Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions—Part I: Review of Anticoagulation Agents and Clinical Considerations

Endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe

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ABBREVIATIONS

ADP = adenosine diphosphate, CI = confidence interval, CKD = chronic kidney disease, CLD = chronic liver disease, COX = cyclooxygenase, DAPT = dual antiplatelet therapy, DIC = disseminated intravascular coagulation, DOAC = direct oral anticoagulant, FDA = Food and Drug Administration, 4F-PCC = 4-factor prothrombin complex concentrate, INR = International Normalized Ratio, ITP = immune thrombocytopenia, LMWH = low molecular weight heparin, PT = prothrombin time, PTT = partial thromboplastin time, ROTEM = rotational thromboelastometry, SSRI = selective serotonin reuptake inhibitor, TEG = thromboelastography, UFH = unfractionated heparin, VKA = vitamin K antagonist, VTE = venous thromboembolic disease, VWF = von Willebrand factor

PREAMBLE

In 2012, the Society of Interventional Radiology (SIR) published its first consensus practice guidelines regarding the periprocedural management of coagulation status for percutaneous image-guided interventions (1), which was subsequently revised in 2013 with a discussion of newer anticoagulant agents (2). The present update to both documents incorporates a multidisciplinary approach to the periprocedural management of coagulation status with emphasis on the patient's clinically relevant comorbidities, and will be divided into 2 parts: part I will review classes of anticoagulation medications and clinical considerations common to patients requiring percutaneous image-guided interventions; part II will discuss recommendations.

METHODOLOGY

The Standards Division of SIR provides evidence-based clinical practice documents to ensure patient safety and enhance the delivery of patient care. Standards Division members are leaders in the field of interventional radiology from the private and academic sectors of medicine who dedicate the vast majority of their professional time to performing interventional

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procedures, and, as such, they represent a broad expert constituency of the subject matter under consideration for standards development.

Topics for standards document development are solicited through an annual survey that allows SIR members the opportunity to submit topics for consideration. The proposed topics are approved and prioritized by the Executive Council. A recognized expert or group of experts is identified to serve as the principal author or writing group for the document. Additional authors or societies may be sought to increase the scope, depth, and quality of the document depending on the magnitude of the project.

An in-depth literature search is performed by using electronic medical literature databases, such as Medline (via PubMed) and The Cochrane Library. A critical review of peer-reviewed articles is performed with regard to the study methodology, results, and conclusions. All documents have adopted an updated methodology for evidence grading and assessment of strength of recommendation (**Appendixes A** and **B**, available online on the article's Supplemental Material page at *www.jvir.org*) to fulfill the Institute of Medicine standards for guidelines development. Accepted definitions of the hierarchical classification of evidence, commonly used by systems such as Oxford and Grading of Recommendations Assessment, Development and Evaluation, are included, and an assessment of the strength of recommendation is defined to assist in clinical decision-making (3,4). Similar classification systems are used by other specialty practice societies such as the American College of Cardiology and the American Heart Association (5). The level of evidence assessment is used to create the evidence tables that inform the standards documents. For documents that incorporate clinical recommendations, the strength of recommendation is used to denote how well the recommendation is supported by systematic evidence.

When the evidence of literature is weak, conflicting, or contradictory, a modified Delphi technique may be used to enhance effective decision-making (6,7), and consensus for the parameter is reached when 80% of panelists are in agreement. The draft document is critically reviewed by the writing group and members of the Standards Division by telephone conference call or face-to-face meeting. Comments are discussed by the members of the Standards Division, and appropriate revisions made to create the final document before peer review, approval by the SIR Operations Committee, and journal publication.

INTRODUCTION

The management of patients with coagulopathies and patients receiving anticoagulation and antiplatelet therapy undergoing minimally invasive image-guided interventions is complex and evolving. As the United States population ages, the American Heart Association anticipates an increased use of long-term anticoagulation medications to prevent stroke associated with nonvalvular atrial fibrillation and to prevent and treat venous thromboembolic disease (VTE) (8). Thus, it is imperative that interventional radiologists understand the causes and pathophysiology of their patients' coagulopathies to determine the best course of action in mitigating bleeding and thromboembolic risks in the periprocedural period. Herein, coagulation physiology, anticoagulant and antiplatelet medications, laboratory testing, and challenges of periprocedural coagulation management in patients with specific clinical conditions such as cirrhosis, renal failure, and cardiac disease are reviewed.

COAGULATION PHYSIOLOGY

Although a full review of coagulation physiology is beyond the scope of this paper, a brief overview can be helpful in discussing commonly used antiplatelet and anticoagulation medications and how they affect bleeding risk. The ultimate goal of the coagulation cascade is to form a platelet-rich cross-linked fibrin clot, which creates a scaffolding across areas of endothelial damage to prevent blood loss from the vessel lumen (9,10). Platelets and von Willebrand factor (VWF) are responsible for primary hemostasis, resulting in the formation of a platelet plug at the site of vascular injury. Platelet adhesion to exposed collagen or injured endothelium is mediated via glycoproteins Ib/IX/V and results in the release of thromboxane A2 and adenosine diphosphate (ADP), which initiate platelet aggregation through glycoprotein IIb/IIIa and fibrinogen. Secondary hemostasis involves activation of the coagulation cascade to form a fibrin clot. **Figure 1** illustrates the coagulation pathways, and **Figure 2** depicts how anticoagulant medications interact within the cascade.

LABORATORY TESTS USED IN THE EVALUATION OF HEMOSTASIS

The prothrombin time (PT) test assesses the tissue factor (ie, extrinsic) pathway, and the activated partial thromboplastin time (PTT) test assesses the intrinsic pathway. These tests are often used to assess bleeding risk before procedures. Both are also affected by the common pathway factors. These tests were developed to identify the cause of bleeding in symptomatic patients, and mild to moderate prolongation of these laboratory values has not been shown to predict bleeding risk in a nonbleeding patient (11,12).

The International Normalized Ratio (INR) was developed to standardize warfarin monitoring because of variability in tissue thromboplastins used in the PT reagent. INR is calculated as $(PTR)^{ISI}$ where PTR= prothrombin time ratio (PT of patient/PT of control) and ISI = international sensitivity index, a value assigned to each PT reagent after calibrating against a WHO standard that has an ISI of 1.0. PTT reagents are even more variable than PT reagents in clinical laboratories, and local standards should be verified.

Other tests include the thrombin time test, fibrinogen assay, and D-dimer assay. D-dimers are produced by the action of plasmin (fibrinolytic system) on a cross-linked fibrin clot and are often used to diagnose disseminated intravascular coagulation (DIC) or to aid in ruling out acute thrombosis. Various coagulopathies, the use of anticoagulant medications, or liver disease can be associated with abnormalities of the results of these routine coagulation tests (**Table 1**). Therefore, the entire clinical picture must be taken into consideration to understand the patient's true bleeding risk.

There are several classes of anticoagulant medications, such as low molecular weight heparin (LMWH) and most direct oral anticoagulants (DOACs), that may not cause derangements in activated PTT and/or PT/INR but still increase bleeding risk. Routine laboratory monitoring, with the exception of periodic assessment of renal function, is not required for patients receiving DOACs because these medications have predictable pharmacokinetics and anticoagulant effects (13), and there is no US Food and Drug Administration (FDA)–approved DOAC laboratory assay (14). All DOACs may affect routine coagulation test results, but not in ways that allow for reliable quantitative measurement of the anticoagulation effect (8). However, the following tests may be used to evaluate for the presence of DOACs: thrombin time, ecarin clotting time (dabigatran), and anti–factor Xa activity (rivaroxaban, apixaban, edoxaban). Most clinical decisions concerning DOACs can be made by knowing the creatinine clearance and time of last drug ingestion (8).

Platelet count is also frequently assessed as part of preprocedure laboratory testing. For normal hemostasis, a platelet count of 5×10^9/L is sufficient; however, moderate to severe thrombocytopenia as well as moderate to severe platelet dysfunction have been shown to increase bleeding risk during procedures (10,15). With normally functioning platelets, a platelet count $> 50 \times 10^9$/L is generally sufficient to reduce bleeding risk for most high-risk image-guided interventional procedures (15,16), whereas a platelet count $< 20 \times 10^9$/L is associated with an increased bleeding risk (15).

Although they are not incorporated into routine laboratory testing, thromboelastography (TEG) and rotational thromboelastometry (ROTEM) deserve mention. TEG/ROTEM has been used for "point-of-display" testing during liver transplantation since the 1980s (17) and more recently to differentiate between coagulopathic versus perioperative surgical-associated bleeding to guide the transfusion of blood products (18,19). Thromboelastography assesses the viscoelastic properties of clot formation in whole blood from the initiation of clot through clot lysis, thereby allowing the evaluation of the kinetics of a patient's coagulation system. Authors have advocated that it has distinct benefits for patients with cirrhosis in whom traditional coagulation tests are known to be inaccurate (17,20). A recent randomized controlled trial suggested that a TEG-guided transfusion strategy may lead to significantly lower use of blood products

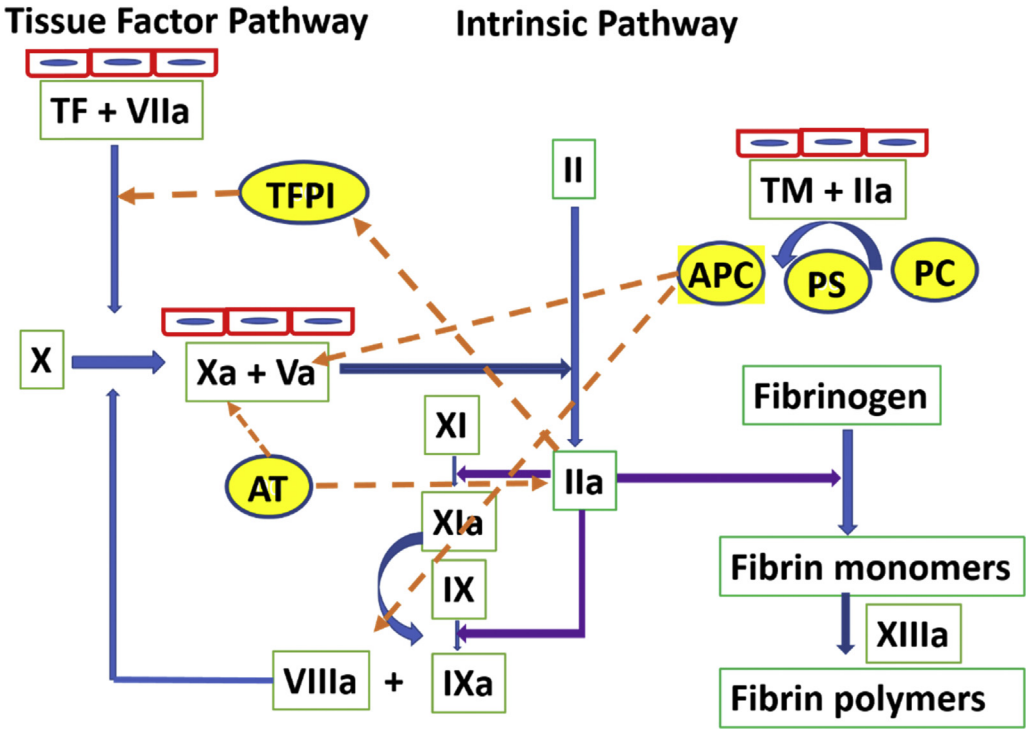

Figure 1. The coagulation cascade. The coagulation cascade is initiated by the tissue factor pathway that includes tissue factor (*TF*) exposed on damaged or altered cell surfaces. When tissue factor binds to small amounts of factor VIIa, the complex is called extrinsic tenase, as it will convert factor X to factor Xa. Factors Xa and Va on the cell surface, along with Ca^{+2}, form prothrombinase complex, which converts prothrombin (factor II) to thrombin (factor IIa). Thrombin has 2 actions. First, it contributes to self-regulation of the tissue factor pathway by activating tissue factor pathway inhibitor (*TFPI*), which will shut down the tissue factor pathway; and second, thrombin will initiate the intrinsic pathway by activating factors XI and IX. Factor XIa will also convert factor IX to factor IXa, which, along with factor VIIIa, forms an intrinsic tenase to convert factor X to factor Xa. This is the main amplification pathway to generate thrombin. The thrombin converts fibrinogen to fibrin monomers. Factor XIIIa cross-links monomers to polymerize and stabilize the clot. Antithrombin (*AT*) inhibits thrombin and factor Xa to regulate thrombin generation. Free thrombin also binds to thrombomodulin (*TM*) on endothelium and converts protein C to activated protein C (*APC*); protein S acts as a cofactor. The APC inactivates factors Va and VIIIa to regulate thrombin generation.

(ie, fresh frozen plasma and platelets) compared with a transfusion strategy guided by traditional coagulation tests (INR, platelet count) in patients with cirrhosis with significant coagulopathy undergoing invasive procedures (20). However, it should be noted that TEG/ROTEM has not been validated to assess bleeding risk in nonbleeding patients to guide blood component therapy, and its value in the preprocedural workup of a patient for an interventional radiologic procedure is unknown (21,22). It is discussed in brief here because there is ongoing research examining how to optimally include this test in treatment algorithms.

MEDICATIONS AFFECTING HEMOSTASIS

Antiplatelet Agents

Platelets play an important role in the pathogenesis of arterial thrombosis in cerebral, coronary, and peripheral arteries. Antiplatelet agents are the mainstay of therapy in the primary and secondary prevention of such thromboses (23). There are no specific reversal agents for antiplatelet agents. Platelet transfusion is often used to provide functional platelets, although clinical evidence to support its effect is sparse (24,25). **Table 2** summarizes the properties of antiplatelet agents.

Cyclooxygenase Inhibitors

Aspirin is one of the most commonly prescribed antiplatelet agents for the prevention of thrombosis. It is used in patients without verified vascular disease and to reduce the risk of vascular events in patients at high risk or those with a history of myocardial infarction or stroke. Aspirin irreversibly inhibits cyclooxygenase (COX)-1, resulting in reduced thromboxane A2 production, which subsequently decreases platelet aggregation and activation. Aspirin has a mild antiplatelet effect, acts within 15–30 minutes, and is rapidly metabolized into its nonactive metabolite. The lifespan of platelets is 8–10 days, and 10% of platelets are produced daily (26,27). Thus, within 3 days of discontinuing aspirin, there will be at least 50–60 $\times$ 10^9/L fully functional platelets (in addition to partially functioning platelets), which should be adequate to normalize bleeding risk, even for high-risk interventions (15,16).

Nonsteroidal antiinflammatory drugs (NSAIDs) reversibly inhibit COX-1 and/or COX-2 and have weak antiplatelet effects (28). Selective COX-2 inhibitors, such as celecoxib, do not interfere with normal mechanisms of platelet aggregation and hemostasis (29,30). NSAIDs are typically taken electively for pain control and can be discontinued without negatively affecting cardiac or cerebrovascular thromboembolic risk (31). Studies on patients undergoing interventional procedures while receiving NSAIDs are limited and inconclusive (32,33) as to whether these agents are associated with an increased bleeding risk. The platelet effects of NSAIDs are directly related to the plasma concentration of the drug, and, after 5 half-lives, most of the drug will have been eliminated (31).

P2Y12 Inhibitors

The oral thienopyridine agents (clopidogrel, ticlopidine, and prasugrel) are prodrugs that are metabolized by cytochrome P450 in the liver and whose metabolites irreversibly inhibit the P2Y12 ADP receptor to reduce platelet aggregation. They are more potent antiplatelet agents than aspirin, and often used in combination with aspirin (ie, dual antiplatelet therapy [DAPT]) to reduce thrombotic events after cardiac interventions. Bleeding risks from

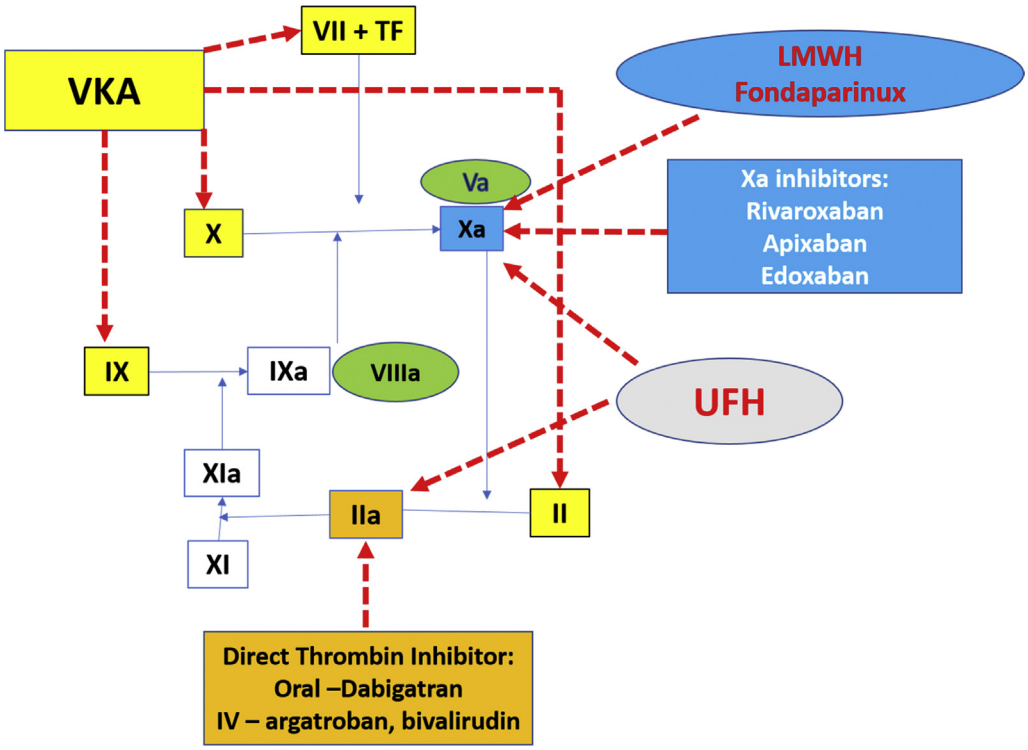

Figure 2. Mechanisms of action of common anticoagulant medications. VKA (warfarin) decreases the functional levels of factors II, VII, IX, and X by 15%–30% versus baseline (administered orally). UFH potentiates the action of antithrombin to predominantly inhibit thrombin (factor IIa) and, to a lesser extent, factor Xa (administered intravenously). LMWH potentiates the action of antithrombin to predominantly inhibit factor Xa and, minimally, thrombin (factor IIa), and fondaparinux potentiates antithrombin to inhibit factor Xa only (both administered via subcutaneous injection). Oral direct factor Xa inhibitors rivaroxaban, apixaban, edoxaban, and betrixaban inhibit factor Xa without antithrombin. Direct thrombin inhibitors can be administered orally (eg, dabigatran) or intravenously (eg, argatroban and bivalirudin).

Table 1. Interpretation of Routine Coagulation Tests

PT/INR	PTT	Fibrinogen	D-Dimers	Thrombin Time	Platelet Count	Interpretation
↑	Normal	Normal	Normal	Normal	Normal	Liver disease, vitamin K antagonist, factor VII deficiency, oral factor Xa inhibitors
Normal	↑	Normal	Normal	↑	Normal	Unfractionated heparin, dabigatran
Normal	↑	Normal	Normal	Normal	Normal	With history of bleeding: factor VIII, IX, or IX deficiency
Normal	↑	Normal	Normal	Normal	Normal	Without history of bleeding: lupus anticoagulant, factor XII deficiency
↑	↑	↓	↑	↑	↓	Acute disseminated intravascular coagulation
Normal	Normal	Normal	↑	Normal	Normal	Acute thrombosis (nonspecific)

INR = International Normalized Ratio; PT = prothrombin time; PTT = partial thromboplastin time.

medications in this group are extrapolated from surgical literature in which 5.6% of coronary bypass patients experienced severe life-threatening hemorrhage with this medication compared with 4.2% receiving placebo, with no statistically significant difference between the groups (34). Ticlopidine is known to cause thrombotic thrombocytopenic purpura and neutropenia and is therefore rarely used today (35). Clopidogrel is commonly used, and less perioperative bleeding was noted when clopidogrel was stopped 5 days before surgery in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events trial (34). Prasugrel has a stronger antiplatelet effect than clopidogrel, and platelet activity normalizes at 7 days after discontinuation (36). Ticagrelor directly inhibits the P2Y12 receptor, with a greater antiplatelet effect than clopidogrel and a faster platelet recovery time (37). Cangrelor is an intravenous, direct P2Y12 inhibitor that has a rapid onset of action with a short half-life of 3–6 minutes. It is used in acute coronary care for the prevention of periprocedural myocardial infarction or stent thrombosis, with patients being transitioned to an oral thienopyridine agent postprocedurally. Cangrelor can also be used as a "bridge" therapy option for patients receiving oral thienopyridines before surgery (38).

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors reduce ADP-induced platelet aggregation. They are weak antiplatelet agents with associated bleeding risk that is considered to be very low. Cilostazol is used in treating symptomatic peripheral arterial disease and improves walking distance and overall quality-of-life metrics (39). It has commonly been associated with minor side effects such as headache and diarrhea, and more recently with reports

Table 2. Properties of Antiplatelet Agents

Drug (Brand Name)	Mechanism of Action	Half-Life	Drug Elimination (h)*	Test to Detect Drug Effect
Thienopyridines				
Cangrelor (Kengreal)†	Thienopyridine (reversible)	3.6 min	0.33	Platelet aggregometry, VerifyNow P2Y12‖
Clopidogrel (Plavix)†	Thienopyridine (irreversible)	6 h	30	Platelet aggregometry, VerifyNow P2Y12‖
Prasugrel (Effient)†,§	Thienopyridine (irreversible)	3.7 h	20	Platelet aggregometry, VerifyNow P2Y12‖
Ticagrelor (Brilinta)†	Thienopyridine (reversible)	7 h	35	Platelet aggregometry, VerifyNow P2Y12‖
Ticlopidine (Ticlid)†	Thienopyridine (irreversible)	13 h	65	Platelet aggregometry, VerifyNow P2Y12‖
NSAIDs				
Aspirin†	COX-1 inhibitor	2–3 h	10–15‡	PFA-100, platelet aggregometry, VerifyNow ASA‖
Aspirin/dipyridamole (Aggrenox)†	COX-1 and phosphodiesterase inhibitor	13 h	65‡	PFA-100
Celecoxib (Celebrex)	COX-2 inhibitor	8–12 h	40–60	NA
Diclofenac (Voltaren)	COX-2 inhibitor	1–2 h	5–10	NA
Diflunisal (Dolobid)	COX-1 and -2 inhibitor	8–12 h	40–60	NA
Ibuprofen (Motrin)	COX-1 inhibitor	2–4 h	10–20‡	NA
Indomethacin	COX-1 inhibitor	5–10 h	25–50	NA
Ketorolac (Toradol)	COX-1 and -2 inhibitor	5–6 h	25–30‡	NA
Ketoprofen (Orudis)	COX-1 and -2 inhibitor	2–5 h	10–25‡	NA
Meloxicam (Mobic)	COX-2 inhibitor	15–20 h	75–100	NA
Nabumetone (Relafen)	COX-2 inhibitor	22–30 h	110–150	NA
Naproxen (Aleve)	COX-1 and -2 inhibitor	12–17 h	60–85‡	NA
Piroxicam (Feldene)	COX-1 and -2 inhibitor	45–50 h	225–250	NA
Sulindac (Clinoril)	COX-1 and -2 inhibitor	16 h (active metabolite)	80	NA
Glycoprotein IIb/IIIa inhibitors				
Abciximab (ReoPro)†	Glycoprotein IIb/IIIa inhibitor	10–30 min	2.5	PFA-100
Eptifibatide (Integrilin)†	Glycoprotein IIb/IIIa inhibitor	2.5 h	12.5	PFA-100
Tirofiban (Aggrastat)†	Glycoprotein IIb/IIIa inhibitor	2 h	10	PFA-100
Phosphodiesterase inhibitors				
Cilostazol (Pletal)	Phosphodiesterase inhibitor	10 h	50‡	NA
Dipyridamole (Persantine)	Phosphodiesterase inhibitor	10 h	50	NA

COX = cyclooxygenase; NA = not applicable; NSAID = nonsteroidal antiinflammatory drug; PFA-100 = platelet function analyzer-100 (this test has replaced bleeding time to assess primary hemostasis, ie, platelet function and von Willebrand disease).

*The plasma concentration of a drug is halved after 1 elimination half-life. After 5 half-lives, the amount of drug remaining is approximately 3%, which is considered to be negligible with regard to therapeutic effect for most classes of drug. However, complete drug elimination may not always reflect the time to return to normal hemostasis for all drug classes (eg, abciximab and aspirin), and specific drug-withholding recommendations are provided in table 6 of part II of this document.

†In cases of antiplatelet-associated life-threatening bleeding requiring reversal, there are no specific antidotes to the medications themselves; however, platelet transfusions may help control bleeding/symptoms.

‡Time to drug elimination may vary with these drugs in patients with renal failure as a result of renal excretion of the medications.

§The US Food and Drug Administration issued a Black Box Warning for prasugrel, which should not be used in patients with active pathologic bleeding, history of ministrokes or stroke, or those requiring an urgent need for surgery, including coronary artery bypass graft surgery.

‖VerifyNow P2Y12 and VerifyNow ASA are point-of-care devices that can detect a patient's resistance to thienopyridines or acetylsalicylic acid (ASA). If a patient is resistant to these medications, the normal recommended withholding times may not apply.

of cardiovascular adverse events and also bleeding (40,41). Cilostazol has not been shown to increase bleeding time when used alone or with acetylsalicylic acid (42,43). If the medication is discontinued, after 5 half-lives, less than 5% of the drug remains in the plasma, and improvements in platelet aggregation have been demonstrated (44,45). Dipyridamole can be used alone or in a combination extended-release form with aspirin for the secondary prevention of stroke or transient ischemic attacks. When used in combination, an increased risk of bleeding has been reported (46,47).

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation by binding to the receptor site on the glycoprotein IIb/IIIa complex where fibrinogen normally attaches. Abciximab, eptifibatide, and tirofiban are very potent antiplatelet agents with very short half-lives (30–45 min) that are given intravenously during percutaneous coronary interventions and used primarily in the acute coronary care setting (48–50). Abciximab causes irreversible inhibition, and, although the half-life is short (10–30 minutes), dissociation from the receptor requires hours and recovery of platelet function is slow, with normal hemostasis achieved between 24 and 48 hours after drug discontinuation (51,52). Eptifibatide and tirofiban have faster dissociation times, with normalization of platelet aggregation occurring between 4 and 8 hours after drug discontinuation (53,54). Increased perioperative bleeding has been noted following cardiac and vascular surgery (55), but there are no studies on interventional procedures for patients receiving glycoprotein IIb/IIIa inhibitors (31). The effects of these medications can be partly reversed with platelet transfusion.

Anticoagulant Agents

Table 3 summarizes the properties of anticoagulant medications.

Vitamin K Antagonists

Warfarin, the most common vitamin K antagonist (VKA) used clinically, inhibits vitamin K epoxide reductase and vitamin K reductase in the liver, thereby decreasing carboxylation of γ-glutamic acid residues, which are required for factors II, VII, IX, and X and proteins C and S to function normally. The full anticoagulation effect of warfarin is achieved at approximately 3–5 days, when the levels of factors II and X are sufficiently decreased (31). When the activity of factors II and X are reduced to 30%–15% of normal, the corresponding INRs are 2.0–3.0, respectively (56). The presence of clotting factors at concentrations of $> 40\%$ is considered adequate for surgical hemostasis (57). Although the use of VKAs has decreased during the past 5 years as a result of the introduction of DOACs, warfarin remains the anticoagulant agent of choice in many clinical conditions, including mechanical heart valves, left ventricular assist devices, and antiphospholipid antibody syndrome. The effect lasts for 5–7 days (10,58).

There are several options for reversing the effects of VKA. A 4-factor prothrombin complex concentrate (4F-PCC; Kcentra; CSL Behring, King of Prussia, Pennsylvania) is the only US FDA-approved drug for VKA reversal and should be administered according to local hospital-based anticoagulation-reversal protocols (59,60). It contains all vitamin K–dependent factors (II, VI, IX, and X) and natural anticoagulants (proteins C and S). A randomized clinical trial comparing 4F-PCC with plasma for VKA reversal (60) showed similar hemostatic efficacy in bleeding patients, whereas another randomized clinical (59) trial showed superior hemostatic efficacy of 4F-PCC versus plasma for VKA reversal in patients needing urgent surgical or invasive procedures The thromboembolic events were similar in both studies for 4F-PCC and plasma, whereas volume overload was higher in the plasma arm than in the 4F-PCC arm (61). Vitamin K–dependent factors achieved hemostatic levels within 30 minutes following 4F-PCC administration, compared with several hours for plasma. If 4F-PCC is unavailable, plasma may be used for VKA reversal; however, plasma requires an infusion time that is 8 times longer than that for 4F-PCC (62). Side effects of plasma infusion include volume overload, acute lung injury, allergic reactions, or infections (63). Oral vitamin K can be administered to reverse the effect of VKA for elective procedures. The intravenous administration of 3 mg of vitamin K, diluted in 25–50 mL of normal saline solution and infused slowly over a period of 15–30 minutes, can also reverse VKA effect within 18 hours before major surgery, with adequate hemostatic levels of factors (64), and has been found to be safe in some studies (58,65). However, the FDA has issued a Black Box Warning for the risk of anaphylactoid reactions associated with the intravenous "push" or subcutaneous administration of vitamin K.

Heparins

Heparins (unfractionated or LMWH) are the most commonly used parenteral anticoagulant agents, particularly for the acute treatment of thromboembolic disease or coronary syndromes. LMWH and unfractionated heparin (UFH) potentiate the anticoagulant effects of antithrombin by many thousand fold to neutralize thrombin and factor Xa. UFH predominantly inhibits thrombin more than factor Xa (4:1 ratio) and hence prolongs PTT. Because of the short half-life of UFH (60–90 min), waiting for 4 hours after discontinuing heparin and checking PTT or anti-Xa level is sufficient to normalize the bleeding risk before any procedure (66). By contrast, LMWH inhibits factor Xa more than thrombin (4:1 ratio) and hence generally does not affect PTT at therapeutic doses. An anti-Xa assay can be used to monitor LWMH if needed, especially in patients at extremes of body weight or with impaired renal function. LMWH has a half-life of 4–6 hours, which requires waiting for at least 24 hours before a procedure to normalize the bleeding risk (67). Fondaparinux is a synthetic pentasaccharide that binds to antithrombin and potentiates its effect only on factor Xa. It is often used in place of LMWH, especially in patients with heparin-induced thrombocytopenia, and should be treated like LMWH.

Protamine is a heparin reversal agent. A 1-mg dose of protamine neutralizes 100 IU of UFH, but the goal should be to neutralize only 80% of UFH estimated at the time of protamine infusion, as excess protamine will itself function as an anticoagulant (68). Similarly, protamine can be used to partially neutralize LMWH at doses of 1 mg per milligram of LMWH within 8 hours of the last dose or 0.5 mg per milligram of LMWH if beyond 8 hours (68).

Parenteral Direct Thrombin Inhibitors

Parenteral direct thrombin inhibitors, including bivalirudin and argatroban, are increasingly encountered in clinical practice because they block thrombin directly, resulting in a more predictable anticoagulant effect compared with UFH. They have very short half-lives (15–40 min) and a rapid onset of action. Argatroban is metabolized by the liver, whereas bivalirudin is metabolized by plasma enzymes, making bivalirudin a safer option for patients with renal or hepatic dysfunction (69). Although there are no reversal agents, bleeding risk should normalize 2–4 hours after discontinuation of these drugs (69).

DOACs

All DOACs are indicated for nonvalvular atrial fibrillation to prevent thromboembolic events and are also FDA-approved for the treatment and prevention of deep vein thrombosis and pulmonary embolism. In clinical trials (70–72), DOACs have shown significantly lower rates of intracerebral hemorrhage compared with VKA, but dabigatran and rivaroxaban were associated with a higher incidence of gastrointestinal bleeding. In general, DOACs have a rapid onset of action (within approximately 2 h) and have short half-lives (approximately 9–17 h). Other advantages include no need for laboratory monitoring, no effect of diet, and fewer drug interactions compared with VKAs. However, certain clinical conditions may require knowledge of DOAC plasma levels and effects, such as patients who require emergent major surgeries and procedures, present with severe bleeding, or develop thrombosis while receiving DOACs.

Direct Thrombin Inhibitor

Dabigatran etexilate is the only currently available oral direct thrombin inhibitor (DTI). It is a prodrug that is metabolized by plasma and intestinal proteases to the active drug dabigatran. It is given twice daily and is excreted by the kidneys. Thus, the risk of bleeding associated with

Table 3. Properties of Anticoagulant Medications

Drug (Brand Name)	Mechanism of Action	Half-Life	Drug Elimination (h)*	Test to Detect Drug Effect or Presence	Reversal Agent (Brand Name)
Vitamin K antagonist					
Warfarin (Coumadin)	Inhibits function of factors II,VII, IX, and X	40 h	200	PT/INR or chromogenic factor X	4F-PCC (Kcentra), plasma†
Heparins					
Low molecular weight: enoxaparin (Lovenox) and dalteparin (Fragmin)	Indirect factor Xa inhibition	2–6 h‡	10–30	Anti-Xa assay	Protamine
Unfractionated	Inhibits thrombin more than factor Xa	1.5–2 h‡	7.5–10	PTT, anti-Xa assay	Protamine
Direct thrombin inhibitors					
Argatroban (Acova)	Direct thrombin inhibitor	50 min	4	PTT or TT	None
Bivalirudin (Angiomax)	Direct thrombin inhibitor	25 min	2§	PTT or TT	None
Dabigatran (Pradaxa)	Direct thrombin inhibitor	12–17 h	60–85§	TT, ecarin clotting time	Idarucizumab (Praxbind)
Factor Xa inhibitors					
Apixaban (Eliquis)	Direct factor Xa inhibitor	15 h	75§	Anti-Xa assay, apixaban assay where available	Andexanet alfa (Andexxa) PCC
Betrixaban (Bevyxxa)	Direct factor Xa inhibitor	37 h	185§	Anti-Xa assay	Andexanet alfa (Andexxa)
Edoxaban (Savaysa)	Direct factor Xa inhibitor	9–14 h	45–70§	Anti-Xa assay	Andexanet alfa (Andexxa) PCC
Fondaparinux (Arixtra)	Indirect factor Xa inhibitor	17–21 h	85–105§	Fondaparinux assay	Andexanet alfa (Andexxa)
Rivaroxaban (Xarelto)	Direct factor Xa inhibitor	9–13 h	45–65§	Anti-Xa assay, rivaroxaban assay where available	Andexanet alfa (Andexxa) PCC

4F-PCC = 4 factor–prothrombin complex concentrate; INR = International Normalized Ratio; PT = prothrombin time; PTT = partial thromboplastin time; TT = thrombin time.

*The plasma concentration of a drug is halved after 1 elimination half-life. After 5 half-lives, the amount of drug remaining is approximately 3%, which is considered to be negligible with regard to therapeutic effect for most classes of drug. However, complete drug elimination may not always reflect the time to return to normal hemostasis for all drug classes, and specific drug-withholding recommendations are provided in table 6 of part II of this document.

†Plasma only if 4F-PCC is unavailable

‡The range of half-life times presented for the heparin classes of drugs reflect times for intravenous and subcutaneous administration.

§Time to normal hemostasis may vary with these drugs in patients with renal failure as a result of renal excretion of the medications.

dabigatran is increased in patients with renal impairment. In a bleeding patient or someone requiring an emergent intervention, the presence of dabigatran can be assessed by thrombin time, which is exquisitely sensitive to even very low levels of dabigatran; a normal thrombin time measurement excludes the presence of dabigatran. Idarucizumab, a humanized antigen-binding fragment monoclonal antibody, is a specific reversal agent for dabigatran with a rapid onset of action; 2 doses of 5 g are given 15 minutes apart (73). Dialysis can also remove dabigatran from the circulation.

Direct Factor Xa Inhibitors

By binding to factor Xa, direct factor Xa inhibitors, including rivaroxaban, apixaban, edoxaban, and betrixaban, decrease the conversion of prothrombin to thrombin, ultimately limiting the conversion of fibrinogen to fibrin clot. These agents are excreted by the kidneys, and thus renal impairment may prolong their clearance. Prolongation of PT/INR is variable with these medications, so measurement of anti-Xa activity, as is done in patients receiving LMWH, may help to detect their presence in the plasma of patients needing urgent or emergent intervention. An anti-Xa activity of < 0.2 U/mL should be safe for most interventional procedures. Andexanet alfa, a recombinant factor Xa molecule that acts as a decoy, was recently approved by the FDA as a specific reversal agent for all factor Xa inhibitors, LMWH, and fondaparinux (74). In animal experiments and human ex vivo and in vitro studies (75), prothrombin complex concentrates (50 U/kg) were shown to be somewhat effective in neutralizing factor Xa inhibitors.

Other Medications

Over-the-counter herbal medications and supplements are commonly used as self-remedies by patients (76,77). The majority of common herbal medications, such as gingko biloba, ginseng, licorice, and garlic, affect hemostasis through a variety of pathways, usually culminating in the inhibition of platelet function. Many of these herbal agents can affect the efficacy of other medications, including DOACs and warfarin. St. John's wort increases the metabolism of warfarin and decreases its circulating blood time, thereby increasing the risk of thrombosis (78). Ginkgo is known to increase bleeding risk in patients who are also taking cilostazol and warfarin (79). Studies do not conclusively demonstrate an increased bleeding risk. Nevertheless, the interventionalist is encouraged to ask the patient about the use of nontraditional treatments and consult with a pharmacist on their potential implications in patient care given their propensity for drug–drug interactions.

Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed antidepressant medications. These drugs decrease platelet serotonin uptake from the blood. As serotonin plays a role in platelet aggregation, SSRIs have an inhibitory effect on platelet aggregation, and risk of bleeding approximates that associated with low-dose ibuprofen (31). However, studies have shown that SSRI use can be associated with surgical bleeding in breast and orthopedic surgery (80,81) and that the risk of gastrointestinal bleeding increases with SSRIs and concurrent antiplatelet therapy (82,83). Combined use of SSRIs and NSAIDs or low-dose aspirin increased the observed/expected ratios of upper gastrointestinal bleeding to 12.2 (95% confidence interval [CI], 7.1–19.5) and 5.2 (95% CI, 3.2–8.0), respectively, in a large epidemiologic study (83). The risk of bleeding was also increased with concomitant anticoagulant agent use and in patients with chronic liver disease (CLD) (84). Although routine discontinuation is not advocated, for patients at high risk, multidisciplinary discussion with the treating physician may be of benefit to aid in clinical decision-making.

NUANCES OF COAGULATION SPECIFIC TO SELECT CLINICAL COMORBIDITIES

CLD

The interpretation of coagulation test results in patients with cirrhosis or CLD can be difficult, and it is incorrect to assume that patients with CLD with prolonged PT/INR are autoanticoagulated; very large epidemiological studies (85) have demonstrated that patients with CLD have almost twice the thrombotic risk as the general population. In fact, patients with CLD have rebalanced primary and secondary hemostasis (**Table 4**) (86). The coagulopathy of CLD is unique because the liver synthesizes procoagulant factors, with the exception of factor VIII and VWF, and all-natural anticoagulants (eg, proteins C and S and antithrombin) that regulate thrombin generation. The routine coagulation tests used to assess hemostasis, PT/INR and PTT, reflect only decreased procoagulant factors, not the concomitantly decreased natural anticoagulants, thereby resulting in an inaccurate assessment of hemostasis. For example, it would be incorrect to interpret an INR of 3 in a patient with CLD as representing a significant increase in bleeding risk: as a result of the decrease in production of procoagulant and natural anticoagulant factors, the plasma of the patient with CLD actually has the same amount of thrombin generation as the plasma of a normal patient (87). Results from TEG support these hypotheses and argue against the use of plasma administration to correct abnormal laboratory values, as patients with CLD with very prolonged PT/INR have normal clotting times or normal reaction times when assessed by ROTEM or TEG, respectively (17). Many patients with advanced CLD also have hypofibrinogenemia (< 100 mg/dL) and a degree of dysfibrinogenemia (86).

Most patients with advanced CLD have moderate thrombocytopenia (platelet counts of 40–80 $\times$ 10^9/L). Thrombocytopenia in CLD is multifactorial: thrombopoietin is reduced, patients are deficient in folate and vitamin B_{12}, there may be an element of bone-marrow suppression especially in the setting of hepatitis C, and as many as 80% of patients have splenomegaly with platelet sequestration (86). However, it is important to note that the adhesive function of these platelets is actually enhanced, as VWF function is increased by 4–5 fold versus normal. The VWF function is further enhanced by the reduced amount of ADAMTS13 enzyme that regulates VWF multimer sizes. Thus, overall primary hemostasis is rebalanced (86), and, similar to the interpretation of PT/INR values, quantitative evidence of thrombocytopenia periprocedurally does not always imply increased bleeding risk. Therefore, the involvement of a transfusion medicine or hemostasis specialist may be in the best interest of a patient with CLD when determining when platelet transfusion or other agents should be used.

A recent prospective study of 363 patients with cirrhosis with thrombocytopenia who underwent 852 invasive procedures (88) showed that postprocedural bleeding is rare in patients with CLD and unrelated to platelet counts. Ten postprocedural bleeding episodes (1 per 84 procedures) were reported, but none of the patients who had platelet counts $< 50 \times 10^9$/L ($n = 49$) experienced any bleeding. The authors concluded that the recommendation to transfuse platelets when the platelet count is $< 50 \times 10^9$/L is not substantiated by this case series and that postprocedural bleeding is not predicted by INR or platelet count (88). Reported results of treatment with agonists of the thrombopoietin receptor, which are designed to increase platelet counts, are mixed. A randomized controlled clinical trial (89) comparing the use of eltrombopag (Promacta; Novartis, Basel, Switzerland) versus placebo in patients with cirrhosis was discontinued because the eltrombopag arm exhibited increased incidences of portal vein thrombosis, even though bleeding events were similar in both arms (89).

Avatrombopag is the newest FDA-approved thrombopoietin receptor agonist for patients with cirrhosis with thrombocytopenia who are scheduled to undergo a procedure. Two randomized controlled studies (90) were conducted with the primary endpoint of whether the use of avatrombopag would result in a platelet count of 50 $\times$ 10^9/L before the procedure, thereby avoiding the need for platelet transfusion (90). The drug must be taken daily for 5 consecutive days with the procedure to be scheduled 5–8 days after the last dose (91). Avatrombopag increased platelet count to $> 50 \times 10^9$/L in 66% of patients receiving a high dose (60 mg for platelet count $< 40 \times 10^9$/L) and 88% of patients receiving a low dose (40 mg for platelet count of 40–50 $\times$ 10^9/L) compared with 23%–38% of patients receiving placebo (90). Patients receiving avatrombopag required fewer platelet transfusions than patients receiving placebo ($P < .0001$). Avatrombopag did not cause increased thrombotic complications, nor was there any difference in bleeding events between groups of patients receiving placebo and avatrombopag. Although both studies met their primary endpoints, the utility of this drug remains questionable in procedures associated with low to medium bleeding risk in view of the results presented by other authors (20,89), which seem to suggest that the accepted thresholds of INR < 1.5 and

Table 4. Rebalanced Hemostasis in Chronic Liver Disease

Primary Hemostasis			
↓Platelets	↓Thrombopoietin ↓Bone marrow function Splenomegaly Nutritional deficiency	↑VWF function	↑↑VWF antigen and activity ↑Large VWF multimers ↓ ADAMTS13
Secondary Hemostasis			
↓Procoagulants	Factors I, II, V,VII, IX, X, XI, XIII	↓Anticoagulants ↑Procoagulant	↓Antithrombin, protein C, protein S ↑↑↑Factor VIII
Fibrinolytic System			
↓ Plasminogen and α2 antiplasmin	–		↑TPA

TPA = tissue plasminogen activator; VWF = von Willebrand factor.

platelet count of 50 × 10^9/L before a procedure do not predict bleeding risk and may not be the correct safety thresholds for patients with cirrhosis undergoing invasive procedures.

Chronic Renal Failure

The pathogenesis of chronic kidney disease (CKD)–related bleeding is tied to (i) primary hemostatic defect secondary to an abnormal platelet–endothelial interaction caused by the presence of a middle molecule that interferes with VWF function and (ii) anemia, as red cell mass has a rheologic effect on platelets and provides ADP for platelet activation (92). As a result, patients with CKD have an increased tendency to experience bleed at baseline (93), during endovascular procedures (94), and when receiving antiplatelet agents or anticoagulation (95). Risk exists at all CKD stages, but is most pronounced in patients with uremia (92,96). Therefore, CKD should be accounted for when considering an endovascular procedure and reinitiation of postprocedural anticoagulation and antiplatelet therapy. Unfortunately, there are no well-validated tests to aid in assessing a patient's periprocedural bleeding risk (92). Other platelet function–related tests (eg, platelet aggregation) are not routinely available in most centers. Finally, CKD should be recognized when offering preprocedural medication-related recommendations, as the bioavailability of many medications is influenced by renal function. This is specifically true for many anticoagulant agents, including LMWH, fondaparinux, and DOAC (97). Typically, "hold" times, particularly before elective procedures, will be relatively prolonged in the presence of CKD.

Thrombocytopenia

A low platelet count is associated with increased bleeding (15,98), but bleeding risk and management options differ depending on the etiology of thrombocytopenia.

Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is defined as a platelet count < 100 × 10^9/L that is caused by autoantibodies, which results in immune destruction of platelets (99,100). Primary ITP is an acquired immune disorder, whereas secondary ITP is associated with other underlying autoimmune disorders, such as systemic lupus erythematosus, HIV, or underlying immune dysregulation syndromes, such as common variable immunodeficiency (101). Most patients with ITP have large platelets in peripheral blood as a result of the rapid and premature release from megakaryocytes, and these are typically hyperfunctional compared with normal-sized platelets (102,103).

First-line therapy for ITP can include corticosteroid agents, with which platelet counts will increase rapidly within 1–2 days in approximately 75% of patients. However, durable benefit is seen in only 25% of patients (104), and intravenous immunoglobulin may have to be used in this patient population. Intravenous immunoglobulin has a short time to therapeutic response (within 24–48 h), but its effect is transient and rarely produces sustained responses longer than 3–4 weeks (104). Second-line therapy includes thrombopoietic receptor agonists such as eltrombopag and romiplostim (Nplate; Novartis). Splenectomy is often used as a last resort: surgical splenectomy and splenic embolization have been used in this setting to provide similar levels of platelet response. Surgical splenectomy has initial responses as high as 80%, with sustained response rates decreasing to 66% (105,106). Platelet transfusions alone are often ineffective in increasing platelet counts because autoantibodies will destroy transfused platelets within minutes unless they are given with intravenous immunoglobulin.

Although the safety of minimally invasive image-guided procedures in patients with hematologic disorders such as ITP has not yet been satisfactorily established, it is widely accepted that there is an increased risk of hemorrhage in these patients. A recent study (107) compared endoscopy procedure–related bleeding in patients with ITP or aplastic anemia versus the procedural outcomes in matched control subjects without hematologic disorders. The endoscopic interventions included low-risk procedures such as endoscopic biopsy and high-risk procedures including polypectomy, endoscopic resection, and endoscopic retrograde cholangiopancreatography with sphincterotomy. The study (107) showed that bleeding occurred in 9.7% of procedures among the patients with thrombocytopenia, compared with 3.1% in the control patients ($P = .003$). Bleeding occurred after 20% of all high-risk procedures, and the incidence of bleeding was significantly increased in patients with a platelet count less than 50 × 10^9/L.

Nonimmune Thrombocytopenia

Patients with non–immune-mediated etiologies of thrombocytopenia will often respond well to platelet transfusions, with the exception of those with splenomegaly, in which cases transfused platelets are sequestered in minutes (108). Cancer-related thrombocytopenia will be discussed in more detail in the following section. Platelet consumption in "platelet-rich thrombi" is the underlying mechanism in heparin-induced thrombocytopenia and thrombotic thrombocytopenic purpura, and platelet transfusions are relatively contraindicated (109).

Cancer

Cancer is associated with increased risk of venous and arterial thrombosis (110). Patients with a history of cancer and VTE > 12 months and no other risk factors, as well as patients with active cancer, defined as having been treated within the previous 6 months or receiving palliative therapy, are considered to be at moderate risk for periprocedural thromboembolism, ie, an annual risk of arterial thromboembolism of 5%–10% and a 1-month VTE risk of 2%–10% (110–112). The risks are even higher for patients with advanced-stage cancer, high-risk cancer histologies (eg, stomach, pancreas, lung), high-risk biomarkers, thrombotic event within 3 months, or thrombophilia, ie, an annual risk of arterial thromboembolism > 10% or 1-month VTE risk > 10% (110–112). Thrombocytopenia is also common as a result of the disease (usually hematologic malignancies) or a consequence of treatment (113). Adequate knowledge of this patient population and the impact of pre- and postprocedural anticoagulation management is essential,

as these patients frequently undergo procedures for diagnosis, curative therapy, or palliation.

It is not uncommon to encounter patients with cancer who are receiving anticoagulation (110). Tafur et al (114) prospectively followed 2,182 chronically anticoagulated patients who were referred for periprocedural anticoagulation management to estimate the 3-month incidences of thromboembolism, major bleeding, and survival. In this cohort, 20% of all patients (n = 435) had active malignancy, and the indication for anticoagulation was VTE in 50% (n = 218). This study (114) showed distinct differences between patients with and without cancer: the VTE rate was higher (1.2% vs 0.2%; $P = .001$), the major bleeding rate was higher (3.4% vs 1.7%; $P = .015$), and the survival rate was reduced in patients with cancer (95% vs 99%; $P < .001$). Patients with cancer receiving anticoagulation and undergoing bridging therapy had higher rates of periprocedural VTE and major bleeding compared with patients without cancer who were receiving chronic anticoagulant therapy (114); however, the procedure-specific bleeding risk (ie, procedures with low vs high bleeding risk) did not significantly impact the incidence of major bleeding in patients with cancer.

Thrombocytopenia and its severity may depend on the type of malignancy, stage of cancer, or treatment (113). However, the bleeding risk has not been well established in patients with cancer with thrombocytopenia undergoing procedures (115,116), a finding acknowledged in the 2018 American Society of Clinical Oncology Clinical Practice Guideline Update "Platelet Transfusion for Patients with Cancer" (117), in which the recommendation for a minimal threshold platelet count for the performance of a major invasive procedure was noted to be supported by low-quality evidence and associated with a weak strength of recommendation.

DIC

DIC is characterized by systemic activation of coagulation, with the potential to cause thrombotic and hemorrhagic events. It is a heterogeneous syndrome that may present as an acute and life-threatening emergency or as a chronic asymptomatic process (118). DIC is typically triggered by an underlying event such as sepsis, trauma, or obstetric complications. The pathophysiology typically includes 4 main steps. First, there is a procoagulant exposure. The source of the procoagulant (eg, tissue factor, bacteria-derived lipopolysaccharide, cancer procoagulant) will vary depending on the underlying cause of DIC. Second, the coagulation cascade is activated, leading to the formation of micro- and macrothrombi consisting of fibrin and platelets in the microvasculature and/or larger vessels. Third, fibrinolysis is activated at sites of thrombi formation, resulting in the production of D-dimers and fibrin degradation products. When present in significant amounts, fibrin degradation products can interfere with systemic fibrin clot formation and platelet aggregation. Finally, end-organ and tissue damage may occur from arterial thrombosis, reduced perfusion, and bleeding (119,120). A patient with DIC can have significant intraprocedural and postprocedural bleeding, which may be difficult to control. Given the complex disease process of DIC and heterogeneous presentation of patients with this syndrome, a multidisciplinary discussion regarding the risks and benefits of any image-guided procedure is necessary before an appropriate periprocedural transfusion management strategy is determined.

Cardiovascular Disease and Arrhythmias

Patients with nonvalvular atrial fibrillation can be expected to be receiving long-term anticoagulation to reduce the risk of stroke and systemic embolization (8). In addition, patients with cardiac stents or those with a history of acute coronary syndrome will likely receive antiplatelet therapy. Current guidelines (121,122) recommend a minimum of 1 month of DAPT for patients receiving a bare metal stent and 6–12 months of DAPT for patients receiving drug-eluting stents. For patients with a history of acute coronary syndrome, irrespective of whether a percutaneous coronary intervention with or without stent placement was performed, the recommendation is for 12 months of DAPT (123). Similar considerations may exist after peripheral intervention and, most significantly, after carotid intervention.

As a result, management of patients with known cardiovascular disease and/or arrhythmias can be particularly challenging, as the interventionalist has to consider the patient's risk of stent thrombosis or major adverse cardiovascular and/or cerebrovascular events. Importantly, premature discontinuation of antiplatelet therapy has been shown to be the most important predictor of stent thrombosis (hazard ratio, 89.78; 95% CI, 29.90–269.60; $P < .001$) in a prospective observation cohort study of 2,229 patients (124). The premature discontinuation of antiplatelet therapy can be associated with a 6% risk of periprocedural stent thrombosis and a 45% mortality rate for periprocedural myocardial infarction secondary to stent thrombosis (124). Therefore, given the complexities inherent in the management of patients with cardiac stents or acute coronary syndrome, particularly if the stent implantation or cardiac event occurred within 1 year, it is recommended that a cardiology or vascular or internal medicine consultation be obtained for patients who are being considered for procedures that require the discontinuation of antiplatelet therapy, and that a discussion of the risks with the patient be documented in the medical record.

CONCLUSIONS

The development of the appropriate management approach to the patient undergoing interventional procedures requires an understanding of the coagulation cascade and how it can be affected by common clinical conditions and antiplatelet or anticoagulation medications. Familiarity with the basic pharmacologic properties and appropriate methods of reversal for each medication class is essential.

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REFERENCES

1. Patel IJ, Davidson JC, Nikolic B, et al; Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2012; 23:727–736.
2. Patel IJ, Davidson JC, Nikolic B, et al; Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Addendum of newer anticoagulants to the SIR consensus guideline. J Vasc Interv Radiol 2013; 24:641–645.
3. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Br Med J 2008; 336:924–926.
4. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence, 2011. Available at https://www.cebm.net/index.aspx?o=5653. Accessed May 16, 2018.
5. Jacobs AK, Anderson JL, Halperin JL, et al. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Circulation 2014; 130:1208–1217.
6. Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. Am J Public Health 1984; 74:979–983.
7. Leape LL, Hilborne LH, Park RE, et al. The appropriateness of use of coronary artery bypass graft surgery in New York State. JAMA 1993; 269:753–760.
8. Raval AN, Cigarroa JE, Chung MK, et al; American Heart Association Clinical Pharmacology Subcommittee of the Acute Cardiac Care and General Cardiology Committee of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Quality of Care and Outcomes Research. Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: a scientific statement from the American Heart Association. Circulation 2017; 135:e604–e633.

9. Beshay JE, Morgan H, Madden C, Yu W, Sarode R. Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. J Neurosurg 2010; 112:307–318.
10. Godfrey EM, Godfrey AL, Perry DJ, Shaw AS. Don't be a clot: a radiologist's guide to haemostasis including novel antiplatelet and anticoagulant therapies. Clin Radiol 2011; 66:693–700.
11. Kitchens CS. To bleed or not to bleed? Is that the question for the PTT? J Thromb Haemost 2005; 3:2607–2611.
12. Pilsczek FH, Rifkin WD, Walerstein S. Overuse of prothrombin and partial thromboplastin coagulation tests in medical inpatients. Heart Lung 2005; 34:402–405.
13. Levy JH, Faraoni D, Spring JL, Douketis JD, Samama CM. Managing new oral anticoagulants in the perioperative and intensive care unit setting. Anesthesiology 2013; 118:1466–1474.
14. Gehrie E, Tormey C. Novel oral anticoagulants: efficacy, laboratory measurement, and approaches to emergent reversal. Arch Pathol Lab Med 2015; 139:687–692.
15. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. Br J Med 2003; 122:10–23.
16. Sarode R, Refaai MA, Matevosyan K, Burner JD, Hampton S, Rutherford C. Prospective monitoring of plasma and platelet transfusions in a large teaching hospital results in significant cost reduction. Transfusion 2010; 50:487–492.
17. Mallett SV. Clinical utility of viscoelastic tests of coagulation (TEG/ROTEM) in patients with liver disease and during liver transplantation. Semin Thromb Hemost 2015; 41:527–537.
18. Afshari A, Wikkelso A, Brok J, Møller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev 2011:CD007871.
19. Baksaas-Aasen K, Van Dieren S, Balvers K, et al; TACTIC/INTRN collaborators. Data-driven development of ROTEM and TEG algorithms for the management of trauma hemorrhage: a prospective observational multicenter study. Ann Surg 2018, https://doi.org/10.1097/SLA.0000000000002825.
20. De Pietri L, Bianchini M, Montalti R, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. Hepatology 2016; 63:566–573.
21. Adler M, Ivic S, Bodmer NS, et al. Thromboelastometry and thrombelastography analysis under normal physiological conditions - systematic review. Transfus Med Hemother 2017; 44:78–83.
22. Chitlur M, Lusher J. Standardization of thromboelastography: values and challenges. Semin Thromb Hemost 2010; 36:707–711.
23. Gremmel T, Michelson AD, Frelinger AL III, Bhatt DL. Novel aspects of antiplatelet therapy in cardiovascular disease. Res Pract Thromb Haemost 2018; 2:439–449.
24. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al; PATCH Investigators. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet 2016; 387:2605–2613.
25. Lam H, Katyal N, Parker C, et al. Thromboelastography with platelet mapping is not an effective measure of platelet inhibition in patients with spontaneous intracerebral hemorrhage on antiplatelet therapy. Cureus 2018; 10:e2515.
26. Sarode R. How do I transfuse platelets (PLTs) to reverse anti-PLT drug effect? Transfusion 2012; 52:695–701.
27. Lebois M, Josefsson EC. Regulation of platelet lifespan by apoptosis. Platelets 2016; 27:497–504.
28. Scott WW, Levy M, Rickert KL, Madden CJ, Beshay JE, Sarode R. Assessment of common nonsteroidal anti-inflammatory medications by whole blood aggregometry: a clinical evaluation for the perioperative setting. World Neurosurg 2014; 82:e633–e638.
29. Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. J Clin Pharmacol 2000; 40:124–132.
30. Simon LS, Lanza FL, Lipsky PE, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum 1998; 41:1591–1602.
31. Narouze S, Benzon HT, Provenzano D, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications (second edition): guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med 2018; 43:225–262.
32. Endres S, Shufelt A, Bogduk N. The risks of continuing or discontinuing anticoagulants for patients undergoing common interventional pain procedures. Pain Med 2017; 18:403–409.
33. Moeschler SM, Warner NS, Lamer TJ, et al. Bleeding complications in patients undergoing percutaneous spinal cord stimulator trials and implantations. Pain Med 2016; 17:2076–2081.
34. Fox KA, Mehta SR, Peters R, et al; Clopidogrel in Unstable angina to prevent Recurrent ischemic Events Trial. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. Circulation 2004; 110:1202–1208.
35. Jacob S, Dunn BL, Qureshi ZP, et al. Ticlopidine-, clopidogrel-, and prasugrel-associated thrombotic thrombocytopenic purpura: a 20-year review from the Southern Network on Adverse Reactions (SONAR). Semin Thromb Hemost 2012; 38:845–853.
36. Asai F, Jakubowski JA, Naganuma H, et al. Platelet inhibitory activity and pharmacokinetics of prasugrel (CS-747) a novel thienopyridine P2Y12 inhibitor: a single ascending dose study in healthy humans. Platelets 2006; 17:209–217.
37. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009; 120:2577–2585.
38. Angiolillo DJ, Firstenberg MS, Price MJ, et al; BRIDGE Investigators. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. JAMA 2012; 307:265–274.
39. Tsigkou V, Siasos G, Rovos K, Tripyla N, Tousoulis D. Peripheral artery disease and antiplatelet treatment. Curr Opin Pharmacol 2018; 39:43–52.
40. Gonzalez-Ruiz M, Cuaresma E, Blanco-Ramos IV, Rodríguez-Dichico G, Montero-Corominas D. Cilostazol: from spontaneous reports of cardiovascular and haemorrhagic reactions to a thorough benefit-risk evaluation in Europe. A signal generation. Basic Clin Pharmacol Toxicol 2011; 109:36.
41. Real J, Serna MC, Giner-Soriano M, et al. Safety of cilostazol in peripheral artery disease: a cohort from a primary healthcare electronic database. BMC Cardiovasc Disord 2018; 18:85.
42. Tamai Y, Takami H, Nakahata R, Ono F, Munakata A. Comparison of the effects of acetylsalicylic acid, ticlopidine and cilostazol on primary hemostasis using a quantitative bleeding time test apparatus. Haemostasis 1999; 29:269–276.
43. Wilhite DB, Comerota AJ, Schmieder FA, Throm RC, Gaughan JP, Rao AK. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. J Vasc Surg 2003; 38:710–713.
44. Kaneda T, Urimoto G, Suzuki T. Spinal epidural hematoma following epidural catheter removal during antiplatelet therapy with cilostazol. J Anesth 2008; 22:290–293.
45. Yasunaga K, Mase K. Antiaggregatory effect of oral cilostazol and recovery of platelet aggregability in patients with cerebrovascular disease. Arzneimittelforschung 1985; 35:1189–1192.
46. Hall R, Mazer CD. Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. Anesth Analg 2011; 112:292–318.
47. Serebruany VL, Malinin AI, Eisert RM, Sane DC. Risk of bleeding complications with antiplatelet agents: meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. Am J Hematol 2004; 75:40–47.
48. *Aggrastat (tirofiban hydrochloride) [package insert].* West Point, PA: Merck; 1998.
49. *Integrilin (eptifibatide) [package insert].* Kenilworth, NJ: Schering-Plough; 2011.
50. *ReoPro (abciximab) [package insert].* Leiden, The Netherlands: Janssen Biologics; 2013.
51. De Luca G. Glycoprotein IIb-IIIa inhibitors. Cardiovasc Ther 2012; 30:e242–e254.

52. Schneider DJ, Aggarwal A. Development of glycoprotein IIb-IIIa antagonists: translation of pharmacodynamic effects into clinical benefit. Expert Rev Cardiovasc Ther 2004; 2:903–913.
53. Phillips DR, Scarborough RM. Clinical pharmacology of eptifibatide. Am J Cardiol 1997; 80:11B–20B.
54. Rosove MH. Platelet glycoprotein IIb/IIIa inhibitors. Best Pract Res Clin Haematol 2004; 17:65–76.
55. Reddy MS, Carmody TJ, Kereiakes DJ. Severe delayed thrombocytopenia associated with abciximab (ReoPro) therapy. Cathet Cardiovasc Interv 2001; 52:486–468.
56. Lind SE, Callas PW, Golden EA, Joyner KA Jr, Ortel TL. Plasma levels of factors II, VII and × and their relationship to the International Normalized Ratio during chronic warfarin therapy. Blood Coagul Fibrinolysis 1997; 8: 48–53.
57. Xi M, Beguin S, Hemker HC. The relative importance of the factors II, VII, IX and X for the prothrombinase activity in plasma of orally anticoagulated patients. Thromb Haemost 1989; 62:788–791.
58. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl):204S–233S.
59. Goldstein JN, Refaai MA, Milling TJ Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet 2015; 385: 2077–2087.
60. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013; 128:1234–1243.
61. Milling TJ Jr, Refaai MA, Sarode R, et al. Safety of a four-factor prothrombin complex concentrate versus plasma for vitamin k antagonist reversal: an integrated analysis of two phase IIIb clinical trials. Acad Emerg Med 2016; 23:466–475.
62. Refaai MA, Kothari TH, Straub S, et al. Four-factor prothrombin complex concentrate reduces time to procedure in vitamin K antagonist-treated patients experiencing gastrointestinal bleeding: a post hoc analysis of two randomized controlled trials. Emerg Med Int 2017; 2017:8024356.
63. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. Br J Haematol 2004; 126:139–152.
64. 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.
65. Raj G, Kumar R, McKinney WP. Time course of reversal of anticoagulant effect of warfarin by intravenous and subcutaneous phytonadione. Arch Intern Med 1999; 159:2721–2724.
66. McAvoy TJ. The biologic half-life of heparin. Clin Pharmacol Ther 1979; 25:372–379.
67. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008; 133(suppl):141S–159S.
68. Simon EM, Streitz MJ, Sessions DJ, Kaide CG. Anticoagulation reversal. Emerg Med Clin North Am 2018; 36:585–601.
69. Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. N Engl J Med 2005; 353:1028–1040.
70. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139–1151.
71. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883–891.
72. Wolfe Z, Khan SU, Nasir F, Raghu Subramanian C, Lash B. A systematic review and Bayesian network meta-analysis of risk of intracranial hemorrhage with direct oral anticoagulants. J Thromb Haemost 2018; 16: 1296–1306.
73. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015; 373:511–520.
74. Rogers KC, Finks SW. A new option for reversing the anticoagulant effect of factor Xa inhibitors: andexanet alfa (Andexxa(R)). Am J Med 2018; 132:38–41.
75. Dickneite G, Hoffman M. Reversing the new oral anticoagulants with prothrombin complex concentrates (PCCs): what is the evidence? Thromb Haemost 2014; 111:189–198.
76. Cordier W, Steenkamp V. Herbal remedies affecting coagulation: a review. Pharm Biol 2012; 50:443–452.
77. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (fourth edition). Reg Anesth Pain Med 2018; 43:263–309.
78. Roby CA, Anderson GD, Kantor E, Dryer DA, Burstein AH. St John's wort: effect on CYP3A4 activity. Clin Pharmacol Ther 2000; 67:451–457.
79. Ryu KH, Han HY, Lee SY, et al. Ginkgo biloba extract enhances antiplatelet and antithrombotic effects of cilostazol without prolongation of bleeding time. Thromb Res 2009; 124:328–334.
80. Gartner R, Cronin-Fenton D, Hundborg HH, et al. Use of selective serotonin reuptake inhibitors and risk of re-operation due to post-surgical bleeding in breast cancer patients: a Danish population-based cohort study. BMC Surg 2010; 10:3.
81. van Haelst IM, Egberts TC, Doodeman HJ, et al. Use of serotonergic antidepressants and bleeding risk in orthopedic patients. Anesthesiology 2010; 112:631–636.
82. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. Clin Gastroenterol Hepatol 2009; 7:1314–1321.
83. Dalton SO, Johansen C, Mellemkjaer L, Nørgård B, Sørensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med 2003; 163:59–64.
84. Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. J Clin Psychiatry 2010; 71:1565–1575.
85. Ambrosino P, Tarantino L, Di Minno G, et al. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. Thromb Haemost 2017; 117:139–148.
86. Tripodi A, Primignani M, Mannucci PM, Caldwell SH. Changing concepts of cirrhotic coagulopathy. Am J Gastroenterol 2017; 112:274–281.
87. Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005; 41:553–558.
88. Napolitano G, Iacobellis A, Merla A, et al. Bleeding after invasive procedures is rare and unpredicted by platelet counts in cirrhotic patients with thrombocytopenia. Eur J Intern Med 2017; 38:79–82.
89. Afdhal NH, Giannini EG, Tayyab G, et al; ELEVATE Study Group. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med 2012; 367:716–724.
90. Terrault N, Chen YC, Izumi N, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology 2018; 155:705–718.
91. Dova Pharmaceuticals. *DOPTELET Highlights of Prescribing Information*. 2018.
92. Pavord S, Myers B. Bleeding and thrombotic complications of kidney disease. Blood Rev 2011; 25:271–278.
93. Castaldi PA, Rozenberg MC, Stewart JH. The bleeding disorder of uraemia. A qualitative platelet defect. Lancet 1966; 2:66–69.
94. Manzano-Fernandez S, Cambronero F, Caro-Martinez C, et al. Mild kidney disease as a risk factor for major bleeding in patients with atrial fibrillation undergoing percutaneous coronary stenting. Thromb Haemost 2012; 107:51–58.
95. Kaufman JS, O'Connor TZ, Zhang JH, et al; Veterans Affairs Cooperative Study Group on Hemodialysis Access Graft Thrombosis. Randomized controlled trial of clopidogrel plus aspirin to prevent hemodialysis access graft thrombosis. J Am Soc Nephrol 2003; 14:2313–2321.
96. Qaseem A, Hopkins RH Jr, Sweet DE, et al; Clinical Guidelines Committee of the American College of Physicians. Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2013; 159:835–847.
97. Bauersachs RM. Managing venous thromboembolism with novel oral anticoagulants in the elderly and other high-risk patient groups. Eur J Intern Med 2014; 25:600–606.
98. Greinacher A, Selleng K. Thrombocytopenia in the intensive care unit patient. Hematology Am Soc Hematol Educ Program 2010; 2010:135–143.

99. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009; 113:2386–2393.
100. Schulze H, Gaedicke G. Immune thrombocytopenia in children and adults: what's the same, what's different? Haematologica 2011; 96:1739–1741.
101. Cines DB, Bussel JB, Liebman HA, Luning Prak ET, et al. The ITP syndrome: pathogenic and clinical diversity. Blood 2009; 113:6511–6521.
102. Middelburg RA, Carbaat-Ham JC, Hesam H, Ragusi MA, Zwaginga JJ. Platelet function in adult ITP patients can be either increased or decreased, compared to healthy controls, and is associated with bleeding risk. Hematology 2016; 21:549–551.
103. Panzer S, Rieger M, Vormittag R, Eichelberger B, Dunkler D, Pabinger I. Platelet function to estimate the bleeding risk in autoimmune thrombocytopenia. Eur J Clin Invest 2007; 37:814–819.
104. Provan D, Newland AC. Current management of primary immune thrombocytopenia. Adv Ther 2015; 32:875–887.
105. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood 2004; 104:2623–2634.
106. Schwartz J, Leber MD, Gillis S, Giunta A, Eldor A, Bussel JB. Long term follow-up after splenectomy performed for immune thrombocytopenic purpura (ITP). Am J Hematol 2003; 72:94–98.
107. Oh HJ, Park JM, Yoon SB, et al. Bleeding after endoscopic procedures in patients with chronic hematologic thrombocytopenia. Dig Dis Sci 2017; 62:746–754.
108. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. J Clin Invest 1966; 45:645–657.
109. Goel R, Ness PM, Takemoto CM, Krishnamurti L, King KE, Tobian AA. Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality. Blood 2015; 125:1470–1476.
110. Pudusseri A, Spyropoulos AC. Management of anticoagulants in the periprocedural period for patients with cancer. J Natl Compr Canc Netw 2014; 12:1713–1720.
111. Connolly GC, Khorana AA. Emerging risk stratification approaches to cancer-associated thrombosis: risk factors, biomarkers and a risk score. Thromb Res 2010; 125(suppl 2):S1–S7.
112. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. Arch Intern Med 2000; 160: 3431–3436.
113. Liebman HA. Thrombocytopenia in cancer patients. Thromb Res 2014; 133(suppl 2):S63–S69.
114. Tafur AJ, Wysokinski WE, McBane RD, et al. Cancer effect on periprocedural thromboembolism and bleeding in anticoagulated patients. Ann Oncol 2012; 23:1998–2005.
115. Gorschluter M, Schmitz V, Mey U, Hahn-Ast C, Schmidt-Wolf IG, Sauerbruch T. Endoscopy in patients with acute leukaemia after intensive chemotherapy. Leuk Res 2008; 32:1510–1517.
116. Soylu AR, Buyukasik Y, Cetiner D, et al. Overt gastrointestinal bleeding in haematologic neoplasms. Dig Liver Dis 2005; 37:917–922.
117. Schiffer CA, Bohlke K, Delaney M, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2018; 36:283–299.
118. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intens Care 2014; 2:15.
119. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol 2009; 145: 24–33.
120. Squizzato A, Hunt BJ, Kinasewitz GT, et al. Supportive management strategies for disseminated intravascular coagulation. An international consensus. Thromb Haemost 2016; 115:896–904.
121. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014; 35:2541–2619.
122. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation 2016; 134:e123–e155.
123. Yusuf S, Zhao F, Mehta SR, et al; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494–502.
124. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005; 293:2126–2130.