

Periprocedural Management of Antithrombotic Agents

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Michael Y. Chan and Thomas J. Savides

Abbreviations

ACC	American College of Cardiology	FFP	Fresh frozen plasma
ACCP	American College of Chest Physicians	FNA	Fine-needle aspiration
ACS	Acute coronary syndrome	GIB	Gastrointestinal bleeding
ACT	Activated clotting time	GPI	Glycoprotein IIb/IIIa inhibitor
ADP	Adenosine diphosphate	HITT	Heparin-induced thrombocytopenia and thrombosis
AF	Atrial fibrillation	INR	International normalized ratio
AHA	American Heart Association	ISTH	International Society of Thrombosis and Haemostasis
aPTT	Activated partial thromboplastin time	IU	International units
AT	Antithrombin	IV	Intravenous
BMS	Bare-metal stent	LMWH	Low-molecular-weight heparin
cAMP	Cyclic adenosine monophosphate	LVAD	Left ventricular assist device
cGMP	Cyclic guanosine monophosphate	MI	Myocardial infarction
CI	Confidence interval	NSAID	Nonsteroidal anti-inflammatory drug
COX	Cyclooxygenase	NSTEMI	Non-ST elevation myocardial infarction
DBE	Double-balloon enteroscopy	OR	Odds ratio
DES	Drug-eluting stent	OS	Orthopedic surgery
DIC	Disseminated intravascular coagulation	PCI	Percutaneous coronary interventions
EGD	Esophagogastroduodenoscopy	PDE	Phosphodiesterase
ERCP	Endoscopic retrograde cholangiopancreatography	PEG	Percutaneous endoscopic gastrostomy
EUS	Endoscopic ultrasound	PGI ₂	Prostacyclin
FDA	Food and Drug Administration	PO	Per oral
		PPB	Post-polypectomy bleeding
		PPI	Proton-pump inhibitor
		rFVIIa	Recombinant activated factor VII
		SC	Subcutaneous
		SEMS	Self-expanding metal stent
		STEMI	ST elevation myocardial infarction
		TF	Tissue factor
		TIMI	Thrombolysis in Myocardial Infarction
		TXA ₂	Thromboxane A ₂

M.Y. Chan, M.D., M.P.H. • T.J. Savides, M.D. (✉)
Division of Gastroenterology, University of
California, San Diego, 9500 Gilman Drive,
La Jolla, CA 92093, USA
e-mail: michaelchan78@yahoo.com;
tsavides@ucsd.edu

UA	Unstable angina
UFH	Unfractionated heparin
UGI	Upper gastrointestinal
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Introduction

Cardiovascular diseases affect approximately one-third of all adults and account for 800,000 deaths each year in the United States [1]. As a result, many patients are on antithrombotic therapies to reduce their risk of thromboembolic complications and pose a dilemma for providers who perform endoscopy due to lack of well-designed studies investigating the optimal approach in managing these agents in patients who require procedures. There is much reliance on retrospective studies and expert opinion that formulate guidelines for management of anti-thrombotic therapies in the periprocedural setting [2–4].

Management of antithrombotic medications at the time of endoscopy involves balancing the risk of thromboembolic events from interruption of these agents versus the risk of procedure-related bleeding and related complications from continuation of therapy. In general, patients who undergo procedures considered low risk for causing bleeding can continue their antithrombotic medications, regardless of their risk for thromboembolism (Table 2.1). Patients at low risk for thromboembolism but who undergo procedures with higher bleeding risk can temporarily discontinue antithrombotic medications and remain in a subtherapeutic range in the periprocedural period. Patients at moderate-to-high risk for thromboembolic events who are undergoing procedures with high bleeding risk are a challenge to manage. Providers need to be familiar with the bleeding risks of planned procedures, identify those at highest risk for thromboembolism, recognize the need for bridging therapy, and know when to interrupt and reinstitute anti-thrombotic therapy.

Table 2.1 Management recommendations based on risks of thromboembolism and procedure-related bleeding

Procedural bleeding risk	Thromboembolism risk	
	Low	High
Low	Continue antithrombotic medications	Continue antithrombotic medications
High	Temporarily discontinue antithrombotic medications without bridging therapy	Continue antithrombotic medications or temporarily discontinue antithrombotic medication with bridging therapy

Bleeding Risk of Endoscopic Procedures

Overview

Procedures considered high risk for bleeding (Table 2.2) are those associated with ≥ 1 % risk of causing clinically significant hemorrhage (i.e., requiring hospitalization, transfusion, endoscopic treatment, or surgery) [4, 5]. Low-risk procedures include diagnostic endoscopy with or without biopsy, endoscopic retrograde cholangiopancreatography (ERCP) without sphincterotomy, endoscopic ultrasound (EUS) without fine-needle aspiration (FNA), and capsule endoscopy. High-risk procedures include polypectomy at any location (≥ 1 cm), ERCP with biliary/pancreatic sphincterotomy, and endoscopic hemostasis, among others. The bleeding risk associated with enteral stent placement but without dilation and ERCP with papillary balloon dilation but without sphincterotomy remains controversial. As a general rule, elective high-risk procedures should be delayed until the patient’s risk for thromboembolism is reduced and/or antithrombotic medications are optimized to minimize bleeding complications. In the setting where emergent endoscopic intervention is required, every effort should be made to conservatively manage these patients (e.g., transfusions) until their periprocedural bleeding and thromboembolic risks are reduced.

Table 2.2 Bleeding risks of endoscopic procedures

Low-risk procedures (<1 %)	Controversial	High-risk procedures (≥1 %)
Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy, BAE)±biopsy	Enteral stent placement without dilation	Polypectomy (any location, ≥1 cm)
ERCP±stenting without sphincterotomy	ERCP papillary balloon dilation without sphincterotomy	ERCP with biliary/pancreatic sphincterotomy
EUS without FNA		EUS with FNA
Capsule endoscopy		PEG placement
		Therapeutic BAE
		Pneumatic or bougie dilation
		Endoscopic hemostasis
		Treatment of varices
		Cystogastrostomy
		EMR, ESD, ampullectomy
		Ablation of tumor or vascular lesion by any technique

BAE balloon-assisted enteroscopy, *EGD* esophagogastroduodenoscopy, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *FNA* fine-needle aspiration, *PEG* percutaneous endoscopic gastrostomy, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

Endoscopic Sphincterotomy

The majority of ERCP-related bleeding is intraluminal and is primarily related to sphincterotomy, including precut papillotomy. In a pooled analysis of 21 prospective cohort studies involving 16,855 patients who underwent ERCP, clinically significant bleeding occurred in 226 patients (1.34 %, 95 % confidence interval [CI] 1.16–1.52 %) [6]. Independent predictors of post-ERCP hemorrhage include sphincterotomy, coagulopathy before the procedure (partial thromboplastin or prothrombin time >2 s above normal, platelet count <80,000 mm³, or ongoing hemodialysis), anticoagulant therapy within 3 days post procedure (oral warfarin or intravenous heparin), cholangitis before the procedure, intraprocedural bleeding (ranging from oozing to requiring endoscopic hemostasis), precut papillotomy, obstruction/stenosis of the orifice of the papilla of Vater, low endoscopist case volume (≤1 sphincterotomy/week), and low center volume (<200 ERCPs/year) [7–9]. Freeman et al. showed that while cirrhosis was not an independent predictor of post-sphincterotomy bleeding ($p=0.06$), the two patients with fatal bleeding complications had Child–Pugh class C cirrhosis [7]. Neither extension of previous sphincterotomy nor the

size of sphincterotomy was associated with increased post-sphincterotomy bleeding [7].

Evidence is conflicting as to the risk of post-sphincterotomy bleeding in the setting of recent aspirin or nonsteroidal anti-inflammatory drug (NSAID) use. Freeman et al. showed no increased risk of bleeding if aspirin or NSAID was used within 3 days of endoscopic sphincterotomy [7]. In another case–control study, there was no increased risk of clinically significant bleeding related to the use of antiplatelet agents [10]. Conversely, one study demonstrated an increased incidence of post-sphincterotomy bleeding in aspirin users relative to nonusers (9.7 % vs. 3.9 %, $p=0.01$), and the withholding of aspirin for 7 days prior to endoscopic sphincterotomy did not decrease the risk for bleeding (9.5 % vs. 3.9 %, $p=0.01$) [11]. Unfortunately, data are lacking regarding the safety of endoscopic sphincterotomy in patients on dual antiplatelet agents and/or anticoagulants or in those who are coagulopathic due to cirrhosis or hemodialysis.

In one study, endoscopic balloon dilation of the biliary sphincter was as effective as biliary sphincterotomy for the removal of common bile duct stones, with significantly reduced bleeding complications (0 % vs. 2.0 %, $p=0.001$) [12]. However, the rate of post-ERCP pancreatitis was

higher in the balloon dilation group (7.4 % vs. 4.3 %, $p=0.05$). Therefore, it cannot be advocated for routine use [12]. There are no well-designed, head-to-head comparisons of the two methods at this time in patients who are on anti-thrombotic therapy.

An endoscopist performing ERCP on an emergent basis is likely already dealing with a patient at high risk for post-procedural bleeding. Based on current evidence, ERCP can be performed with low risk of post-procedural bleeding if sphincterotomy is not necessary or can be deferred until the patient's bleeding risk is reduced. If the patient is medically stable, transfer to a high-volume center for ERCP should be considered.

Endoscopic Hemostasis

Contribution of Antithrombotic Medications to Gastrointestinal Bleeding

In the setting of antiplatelet use, recurring patient-related risk factors for gastrointestinal bleeding (GIB) include prior history of GIB, history of *H. pylori* infection, and advanced age. Concurrent use of anticoagulants, steroids, or NSAIDs is also a consistent predictor of GIB. GIB risk increases with the number of risk factors present in the patient [13]. Among patients using low-dose aspirin (75–325 mg daily), a meta-analysis of placebo-controlled trials for vascular protection demonstrated a relative risk of 2.07 (95 % CI, 1.61–2.66), conferring an increased annual incidence of 0.12 % (95 % CI 0.07–0.19 %) for major GIB attributed to low-dose aspirin use [14].

The risk of GIB with combination antithrombotic agents is increased when compared with low-dose aspirin alone. A meta-analysis showed an increased risk of major GIB when aspirin was combined with clopidogrel (odds ratio [OR] 1.86, 95 % CI, 1.49–2.31) or with an anticoagulant (OR 1.93, 95 % CI, 1.42–2.61) compared with aspirin alone [15]. In the same study, proton-pump inhibitor (PPI) therapy significantly reduced the risk of GIB events in patients given low-dose aspirin [15]. The routine use of PPI

with clopidogrel is controversial due to impairment of antiplatelet effects of clopidogrel by PPI in in vitro studies [13]. Although findings from clinical studies are inconsistent, product labeling of omeprazole and esomeprazole includes warnings about possible interactions with clopidogrel.

Patients who undergo careful monitoring of anticoagulant intensity have a 0.3–0.5 % increased annual risk of major bleeding compared with controls [16]. Independent predictors of anticoagulant-related bleeding include intensity of anticoagulant effect, age >75, concomitant use of antiplatelets, and length of therapy [17].

Holster et al. performed a meta-analysis of 43 randomized trials comparing bleeding risk of the new oral anticoagulants versus standard therapy [18]. While all the studies included bleeding events as a safety outcome, only 19 of these trials assessed GIB as a separate subgroup (Table 2.3). The overall OR for GIB among patients taking the new oral anticoagulants was 1.45 (95 % CI, 1.07–1.97), and the OR for clinically relevant bleeding (as defined by the International Society of Thrombosis and Haemostasis [ISTH] and Thrombolysis in Myocardial Infarction [TIMI] study group) was 1.16 (95 % CI, 1.00–1.34). Subgroup analyses demonstrated significantly

Table 2.3 Bleeding risk of new oral anticoagulants [18]

Group	OR (95 % CI)
Clinically relevant bleeding	1.2 (1.0–1.3)
Gastrointestinal bleeding	1.5 (1.1–2.0)
Indication	
ACS	5.2 (2.6–10.5)
Venous thrombosis	1.6 (1.0–2.4)
AF	1.2 (0.9–1.6)
OS thromboprophylaxis	0.8 (0.3–2.0)
Drug-specific GIB ^a	
Dabigatran	1.6 (1.3–1.9)
Rivaroxaban	1.5 (1.2–1.8)
Apixaban	1.2 (0.6–2.7)
Edoxaban	0.3 (0.0–7.7)

OR odds ratio, CI confidence interval, ACS acute coronary syndrome, AF atrial fibrillation, OS orthopedic surgery, GIB gastrointestinal bleeding

^aResults based on three studies for dabigatran, five studies for rivaroxaban, eight studies for apixaban, and one study for edoxaban

increased bleeding risk of the new oral anticoagulants versus standard therapy if the indications included acute coronary syndrome (ACS) and treatment of venous thrombosis, but not atrial fibrillation (AF) or thromboprophylaxis after orthopedic surgery (OS). Dabigatran and rivaroxaban were also associated with significantly increased risk for GIB. The meta-analysis was limited by substantial heterogeneity between studies with an I^2 of 60.8 % ($p < 0.05$) for studies assessing GIB and I^2 of 83.5 % ($p < 0.05$) for studies assessing clinically relevant bleeding. Further studies assessing specific GIB-related outcomes in patients taking the new oral anticoagulants are warranted.

Considerations Regarding Hemostatic Techniques

Most studies evaluating endoscopic hemostasis in anticoagulated patients are retrospective in nature. In these studies, identifying the site of GIB was successful in >80 % of patients [19, 20]. Gastroduodenal ulcers and erosions accounted for >50 % of lesions causing upper GIB. Studies evaluating specific lower GI sources of bleeding are lacking, although common causes include polyps, diverticula, and angiodysplasia. Among patients with GIB on antiplatelets or anticoagulants, 17–29 % will have no mucosal abnormality on endoscopic evaluation [21].

Endoscopic clips are safe and effective in the treatment of bleeding peptic ulcers, Dieulafoy lesions, and Mallory–Weiss tears, as well as for prophylaxis or treatment of post-polypectomy bleeding and diverticular hemorrhage [22]. Clip placement has been demonstrated to be superior to injection alone and comparable to thermal coagulation for the treatment of non-variceal upper gastrointestinal bleeding [23]. Endoscopic clip placement, when technically feasible, may be preferable to thermal therapies in patients on antithrombotic therapy for several reasons. Thermal therapies induce or extend ulcer formation and may exacerbate bleeding from tissue injury. Clips have the theoretical advantage of applying mechanical compression to bleeding lesions and can be applied with minimal tissue injury. Additionally, clips can serve as angio-

graphic or surgical markers if bleeding cannot be controlled endoscopically. Clips achieve high rates of primary hemostasis (85–100 %) with low rebleeding rates (2–20 %), although their effectiveness in the setting of antithrombotic therapy is unclear [22]. Studies comparing the different modalities for endoscopic hemostasis in patients on antithrombotic agents are lacking.

Polypectomy

Polypectomy is usually performed in the elective setting with outpatient antithrombotic medications optimized prior to the procedure. Moreover, immediate post-polypectomy bleeding (PPB) can usually be treated effectively with traditional hemostatic techniques. However, severe delayed PPB (1–14 days post procedure) may require emergent endoscopic intervention and often occurs in patients on antithrombotic therapy [24, 25]. Independent predictors of delayed PPB include resumption of anticoagulation following polypectomy, polyp diameter (≥ 10 mm), number of polyps removed, proximal colonic location, history of cardiovascular disease, and hypertension [24–28].

Aspirin/NSAID use alone has not been shown to increase the risk of delayed PPB [24, 29]. Current data suggest that there is an increased risk of PPB in patients who continue clopidogrel alone or in combination with aspirin, with an event rate ranging from 2.4 to 3.5 % [27, 28, 30]; however, bleeding was controlled without the need for angiographic or surgical intervention. Thus, in patients who are at high risk for cardiovascular complications, such as those with recent ACS or stent placement, continuation of dual antiplatelet therapy may be reasonable.

Endoscopic clip placement over the polypectomy defect may decrease the risk of delayed PPB. In the only randomized controlled trial to evaluate this intervention, no difference was seen in the rates of delayed PPB in the prophylactic clip placement group compared with the group that received no clip; however, the polyps removed were generally low-risk, small (mean size 7.8 ± 4.0 mm) lesions [31]. On the other hand, a large retro-

spective study of patients with resected polyps of ≥ 2 cm showed that prophylactic clip closure significantly reduced the risk of PPB compared with no clip closure (1.8 % vs. 9.7 %) [32].

Data are limited on the effectiveness of prophylactic clip placement after polypectomy in the setting of uninterrupted anticoagulation. A small retrospective study of 21 patients (41 polypectomies) on uninterrupted warfarin (mean international normalized ratio [INR] 2.3, range 1.4–4.9) who underwent hot snare resection of small polyps (≤ 10 mm) had no PPB events when one or two clips were placed immediately after polyp resection. Warfarin was withheld for 36 h before the procedure, while patients remained on a modified diet to avoid supra-therapeutic INR and without concomitant antiplatelet agents. Warfarin was resumed according to the patient's standard schedule [33]. Prophylactic clip placement after polypectomy may be effective in preventing PPB in select patients on uninterrupted anticoagulation, although confirmatory data are needed.

Left Ventricular Assist Devices

Left ventricular assist devices (LVADs) are increasingly being used in patients with advanced cardiac failure as a bridge to cardiac transplantation or destination therapy (i.e., ineligible for transplantation). Bleeding complications after LVAD implantation are common, with 30 % requiring surgery and 50–80 % requiring at least 2 units of packed red blood cells [34, 35]. Risk factors for GIB after LVAD implantation include use of nonpulsatile device and history of GIB prior to device placement [36, 37]. Retrospective studies show rates of GIB varying from 8 to 40 %, likely due to differences in the definition of GIB, and rebleeding is common [37–41]. Endoscopy is safe in LVAD patients and identifies the etiology of GIB in 60–70 % of cases, with peptic ulcer bleeding and vascular malformations of the upper GI tract being the more common sources [39, 42]. Endoscopic hemostasis is generally successful, but data are limited to small

studies [42]. The cardiologist and/or cardiac surgeon should be involved in any plan to modify antithrombotic medications.

Endoscopic Bleeding Risks for Other Situations

Foreign Body Ingestion/Food Impaction

Data from two large retrospective studies found bleeding related to endoscopic foreign body removal ranging from 1 to 3 % [43, 44]. Bleeding associated with endoscopic esophageal food disimpaction ranged from 0 to 1 % in two retrospective studies [45, 46].

Colonic Decompression

The risk of causing bleeding from endoscopic decompression of colonic pseudo-obstruction is uncommon [47].

Luminal Stents

A systematic review of gastroduodenal self-expanding metal stents (SEMS) found a 0.5 % risk of bleeding in a pooled analysis of 606 patients [48]. Data regarding bleeding complications from placement of esophageal and colonic SEMS are scant.

Assessing Risk for Thromboembolism

Bleeding complications from endoscopy can be problematic but are rarely catastrophic. Conversely, thromboembolic events are associated with high rates of morbidity and mortality. The following is an approach to risk stratify patients according to their risk of thromboembolic events. Patients with prosthetic heart valves, AF, and venous thromboembolism (VTE) frequently require chronic anticoagulation therapy. A strategy has been proposed for risk stratifying patients susceptible to perioperative thromboembolism according to indication for anticoagulant therapy (Table 2.4) [49]. Patients

Table 2.4 Proposed perioperative risk stratification for patients at risk for thromboembolism on anticoagulation [49]

Condition	Annual risk for thromboembolism		
	Low (<5 %)	Moderate (5–10 %)	High (>10 %)
Mechanical heart valve	– Bileaflet aortic valve without atrial fibrillation or risk factors ^a	– Bileaflet aortic valve with at least 1 risk factor ^a	– Any mechanical mitral valve – Older aortic mechanical valve (caged ball, tilting disk) – Recent (<6 months) stroke/TIA
Atrial fibrillation	– CHADS ₂ score 0–2 without previous stroke/TIA	– CHADS ₂ score 3 or 4	– CHADS ₂ score 5 or 6 – Rheumatic or severe valvular disease – Recent (<3 months) stroke/TIA
Venous thromboembolism	– VTE >12 months previously without other risk factors	– VTE within the past 3–12 months – Non-severe thrombophilia ^b – Recurrent VTE – Active cancer (diagnosis <6 months or undergoing treatment)	– Recent (<3 months) VTE – Severe thrombophilia ^c

CHADS₂ score (range 0–6): congestive heart failure, hypertension, age >75 years, and diabetes mellitus are assigned 1 point apiece, while previous stroke or TIA is assigned 2 points

CHADS₂ cardiac failure–hypertension–age–diabetes–stroke, TIA transient ischemic attack, VTE venous thromboembolism

^aRisk factors for stroke without atrial fibrillation: congestive heart failure, hypertension, age >75 years, diabetes, prior stroke/TIA

^bNon-severe thrombophilia: heterozygous factor V Leiden or prothrombin gene G20210A mutation

^cSevere thrombophilia: deficiency of protein C, protein S, or antithrombin, antiphospholipid syndrome (presence of antiphospholipid antibodies or lupus anticoagulant), homozygous for factor V Leiden, homozygous for prothrombin gene G20210A, compound heterozygous mutations of latter two genes

with a >10 % annual risk for thromboembolism are classified as “high risk,” 5–10 % annual risk as “moderate risk,” and <5 % annual risk as “low risk.” While this classification system can provide some guidance for the risk of developing a thromboembolic event, a patient’s risk assessment should be individualized according to patient- and procedure-related factors.

Atrial Fibrillation

In patients with AF, the CHADS₂ score is useful to risk stratify a patient’s annual risk for stroke, although it has not been validated in the perioperative setting [50]. The CHADS₂ score scheme is based on a scale of 0–6. Congestive heart failure, hypertension, age >75 years, and diabetes

mellitus are assigned 1 point apiece, while previous stroke or transient ischemic attack (TIA) is assigned 2 points. Patients with AF at highest risk for stroke (>10 % annual stroke risk) include a CHADS₂ score of 5 or 6, recent (<3 months) ischemic stroke or TIA, or the presence of rheumatic or severe valvular heart disease. Patients with a CHADS₂ score of 3 or 4 are considered moderate risk (5–10 % annual risk) and 0–2 are low risk (<5 % annual risk) for stroke [49].

Mechanical Heart Valves

Patients with mechanical heart valves who are at high risk for thromboembolic events include a prosthesis in the mitral position, any caged-ball or tilting disk aortic valve prosthesis, and recent

(<6 months) ischemic stroke or TIA. Patients with bileaflet aortic valve prostheses with one or more risk factors, including AF, prior stroke or TIA, hypertension, diabetes, congestive heart failure (CHF), or age >75 years, are at moderate risk. Patients with bileaflet aortic valve prostheses without AF or other risk factors for stroke are at low risk [49].

Deep Vein Thrombosis/Pulmonary Emboli

Patients with recent (<3 months) VTE and severe thrombophilia are considered high risk for additional thromboembolic events. Those at moderate risk are patients with VTE within the past 3–12 months, recurrent VTE, active cancer (diagnosis <6 months or undergoing treatment), and non-severe thrombophilia. Remote VTE (>12 months) with no other risk factors is considered low risk (Table 2.4) [49].

Coronary Stents and Recent Acute Coronary Syndrome

Dual antiplatelet therapy with combination aspirin and thienopyridine has been shown to reduce adverse events in patients receiving coronary artery stents. Premature discontinuation of antiplatelet therapy is associated with increased risk of stent thrombosis, myocardial infarction, and death. Stent thrombosis can have catastrophic consequences, with incidence of death ranging from 20 to 45 % and myocardial infarction in up to 64 % of cases [51]. Patients at highest risk for stent thrombosis are those with bare-metal stents (BMS) placed within 6 weeks and drug-eluting stents (DES) placed within 12 months [3]. Guidelines vary in regards to when dual antiplatelet therapy can be interrupted (while aspirin is continued) for elective procedures: 4–6 weeks after placement of BMS and 6–12 months after placement of DES [2–5]. Individuals at higher risk for thrombotic events (diabetes, renal failure, cancer, heart failure, complex coronary dis-

ease, or history of coronary stent thrombosis) or with stent placement in the setting of ACS may need longer periods of uninterrupted dual antiplatelet therapy prior to elective/urgent procedures [52]. Dual antiplatelet therapy should be resumed after bleeding risk is minimized from the endoscopic intervention and continued for the recommended duration (up to 12 months for patients with BMS and at least 12 months for patients with DES) [53].

Non-cardioembolic Stroke and Transient Ischemic Attack Prevention

Risk factors for non-cardioembolic stroke include hypertension, diabetes, and hyperlipidemia. Aggressive control of risk factors and lifestyle changes (smoking and alcohol cessation) are recommended to prevent a stroke [54]. Aspirin reduces the risk for secondary stroke by 15 % (95 % CI, 6–23 %) compared with placebo. Aspirin monotherapy, combination aspirin/dipyridamole, and clopidogrel monotherapy are all acceptable options for stroke prevention. Use of an antiplatelet agent is preferred over oral anticoagulants for non-cardioembolic stroke prevention [54].

Left Ventricular Assist Devices

LVADs induce hypercoagulability and persistent platelet activation through various mechanisms, frequently requiring combination anticoagulation and antiplatelet therapy depending on the device implanted [55]. Two randomized controlled trials investigating one of the most common LVADs (HeartMate II, Thoratec, Pleasanton, CA) found low rates of thrombotic complications (ischemic stroke ranging from 3 to 8 %; device thrombosis ranging from 2 to 4 %) in patients on combination warfarin and aspirin [34, 35]. Ischemic strokes are more common with lower INR (<1.5), and hemorrhagic strokes are more common with higher INR (>3.0) [56].

Management of Antithrombotic Medications

Anticoagulants

Overview of Anticoagulants

Indications for anticoagulation therapy encompass a heterogeneous group of conditions that have varying risks of developing into thromboembolism, including patients with prosthetic heart valves, AF, VTE, and hypercoagulable states (e.g., thrombophilia, active cancer). Anticoagulants exert their effects at various points in the coagulation cascade, which include coagulation initiation and propagation, as well as fibrin formation (Fig. 2.1). An overview of currently available anticoagulants is provided in Table 2.5.

Vitamin K antagonists (VKAs), such as warfarin, are the mainstay of chronic anticoagulation therapy. VKAs inhibit γ -carboxylation of vitamin

K epoxide reductase in the liver, which inhibits the production of factors II, VII, IX, and X in the coagulation cascade. While VKAs are effective at reducing thromboembolic events, they have several limitations, including slow onset of action (~5 to 7 days to therapeutic INR), need for regular monitoring, variability in drug metabolism, narrow therapeutic window (usually an INR between 2.0 and 3.0), and several drug and dietary interactions. Approximately 5 days are needed for the INR to normalize after VKA cessation. The effects of VKAs can be reversed more rapidly with administration of vitamin K and fresh frozen plasma (FFP) primarily.

Unfractionated heparin (UFH) can be administered in intravenous (IV) and subcutaneous (SC) forms. Its mode of action is through anti-thrombin (AT) III-mediated inhibition of factor Xa and thrombin (factor IIa) of the coagulation cascade. Intravenous formulations are used for

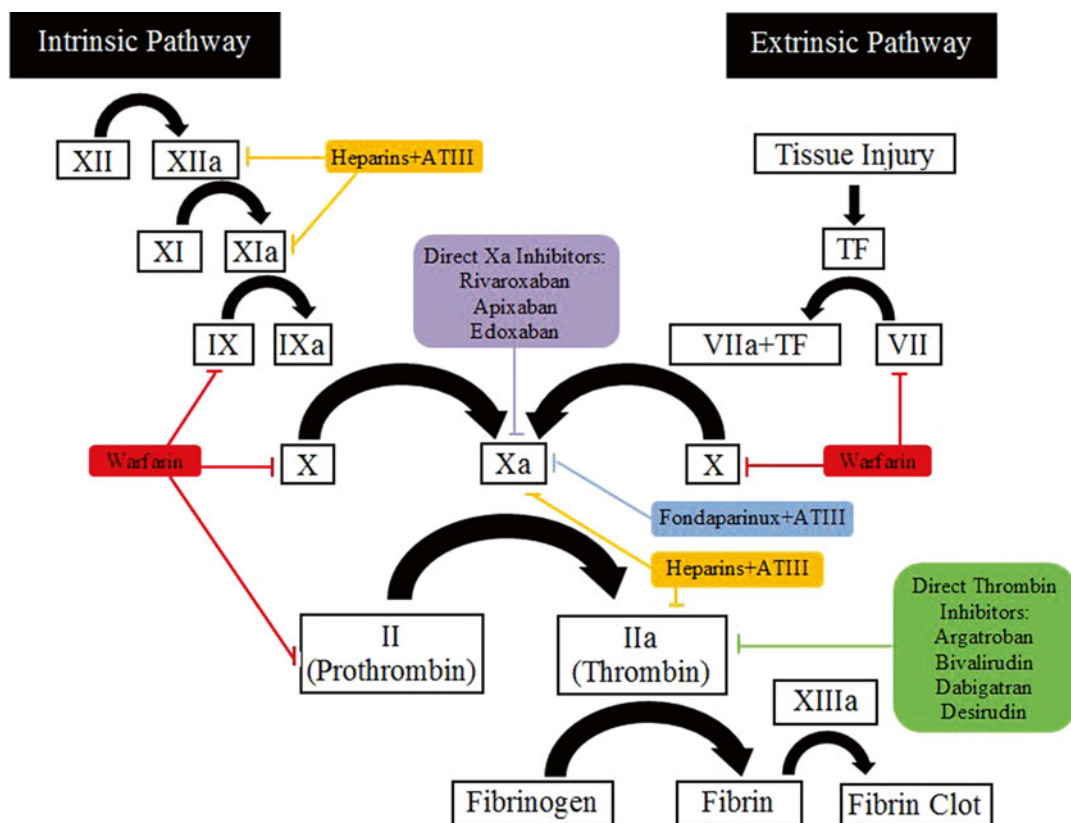


Fig. 2.1 Simplified diagram of coagulation cascade with sites targeted by anticoagulant drugs

Table 2.5 Current anticoagulant agents

Drug	Main indications	Route	Mechanism of action	Time to maximal effect	Elimination half-life ^a	Return of normal coagulation after cessation	Reversal agent or antidote
Warfarin (Coumadin, Bristol-Myers Squibb) [57–59]	VTE treatment; AF, post-MI, mechanical valve, bioprosthetic valve, others	PO	Vitamin K-dependent inhibition of clotting factors II, VII, IX, and X	5–7 days for therapeutic INR	36–42 h	~5 days to normalize INR	Vitamin K, FFP, PCC, rFVIIa
Unfractionated heparin (Fresenius Kabi USA) [60, 61]	ACS, VTE treatment or prophylaxis, bridge therapy for AF/ cardioversion	IV or SC	AT-mediated indirect inhibition of factors XIIa, IXa, XIa, and Xa and thrombin	Immediate (IV) Within 6 h (SC)	30–120 min	4 h	Hold or protamine sulfate
Low-molecular-weight heparin (enoxaparin [Lovenox, Sanofi Aventis], dalteparin [Fragmin, Eisai]) [60, 62, 63]	ACS, VTE treatment or prophylaxis, bridge therapy for AF/ cardioversion	SC	AT-mediated indirect inhibition of factors XIIa, IXa, XIa, and Xa and thrombin	3–5 h	3–6 h	24 h	Hold or protamine sulfate
Fondaparinux (Arixtra, GlaxoSmithKline) [60, 64]	VTE treatment and prophylaxis	SC	AT-mediated indirect inhibition of factor Xa	3–5 h	17–21 h	2–4 days	No antidote; consider rFVIIa
Bivalirudin (Angiomax, The Medicines Company) [60, 65]	PCI; ACS; HIT treatment and prophylaxis	IV	Reversible direct thrombin inhibition	Immediate	20–30 min	1 h	No antidote; consider hemodialysis
Desirudin (Privask, Canyon Pharmaceuticals) [66, 67]	VTE prophylaxis	SC	Reversible direct thrombin inhibition	60–90 min	2–3 h	16–36 h	No antidote; consider hemodialysis
Argatroban (Eagle Pharmaceuticals) [60, 68]	PCI (patients with heparin allergy); HIT treatment and prophylaxis	IV	Reversible direct thrombin inhibition	Immediate	40–50 min	2–4 h	No antidote; consider hemodialysis

Dabigatran (Pradaxa, Boehringer Ingelheim) [57, 58, 69]	Non-valvular AF	PO	Reversible direct thrombin inhibition	0.5–2 h	12–17 h	24–36 h	No antidote; charcoal for overdose (ingestion <2 h); consider hemodialysis (~60 % removal), rFVIIa, PCC, or FEIBA
Rivaroxaban (Xarelto, Janssen Pharmaceuticals) [57, 58, 70]	VTE treatment and prophylaxis; non-valvular AF	PO	Reversible direct factor Xa inhibition	1–4 h	5–13 h	24 h	No antidote; charcoal for overdose (ingestion <2 h); consider PCC
Apixaban (Eliquis, Bristol-Myers Squibb) [71]	Non-valvular AF; phase III studies: VTE treatment and prophylaxis	PO	Reversible direct factor Xa inhibition	1–4 h	8–15 h	24 h	No antidote; charcoal for overdose (ingestion <2 h); consider PCC
Edoxaban (Daiichi Sankyo) (investigational) [72, 73]	Phase III studies: VTE treatment and prophylaxis (Japan); non-valvular AF (USA)	PO	Reversible direct factor Xa inhibition	1–2 h	6–11 h	24–36 h	No antidote; charcoal for overdose (ingestion <2 h); consider PCC

VTE venous thromboembolism, AF atrial fibrillation, MI myocardial infarction, PO per oral, INR international normalized ratio, FFP fresh frozen plasma, PCC prothrombin complex concentrates, rFVIIa recombinant activated factor VIIa, ACS acute coronary syndrome, IV intravenous, SC subcutaneous, AT antithrombin, PCI percutaneous coronary intervention, HIT heparin-induced thrombocytopenia and thrombosis

^aNote: elimination half-life is dose dependent

treatment of VTE, ACS, and bridging anticoagulation for AF and cardioversion. Subcutaneous formulations are used for VTE prophylaxis. The IV UFH anticoagulant response is monitored by measuring the activated partial thromboplastin time (aPTT) at 6 h intervals. UFH is favored over low-molecular-weight heparin (LMWH) in certain clinical situations given its short half-life, reversal capabilities, and safe use in patients with renal dysfunction. Urgent reversal can be achieved with protamine sulfate [57].

LMWHs have increased bioavailability over UFH when administered subcutaneously. LMWHs inhibit factor Xa and, to a lesser degree, thrombin (IIa) to achieve their anticoagulant effects. Laboratory monitoring is usually not needed, but anti-Xa assays are used in select patients. Clinical indications are similar to UFH, and urgent reversal of anticoagulant effects can partially be achieved with protamine sulfate [57].

Fondaparinux is administered subcutaneously and inhibits factor Xa [57, 60]. This agent is approved for use in the prophylaxis and treatment of VTE and may be employed in situations where UFH and LMWH cannot be used, such as in the setting of heparin-induced thrombocytopenia and thrombosis (HITT). Monitoring is not usually necessary, but an anti-Xa assay may be used to identify if activity is present [74]. Recombinant activated factor VII (rFVIIa) can be considered for emergent reversal [60].

Bivalirudin and desirudin are synthetic analogs of r-hirudin. They reversibly bind to the enzymatic catalytic site and anion binding site of thrombin [57]. The short half-life of bivalirudin enables its use in the periprocedural setting. It is an accepted alternative anticoagulant to UFH for percutaneous coronary interventions (PCI) and ST elevation myocardial infarction (STEMI), as well as in select patients with unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI) [53, 75]. There is some evidence that bleeding complications are lower with bivalirudin than with combination UFH and glycoprotein IIb/IIIa inhibitors (GPI) in the setting of ACS [53, 76]. Bivalirudin may be monitored by activated clotting time (ACT) [74]. Desirudin

has been used mainly for VTE prophylaxis [66]. Monitoring can be done by following the aPTT [74]. Serious bleeding complications with desirudin are comparable to SC UFH and LMWH [66]. There are no known reversal agents for bivalirudin and desirudin.

Argatroban is an IV anticoagulant derived from the amino acid arginine and reversibly binds to the thrombin active site. It has a short half-life, and coagulation parameters normalize within hours of infusion cessation but may take longer in patients with hepatic impairment. The aPTT or ACT should be followed for appropriate dosing. It is used primarily in the management of HITT and as a potential alternative to UFH during PCI in patients with heparin allergy [52, 57, 60]. There is no known reversal agent for argatroban.

Several novel oral anticoagulants have recently been marketed for use or are in late phases of clinical trials. These new agents provide the convenience of oral administration and avoid many of the limitations of warfarin. However, there are reports of increased clinically relevant bleeding complications, including GIB, with the new oral anticoagulant agents compared with standard therapies [18]. Dabigatran is a direct thrombin inhibitor approved for use in non-valvular AF [77]. Time to maximal effect is 0.5–2 h with a terminal half-life of 12–17 h at steady-state levels [58]. There is no specific reversal agent. Because dabigatran is a direct thrombin inhibitor, administration of FFP or prothrombin complex concentrate (PCC) may not be completely effective in reversing its effects. Hemodialysis may be effective at removing dabigatran (~60 %) from the bloodstream, and activated charcoal may be helpful in the setting of overdose [77]. Rivaroxaban is a direct factor Xa inhibitor and is approved for treatment and prophylaxis of VTE and stroke prevention in the setting of non-valvular AF [57, 58]. Time to maximal inhibition is 1–4 h. Its half-life is 5–13 h [58]. There is no specific reversal agent. Activated charcoal may be useful in the setting of overdose. However, given that rivaroxaban is highly protein bound, hemodialysis will not be effective in removing it from plasma. As it is an

upstream inhibitor of coagulation, administration of FFP, PCC, or rFVIIa may reverse its effects [57]. Apixaban (recently FDA approved) and edoxaban (in phase III clinical trials) are both direct factor Xa inhibitors with similar indications and pharmacologic properties as rivaroxaban [57].

Bridging Therapy

Once it is determined that a patient's thromboembolic risk and procedure-related bleeding risk warrant a change in antithrombotic therapy, the ultimate goal is to minimize the interval that a patient remains off anticoagulation. Anticoagulation interruption may be performed with or without "bridging." Bridging therapy usually refers to the administration of a short-acting anticoagulant, usually IV UFH or SC LMWH, during interruption of warfarin [49]. The following sections will discuss which patients need bridging anticoagulation, when to stop and restart anticoagulants in the periprocedural setting, and methods of reversing anticoagulation.

Patients at high risk for developing thromboembolism are recommended to receive bridging therapy (Table 2.4) [49]. In moderate-risk patients, the decision to proceed with bridging therapy should be based on individual patient- and procedure-related factors. Bridging therapy is not recommended for low-risk patients [49].

Interruption of Anticoagulants before Procedure

Patients requiring temporary interruption of warfarin before endoscopy should stop a minimum of 5 days prior to the procedure; shorter time intervals are discouraged [49]. Patients receiving therapeutic dose IV UFH should stop the agent at least 4–6 h before the procedure [49]. Patients on therapeutic dose SC LMWH should receive their last dose a minimum of 24 h prior to the procedure [49]. Because reversal agents are not available for the new oral anticoagulants (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban), these agents should be held at least 1–2 days prior to the procedure and even longer in the setting of renal impairment.

Resumption of Anticoagulants after Procedure

Patients may resume warfarin within 12–24 h after endoscopy as long as the procedure was completed with adequate hemostasis [49]. UFH and LMWH should not be resumed at a fixed time after the procedure without consideration of anticipated bleeding risk or adequacy of post-procedural hemostasis. Following procedures with low bleeding risk, patients receiving therapeutic dose IV UFH or SC LMWH (whether for bridging purposes or not) may resume therapy approximately 24 h after the procedure. Following procedures with high bleeding risk, resumption of therapeutic dose IV UFH or SC LMWH (whether for bridging purposes or not) should be delayed for 48–72 h at which time adequate hemostasis has been assured [49]. When resuming IV UFH, it should be done without bolus injection and at the same infusion rate used prior to the procedure [49]. If bleeding continues beyond 72 h, use of low-dose heparin bridging regimens and resumption of warfarin alone without post-procedural bridging are therapeutic options [49].

Reversal

If reversal of anticoagulation status is necessary, the severity of bleeding and urgency of reversal will often dictate the method of anticoagulation reversal, selection of reversal agent, and dosing of the agent. Table 2.6 provides a general overview of reversal agents when urgent reversal is needed or in the setting of severe bleeding. Of note, anticoagulation reversal guidelines are institution specific, taking into account the institution's clinical experience and formulary availability. One can seek the guidance of a hospital's hematology, pharmacy, or anticoagulation service to assist with anticoagulation reversal.

Protamine sulfate is the antidote for heparin-based anticoagulants and can be used for emergent reversal. For treatment of UFH overdose, 1 mg of protamine sulfate per 100 units of heparin is usually administered (not to exceed 50 mg in a single dose) [60]. Given the short half-life of IV UFH (60–90 min), the dose of protamine sulfate given should be calculated based on the amount of UFH adminis-

Table 2.6 Antithrombotic reversal agents [5, 17, 60, 78–80]

Reversal agent	Antithrombotic agents	Dosage	Contraindications	Notes
Protamine sulfate	UFH, LMWH	1 mg protamine sulfate per 100 units of heparin (not to exceed 50 mg in single dose) 1 mg per 1 mg enoxaparin or 100 units dalteparin in previous 8 h (not to exceed 50 mg in single dose) [60]	<ul style="list-style-type: none"> Allergy to protamine sulfate 	<ul style="list-style-type: none"> Patients who previously received protamine sulfate-containing insulin, undergone vasectomy, or have known sensitivity to fish are at increased risk of preformed antibodies and allergic reactions 60–80 % reversal of LMWH
Vitamin K	Vitamin K antagonist	10 mg IV infusion over 20–30 min	<ul style="list-style-type: none"> Allergy to vitamin K 	<ul style="list-style-type: none"> AHA and ACC recommend FFP over high-dose vitamin K (10 mg) in patients with mechanical valves requiring emergent reversal given the risk of creating a hypercoagulable condition with vitamin K [78] IV more rapid onset than oral; SC injection not recommended
FFP	Vitamin K antagonist	10–30 mL/kg (1 unit = ~250 ml)	<ul style="list-style-type: none"> Should not be given for vitamin K deficiency or nonurgent vitamin K antagonist reversal 	<ul style="list-style-type: none"> Replaces all coagulation factors but cannot fully correct May need repeat after 6 h for continued bleeding 15–20 min to thaw each unit Requires ABO compatibility testing Risk of intravascular volume overload
PCC Three-factor PCC (Bebulin, Baxter; Profilnine, Grifols) Four-factor PCC (Kcentra, CSL Behring)	Off-label use: vitamin K antagonist, dabigatran, rivaroxaban, apixaban	25–50 IU/kg IV sufficient in most patients	<ul style="list-style-type: none"> DIC HITT Hypersensitivity to any components in the product 	<ul style="list-style-type: none"> Derived from human plasma Factors require activation via coagulation cascade Rapid correction of INR in warfarin patients Small-volume infusion over 10–30 min Risk of thrombosis 1.4 % May need repeat dose after 6 h Consider adding FFP if three-factor PCC used

(continued)

Table 2.6 (continued)

Reversal agent	Antithrombotic agents	Dosage	Contraindications	Notes
rFVIIa (NovoSeven RT, Novo Nordisk)	Off-label use: vitamin K antagonist, fondaparinux, dabigatran	15–90 µg/kg IV bolus every 2–6 h until hemostasis achieved	<ul style="list-style-type: none"> None known 	<ul style="list-style-type: none"> Non-plasma-derived form Rapid infusion of small volume Rapid INR correction of warfarin but may not correct bleeding because only restores rFVIIa Risk of thrombosis 5–10 %
Factor VIII inhibitor bypass activity (FEIBA NF, Baxter)	Off-label use: vitamin K antagonist, dabigatran	50–100 units/kg every 6–12 h, depending on indication (not to exceed single dose of 100 units/kg and daily dose of 200 units/kg)	<ul style="list-style-type: none"> Known anaphylactic or severe systemic reactions Normal coagulation mechanism Treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to coagulation factor VII or IX DIC Acute thrombosis or embolism (including MI) 	<ul style="list-style-type: none"> Derived from human plasma
Platelets	Aspirin, thienopyridines, ticagrelor	1 apheresis unit		<ul style="list-style-type: none"> Each unit raises platelet count by $30 \times 10^9/L$
Desmopressin (DDAVP, Sanofi Aventis)	Off-label use: aspirin, thienopyridines	0.3–0.4 µg/kg IV	<ul style="list-style-type: none"> Hypersensitivity to drug or components CrCl <50 ml/min History of hyponatremia 	

UFH unfractionated heparin, *LMWH* low-molecular-weight heparin, *IV* intravenous, *SC* subcutaneous, *AHA* American Heart Association, *ACC* American College of Cardiology, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate, *IU* international units, *DIC* disseminated intravascular coagulation, *HITT* heparin-induced thrombocytopenia and thrombosis, *rFVIIa* recombinant activated factor VII, *MI* myocardial infarction

tered over the previous several hours. Rapid administration of protamine sulfate can cause severe hypotension or anaphylaxis. Protamine sulfate is not as effective in reversing the anticoagulant effects of LMWHs. The American College of Chest Physicians (ACCP) recommends that if LMWH is given within 8 h, protamine sulfate should be given in a dose of 1 mg per 100 anti-Xa units of LMWH (not to exceed 50 mg in a single dose) [60]. One milligram of enoxaparin is equivalent to approximately 100 anti-Xa units. If bleeding continues, a second dose of protamine sulfate at 0.5 mg per 100 anti-Xa units can be given [60].

Recommendations for reversing anticoagulation in patients on VKA therapy vary accord-

ing to differences in society guidelines. The ACCP recommends reversal with vitamin K (10 mg) by slow IV infusion (over 30 min) in all patients with serious bleeding and elevated INR, supplemented with FFP, PCC, or rFVIIa, depending on the urgency of the clinical situation [17]. Repeat vitamin K infusion may be given every 12 h, as needed, for persistent INR elevation [17]. In patients with life-threatening bleeding (e.g., intracranial hemorrhage), administration of FFP, PCC, or rFVIIa is recommended, supplemented with vitamin K (10 mg) by slow IV infusion [17]. The American Heart Association and American College of Cardiology recommend FFP over high-dose

vitamin K (10 mg) in patients with mechanical valves requiring emergent reversal due to the risk of creating a hypercoagulable state with the use of the latter. Low-dose vitamin K (1 mg) IV may be a safe alternative [78].

There are no known reversal agents for the newer oral anticoagulant agents, which include direct factor Xa inhibitors (i.e., rivaroxaban, apixaban) and direct thrombin inhibitors (i.e., dabigatran). The use of FFP, PCC, rFVIIa, and FEIBA for anticoagulation reversal can be considered, but data are limited to anecdotal experience and small studies (Table 2.6).

PCCs come in three-factor or four-factor concentrates. Three-factor PCCs have therapeutically useful levels of factors II, IX, and X, but only small amounts of factor VII [81]. There are currently two three-factor PCCs available in the United States: Bebulin (Baxter) and Profilnine (Grifols). Four-factor PCCs contain factors II, VII, IX, and X, as well as proteins C and S. Kcentra (CSL Behring) is the only four-factor PCC approved for use in the United States. Because three-factor PCCs lack factor VII, their use alone for reversing VKA-induced coagulopathy may not be completely effective [81]. When comparing four-factor PCCs with FFP for reversing VKA-induced coagulopathy, the former delivers a higher concentration of coagulation factors more rapidly and in a smaller volume than FFP, although at significant expense [81].

Algorithm

Figure 2.2 is a proposed algorithm for the management of anticoagulants in the periprocedural period.

Antiplatelets

Overview of Antiplatelets

Antiplatelet agents are used for the management of atherosclerotic thrombotic diseases, a spectrum of conditions that includes stroke, ACS, and peripheral vascular disease, as well as in patients undergoing cardiac surgery and PCI [82]. An overview of current antiplatelet drugs is shown in Table 2.7.

Aspirin is an irreversible inhibitor of cyclooxygenase (COX), causing decreased production of thromboxane A₂ (TXA₂) and prostacyclin (PGI₂) and leading to impaired platelet aggregation [82]. The thienopyridines are a class of drugs that include clopidogrel, ticlopidine, and prasugrel. They are prodrugs whose active metabolites bind to platelet P2Y₁₂ receptor to form disulfide bridges between extracellular cysteine residues that irreversibly inhibit adenosine diphosphate (ADP)-induced platelet aggregation [82]. In patients treated with aspirin or thienopyridines, normal platelet function returns with the production of new platelets, which usually occurs over a period of 5–10 days.

Dipyridamole is a phosphodiesterase (PDE) inhibitor that causes an increase in cyclic adenos-

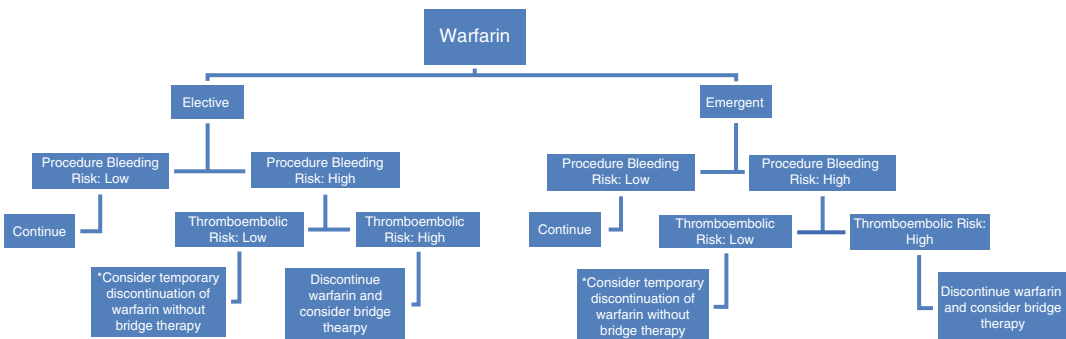


Fig. 2.2 Anticoagulant therapy management algorithm

Table 2.7 Current antiplatelet agents

Drug	Main indications	Route	Mechanism of action	Time to maximal IPA	Elimination half-life ^a	Return of platelet function after cessation	Reversal agent or antidote
Aspirin (generic) [49, 83]	ACS, PCI, stroke treatment and prophylaxis, MI prophylaxis, others	PO	Irreversible inhibition of COX → ↓ thromboxane A ₂ and prostacyclin	Minutes to hours (delayed with enteric coating)	6 h 15–20 min (plasma half-life)	5–10 days (lifespan of platelet)	Platelet transfusion ± desmopressin
Clopidogrel (Plavix, Sanofi Aventis) [49, 84]	ACS, PCI, stroke, peripheral arterial disease	PO	Irreversible inhibition of P2Y ₁₂ ADP receptor	12–15 h after loading dose 5–10 days after maintenance dose	8 h	7–10 days	Platelet transfusion ± desmopressin
Ticlopidine (Ticlid, Apotex) [83, 85]	Stroke, PCI	PO	Irreversible inhibition of P2Y ₁₂ ADP receptor	8–11 days after maintenance dose	24–36 h	7–10 days	Platelet transfusion ± desmopressin
Prasugrel (Effient, Eli Lilly) [86]	ACS, PCI	PO	Irreversible inhibitor of P2Y ₁₂ ADP receptor	4 h after loading dose	~7 h (range 2–15 h)	7–9 days	Platelet transfusion ± desmopressin
Dipyridamole + aspirin (Aggrenox, Boehringer Ingelheim) [87–89]	Stroke prophylaxis (combined with aspirin); prosthetic heart valve thromboembolism prophylaxis adjunct	PO	PDE3/5 inhibition → ↑ cAMP/cGMP in platelets → ↓ platelet aggregation through multiple mechanisms	Hours	9–12 h	See aspirin	Platelet transfusion ± desmopressin
Cilostazol (Pletal, Otsuka Pharmaceutical) [87, 90–92]	Intermittent claudication (USA); peripheral arterial disease (Japan)	PO	PDE3 inhibition → ↑ cAMP in platelets → ↓ platelet aggregation through multiple mechanisms	6–8 h	11–13 h	24–48 h	Platelet transfusion ± desmopressin
Ticagrelor (Brilinta, AstraZeneca) [93]	ACS, PCI	PO	Reversible inhibition of P2Y ₁₂ ADP receptor	1–2 h after loading dose	9 h	5 days	Platelet transfusion ± desmopressin
Cangrelor (The Medicines Company) (investigational) [94]	Phase III studies: ACS, PCI	IV	Reversible inhibition of P2Y ₁₂ ADP receptor	30 min	3–6 min	60–90 min	Rapid reversal with cessation

(continued)

Table 2.7 (continued)

Drug	Main indications	Route	Mechanism of action	Time to maximal IPA	Elimination half-life ^a	Return of platelet function after cessation	Reversal agent or antidote
Abciximab (ReoPro, Eli Lilly) [95, 96]	PCI with STEMI or high-risk UA/NSTEMI Treatment of patients undergoing PCI. Treatment of patients with UA not responding to conventional medical therapy when PCI is planned within 24 h.	IV	Noncompetitive, irreversible inhibition of GP IIb/IIIa	2 h	10–30 min	24–48 h	Platelet transfusion ± desmopressin
Eptifibatide (Integrilin, Merck) [95, 97]	PCI with STEMI or high-risk UA/NSTEMI Treatment of ACS managed medically or with PCI. Treatment of patients undergoing PCI	IV	Competitive, reversible inhibition of GP IIb/IIIa	Immediate	2.5 h	<4 h	Platelet transfusion ± desmopressin
Tirofiban (Aggrastat, Medicure) [95, 98]	PCI with STEMI or high-risk UA/NSTEMI	IV	Competitive, reversible inhibition of GP IIb/IIIa	Immediate	2 h	4–8 h	Platelet transfusion ± desmopressin

IPA inhibition of platelet aggregation, ACS acute coronary syndrome, PCI percutaneous coronary intervention, MI myocardial infarction, PO per oral, IV intravenous, COX cyclooxygenase, ADP adenosine diphosphate, PDE phosphodiesterase, STEMI ST segment elevation myocardial infarction, UA unstable angina, NSTEMI non-ST segment elevation myocardial infarction, GP glycoprotein

^aNote: elimination half-life is dose dependent

ine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in platelets, leading to a decrease in platelet aggregation through multiple mechanisms [87]. Dipyridamole is frequently used in combination with aspirin for secondary prophylaxis of non-cardioembolic transient ischemic attacks or stroke. Dipyridamole alone is not associated with increased bleeding risk but, when used in combination with aspirin, may require 5–10 days for platelet function to return. Cilostazol is a PDE3 inhibitor that also causes an increase in cAMP in platelets, leading to inhibited platelet aggregation. It is approved for use in the treatment of intermittent claudication [87]. Cilostazol has not been associated with increased bleeding risk in clinical studies [87].

Agents with reversible effects on the P2Y₁₂ receptor include ticagrelor and cangrelor. Ticagrelor, a cyclopentyltriazolopyrimidine, is an oral reversible P2Y₁₂ receptor inhibitor with more rapid onset and return of platelet function than clopidogrel and is approved for use in ACS and PCI [82]. Compared with clopidogrel, ticagrelor is associated with a higher rate of major bleeding not related to coronary artery bypass grafting surgery [99]. Cangrelor is an intravenously administered reversible P2Y₁₂ receptor inhibitor currently in phase III clinical trials for treatment of ACS. Unlike other P2Y₁₂ receptor inhibitors, cangrelor has a rapid onset of action (maximal inhibition of ADP-induced platelet aggregation at 30 min) as well as rapid return of platelet function (within 60 min) [94]. Overall bleeding complications related to cangrelor are low and comparable to clopidogrel [100].

Both prasugrel and ticagrelor now form part of ACS management algorithms, based on data from head-to-head comparison trials demonstrating reduced cardiovascular events relative to clopidogrel, but at the expense of increased bleeding complications [53, 99, 101].

GPIs prevent the binding of fibrinogen to GP IIb/IIIa receptors, interfering with interplatelet bridging mediated by fibrinogen, which is the final common pathway of platelet aggregation. GPIs primarily serve as adjunctive therapy when used in combination with dual antiplatelet and anticoagulant (UFH or bivalirudin) therapy at the time of PCI in the setting of STEMI or high-risk

UA/NSTEMI [53, 75]. Abciximab is a monoclonal antibody fragment that exerts noncompetitive, irreversible inhibition of GP IIb/IIIa. Although the plasma half-life of abciximab is short (few min), its platelet-bound half-life lasts hours. Therefore, it may take 24–48 h for platelet function to return in the absence of platelet transfusion [83]. Eptifibatide and tirofiban are small-molecule GPIs which exert competitive inhibition of GP IIb/IIIa. Their effects on platelet aggregation are closely related to plasma concentrations, and return of platelet function occurs within hours (~4 h) of stopping infusion [83]. Bleeding complications are higher with the use of GPIs [102].

Bridging Therapy

There are currently no proven bridging therapies for patients who must consider discontinuing dual antiplatelet therapy. The use of anticoagulants has not been satisfactory in this regard and there are no data supporting the use of GPIs in this situation [103]. Given the lack of uniform guidelines in regard to the discontinuation and resumption of antiplatelet agents in the periprocedural period, endoscopists should consult with the appropriate specialist for the optimal management of these high-risk patients.

Interruption of Antiplatelets before Procedure

In general, patients on aspirin monotherapy may proceed with most endoscopic procedures without interruption in the absence of pre-existing bleeding disorders [2–4]. Exceptions may include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), ampullary resections, EUS-FNA of large cystic lesions, and ERCP with combination sphincterotomy and large papillary balloon dilation [4]. Patients at low risk for cardiovascular events who are receiving aspirin monotherapy should stop the drug 7–10 days pre-procedure; those on clopidogrel monotherapy should stop the drug 5–10 days pre-procedure [5, 49].

In patients with coronary stents who are receiving dual antiplatelet therapy and require an endoscopy, it is recommended to defer endoscopy, if feasible, for at least 4–6 weeks after placement of

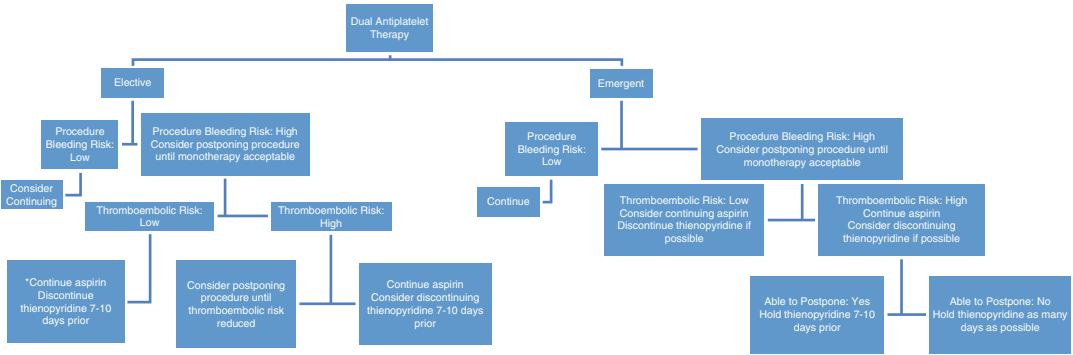


Fig. 2.3 Dual antiplatelet therapy management algorithm

a BMS and for at least 6–12 months after placement of a DES [2–5, 49]. In patients who require a procedure within 6 weeks of placement of a BMS or within 6 months of placement of a DES, it is recommended that dual antiplatelet therapy be continued at the time of the procedure [49].

Resumption of Antiplatelets after Procedure

In general, dual antiplatelet therapy should be resumed after the bleeding risk is minimized from the endoscopic intervention and continued for the recommended duration. Platelet inhibition is rapid with aspirin (minutes to hours) compared with maintenance-dose clopidogrel, which may take 5–10 days to reach maximal inhibition of platelet function [49]. Aspirin and maintenance-dose clopidogrel can usually be resumed within 24 h post procedure (similar to warfarin) [5, 49]. Loading-dose clopidogrel has a more rapid onset and can be considered if bleeding risk is low [5]. The optimal timing regarding resumption of prasugrel and ticagrelor is unclear, but likely more than 24 h post procedure [5].

Reversal

The effects of antiplatelet agents with irreversible inhibition of platelet aggregation will last for the lifespan of the platelets, and function will return after the platelet pool is replenished (~7–10 days). Patients requiring reversal of antiplatelet effects may require platelet infusion and, in some cases, desmopressin to help restore platelet function. The GPIs have short half-lives and may only require supportive care and holding the infusion.

Algorithm

Figure 2.3 is a proposed algorithm for the management of antiplatelet therapy in the periprocedural period.

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