who experience a first thrombosis will experience a second stent occlusion at a rate of .6% per year over the first 3 years,[34,35] with a cumulative risk of cardiac death of 27.9%. Patients with ACS or ST elevation MI, multivessel percutaneous coronary intervention, diabetes, renal failure, or diffuse coronary artery disease are also at higher risk of stent occlusion or ACS events with alteration of antithrombotic therapy.[36]

Patients with previous venous thromboembolism (VTE) on anticoagulation or 1 or more mechanical heart valves have different risk factors for thromboembolic events (Table 5). Specific clinical variables divide patients into low-, medium-, and high-risk groups. Among patients with VTE, time from initial VTE, history of recurrent VTE with antithrombotic interruption, and presence of underlying thrombophilia are most predictive of future thromboembolic risk. For patients with mechanical heart valves the type, number, and location of valvular prostheses and the presence or absence of associated heart failure and AF determine the annual risk of thromboembolic events. Bioprosthetic valves are considered low risk.[37]

ANTIPLATELET AGENTS

ASA is a cyclooxygenase inhibitor that is used alone or in combination with other APAs. It is used to inhibit platelet aggregation for prophylaxis of secondary cardioembolic phenomena after occurrence of a stroke or MI. In patients with a >10% 10-year risk of heart attack or stroke,[38] primary cardioprophylaxis with low-dose ASA therapy is recommended. ASA causes irreversible inhibition of the cyclooxygenase 1 and 2 enzyme systems. After cessation of ASA, 7 to 9 days are required to regain full platelet function.[39]

Dipyridamole (Persantine, Teva Pharmaceuticals USA, Sellersville, Pa, USA) reversibly inhibits platelet aggregation. This drug is used in combination with ASA in the secondary prevention of stroke and off-label for primary stroke prevention. The mechanism of action of this drug is controversial[40]; both inhibition of cyclic nucleotide phosphodiesterase and blockade of the uptake of adenosine have been suggested. Dipyridamole has an elimination half-life of 12 hours and duration of action of about 2 days after discontinuation.

The most common APAs used after ASA therapy are the thienopyridine agents. These drugs bind to the P2Y12 component of the ADP receptors, which prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. The class includes ticlopidine (Ticlid),

clopidogrel (Plavix), prasugrel (Effient), and ticagrelor (Brilinta). Ticlopidine (Ticlid), the first widely available thienopyridine agent, has largely been supplanted in clinical use by newer second-generation agents because of concerns regarding hematologic side effects (such as neutropenia, thrombotic thrombocytopenia purpura, and hemolytic uremic syndrome). Clopidogrel (Plavix) is approved for secondary prevention of MI or stroke and in the primary management of established peripheral vascular disease. Clopidogrel (Plavix) efficacy can be limited by variations of the ABCB13435 TT and CYP2C19 genotypes of cytochrome P450 enzymes, which alter hepatic metabolism of the clopidogrel prodrug to its active thiol metabolite.[41,42] This altered metabolism results in variable antiplatelet effects and adverse cardiac events,[43] including stent thrombosis[44] and post–percutaneous coronary intervention ischemic events.[45] The minimum duration of discontinuation of clopidogrel that allows for restoration of normal platelet aggregation is 5 to 7 days.[37]

Third-generation thienopyridine agents include prasugrel (Effient) and ticagrelor (Brilinta). Similar to clopidogrel (Plavix), prasugrel (Effient) is a prodrug that requires conversion by the cytochrome P450 hepatic enzymes; however, unlike clopidogrel's (Plavix) multistep conversion process to an active metabolite, the activation of prasugrel (Effient) occurs in a single hepatic step. The pharmacologic characteristics of prasugrel (Effient) overcome some of the limitations of clopidogrel (Plavix) but at the risk of increased bleeding. Because of this, the U.S. Food and Drug Administration (FDA) approved the drug with a black box warning specifically noting that prasugrel (Effient) should not be used in patients with active bleeding, a history of transient ischemic attack or CVA, or likely to undergo urgent coronary bypass graft surgery. Similar to clopidogrel (Plavix), the mechanism of action is the irreversible inhibition of the P2Y12 receptor; thus, the minimum duration of discontinuation of prasugrel that allows for restoration of normal platelet aggregation is 5 to 7 days. Unlike clopidogrel (Plavix), prasugrel (Effient) achieves a much higher level of platelet inhibition and is unaffected by variants of the CYP2C19 or ABCB1 genotypes.[46-48]

Ticagrelor (Brilinta) is the first reversible oral P2Y12 antagonist and an alternative therapy for ACS. This drug is quickly absorbed, does not require metabolic activation, and has a rapid antiplatelet effect that closely parallels drug-exposure levels. Unlike clopidogrel (Plavix) and prasugrel (Effient), the reversible inhibition of the P2Y12 receptor permits a shorter interval of discontinuation, 3 to 5 days, to recover adequate platelet function.[49]

In January 2014 the FDA approved a first-in-class antiplatelet medication, vorapaxar (Zontivity). This agent is a competitive and selective inhibitor of PAR-1, the major thrombin receptor on human platelets. It has been shown in clinical trials to reduce the risk of MI, stroke, CV death, and need for revascularization procedures in patients with a previous MI or peripheral artery disease when prescribed in conjunction with traditional dual antiplatelet therapy (DAPT).[50] However, this intensification of antiplatelet effect, via a novel pathway, is associated with an increased risk of moderate or severe bleeding in 4.2% versus 2.5% (placebo) and a 66% increased risk of bleeding overall. Currently, this agent is associated with a black box warning identifying a high risk of bleeding and contraindication in patients with a history of stroke, transient ischemic attack, or intracranial hemorrhage. Vorapaxar displays significant inhibition of platelet aggregation that remains up to 4 weeks after discontinuation.[51] The actual impact of this drug on the GI tract is relatively unknown, and postmarketing data are needed to identify these risks.

ANTICOAGULANT AGENTS

Warfarin

Warfarin (Coumadin, Bristol-Myers Squibb Company, Princeton, NJ, USA) is an oral anticoagulant that inhibits the vitamin K–dependent clotting factors II, VII, IX, and X and proteins C and S. Its activity is measured via the International Normalized Ratio (INR). The INR decreases to $\leq$1.5 in approximately 93% of patients within 5 days of discontinuing therapy.[52]

Novel oral anticoagulants

The novel oral anticoagulants (NOACs) include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors (eg, rivaroxaban [Xarelto], apixaban [Eliquis], edoxaban [Savaysa]) (Table 2). Dabigatran (Pradaxa) was the first NOAC approved in the United States for prevention of CVA and systemic embolism in patients with nonvalvular AF. It is metabolized and excreted primarily by the kidneys, reaching maximum effect 1.25 to 3 hours after ingestion, with a half-life of 12 to 14 hours. Assessment of the degree of anticoagulation is best achieved by assessment of the Ecarin Clotting Time or the dilute thrombin time, neither of which is readily available in the acute clinical setting. Partial thromboplastin time and prothrombin time vary in their sensitivities to dabigatran depending on the reagents used and can be normal in spite of circulating therapeutic levels of dabigatran. However, a normal activated partial thromboplastin time effectively rules out a clinically significant circulating drug level. Timing of discontinuation before an endoscopic procedure is dictated by the patient's creatinine clearance because 80% of excretion occurs via the kidneys (Table 6).[53]

Rivaroxaban (Xarelto) is approved in the United States for prevention of VTE after orthopedic surgery, treatment of VTE, and prevention of CVA and systemic embolism in patients with AF. Apixaban (Eliquis) is FDA

TABLE 6. Periprocedural management of dabigatran (Pradaxa)[53]

Creatinine clearance (mL/min)	Time to onset of action (h)	Half-life (h)	Timing of discontinuation before procedure	
			Moderate procedural bleeding risk (2-3 half-lives)	High procedural bleeding risk (4-5 half-lives)
>80	1.25-3	13 (11-22)	1-1.5 days	2-3 days
50-80	1.25-3	15 (12-34)	1-2 days	2-3 days
30-49	1.25-3	18 (13-23)	1.5-2 days	3-4 days
≤29	1.25-3	27 (22-35)	2-3 days	4-6 days

approved for prevention of systemic embolism in AF patients, postorthopedic surgery prevention of VTE, and for treatment and reduction of recurrence of VTE. Edoxaban (Savaysa) is FDA approved for AF and VTE treatment indications. The effect of the anti-Xa anticoagulants is best assessed by measuring anti-Xa levels with drug-specific calibrators. Prothrombin time and activated partial thromboplastin time are crude measures of drug effect and are insensitive tests, often only minimally prolonged or even normal in spite of therapeutic drug levels. However, normal test results rule out high circulating drug levels. There is no reliable serum assay to assess the degree of anticoagulant activity with these agents at this time. Caution should be used in interpretation of the activated partial thromboplastin time in situations of drug toxicity because the assay is subject to a ceiling effect and does not reliably capture the severity of the anticoagulant effect.[53]

In the periendoscopic period there are 3 important pharmacodynamic considerations when holding and restarting an anticoagulant: (1) time to maximum effect, (2) half-life, and (3) excretion of the drug. Rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) all have a relatively short time to maximal effect (eg, 2-4 hours with rivaroxaban [Xarelto], 1-3 hours with apixaban [Eliquis]), a half-life ranging from 8 to 15 hours, and variable excretion by the kidneys (rivaroxaban [Xarelto] 66% and apixaban [Eliquis] 25%). To minimize the risk of bleeding, these medications should be stopped for at least 2 half-lives before high-risk procedures, and their dosing should be adjusted in the setting of renal impairment (Tables 7-9).[54]

An antidote for dabigatran (Pradaxa) has been approved following accelerated review by the FDA.[55] This antidote is idarucizumab (Praxbind, Boehringer Ingelheim, Inc, Ridgefield, CT, USA) and is approved for use in cases of life-threatening, uncontrolled bleeding or prior to emergency surgery. Another reversal agent that is currently under evaluation is Aripazine (PER977, Perosphere, Inc, Danbury, CT, USA), which binds to UFH and LMWH; factor Xa inhibitors; edoxaban (Savaysa); rivaroxaban (Xarelto) and apixaban (Eliquis); and dabigatran (Pradaxa).[56] Animal studies and pharmacodynamics studies with Aripazine have demonstrated reversal of edoxaban (Savaysa) to 10% of baseline values within 10 minutes of drug delivery. Finally,

TABLE 7. Periprocedural management of apixaban (Eliquis)[54]

Creatinine clearance (mL/min)	Time to onset of action (h)	Timing of discontinuation before high-risk endoscopic procedure (day)
>60	1-3	1 or 2
30-59	1-3	3
15-29	1-3	4

TABLE 8. Periprocedural management of rivaroxaban (Xarelto)[54]

Creatinine clearance (mL/min)	Time to onset of action (h)	Timing of discontinuation before high-risk endoscopic procedure (day)
>90	2-4	≥1
60-90	2-4	2
30-59	2-4	3
15-29	2-4	4

Andexanet alfa has been studied in a phase II trial and shows promise as yet another reversal agent, by decreasing anti-Xa activity and reducing plasma concentrations of free apixaban (Eliquis) in healthy volunteers.[57] Future studies are needed to demonstrate efficacy in humans and in the setting of major hemorrhage.

Parenteral and subcutaneously administered anticoagulants

UFH administered intravenously has a half-life of 60 to 90 minutes, and anticoagulant effects dissipate 3 to 4 hours after discontinuation. LMWH (enoxaparin [Lovenox, Sanofi-Aventis U.S., LLC, Bridgewater, NJ, USA] and dalteparin [Fragmin, Pfizer Inc, New York, NY, USA]) is administered subcutaneously at therapeutic doses for bridging and for the treatment of VTE. It is also prescribed at reduced doses for the prevention of VTE in low-risk patients. The last dose of these agents should be given 24 hours before the anticipated procedure at 50% of the total daily dose.[37]

Fondaparinux (Arixtra) is a synthetic and specific inhibitor of factor Xa. It is approved in the United States for

TABLE 9. Periprocedural management of edoxaban (Savaysa)[99]

Creatinine clearance (mL/min)	Time to onset of action (h)	Half-life (h)	Timing of discontinuation before high-risk procedure (h)
>60	1-2	8.6	At least 24
30-60	1-2	9.4	At least 24
15-30	1-2	16.9	At least 24
≤15	1-2	No data	No data

perioperative DVT prophylaxis and for the initial treatment of acute DVT/pulmonary embolism. It is administered subcutaneously and is distinct from LMWH. Fondaparinux (Arixtra) has a high affinity for antithrombin III, which potentiates inhibition of factor Xa. The minimum recommended time for discontinuation of this drug before a high-risk procedure is 36 hours.[58]

Desirudin (Iprivask, Aventis Pharmaceuticals Inc., Bridgewater, NJ, USA) is a direct thrombin inhibitor approved for DVT prophylaxis after hip replacement and is administered subcutaneously. Recommendations are to discontinue this medication 10 hours before a high-risk procedure.[59]

COMMON ELECTIVE ENDOSCOPIC PROCEDURES IN PATIENTS ON ANTITHROMBOTIC THERAPY

Because of the paucity of high-quality evidence regarding bleeding risks associated with antithrombotic therapies prescribed in dual (ASA + thienopyridine; ASA + anticoagulant) and triple combinations (ASA + thienopyridine + anticoagulant), a "one-size-fits-all approach" to recommendations regarding the periprocedural management of antithrombotic agents undergoing endoscopy is not possible at this time. A summary of the available evidence is presented below (Table 10), with the awareness that additional research is required and will likely influence future recommendations regarding periendoscopic management of third-generation thienopyridines, PAR-1 inhibitors, and NOAC prescribed in combination with ASA.[60]

With regard to polypectomy, there are modest data to support the use of cold snare rather than conventional polypectomy in those patients anticoagulated with warfarin (Coumadin). In a small study of warfarin (Coumadin), 70 patients with 159 polyps up to 10 mm were randomized to cold polypectomy versus conventional snare. Delayed bleeding requiring hemostasis occurred less commonly after cold snare polypectomy than conventional polypectomy despite continuation of anticoagulants (0% vs 14%, $P = .027$).[61] Further data in the area of optimal endoscopic technique for patients prescribed antithrombotic agents are necessary to better inform endoscopic decisions and clinical best practice.

RISK OF STOPPING ANTITHROMBOTIC THERAPY BEFORE ELECTIVE ENDOSCOPY

When antithrombotic therapy is required for a short period of time (ie, after VTE or bare metal stent insertion), elective procedures should be delayed until such therapy is no longer indicated. In patients who need antithrombotic therapy for a longer period of time (ie, after drug-eluting stent placement or post-ACS), careful consideration of the cardioembolic risk must be made before temporary drug cessation to avoid spontaneous stent occlusion, ACS, and death.[62-64] Decisions about discontinuing or temporary cessation of these agents should be individualized and discussed, before the endoscopic procedure, with the patient and, optimally, the prescribing provider (cardiologist, neurologist, hematologist, primary care physician). It is important to recognize that in some high-risk patients, antithrombotic agents may not be able to be stopped.

Cessation of anticoagulant

Current guidelines from the American College of Chest Physicians (ACCP) regarding the management of anticoagulation in patients with AF and/or valvular heart disease undergoing elective invasive procedures are summarized in Table 6.[42] The absolute risk of an embolic event in patients whose anticoagulation is interrupted for 4 to 7 days is approximately 1%.[65,66] After temporary discontinuation of warfarin (Coumadin), reinitiation of drug should occur within 4 to 7 days of initial drug discontinuation to ensure no increased risk of thromboembolic event and can occur on the same day in many patients.[67]

Role of bridge therapy

To reduce the risk of thromboembolic events, patients on warfarin (Coumadin) may be switched to a shorter-acting (ie, bridge [Table 11]) anticoagulant in the periendoscopic period. Evidence for the use of UFH and LMWH (enoxaparin) as bridge therapies for endoscopic procedures in patients on warfarin (Coumadin) is limited. One study of 98 patients undergoing endoscopy (EGD and/or colonoscopy) with bridge therapy using bemiparin, an ultra-LMWH, found no thromboembolic events and only 2 major bleeding episodes that were unrelated to endoscopy.[68] Current guidelines (2011 American College of Cardiology Foundation/American Heart Association [AHA]/Heart Rhythm Society guideline on AF and the 2014 AHA/American College of Cardiology [ACC] guideline on valvular heart disease) regarding the management of anticoagulation in patients with AF and/or valvular heart disease undergoing elective invasive procedures are summarized in Table 10.[69,70] A meta-analysis[71] showed that vitamin K antagonist–treated patients receiving periprocedural bridging therapy with heparin appear to be at increased risk of both overall and major

TABLE 10. Summary for available evidence for bleeding risk with common endoscopic procedures on antithrombotic agents

	Therapeutic warfarin/heparin	Thienopyridine	ASA/NSAID
Diagnostic EGD/colonoscopy +/- biopsy	Low risk[100]	Low[112]	Low[104]
Colonoscopic polypectomy	High risk[75,101-109]	High[113]	Low[75,98,115]
Sphincterotomy	High[110]	Unknown	Low[17]
EUS/FNA	High[111]	Unknown	Low[111]
PEG (does not apply to DAPT)	Unknown	Low for clopidogrel only[114]	Low[114]

ASA, acetylsalicylic acid, or aspirin; *NSAID*, nonsteroidal anti-inflammatory drug; *DAPT*, dual antiplatelet therapy.

TABLE 11. Approach to bridge therapy for warfarin (Coumadin)[69-70]

Condition	Associated diagnosis	Management
AF	None CHA_2DS_2-VASc score < 2	No bridge recommended
	Mechanical valves History of CVA CHA_2DS_2-VASc score ≥ 2	Bridge therapy recommended
Valvular heart disease	Bileaflet mechanical AVR	No bridge recommended
	Mechanical AVR and any thromboembolic risk factor Older-generation mechanical AVR Mechanical mitral valve replacement	Bridge therapy recommended

AF, atrial fibrillation; *CHA_2DS_2-VASc*, Congestive heart failure, Hypertension, Age ≥ 75 years [2 points], Diabetes Mellitus, Stroke [2 points], Vascular disease, Age 65-74 years, Sex category [ie, female sex]; *CVA*, cerebrovascular accident; *AVR*, aortic valve replacement.

bleeding and at similar risk of thromboembolic events compared with nonbridged patients.

A recently published randomized controlled trial[72] sought to better define the role of periprocedural heparin bridging in 1884 patients with nonvalvular AF undergoing an elective invasive procedure. Patients were randomized to bridging versus no-bridging, and results demonstrated the heparin-bridged group experienced more major bleeding (3.2% vs 1.3%) than the nonbridged group, with no difference in arterial thromboembolism (.3% vs .4%). Of note, these data should not be applied to those patients with higher risk for thromboembolism, such as patients with valvular AF, mechanical valves, left ventricular assist devices, recently diagnosed thromboembolism, AF with congestive heart failure, or in the post-ACS setting.[72]

Cessation of APA (including DAPT)

The most common antithrombotic strategy prescribed in the United States with regard to patients on DAPT is to hold the thienopyridine in the periendoscopic period and continue the aspirin. Eisenberg et al[73] performed a systematic review of 161 reported cases of late stent thrombosis (>30 days but <1 year after stent placement) and very late stent thrombosis (>1 year after stent placement). Patients who discontinued both ASA and a thienopyridine had a median time to event of 7 days. In those who discontinued thienopyridine but remained on ASA, the median time to an event was 122 days. There were a total of 6 cases (6%) of stent thrombosis within 10 days of thienopyridine cessation, suggesting short-term discontinuation between 30 days and 1 year from drug-eluting coronary stent placement (late stent thrombosis) might be relatively safe but still carry some risk. Best practice recommendations for the management of DAPT (ie, ASA + thienopyridine APA) are summarized in the American College of Cardiology Foundation and American College of Gastroenterology consensus statement (Table 12).[36]

REINITIATION OF ANTITHROMBOTIC AGENTS AFTER ELECTIVE ENDOSCOPY

There is consensus that antithrombotic therapy should be resumed upon completion of the procedure.[36,74] The benefits of immediate reinitiation of antithrombotic therapy for the prevention of thromboembolic events should be weighed against the risk of hemorrhage associated with the specific agent, the time to onset of the medication, and on procedure-specific circumstances (eg, risk of bleeding after sphincterotomy, polypectomy, or EMR). Most existing literature on this topic addresses reinitiation of warfarin or heparin and heparin-like products. Less is known regarding timing to reinitiation of APAs and NOACs.

In 1 study involving 94 patients who had undergone 109 colonoscopies (including hot biopsy or snare polypectomy in 47%), patients were instructed to restart warfarin (Coumadin) therapy on the day after endoscopy.[75] Only 1 case (0.9%) of procedure-related bleeding occurred after 7 days of warfarin (Coumadin) therapy and required hospitalization and transfusion. None of the patients undergoing diagnostic colonoscopy experienced bleeding. Conversely, a second study involving 173 patients found that resuming warfarin (Coumadin) or heparin within 1 week after polypectomy was associated with an increased risk of bleeding (OR 5.2; 95% CI, 2.2-12.5).[76] Because of the ongoing risk of thromboembolic events, the 2014 AHA/ACC guideline (on the management of valvular heart disease) recommends that warfarin (Coumadin) be restarted within 24 hours of the procedure in patients with valvular heart disease and a low-risk for thromboembolism. In patients at high risk

TABLE 12. Best practice recommendations for the management of DAPT[36]

Avoid cessation of all antiplatelet therapies after PCI with stent placement.
Avoid cessation of clopidogrel (even when aspirin is continued) within the first 30 days after PCI and either DES or BMS placement when possible.
Defer elective endoscopic procedures, possibly up to 12 months, if clinically acceptable from the time of PCI to DES placement.
Perform endoscopic procedures, particularly those associated with bleeding risk, 5-7 days after thienopyridine drug cessation. ASA should be continued.
Resume thienopyridine and ASA drug therapy after the procedure once hemostasis is achieved. A loading dose of the former should be considered among patients at risk for thrombosis.
Continue platelet-directed therapy in patients undergoing elective endoscopy procedures associated with a low-risk for bleeding.

DAPT, dual antiplatelet therapy; *BMS*, Bare metal stent(s); *DES*, drug-eluting stent(s); *PCI*, percutaneous coronary intervention; *ASA*, acetylsalicylic acid, or aspirin.

for thromboembolism, UFH or LMWH should be restarted as soon as "bleeding stability allows" and continued until the INR reaches an appropriate therapeutic level.[70] UFH may be restarted 2 to 6 hours after a therapeutic procedure. The optimal time to restart LMWH after endoscopy has not been determined. The 2012 ACCP guidelines recommend delaying reinitiation of LMWH 48 to 72 hours after surgery in patients believed to be at high risk for bleeding adverse events.[37]

There are no data to inform optimal timing of resumption of NOACs after endoscopic procedures. Because these agents have a short onset of action (Tables 7-10), if a NOAC cannot be restarted within 24 hours after a high-risk procedure because of concern regarding the adequate hemostasis, then thromboprophylaxis (ie, UFH bridge) should be considered for patients at high risk for thromboembolism.[53,54]

Cardiac ASA should not be discontinued in most cases. Other APAs should be resumed once hemostasis has been achieved (Table 12).

ENDOSCOPIC PROCEDURES IN THE ACUTELY BLEEDING PATIENT ON ANTITHROMBOTIC THERAPY

Endoscopic evaluation and therapy in patients using antithrombotics with active GI bleeding is both warranted and safe.[7] The most common etiologies for upper GI blood loss in these patients are peptic ulcer disease and erosive diseases of the esophagus, stomach, and duodenum.[77] Diverticular bleeding is the most common cause of lower GI bleeding.[78,79]

Anticoagulants

In 1 retrospective series of 52 patients, correction of the INR to between 1.5 and 2.5 allowed successful endoscopic diagnosis and therapy at rates comparable with those achieved in non-anticoagulated patients.[80] In a large series in which 95% of patients had an INR between 1.3 and 2.7, endoscopic therapy achieved initial success in 95% of patients (233/246) using a variety of hemostatic techniques, including injection therapy, heater probe, and hemoclips.[81] Although the rebleeding rate in this series was 23%, the INR level before endoscopy was not a predictor of rebleeding. In another retrospective study, rates of rebleeding in patients with supratherapeutic INRs ($\geq$4.0) were not significantly different from those with INRs in the therapeutic range (2.0-3.9).[79] Finally, in a systematic review of 1869 patients with nonvariceal upper GI bleeding, INR at initial presentation was found not to predict the risk of rebleeding.[82] These data suggest that endoscopic hemostatic therapy is very effective even in patients with moderately elevated INR, normalizing the INR does not reduce rebleeding but does delay time to endoscopy, and INR at the time of endoscopy may not be predictive of rebleeding. Pending further data, performing endoscopic therapy in bleeding patients with INRs < 2.5 is reasonable.

The decision to stop, reduce, and/or reverse antithrombotic therapy (and thereby risking thromboembolic consequences) must be weighed against the risk of continued bleeding. The risk of thromboembolic events was shown to be low in 2 small studies that withheld warfarin (Coumadin) for 4 to 15 days before endoscopy (1/27 patients and 0/28 patients, respectively).[83,84] The ACCP recommends that warfarin (Coumadin) be held and rapid reversal of anticoagulation with 4-factor prothrombin complex (PCC) be used for patients with vitamin K antagonist-associated major bleeding rather than fresh frozen plasma. They also suggest the additional use of vitamin K be given (5-10 mg by slow IV) rather than reversal with coagulation factors alone.[85] PCC contains the vitamin K–dependent factors II, VII, IX, and X either in nonactivated form (nonactivated PCCs) or partially activated form (activated PCCs; individual drug: Feiba). Some of the nonactivated PCCs contain relatively little factor VII, and these PCCs are referred to as 3-factor PCCs (Bebulin, Baxter Healthcare Corporation, Westlake Village, Calif, USA; Profilnine, Grifols Biologicals Inc, Los Angeles, Calif, USA). In 2012 the FDA approved a 4-factor PCC (Kcentra, CSL Behring LLC, Kankakee, Ill, USA) for vitamin K antagonist reversal in patients with acute major bleeding or need for an urgent surgery/invasive procedure. For warfarin (Coumadin) reversal, the 4-factor PCC is the appropriate reversal agent. However, a combination of 3-factor PCC and low dose of recombinant factor VIIa can also be used when the 4-factor agent is unavailable.[86] The 2014 AHA/ACC guideline on the management of valvular heart disease recommends that fresh frozen plasma (which is not recommended in the ACCP 2012 guideline on the management of anticoagulant therapy, mentioned earlier in this paragraph) or PCC is reasonable in patients with

mechanical valves and uncontrollable bleeding who require reversal of anticoagulation. High-dose vitamin K should not be given routinely because this may create a hypercoagulable condition.[70]

In the event of massive hemorrhage, hemodialysis can be used in patients receiving dabigatran (Pradaxa) but not for rivaroxaban (Xarelto), edoxaban (Savaysa), and apixaban (Eliquis) because of their decreased renal excretion and because they are highly protein bound. Although factor VIIa and 4-factor PCC have been used in these situations, their value in reversing the clinical anticoagulant effects, and controlling clinical hemorrhage is uncertain.[87]

Antiplatelet agents

For patients on APAs with life-threatening or serious bleeding, options include stopping these agents and/or administration of platelets. Most patients will require resumption of antithrombotic therapy after endoscopic control of GI bleeding. There are very limited data to guide the timing of reinitiation of antiplatelet therapy; however, current multidisciplinary cardiac and GI society consensus statements recommend reinitiation of antiplatelet therapy as soon as hemostasis is achieved.[36,74] For patients who develop ASA-related peptic ulcer disease bleeding, resumption of ASA with concurrent proton pump inhibitor therapy is superior to switching to clopidogrel alone for the prevention of recurrent GI bleeding.[88,89] The importance of prompt resumption of cardiac aspirin is critical as demonstrated by a randomized control trial by Sung et al[90] that showed no increased risk of postprocedural bleeding associated with continued ASA use but a clear increase in 30-day mortality in cardiac patients in whom ASA was not resumed.

ENDOSCOPY IN THE PATIENT WITH INTRACORONARY STENTS OR ACS TAKING ANTITHROMBOTIC DRUGS

Elective endoscopy in the patient with an intracoronary stent

Use of DAPT may confer a 3-fold increase in the risk of upper GI bleeding over single-agent antithrombotic therapy.[2,3,91] Given the current evidence, all elective high-risk endoscopic procedures in patients on DAPT should be delayed until the patient has received the minimum length of therapy as recommended by American College of Cardiology Foundation/ACG guidelines.[36] Once this period has elapsed, the decision to proceed with such procedures should be made after discussion of the associated risks and benefits with the patient and relevant medical professionals.

Urgent endoscopy in the patient with ACS or recently placed vascular stent

Antithrombotic agents are commonly used in the management of ACS in patients with recently placed intracoronary stents. Many of these patients receive several agents simultaneously, including the potent platelet GPIIb/IIIa receptor antagonists. It is estimated that 1% to 3% of patients with an ACS will present with or develop GI bleeding during their index hospitalization.[92-95] Patients who develop GI bleeding in the setting of ACS have an almost 4- to 7-fold increased risk of in-hospital mortality over patients with ACS and no GI bleeding.[93,94] In this context, clinicians are faced with the dilemma with proceeding with endoscopic evaluation in a patient at an increased risk of procedural complications. Despite the clinical significance of GI bleeding during ACS, there are sparse data on outcomes of patients with GI bleeding in the setting of ACS. In 1 retrospective case-control study, 200 patients underwent endoscopy within 30 days (mean, 9.1 $\pm$ 8.9) of an acute MI.[94] Serious adverse events (fatal ventricular tachycardia and near respiratory arrest) occurred in 2 patients (1%). In another study, ACS patients with an upper GI bleed were associated with markedly increased mortality.[96]

Patients may develop an acute MI after a GI bleed, and these patients are likely to benefit from endoscopic evaluation. A retrospective study showed that patients who presented with upper GI bleeding leading to acute MI were more likely to require endoscopic therapy than patients who developed GI bleeding after being treated for acute MI (OR 3.9; 95% CI, 1.8-8.5).[95] Other factors associated with the need for endoscopic therapy included hemodynamic instability and hematemesis on presentation. The benefit of endoscopy in the patient with significant GI bleeding in the setting of acute MI is supported by a decision analysis that showed upper endoscopy before cardiac catheterization to be beneficial in patients who presented with overt GI bleeding in the setting of ACS, reducing overall deaths from 600 to 97 per 10,000 patients. However, endoscopy was not found to be beneficial in patients who presented with occult GI bleeding and acute MI.[97] Our understanding of the safety of endoscopy in patients with ACS and/or recently placed intracoronary stents on antithrombotic medications, including DAPT and GPIIb/IIIa inhibitors, is rapidly evolving and is likely to change as knowledge and experience are accumulated.

RECOMMENDATIONS (SUMMARIZED IN TABLE 13)

A. Elective endoscopic procedures

Patients receiving anticoagulant therapy

1. We recommend that elective endoscopic procedures be deferred until short-term anticoagulation therapy (eg, warfarin for VTE) is completed. ⊕⊕⊕○
2. We suggest discontinuing anticoagulation (ie, warfarin [Coumadin], NOACs) for the appropriate drug-specific interval in the periendoscopic period if high-risk

TABLE 13. Management of antithrombotic agents in the elective endoscopic setting

			Endoscopy-induced bleeding risk		
			Low		High
CV risk	Low	AC	1. Continue warfarin and NOAC	AC	1. Discontinue AC 2. Restart warfarin on same day of procedure 3. Delay reinitiating NOACs until adequate hemostasis is achieved
		APA	1. Continue standard doses of ASA/NSAIDs 2. Continue thienopyridines	APA	1. Continue standard doses of ASA/NSAIDs* 2. Discontinue thienopyridines at least 5 days before switch to ASA† 3. Dual APA, hold thienopyridines for at least 5 days, continue ASA†
	High	AC	1. Continue warfarin and NOAC	AC	1. Discontinue AC 2. Bridge therapy‡ 3. Restart warfarin on same day of procedure 4. Delay reinitiating NOACs until adequate hemostasis is achieved
		APA	1. Continue standard doses of ASA/NSAIDs 2. Continue thienopyridines	APA	1. Continue standard doses of ASA/NSAIDs 2. Discontinue thienopyridines at least 5 days before endoscopy or switch to ASA† 3. Dual APA, hold thienopyridines for at least 5 days, continue ASA†

AC, Anticoagulants; *APA*, antiplatelet agent; *NOAC*, novel oral anticoagulant; *ASA*, acetylsalicylic acid, or aspirin; *NSAID*, nonsteroidal anti-inflammatory drug; *CV*, cardiovascular.
*There is evidence to hold APA in patients undergoing ESD and EMR who have a low risk for a thromboembolic event.[116]
†Ticagrelor should be held for 3-5 days, and all other thienopyridines should be held for 5-7 days.
‡In moderate-risk patients (from Table 5), the decision to use bridging therapy and the degree of intensity should be individualized and the patient's wishes considered.[40]

endoscopic procedures are planned in a patient at low risk for thromboembolic events. ⊕⊕○○
3. We suggest continuing warfarin and NOAC in the periendoscopic period in patients undergoing low-risk endoscopic procedures. ⊕⊕○○
4. We suggest bridge therapy for patients undergoing high-risk endoscopic procedures who are at high risk for thromboembolic events. ⊕⊕○○
5. We suggest that warfarin (Coumadin) be restarted on the same day as the procedure in all patients who do not have ongoing bleeding. ⊕⊕○○
6. We suggest that the reinitiation of NOACs after high-risk endoscopic procedures be delayed until adequate hemostasis is ensured, given their rapid onset of action and lack of reversal agents. If therapeutic doses of NOACs cannot be restarted within 12 to 24 hours after a high-risk endoscopic procedure, thromboprophylaxis (ie, UFH bridge) should be considered to decrease risk of thromboembolism, given the short half-life of the NOAC agent, in those with a high risk for thromboembolism. ⊕⊕○○

Patients receiving APA therapy

1. We suggest that continuation of low doses of ASA and nonsteroidal anti-inflammatory drugs may be continued safely in the periendoscopic period. ⊕⊕⊕○
2. We recommend that thienopyridines be continued for all low-risk endoscopic procedures. ⊕⊕⊕○
3. We recommend discontinuation of thienopyridines at least 5 to 7 days before high-risk endoscopic procedure or switching to ASA monotherapy and continuing until the thienopyridine can be safely resumed. ⊕⊕⊕○
4. We recommend that elective endoscopic procedures be deferred in patients with recently placed intracoronary stents and/or ACS until the patient has received antithrombotic therapy for the minimum recommended duration. ⊕⊕⊕○
5. We suggest that thienopyridines be withheld for at least 5 to 7 days (ticagrelor 3-5 days) before high-risk endoscopic procedures and that ASA be continued for patients requiring dual APA. ⊕⊕⊕○

B. Urgent and emergent endoscopic procedures

Patients receiving anticoagulant therapy

1. We recommend patients with acute GI bleeding on anticoagulation therapy have anticoagulant agents held to facilitate achievement of hemostasis. ⊕⊕⊕○
2. We recommend either (1) 4-factor PCC and vitamin K or (2) fresh frozen plasma be given for life-threatening GI bleeding in patients on warfarin anticoagulant therapy. Please note the ACCP only advocates option 1. The AHA/ACC supports option 1 or 2. ⊕⊕⊕○
3. We suggest endoscopic therapy not be delayed in patients with serious GI bleeding and an INR < 2.5. ⊕⊕○○
4. We suggest patients who require anticoagulation receive UFH because of its relatively short half-life after successful endoscopic hemostasis for high-risk stigmata. ⊕⊕○○

Patients receiving APA therapy

1. We recommend consultation with the prescribing specialist (or their colleague) before stopping APAs in situations of significant GI bleeding in patients (1) with recently (<1 year) placed drug eluting intracoronary stents, (2) within 30 days after insertion of a bare metal intracoronary stent, or (3) within 90 days of ACS. The risk of an adverse cardiac event associated

with cessation of the APA therapy likely exceeds the benefit of decreasing postendoscopic bleeding. ⊕⊕⊕○

2. We recommend patients on APAs with life-threatening or serious GI bleeding should have these agents held after discussion with their cardiologist. ⊕⊕⊕○

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Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; APA, antiplatelet agent; ASA, acetylsalicylic acid, or aspirin; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; DVT, deep vein thrombosis; FDA, U.S. Food and Drug Administration; GP, glycoprotein; INR, International Normalized Ratio; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NOAC, novel oral anticoagulant; PAR-1, protease-activated receptor-1; PCC, prothrombin complex concentrate; UFH, unfractionated heparin; VTE, venous thromboembolism.

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