Management of Anticoagulant and Antiplatelet Medications in Adults Undergoing Percutaneous Interventions

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OBJECTIVE. Many radiologists are unfamiliar with the new antithrombogenic medications and how to modify patient management before nonvascular percutaneous procedures performed in a radiology department. In this article, we review the indications for use, mechanism of action, pharmacokinetics, dosing, and recommendations for periprocedural management of patients using these medications.

CONCLUSION. To improve patient safety, radiologists involved in percutaneous procedures should have knowledge of the antithrombotics that will be encountered routinely in clinical practice.

Keywords: anticoagulant, antiplatelet, percutaneous, procedure

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Arterial and venous thromboembolic diseases are a leading cause of morbidity and mortality in the United States [1]. Millions of patients in the United States and worldwide require long-term treatment with antithrombogenic therapy, including anticoagulant and antiplatelet agents for the treatment and prevention of thromboembolic disease [2–5]. Advances in the diagnosis and treatment of cardiovascular disease and venous thromboembolism (VTE) have resulted in a complex assortment of available anticoagulation and antiplatelet medications. Unlike their predecessors, these new antithrombogenic agents cannot be monitored with routine laboratory tests and there are no readily available reversal agents. Every year approximately 10% of patients taking antithrombotic medications will undergo a surgical or other invasive procedure that requires discontinuation of therapy [6]. It is important for all radiologists performing percutaneous procedures to be familiar with these medications to optimize management of these patients before and after procedures to minimize risk of procedure-related complications.

The Society of Interventional Radiology and the American Society of Gastrointestinal Endoscopy have published guidelines defining risk for bleeding associated with percutaneous and endoscopic procedures in the setting of antithrombogenic medication use [7, 8]. This article will review the spectrum of current and commonly used antithrombogenic medications including the indications for use, mechanism of action, pharmacokinetics, and periprocedural bleeding risks and will provide recommendations for management of these medications in the radiology department based on extrapolation of the available data in the medical and pharmacologic literature.

General Concepts

The Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis defines "major bleeding" as events that result in death, are life-threatening, cause chronic sequelae, or consume major health care resources [9]. As a general rule, the most important risk factor for hemorrhage in a patient taking antithrombogenic medications is the intensity of the antithrombogenic effect. Because of the lack of randomized controlled studies or other high-level evidence regarding these risks, a panel of experts from the Society of Interventional Radiology Consensus developed guidelines that include an assessment of procedural risk with stratification into three categories: low risk (easily detected and controllable), moderate risk, and high risk (difficult to detect or control) [8, 10]. Stratification of percutaneous procedures based on bleeding risk can be found in Table 1.

The decision to alter antithrombotic therapy in a patient who will be undergoing a

percutaneous procedure involves balancing the risk of postprocedural bleeding with continued treatment against the thrombotic risk. The decision to use bridging anticoagulation therapy, which is designed to minimize thrombotic events in high-risk patients and minimize bleeding after high-risk procedures, is made by weighing the overall thromboembolic risk for the patient if the medication is discontinued [11]. In most cases, bridging is performed in patients on warfarin therapy who have had a recent stroke or systemic embolic event, who have a mechanical heart valve, who have recently undergone coronary stent placement, and who have had a recent VTE (< 3 months) or a prior VTE during interruption of chronic anticoagulation therapy [12, 13]. A discussion with the patient's referring physician and an anticoagulation specialist may be necessary to create a treatment plan that is optimized for individual patient care.

Anticoagulants

The mechanism of action, route of administration, and dosing of anticoagulants and their reversal agents are listed in Table 2. Recommendations for periprocedural management in patients taking anticoagulants are included in Table 3. The coagulation cascade and point of activity of anticoagulants are illustrated in Figure 1.

Warfarin

For more than 50 years, warfarin was the only approved oral anticoagulant in the United States. This medication is used for the prophylaxis and treatment of VTE, thromboembolic complications associated with atrial fibrillation or cardiac valve replacement, and secondary prevention of thrombotic events after myocardial infarction (MI). Warfarin antagonizes the production of vitamin K–dependent clotting factors (factors II, VII, IX, X) and proteins C and S. The onset of action is slow: The peak anticoagulant effect is delayed 72–96 hours after administration and a mean half-life of 40 hours [14]. The effect of warfarin is measured by the prothrombin time (PT), which is commonly expressed as the international normalized ratio (INR) to standardize variability in PT measurements that exists across laboratories. The therapeutic window is narrow (based on indication) but predominately falls in a target INR range of 2–3 [14]. Because comorbidities, concomitant medications, diet, and pharmacogenetics may affect a patient's response to warfarin, regular PT and INR testing must be performed to titrate to the appropriate dose and maximize time spent in the desired INR range [15].

In 2013, the U.S. Food and Drug Administration (FDA) approved four-factor prothrombin complex concentrate (PCC) (Kcentra, CSL Behring) for the urgent reversal of warfarin-acquired factor deficiency in adults with acute major bleeding or preoperatively before urgent surgery or an invasive procedure [16]. Warfarin anticoagulation can be also reversed with the closely monitored administration of 1–2 U of fresh frozen plasma (FFP) and vitamin K [17–20]. Based on our clinical experience, we hold warfarin therapy for 5 days before all nonvascular interventional procedures and confirm INR before the procedure with a goal of an INR of 1.5 or less [6, 8]. For patients who cannot be off anticoagulation therapy for 5 days, the need for heparin bridge therapy is determined by the clinical team. We resume warfarin use within 12 hours after low- and moderate-risk procedures and 24 hours after high-risk procedures.

Heparin

Unfractionated heparin (UFH), an IV or subcutaneously administered anticoagulation medication, is used as prophylaxis and treatment of VTE disorders and as an adjunct anticoagulant for the treatment of MI and cardiac, neurologic, and peripheral vascular diseases [15] (heparin package insert, Pfizer). Heparin potentiates the action of antithrombin III and inactivates thrombin and inactivates activated coagulation factors IX, X, XI, and XII and plasmin, thus preventing conversion of fibrinogen to fibrin [15]. Its onset of action is immediate if delivered IV and 20–30 minutes if administered subcutaneously, which is primarily used for routine deep venous thrombosis (DVT) prophylaxis [15]. If administered subcutaneously, peak plasma levels are achieved 2–4 hours after administration (heparin package insert, Pfizer). The half-life of heparin ranges from 1 to 2 hours but is variable depending on comorbidities.

Heparin is a medication that requires an initial bolus followed by a steady infusion that is titrated according to the therapeutic goal. The effect of heparin can be monitored by activated partial thromboplastin time (APTT) with a target therapeutic window of between 1.5 and 2.5 times the normal value. Protamine is used as the reversal agent for heparin: 1 mg of protamine reverses approximately 100 IU of UFH [21]. Platelet count should also be monitored to evaluate for heparin-induced thrombocytopenia (HIT), which occurs in 1–2% of patients on

TABLE 1: Nonvascular Percutaneous Procedures and Risk of Bleeding

Low Risk	Moderate Risk	High Risk
Thoracentesis	Intraabdominal (excluding liver and spleen) and retroperitoneal (excluding renal) biopsy or drainage, lung, chest wall, or retroperitoneal biopsy or drainage	Renal, hepatic, or splenic parenchymal biopsy
Paracentesis	Percutaneous cholecystostomy tube (original placement and exchanges)	Biliary intervention (new tract)
Superficial aspiration or drainage (excluding intrathoracic or intraabdominal sites)	Simple RFA procedure	Complex[a] RFA procedure
Superficial biopsy (thyroid, peripheral lymph nodes, breast)	Gastrostomy tube placement (original placement and exchanges)	Nephrostomy tube placement (original placement and exchanges)
Drainage catheter exchange	Biliary tube exchange	Lumbar puncture, myelography, epidural injection

Note—RFA = radiofrequency ablation.
[a]A complex RFA procedure entails treatment of a lesion in a location near major vessels or when a large amount of hepatic or nonhepatic parenchyma must be traversed to access the lesion.

TABLE 2: Anticoagulants Dosing and Reversal Agents

Medication	Class of Agent	Laboratory Monitoring	Route of Administration	Dosing	Reversal Agent (Dose)
Warfarin	Vitamin K inhibitor	INR	PO	2–10 mg	Vitamin K (2.5–5 mg for low-risk procedure, 5–10 mg for high-risk procedure) FFP (1–2 IU) Four-factor PCC (dose relative to pretreatment INR[a])
UFH	Antithrombin III activation	APTT	IV	Cardiac therapy: initial bolus of 60 IU/kg and then 12 IU/kg/h DVT therapy: initial bolus of 80 IU/kg and then 18 IU/kg/h	Protamine (1 mg of protamine for each 100 IU of UFH [maximum dose, 50 mg])
UFH	Antithrombin III activation	APTT	SQ	DVT therapy: initial bolus of 333 IU/kg and then 50–70 IU/kg every 4–6 h	Protamine (1 mg protamine for each 100 IU of UFH [maximum dose, 50 mg])
LMWH	Antithrombin III activation	None	SQ	Enoxaparin: 1 mg/kg every 12 h Dalteparin: 150–200 IU/kg/d Tinzaparin: 175 IU/kg/d	Incomplete: protamine (1 mg/100 IU, repeat at half dose if needed)
Dabigatran	Direct thrombin inhibitor	None	PO	150 mg twice daily	None
Rivaroxaban	Direct factor Xa inhibitor	None	PO	20 mg once daily	None
Apixaban	Direct factor Xa inhibitor	None		Atrial fibrillation: 5 mg twice daily PE therapy: 5 mg twice daily DVT prophylaxis: 2.5 mg twice daily	None
Fondaparinux	Select factor Xa inhibitor	None	PO	Acute VTE: 5–10 mg (weight based) once daily DVT prophylaxis: 2.5 mg once daily	None
Argatroban	Direct thrombin inhibitor	APTT	IV	Loading dose 2 mcg/kg/min, titrate upward to keep APTT 1.5–3 times baseline (maximum dose, 10 mcg/kg/min)	None
Desirudin	Direct thrombin inhibitor	APTT	SQ	15 mg every 12 h	None
Bivalirudin	Direct thrombin inhibitor	APTT	IV	Initial bolus of 0.75 mg/kg and then continuous rate of 1.75 mg/kg/h	None

Note—INR = international normalized ratio, PO = oral, FFP = fresh frozen plasma, PCC = prothrombin complex concentrate, DVT = deep venous thrombosis, UFH = unfractionated heparin, APTT= activated partial thromboplastin time, SQ = subcutaneous, LMWH = low-molecular-weight heparin, PE = pulmonary embolism, VTE = venous thromboembolism.

[a]Dose of four-factor PCC is determined by pretreatment INR: 25 IU/kg (maximum dose, 2500 U) for pretreatment INR ranging from 2 to less than 4, 35 IU/kg (maximum dose, 3500 IU) for pretreatment INR of 4–6, and 50 IU/kg (maximum dose, 5000 IU) for pretreatment INR of greater than 6.

TABLE 3: Recommendations for Management of Anticoagulants

	Interval Between Last Dose and Procedure			Resumption After Procedure		
Medication	Low Bleeding Risk	Medium Bleeding Risk	High Bleeding Risk	Low Bleeding Risk	Medium Bleeding Risk	High Bleeding Risk
Warfarin	5 d	5 d	5 d	12 h	12 h	12–24 h
UFH (IV)	1 h	4 h	4 h	1 h	1 h	1 h
UFH (SQ)	4 h	4 h	6 h	Immediate	Immediate	1 h
LMWH (SQ)	12 h	12 h	12 h	6 h	6 h	6 h
Dabigatran	24 h	48 h	72 h	24 h	48 h	48 h
Rivaroxaban	24 h	48 h	48 h	24 h	48 h	48 h
Apixaban	24 h	48 h	72 h	24 h	48 h	48 h
Fondaparinux	24 h	36 h	48 h	6 h	6 h	6 h
Argatroban	None	4 h	4 h	1 h	1 h	1 h
Desirudin	None	4 h	4 h	1 h	1 h	1 h
Bivalirudin	None	4 h	4 h	1 h	1 h	1 h

Note—UFH = unfractionated heparin, SQ = subcutaneous, LMWH = low-molecular-weight heparin. Data from [6–9, 13, 19].

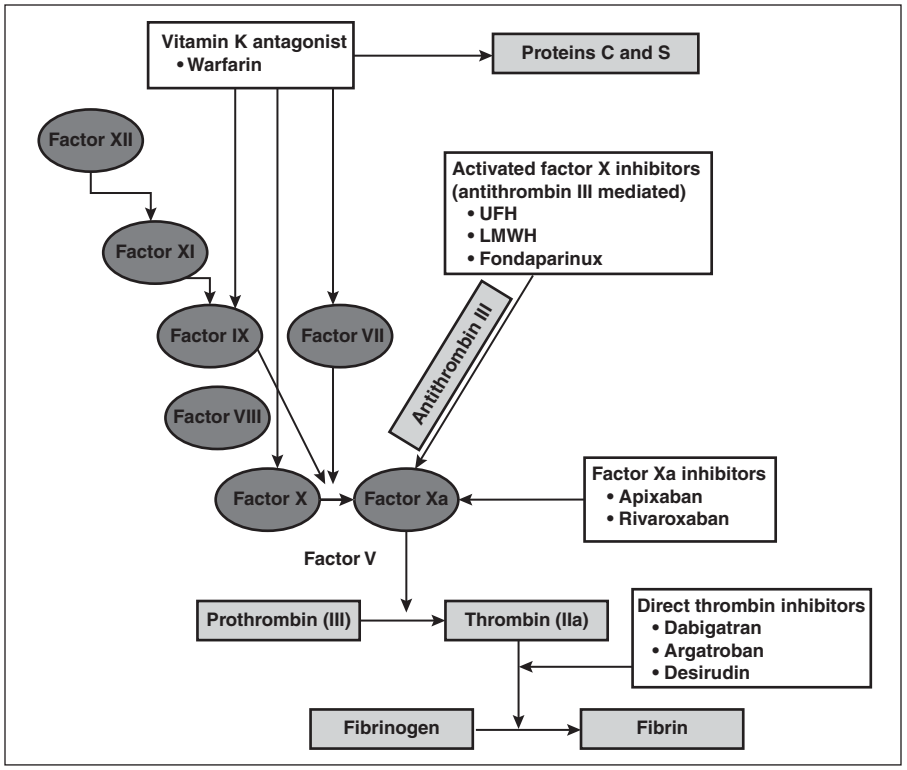

Fig. 1—Flowchart shows pathways of coagulation and modes of action of various anticoagulant classes. UFH = unfractionated heparin, LMWH = low-molecular-weight heparin.

UHF [15]. In our practice, we hold all forms of UFH for 1 hour for low-risk procedures, 4 hours for medium-risk procedures, and 4–6 hours for high-risk procedures [6, 8, 10]. We resume use of UFH within 1 hour of procedures of all bleeding risks.

Low-molecular-weight heparins (LMWHs) (enoxaparin [Lovenox, Sanofi], dalteparin [Fragmin, Eisai], and tinzaparin [Innohep, Leo Pharma]) are derived from UFH and administered either IV and subcutaneously. Although LMWH can be given IV during a coronary intervention and for DVT treatment, most of the utilization of this medication is subcutaneous for the treatment of and prophylaxis against VTE. The advantages for using LMWH include its ease of administration in the outpatient setting, greater bioavailability in a subcutaneous injection, greater duration of anticoagulant effect, ease of fixed-dose administration, and lack of necessity for laboratory monitoring [22]. The mechanism of action of these preparations is the same as that of UFH. The LMWH medications have a small effect on APTT and strongly inhibit factor Xa. Onsets of action are 3–5 hours for enoxaparin, 1–2 hours for dalteparin, and 2–3 hours for tinzaparin. The duration is approximately 12 hours for enoxaparin, more than 12 hours for dalteparin, and more than 24 hours for tinzaparin [23–25] (Lovenox package insert, Sanofi-Aventis). LMWH formulations have a half-life of 2–4 times UFH (4.5 hours after a single dose; 7 hours after repeated doses). Routine monitoring of coagulation parameters is not required. There is no direct antidote for LMWH, but protamine exhibits partial temporary reversal of the anticoagulant effect in the setting of LMWH overdose [23–26]. We do not hold LMWH for low-risk procedures. We prefer that the last dose of all formulations of LMWH be held for 12 and 24 hours for moderate- and high-risk procedures, respectively [6, 8]. We resume LMWH within 6 hours after all procedures.

Target-Specific Oral Anticoagulants

Dabigatran (Pradaxa, Boehringer Ingelheim Pharmaceuticals) is a direct thrombin inhibitor used for the prevention of thromboembolic stroke in patients with nonvalvular atrial fibrillation and for the treatment of VTE. Its mechanism of action is direct inhibition of both free and clot-bound thrombin, which decreases the conversion of fibrinogen into fibrin. It is rapidly absorbed and has a half-life of 12–17 hours in healthy patients; however, the pharmacokinetics of this medication can be severely altered in elderly patients or patients with renal impairment. Thrombin time is the most sensitive assay for dabigatran effect, although it is not routinely monitored [27]. There is no reversal agent for dabigatran, but PCCs have been used emergently in case reports [26, 28, 29]. We hold dabigatran for 48 hours for low- and moderate-risk procedures and 72 hours for high-risk procedures and make adjustments for patients with impaired renal function [6]. We resume dabigatran within 24 hours after low- and medium-risk procedures and 48 hours after high-risk procedures.

Rivaroxaban (Xarelto, Janssen Pharmaceuticals) is an oral anticoagulant indicated to treat DVT and pulmonary embolism and reduce the risk of thrombotic disease in patients after hip or knee replacement surgery or in patients with nonvalvular atrial fibrillation. Rivaroxaban inhibits platelet activation and fibrin clot formation by direct, selective, and reversible inhibition of factor Xa [30]. Through direct inhibition of factor Xa, rivaroxaban decreases the generation of thrombin. Absorption of the medication is rapid, with maximum concentrations occurring 2–4 hours after administration. The half-life of rivaroxaban is 5–9 hours in healthy patients 20–45 years old and is prolonged to 11–13 hours in elderly patients. It is similar to dabigatran in that specific laboratory monitoring is not indicated and there is no FDA-approved reversal agent. We hold rivaroxaban for 24 hours for low-risk procedures and 48 hours for moderate- and high-risk procedures [31, 32]. We resume the medication within 24 hours after low-risk procedures and within 48 hours after moderate- and high-risk procedures.

Apixaban (Eliquis, Bristol-Myers Squibb), another oral direct factor Xa inhibitor, is approved to reduce the risk of stroke or systemic embolism in patients with nonvalvular atrial fibrillation and is also used as treatment for VTE and prevention of VTE recurrence (Eliquis package insert, Bristol-Myers Squibb). Maximum concentrations are achieved 3–4 hours after dose administration with a 12-hour half-life. There is no reversal agent for apixaban. We halt therapy 24 hours before low-risk procedures and 48 hours before moderate- and high-risk procedures [31, 32]. We resume apixaban 24 hours after low-risk procedures and 48 hours after moderate- and high-risk procedures.

Target-Specific Injectable Anticoagulants

Fondaparinux (Arixtra, GlaxoSmithKline) is a subcutaneously administrated anticoagulant indicated for DVT prophylaxis, acute DVT therapy, and acute thrombosis in a patient with a history of HIT [33] (Arixtra package insert, GlaxoSmithKline). It causes antithrombin III–mediated selective inhibition of factor Xa. The onset of activity is 2–3 hours, and its half-life is 17–21 hours. Fondaparinux has no effect on PT and minimal effect on APTT, and there is no established reversal agent; however, agents such as recombinant factor VIIa and activated PCC have been previously evaluated [34, 35]. We withhold this medication for 24 hours for low-risk procedures, 36 hours for moderate-risk procedures, and 48 hours for high-risk group and make modifications for patients with impaired renal function [10, 32]. We resume fondaparinux within 6 hours after all procedures.

Argatroban (Aggrastat, Medicure Pharma), desirudin (Iprivask, Marathon Pharmaceuticals), and bivalirudin (Angiomax, The Medicines) are all reversible direct thrombin inhibitors. Argatroban is administered IV and is used for HIT [36]. Desirudin is administered subcutaneously for DVT prophylaxis in patients undergoing hip replacement (Iprivask package insert, Canyon Pharmaceuticals). Bivalirudin is used as an IV anticoagulant during percutaneous cardiac intervention, during cardiac surgery, or to treat HIT (Angiomax package insert, The Medicines). All three drugs have an immediate onset of action and their half-lives range from 25 to 120 minutes (Iprivask package insert, Canyon Pharmaceuticals; Angiomax package insert, The Medicines; Argatroban package insert, GlaxoSmithKline). There is no reversal agent for these medications. We do not hold any of these medications before low-risk procedures, but we do wait 4 hours after discontinuation before beginning moderate- and high-risk procedures [10]. We resume these medications within 1 hour after all procedures.

Antiplatelet Agents: Oral

The platelet aggregation pathway and point of activity of antiplatelet agents are illustrated in Figure 2. The mechanism of action, route of administration, and dosing of antiplatelet agents and their reversal agents are listed in Table 4. Recommendations for periprocedural management in patients taking antiplatelet agents are included in Table 5.

Acetylsalicylic acid (ASA), or aspirin, is the oral antiplatelet agent routinely given to patients with cardiac disease and peripheral artery disease (PAD). ASA irreversibly inhibits platelet cyclooxygenase enzyme 1 (COX-1), which decreases prostaglandin precursors and ultimately results in inhibition of platelet aggregation. Within plasma, ASA is rapidly hydrolyzed to salicylic acid, with peak plasma levels occurring 1–2 hours after dosing. Doses range from 81 to 325 mg based on the indication. At therapeutic doses, ASA has a plasma half-life of approximately 6 hours, although this half-life may be extended to 20 or more hours in toxic (> 10 g) doses (Aspirin package insert, Bayer). In patients with normal bone marrow function, platelet life span is approximately 10 days. Desmopressin acetate (DDAVP), platelet transfusion, or both can be considered for the reversal of ASA [37]. In our practice, we do not discontinue low-dose ASA for any procedure. In patients taking high-dose ASA, we hold ASA for 5 days before moderate- and high-risk procedures [10, 32]. We resume the medication immediately after all procedures.

Dipyridamole inhibits adenosine uptake into platelets and potentiates the antiplatelet effects of prostacyclin [38]. It has a half-life of 10–12 hours and a duration of action lasting approximately 2 days after discontinuation [6]. The combination of ASA and dipyridamole is administered orally and is used for thromboembolic stroke prophylaxis. Although ASA and dipyridamole individually do not substantially increase the risk of bleeding, the use of the combined agents (Aggrenox, Boehringer Ingelheim) should be considered a bleeding risk. DDAVP, platelet transfusion, or both can be considered for reversal of this antiplatelet agent combination. We hold the ASA-dipyridamole agent for 2 days before low- and moderate-risk procedures and 5 days before high-risk procedures. We resume this medication the same day as the procedure.

Nonsteroidal antiinflammatory drugs (NSAIDs) are oral antithrombotics that are used for treatment of pain and inflammation. NSAIDs are also COX-1 and cyclooxygenase enzyme 2 (COX-2) inhibitors, but unlike ASA, this class of antithrombotic agents produces a reversible platelet aggregation. NSAIDs vary in their half-lives and can be classified into short-acting (ibuprofen, diclofenac, ketoprofen, and indomethacin: 2–6 hours), intermediate-acting (naproxen, sulindac, diflunisal, and celecoxib: 7–15 hours), and long-acting (meloxicam, nabumetone, and piroxicam: > 20 hours) [10]. There are no reversal agents for NSAIDs. We do not discontinue short-acting NSAIDS before low-risk procedures, and we hold short-acting NSAIDs for 24 hours before moderate- and high-risk procedures [10]. We hold longer-acting NSAIDs for 24 hours before low-risk procedures and 48–72 hours before moderate- and high-risk procedures. We allow resumption of NSAIDs within 24 hours after all procedures.

Cilostazol (Pletal, Otsuka Pharmaceutical) is another oral antithrombotic used to treat intermittent claudication in patients with peripheral vascular disease [39]. Cilostazol

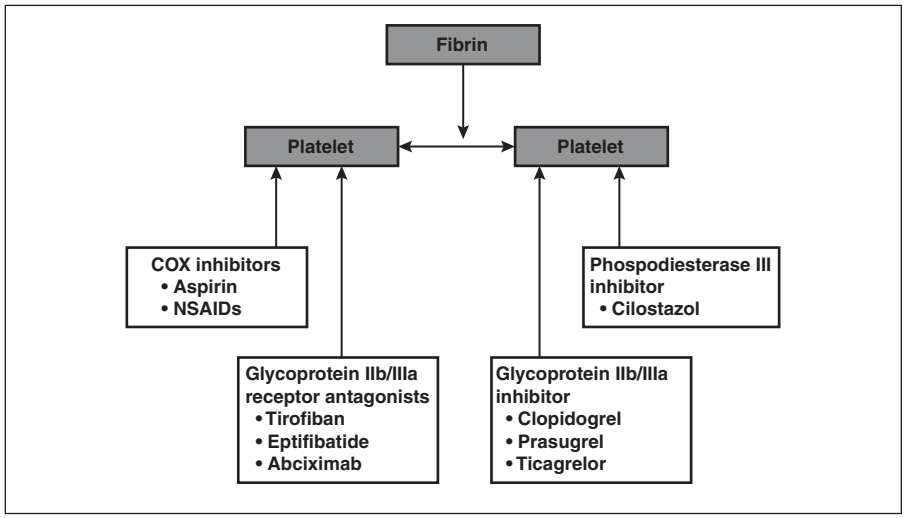

Fig. 2—Flowchart shows pathways of platelet aggregation and fibrin clot formation and modes of action of various antiplatelet classes. COX = cyclooxygenase, NSAIDs = nonsteroidal antiinflammatory drugs.

TABLE 4: Antiplatelet Dosing and Reversal Agents

Medication	Class of Agent	Laboratory Monitoring	Route of Administration	Dosing	Reversal Agent (Dose)
ASA, low dose	COX inhibitor	None	PO	81 mg once daily	DDAVP (0.3–0.4 mcg/kg)
ASA, high dose	COX inhibitor	None	PO	325 mg once daily	DDAVP (0.3–0.4 mcg/kg), platelet transfusion, or both
ASA and dipyridamole	Phosphodiesterase inhibitor	None	PO	ASA: 25 mg Extended release dipyridamole: 200 mg twice daily	DDAVP (0.3–0.4 mcg/kg), platelet transfusion, or both
NSAIDs	COX inhibitor	None	PO	Ibuprofen: 200–400 mg every 4–6 h Diclofenac: 50 mg three times daily Ketoprofen: 20–50 mg every 6–8 h Indomethacin: 20–50 mg three times daily Naproxen: 550 mg every 12 h Sulindac: 150–200 mg twice daily Diflunisal: 500 mg every 12 h Celecoxib: 200 mg twice daily Meloxicam: 7.5 mg once daily Nabumetone: 1000–2000 mg split into two doses daily Piroxicam: 10–20 mg once daily	None
Cilostazol	Phosphodiesterase inhibitor	None	PO	100 mg twice daily	DDAVP (0.3–0.4 mcg/kg), platelet transfusion, or both
Clopidogrel	ADP receptor antagonist	Bleeding time	PO	Recent MI, stroke, or established PAD: 75 mg once daily ACS: 300-mg loading dose and then 75 mg once daily	DDAVP (0.3–0.4 mcg/kg), platelet transfusion, or both
Prasugrel	ADP receptor antagonist	None	PO	ACS: 60-mg loading dose and then 10 mg once daily	DDAVP (0.3–0.4 mcg/kg), platelet transfusion, or both
Ticagrelor	ADP receptor antagonist	None	PO	ACS: 180-mg loading dose and then 90 mg twice daily	DDAVP (0.3–0.4 mcg/kg), platelet transfusion, or both
Tirofiban	GP IIb/IIIa inhibitor	None	IV	Unstable angina or NSTEMI: loading dose 25 mcg/kg and then 0.15 mcg/kg/min	DDAVP (0.3–0.4 mcg/kg), platelet transfusion, or both
Eptifibatide	GP IIb/IIIa inhibitor	None	IV	ACS and PCI: 180 mcg/kg bolus and then 2 mcg/kg/min	DDAVP (0.3–0.4 mcg/kg), platelet transfusion, or both
Abciximab	GP IIb/IIIa inhibitor	None	IV	PCI and unstable angina or NSTEMI: initial bolus of 0.25 mg/kg and then 0.125 mcg/kg/min	Platelet transfusion

Note—ASA = acetylsalicylic acid (aspirin), COX = cyclooxygenase, DDAVP = desmopressin acetate, NSAIDs = nonsteroidal antiinflammatory drugs, ADP = adenosine diphosphonate, GP = glycoprotein, MI = myocardial infarction, PAD = peripheral arterial disease, PO = oral, ACS = acute coronary syndrome, NSTEMI = non–ST-segment elevation myocardial infarction, PCI = percutaneous coronary intervention.

TABLE 5: Recommendations for Management of Antithrombotics

	Interval Between Last Dose and Procedure			Resumption After Procedure			
Medication	Low Bleeding Risk	Medium Bleeding Risk	High Bleeding Risk	Low Bleeding Risk	Medium Bleeding Risk	High Bleeding Risk	Comment
ASA, low dose	None	None	None	Immediate	Immediate	Immediate	
ASA, high dose	None	5 d	5 d	Immediate	Immediate	Immediate	
ASA and dipyridamole	2 d	5 d	5 d	Immediate	Immediate	Immediate	
NSAIDs	None	None	24 h–10 d	Immediate	Immediate	Immediate	Variability in duration of action, long acting NSAIDs require longer interval before procedure
Cilostazol	None	None	24 h	Immediate	Immediate	Immediate	
Clopidogrel	5 d	5 d	5 d	Immediate	Immediate	Immediate	
Prasugrel	5 d	5 d	7 d	24 h	24 h	24 h	
Ticagrelor	5 d	5 d	7 d	24 h	24 h	24 h	
Tirofiban	—	—	—	—	—	—	Recent surgery is a contraindication (within 4 wk)
Eptifibatide	—	—	—	—	—	—	Recent surgery is a contraindication (within 6 wk)
Abciximab	NR	NR	NR	—	—	—	Recent surgery is a contraindication (within 6 wk)

Note—Dash (—) indicates that there are no recommendations available. ASA = acetylsalicylic acid (aspirin), NSAIDs = nonsteroidal antiinflammatory drugs, NR = not recommended. Data from [6–9, 13, 19, 41].

acts as an inhibitor to phosphodiesterase III, which leads to reversible inhibition of platelet aggregation. Its onset of action is 2–4 weeks with a half-life of approximately 10 hours [39]. DDAVP, platelet transfusion, or both can be considered for reversal of this agent. We do not withhold cilostazol before low- and moderate-risk procedures. We hold the agent for 24 hours before high-risk procedures. We resume cilostazol immediately after high-risk procedures.

Clopidogrel (Plavix, Bristol-Myers Squibb), prasugrel (Effient, Daiichi Sankyo and Eli Lilly and Company), and ticagrelor (Brilinta, AstraZeneca) are all oral antiplatelet agents that inhibit binding of adenosine diphosphate (ADP) to the platelet $P2Y_{12}$ receptor. These agents are used for a variety of antithrombotic indications: clopidogrel for coronary arterial, peripheral vascular, and cerebrovascular diseases; prasugrel for percutaneous coronary interventions; and ticagrelor for acute coronary syndrome or MI. These agents inhibit binding of ADP to the platelet $P2Y_{12}$ receptor, preventing the activation of the glycoprotein IIb/IIIa receptor complex, thus inhibiting platelet aggregation. The onset of maximum antiplatelet action for clopidogrel is dose-dependent, taking 4–5 days with daily doses of 75 mg and 2–5 hours with a loading dose of 300–600 mg (Plavix package insert, Bristol-Myers Squibb), and its irreversible binding results in recovery of only 40% of normal platelet function after discontinuation [40].

Prasugrel possesses antiplatelet activity as a result of its active metabolite irreversibly binding to platelets [40]. A loading dose of prasugrel inhibits platelet aggregation more quickly than clopidogrel, and the extent of platelet inhibition is inversely related to patient weight [41] (Effient package insert, Eli-Lilly and Company). Like prasugrel, ticagrelor has a faster onset of antiplatelet activity than clopidogrel [42]. Because it is a reversible antagonist, platelet function is restored more quickly than with clopidogrel or prasugrel, with nearly 60% of function restored within 24 hours after discontinuation [40]. Although there is no specific reversal agent for these medications, it is thought that transfusion of DDAVP or normal platelets may overcome some of these medications' effects [19, 26]. If patients can tolerate discontinuation of clopidogrel, we hold the medication for 5 days before all risk procedures [10, 32]. We hold prasugrel and ticlopidine for 5 days for low-risk procedures and 7 days before moderate- and high-risk procedures [34]. We resume clopidogrel immediately after the procedure and prasugrel and ticagrelor 24 hours after the procedure.

Antiplatelet Agents: IV

Tirofiban (Aggrastat, Medicure Pharma), eptifibatide (Integrilin, Merck & Company), and abciximab (ReoPro, Janssen Biotech) are fast-acting IV antiplatelet agents used in the setting of acute MI and percutaneous coronary interventions. These antiplatelet agents are classified as glycoprotein IIb/IIIa receptor antagonists. The onset of action for these agents is rapid (≈ 10 minutes for tirofiban and abciximab; within 15 minutes after an eptifibatide bolus), and plasma half-lives range between 30 minutes to 2.5 hours (Aggrastat package insert, Medicare Pharma; Integrilin package insert, Merck & Company; ReoPro package insert, Eli Lilly and Company). However, the high-affinity binding of abciximab to the glycoprotein IIb/IIIa receptor—that is, the antiplatelet effects of the drug—persist for at least 24–48 hours [43]. For tirofiban and eptifibatide, platelet aggregation returns to baseline approximately 4 hours from when the drug infusion ends [43, 44]. Percutaneous procedures are only recommended in emergent settings. Platelet transfusion may be used to overcome the effect of glycoprotein IIb/IIIa receptor antagonists [19].

Recommendations for Observation After an Interventional Procedure in Patients on Antithrombogenic Medications

As a general rule, patients who have undergone procedures with a low bleeding risk do not need to be monitored after the procedure: Hospitalized patients may return to their room and outpatients may be discharged from the hospital without observation. Patients who undergo procedures with a moderate or high bleeding risk are closely monitored for changes in hemodynamic status after the procedures. Outpatients in this patient population should be observed 1–2 hours before discharge from the hospital to ensure hemodynamic stability. Inpatients are returned to their floor with instructions for vitals monitoring for the first 2 hours after the procedure. Pain out of proportion to expected postprocedural discomfort and hemodynamic instability should be evaluated immediately by the radiologist. CT remains the imaging choice for the identification of bleeding complications after percutaneous interventions. Occasionally these complications are severe enough to warrant diagnostic angiography and embolization.

Individualized Approach to Periprocedural Use of Antithrombotic Agents

Although there are available recommendations for the periprocedural management of antithrombotic medications, the approach to the use of these agents should be individualized for patients on the basis of a multitude of factors including the risk of complications of a thrombotic event when antithrombotic therapy is withheld, individualized variations in pharmacokinetics of certain agents (renal or hepatic impairment), and risk of complications from postprocedural hemorrhage. Communication among health care providers should be clear, and whenever possible, procedures should be performed when the risks are as low as possible. These recommendations are conservative estimates and intended for use in elective procedures. Clinical necessity may ultimately determine the timing of a radiology procedure.

Conclusion

Radiologists are frequently asked to perform percutaneous procedures on patients being treated with antithrombogenic agents in this era of rapid growth in drug research and development. Appropriate discontinuation and resumption of these medications coordinated around procedures will minimize bleeding risk. Awareness of and familiarity with the pharmacokinetics of these agents are essential for optimizing outcomes after percutaneous interventions.

References

1. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. *Natl Vital Stat Rep* 2013; 61:1–117
2. Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC. National trends in oral anticoagulant use in the United States, 2007 to 2011. *Circ Cardiovasc Qual Outcomes* 2012; 5:615–621
3. Cushman M. Treating acute venous thromboembolism: shift with care. *N Engl J Med* 2013; 369:865–866
4. Jacobs JM, Stessman J. New anticoagulant drugs among elderly patients is caution necessary?: Comment on "The use of dabigatran in elderly patients." *Arch Intern Med* 2011; 171:1287–1288
5. Pengo V, Pegoraro C, Cucchini U, Iliceto S. Worldwide management of oral anticoagulant therapy: the ISAM study. *J Thromb Thrombolysis* 2006; 21:73–77

6. Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. *N Engl J Med* 2013; 368:2113–2124
7. Anderson MA, Ben-Menachem T, Gan SI, et al. Management of antithrombotic agents for endoscopic procedures. *Gastrointest Endosc* 2009; 70:1060–1070
8. Patel IJ, Davidson JC, Nikolic B, et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J Vasc Interv Radiol* 2012; 23:727–736
9. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in nonsurgical patients. *J Thromb Haemost* 2005; 3:692–694
10. Patel IJ, Davidson JC, Nikolic B, et al.; Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement; Standards of Practice Committee of the Society of Interventional Radiology. Addendum of newer anticoagulants to the SIR consensus guideline. *J Vasc Interv Radiol* 2013; 24:641–645
11. Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. *Hematology Am Soc Hematol Educ Program* 2012; 2012:529–535
12. Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. *Blood* 2011; 117:5044–5049
13. Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. *Blood* 2012; 120:4699–4705
14. Lexicomp Online. Oral anticoagulant comparison chart. Hudson, OH: Lexi-Comp, 2014
15. Lexicomp Online. Heparin (Lexi-Drug). Hudson, OH: Lexi-Comp, 2014
16. Lexicomp Online. Prothrombin complex concentrate (human) (factors II, VII, IX, X), protein C, and protein S. Hudson, OH: Lexi-Comp, 2014
17. Woods K, Douketis JD, Kathirgamanathan K, Yi Q, Crowther MA. Low-dose oral vitamin K to normalize the international normalized ratio prior to surgery in patients who require temporary interruption of warfarin. *J Thromb Thrombolysis* 2007; 24:93–97
18. Burbury KL, Milner A, Snooks B, Jupe D, Westerman DA. Short-term warfarin reversal for elective surgery: using low-dose intravenous vitamin K—safe, reliable and convenient. *Br J Haematol* 2011; 154:626–634
19. Yorkgitis BK, Ruggia-Check C, Dujon JE. Antiplatelet and anticoagulation medications and the surgical patient. *Am J Surg* 2014; 207:95–101
20. Lexicomp Online. Treatment of elevated INR due to warfarin. Hudson, OH: Lexi-Comp, 2014
21. Lexicomp Online. Protamine. Hudson, OH: Lexi-Comp, 2014
22. UpToDate website. Hull RD, Garcia DA. Therapeutic use of heparin and low molecular weight heparin. www.uptodate.com/contents/therapeutic-use-of-heparin-and-low-molecular-weight-heparin. Waltham, MA. Updated May 6, 2014. Accessed August 5, 2014
23. Lexicomp Online. Enoxaparin (Lexi-Drug). Hudson, OH: Lexi-Comp, 2014
24. Lexicomp Online. Dalteparin (Lexi-Drug). Hudson, OH: Lexi-Comp, 2014
25. Lexicomp Online. Tinzaparin. Hudson, OH: Lexi-Comp, 2014
26. McCoy CC, Lawson JH, Shapiro ML. Management of anticoagulation agents in trauma patients. *Clin Lab Med* 2014; 34:563–574
27. Lexicomp Online. Dabigitran Etexilate (Lexi-Drug). Hudson, OH: Lexi-Comp, 2014
28. Faust AC, Peterson EJ. Management of dabigatran-associated intracerebral and intraventricular hemorrhage: a case report. *J Emerg Med* 2014; 46:525–529
29. Dumkow LE, Voss JR, Peters M, Jennings DL. Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma. *Am J Health Syst Pharm* 2012; 69:1646–1650
30. Lexicomp Online. Rivaroxaban (Lexi-Drug). Hudson, OH: Lexi-Comp, 2014
31. Crockett MT, Moynagh MR, Kavanagh EC. The novel oral anticoagulants: an update for the interventional radiologist. *AJR* 2012; 199[web]:W376–W379
32. Baron TH, Kamath PS, McBane RD. New anticoagulant and antiplatelet agents: a primer for the gastroenterologist. *Clin Gastroenterol Hepatol* 2014; 12:187–195
33. Connolly G, Spyropoulos AC. Practical issues, limitations, and periprocedural management of the NOAC's. *J Thromb Thrombolysis* 2013; 36:212–222
34. Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002; 106:2550–2554
35. Desmurs-Clavel H, Huchon C, Chatard B, Negrier C, Dargaud Y. Reversal of the inhibitory effect of fondaparinux on thrombin generation by rFVIIa, aCCP and PCC. *Thromb Res* 2009; 123:796–798
36. Lexicomp Online. Argatroban. Hudson, OH: Lexi-Comp, 2014
37. Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. *J Thromb Haemost* 2011; 9:1705–1712
38. Diener H-C, Cunha L, Forbes Ce, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 143:1–13
39. Lexicomp Online. Cilostazol (Lexi-Drug). Hudson, OH: Lexi-Comp, 2014
40. Cattaneo M. Advances in antiplatelet therapy: overview of new $P2Y_{12}$ receptor antagonists in development. *Eur Heart J Suppl* 2008; 10(suppl I):I33–I37
41. Hall R, Mazer CD. Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. *Anesth Analg* 2011; 112:292–318
42. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361:1045–1057
43. Tcheng JE. Differences among the parenteral platelet glycoprotein IIb/IIIa inhibitors and implications for treatment. *Am J Cardiol* 1999; 83:7–11
44. Alton KB, Kosoglou T, Baker S, Affrime MB, Cayen MN, Patrick JE. Disposition of ^{14}C-eptifibatide after intravenous administration to healthy men. *Clin Ther* 1998; 20:307–323

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