Chapter

22 HEMOSTASIS

Lindsey L. Huddleston and Linda L. Liu

Hemostasis is the formation of blood clot at the site of vessel injury. Physiologic hemostasis involves a complex interplay of four components: vascular endothelium, platelets, coagulation factors, and the fibrinolytic system. This intricate system of checks and balances allows blood to maintain its fluidity within a vessel, promotes clot at the site of vessel injury, dismantles clot, and prevents thrombus formation at other sites. If dysfunction of one component or imbalance between components occurs, abnormal bleeding or pathologic thrombosis may occur. Both congenital and acquired disease states, as well as medications, can disrupt the equilibrium of this complex system and lead to bleeding or thrombosis.

PRIMARY HEMOSTASIS

Primary hemostasis refers to initial vascular endothelial injury leading to platelet deposition at the site of injury (or platelet plug). Under normal conditions and blood flow, platelets do not adhere to the endothelial surface or aggregate with each other, but with vascular injury, the endothelial matrix is exposed. This initial trigger leads to platelet adhesion to collagen or von Willebrand factor (vWF) via multiple surface receptors.

Platelet activation then plays a critical role in the aggregation of platelets. Integrins that are normally present on the platelet surface in inactive forms are activated and bind multiple ligands, including vWF, collagen, fibrinogen, fibronectin, and vitronectin. The activated platelets degranulate and release agonists that act on G protein–coupled receptors to further propagate aggregation and formation of the platelet plug. These agonists include adenosine diphosphate (ADP), thromboxane A_2 (TxA_2), serotonin, epinephrine, and vasopressin. Along

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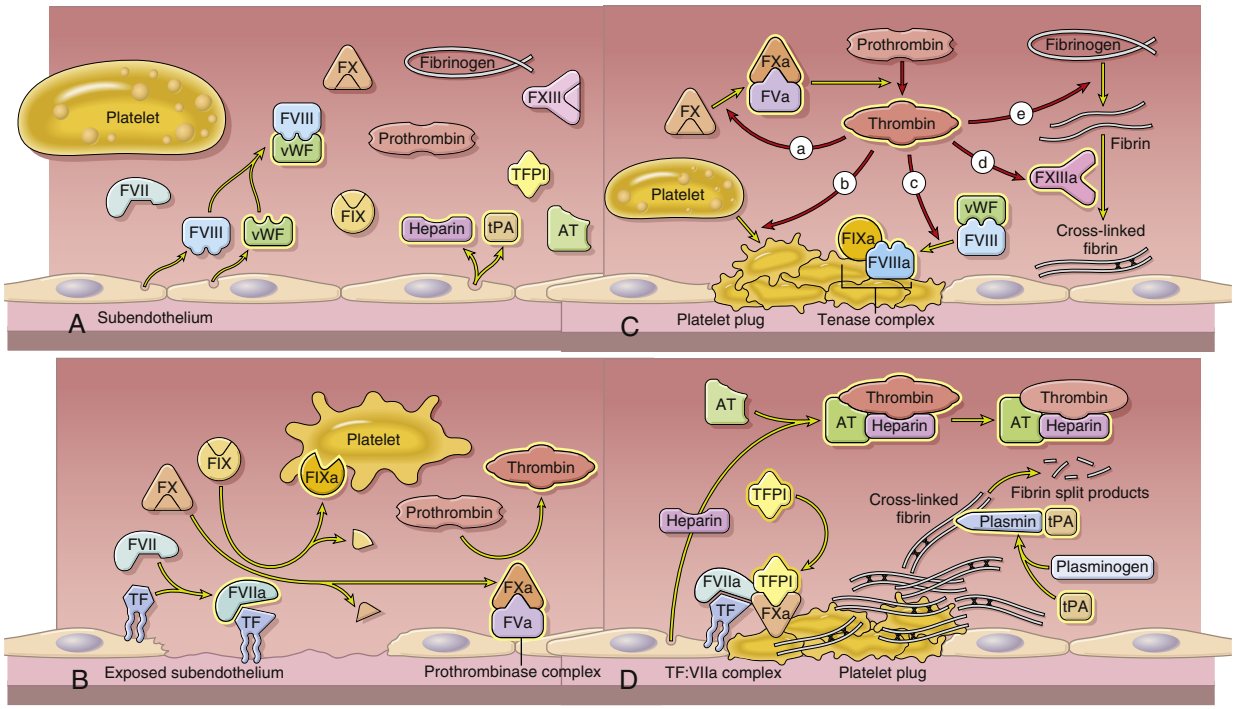


Fig. 22.1 (A) Normal endothelium. Procoagulants (factors [F] VII, VIII, IX, X, XIII, prothrombin), fibrinogen, and platelets circulate in their inactive forms. Anticoagulants (tissue factor pathway inhibitor [TFPI], heparin, and tissue plasminogen activator [tPA]) actively prevent endothelial spontaneous thrombus formation. (B) Vascular injury, initial phase. Subendothelial tissue factor (TF) exposed to circulating FVII forms a TF:VII complex. TF:VII activates FIX and FX. FIXa binds to platelets. FXa activates FV (FVa) to form prothrombinase complex, which converts localized, small amounts of prothrombin to thrombin. (C) Vascular injury, role of thrombin. Thrombin (a) activates FX and FV to form prothrombinase complexes that generate the secondary thrombin burst, (b) activates platelets, (c) separates FVIII from von Willebrand factor (vWF) and activates FVIII, (d) converts fibrinogen to fibrin, (e) activates factor XI, and (f) activates FXIII, the stabilizer of cross-linked fibrin. Stable clot is formed. (D) Control of coagulation and fibrin clot dissolution. Antithrombin (AT) binds heparin and potently inhibits thrombin activity. TFPI binds to FXa to inhibit the TF:VIIa complex. Plasminogen is activated to plasmin by tPA and cleaves fibrin into soluble fibrin split products. (From Stratmann G. Hemostasis. In Miller RD, Pardo MC, eds. *Basics of Anesthesia*. 6th ed. Philadelphia: Elsevier; 2011.)

with the activated integrins on platelet surfaces, each of these agonists target and activate phospholipase C (PLC). PLC activation leads to the release of large amounts of calcium, which catalyzes degranulation and induces a change in the platelet shape, making them extremely adhesive.

Following platelet activation, the most abundant receptor on the platelet surface, glycoprotein IIb/IIIa (GPIIb/IIIa), undergoes a conformational change and gains high affinity for fibrinogen, thus promoting platelet aggregation and stablization of the platelet plug. In addition, the cytosolic portion of GPIIb/IIIa binds to the platelet cytoskeleton to mediate platelet spreading and clot retraction. By integrating receptor-ligand interactions with cytosolic events, GPIIb/IIIa is the final common pathway for platelet aggregation.[1]

SECONDARY HEMOSTASIS

Clotting Cascade and Propagation of the Clot

Proteases cleave inactive precursor proteins (zymogens) to active enzymes that assemble into complexes that subsequently activate thrombin and propagate clot formation. Traditionally, the clotting cascade has been described as consisting of intrinsic, extrinsic, and common pathways. Although this view is useful for providing a structural framework to understand coagulation and to interpret in vivo coagulation tests (e.g., prothrombin time [PT], partial thromboplastin time [PTT]), the current view is that after formation of the platelet plug, coagulation proceeds via an interplay of mechanisms, which include tissue factor (TF) activation of clotting factors, amplification of clotting factors, and propagation of clot formation by thrombin[2] (Fig. 22.1).

The primary physiologic event thought to initiate clotting is the interaction of TF at the site of vascular injury with activated factor VII (factor VIIa). The TF-VIIa complex then activates factors X and IX. Factor Xa then complexes with and activates factor V (which is released from platelet granules during platelet activation) forming the prothrombinase complex. This complex converts a small amount of prothrombin (factor II) to thrombin. This small amount of thrombin amplifies the cascade by activating additional factors V, VIII, XI, and platelets. Factor IXa and factor VIIIa form a complex (the tenase complex) on the surface of activated platelets. The tenase complex activates additional factor X, leading to increased production of the prothrombinase complex and increased thrombin formation. Once sufficient levels of thrombin are available, fibrin is generated from fibrinogen. Finally, to form a strong blood clot, fibrin activates factor XIII to cross-link the fibrin monomers.

Control and Termination of Coagulation

Three main regulatory molecules control coagulation and facilitate the termination of the coagulation cascade: (1) antithrombin (AT) (formerly antithrombin III), (2) TF pathway inhibitor (TFPI), and (3) activated protein C (aPC). AT inhibits thrombin (factor IIa) and factors Xa, IXa, XIa, and VIIa. When heparin binds to AT, a conformational change occurs and the inactivating process is accelerated by over 100-fold. Endogenous heparin is found on normal endothelial cell surface and prevents spontaneous clot formation, thus limiting the coagulation process to only damaged endothelium. TFPI directly inhibits factor Xa and also complexes with factor Xa to inhibit the TF–factor VIIa complex. Protein C becomes activated when thrombin binds to thrombomodulin on the endothelial cell surface as clot progresses. The thrombin-thrombomodulin complex no longer promotes platelet activation or the formation of fibrin, but instead activates protein C. aPC inactivates factors Va and VIIIa, thus inactivating the prothrombinase and intrinsic tenase complexes. This process is greatly enhanced by the presence of protein S.

Fibrinolysis

Under normal physiologic conditions, plasmin circulates in its inactive plasminogen form. Plasminogen activator inhibitor type 1 (PAI-1) is synthesized by endothelial cells and secreted to prevent the activation of plasminogen. Injured endothelium secretes tissue plasminogen activator (tPA), which cleaves plasminogen to its active form, plasmin. Because tPA also binds fibrin, the generation of plasmin takes place on the fibrin clot surface, localizing the action of plasmin to the area of clot. Fibrin is cleaved by plasmin into soluble products (D-dimer, fibrin degradation products), which also inhibit thrombin activity. Like the formation of clot, clot resolution is a highly regulated process. Plasmin that is unbound to the fibrin clot and circulating is inhibited by α_2-antiplasmin. If plasmin activation goes unchecked, systemic fibrinolysis and massive hemorrhage may develop.[3]

DISEASES ASSOCIATED WITH BLEEDING

Certain hereditary or acquired disorders, systemic diseases, and environmental conditions can predispose a patient to excessive bleeding after tissue injury, including surgery. This is the result of a disruption of the hemostatic process and involves a complex interaction between coagulation factors, platelets, fibrinolysis, and vascular integrity. Patients with less than 20% to 30% normal coagulation factor values or platelet counts of less than 50,000 cells/μL are more likely than patients with normal values to have uncontrolled intraoperative bleeding. Bleeding diatheses vary in clinical presentation depending on what component of the hemostatic system is affected.

Diseases involving coagulation factor deficiencies may present in early childhood with subcutaneous, intramuscular, or intra-articular hemorrhage after only minor trauma. Diseases involving decreased or dysfunctional platelets are typically associated with mucosal bleeding, epistaxis, prolonged bleeding after dental procedures, and menorrhagia. A careful history and physical examination, laboratory evaluation, and consultation with a hematologist when appropriate are necessary to evaluate any patient with suspected bleeding disorders.

Inherited Coagulation Factor Deficiencies

Hemophilia A and B

Hemophilia A and hemophilia B are X-linked recessive disorders that are the most common inherited deficiencies of specific coagulation factors. Hemophilia A is a deficiency of factor VIII and occurs in approximately 1 in 5000 live male births. Hemophilia B is a deficiency of factor IX and occurs in approximately 1 in 30,000 live male births. Severe disease, defined by less than 1% of coagulation factor activity, occurs in approximately two thirds of patients with hemophilia A and one half of patients with hemophilia B. Laboratory evaluation shows a prolonged activated PTT (aPTT) that corrects in mixing studies, with a normal platelet count and PT. Plasma von Willebrand factor antigen (vWF:Ag) is normal in hemophilia, distinguishing factor VIII deficiency from von Willebrand disease (vWD). Many patients with hemophilia A (up to 25%) and some with hemophilia B (approximately 3% to 5%) will develop inhibitory antibodies as a response to exogenous factor. In these cases, the aPTT does not correct in mixing studies and alternative treatment is necessary.

Acquired factor deficiencies are caused by autoantibodies, most commonly to factor VIII. Acquired factor inhibitors can develop in patients who have received infusions of factor concentrates, are pregnant (also see Chapter 33), or have underlying systemic disease such as lupus erythematosus or rheumatoid arthritis, or as a drug reaction. In contrast to hemophilia, these acquired factor inhibitors typically occur in adulthood. In addition, mixing studies fail to show correction of the aPTT that is characteristic of hemophilia.

Other Factor Deficiencies

Less common inherited factor deficiencies include deficiencies of factors XI, XII, and XIII. Factor XI deficiency, also known as hemophilia C or Rosenthal disease, is an autosomal recessive disorder that can be associated with bleeding and is characterized by a prolonged aPTT. Factor XII deficiency can result in a prolonged aPTT but is associated with clotting rather than bleeding. Factor XIII is involved in stabilizing the fibrin clot. Patients with factor XIII deficiency present with delayed bleeding after hemostasis, impaired wound healing, and, occasionally, pregnancy loss. Laboratory evaluation shows a normal aPTT and PT with low factor XIII levels.

von Willebrand Disease

vWD is the most common inherited bleeding disorder. The estimated prevalence is 1% of the general population; however, the true prevalence is likely more frequent because of the highly polymorphic von Willebrand gene and variable phenotypes of the disorder. vWF is synthesized by megakaryocytes and endothelial cells. Once released from these cells, it circulates as a series of multimers formed from a basic dimer subunit. The most active forms of vWF are high-molecular-weight multimers that have multiple binding sites for both platelet receptors and subendothelial structures. In normal hemostasis, vWF binds to both platelets and the extracellular matrix at the site of endothelial injury, thus contributing to primary hemostasis by facilitating platelet adhesion. vWF also plays a role in the coagulation cascade and fibrin clot formation by acting as a carrier protein for factor VIII, increasing its concentration and prolonging its half-life. vWD is classified into three types according to vWF levels and protein function (Table 22.1).

In addition to the inherited forms for vWD, several disease states are associated with acquired vWD. These consist of autoimmune, lymphoproliferative, myeloproliferative, neoplastic, and cardiovascular disorders. The underlying pathophysiology of acquired vWD includes autoantibodies to vWF, increased clearance of vWF from plasma, enhanced proteolysis after shear stress, and decreased synthesis.

Acquired Coagulation Factor Disorders

Vitamin K Deficiency

Vitamin K is an essential fat-soluble vitamin that is required for the carboxylation of factors II, VII, IX, and X and proteins C and S. Without carboxylation, these factors

Table 22.1 Classification of von Willebrand Disease

Type	Characteristic	Frequency	Inheritance	Diagnosis	Treatment
1	Not enough vWF	70-80%	AD	vWF:Ag, vWF:RCo, FVIII	1. DDAVP 2. FVIII/vWF concentrate
2	Qualitative defect of vWF	15-20%	AD		
A	↓ binding of vWF to platelets, ↓ large multimers	Common		vWF:RCo << vWF:Ag (↓ large multimers)	
B	↑ binding of vWF to platelets, ↓ large multimers			RIPA (much less ristocetin required for aggregation)	FVIII/vWF concentrate (DDAVP contraindicated)
M	↓ vWF function despite normal large multimers	Rare		↓ vWF:RCo compared with vWF:Ag	1. FVIII/vWF concentrate 2. DDAVP
N	↓ binding of VWF to FVIII	Rare			1. FVIII/vWF concentrate? 2. DDAVP?
3	Absent vWF	Very rare	AR	vWF:Ag	1. FVIII/vWF concentrate/rFVIII 2. Platelet concentrate

AD, Autosomal dominant; *AR*, autosomal recessive; *DDAVP*, desmopressin acetate; *FVIII*, coagulation factor VIII; *rFVIIa*, recombinant factor VIIa; *RIPA*, ristocetin-induced platelet aggregation; *vWF*, von Willebrand factor; *vWF:Ag*, von Willebrand factor antigen; *vWF:RCo*, von Willebrand factor ristocetin cofactor activity; ↓, decreased; ↑, increased; <<, much lower than; *?*, uncertain.
From Stratmann G. Hemostasis. In Miller RD, Pardo MC, eds. *Basics of Anesthesia*. 6th ed. Philadelphia: Elsevier; 2011.

cannot bind to the phospholipid membrane of platelets during secondary hemostasis. Vitamin K is in dietary sources (leafy greens) and is also synthesized by bacteria in the gastrointestinal tract. Patients who are fasting, who have poor dietary intake or are receiving total parenteral nutrition, and those with impaired intestinal absorption (obstructive jaundice, intestinal ileus or obstruction, or total parenteral nutrition) are susceptible to vitamin K deficiency. Newborns, who have not yet developed normal intestinal flora, and patients undergoing oral antibiotic therapy that alters gut flora are also prone to vitamin K deficiency.

Liver Disease

Multiple causes for bleeding diatheses occur in patients with severe liver disease. Primary hemostasis may be impaired because of thrombocytopenia secondary to platelet sequestration by the spleen in patients with portal hypertension and decreased production of thrombopoietic factors. In addition, comorbid conditions such as renal failure and infection can lead to dysfunctional platelets. Secondary hemostasis can be compromised because plasma clotting factors, with the exception of factor VIII, are synthesized in the liver. Laboratory values of platelets, PT, and aPTT may overestimate the bleeding risk in these patients, because the liver is also responsible for the synthesis of anticoagulant factors: protein C, protein S, and AT. Often, this deficiency of both procoagulant and anticoagulant factors leads to a tenuous hemostatic balance, which can be altered by any small disturbance.

Treatment of Clotting Factor Deficiencies

Hemophilia A and Hemophilia B

Patients with known hemophilia should have a thorough preoperative evaluation, including bleeding history, and laboratory evaluation for levels of factor and presence of inhibitors. Given the significant variability of individual response to factor replacement, consultation with a hematologist is necessary to manage perioperative care. Factor concentrates are the treatment of choice for patients with hemophilia A (factor VIII concentrate) and hemophilia B (factor IX concentrate). Dose calculations are targeted to achieve at lease 50% of normal factor activity levels for minor surgery and 80% to 100% of normal factor activity levels for major surgery. Treatment with factor concentrates should continue postoperatively until wound healing is complete. Patient response and the type of surgery determine the necessary duration of treatment.

In resource-limited areas, treatment with cryoprecipitate and fresh frozen plasma (FFP) may be necessary, although not optimal. Cryoprecipitate contains large quantities of factor VIII, vWF, fibrinogen, and factor XIII, but it does not contain factor IX and should not be used for replacement therapy in hemophilia B. Sufficient levels of factor VIII or factor IX levels are difficult to achieve with FFP alone because of inadequate levels of factor and the need for a large volume administration. Prothrombin complex concentrates (PCCs) contain factor IX and can be used for bleeding control in hemophilia B when factor IX concentrates are unavailable. However, PCCs induce a higher thrombotic risk than pure factor IX concentrate and extreme caution should be used when administering concomitant antifibrinolytics. Other adjuvant therapies include desmopressin acetate (DDAVP), which increases plasma levels of factor VIII and vWF and can be useful for hemophilia A, and antifibrinolytics (tranexamic acid [TXA], ε-aminocaproic acid [EACA]), which may decrease the bleeding risk.

von Willebrand Disease

DDAVP is the treatment of choice in type 1 vWD. One dose of DDAVP (0.3 μg/kg) will produce a complete or near complete response in the majority of patients.[4] In addition, cryoprecipitate and intermediate-purity factor VIII concentrates, which both contain high levels of vWF, can be used to attenuate surgical bleeding. DDAVP is contraindicated in type 2b vWD because it causes a transient thrombocytopenia. In addition, patients with severe vWD (type 3) do not respond to DDAVP and should be treated with a combination of factor VIII and vWF concentrates. Antifibrinolytics may also be useful adjuvants in the management of perioperative bleeding in this patient population.

Acquired Coagulation Disorders

Vitamin K deficiency can be treated with vitamin K replacement via oral, intravenous, intramuscular, or subcutaneous administration. In cases of serious bleeding, intravenous vitamin K is the recommended therapy, beginning with a dose of 5 mg. In isolated vitamin K deficiency, correction of the PT will occur within 3 to 4 hours of intravenous vitamin K administration.

Treatment of severe bleeding in the setting of liver failure is most often guided by laboratory abnormalities (also see Chapter 28). Platelets are administered for thrombocytopenia, FFP for prolonged PT, and cryoprecipitate may be necessary to treat bleeding in the setting of hypofibrinogenemia (also see Chapter 24). Because of the complex balance between deficiencies of procoagulant and anticoagulant factors, routine administration of blood products to correct laboratory values in the absence of bleeding or major surgery is not recommended in these patients. Whether blood product replacement in nonbleeding patients with liver failure should be used for minimal risk procedures, such as central line placement, is not well established.

Treatment of patients with acquired factor inhibitors is complex, as these patients may not respond to standard therapy with factor concentrates. “Bypassing agents” treat bleeding by producing thrombin through pathways that

do not require factor VIII or factor IX. "Bypassing agents" are the mainstay of therapy for bleeding patients with high levels of inhibitor in whom administration of factor concentrate is ineffective.[5] Currently available "bypassing agents" include recombinant factor VIIa (rFVIIa) and PCCs. Another treatment strategy in the nonurgent clinical setting is "immune tolerance induction" when patients are exposed to prolonged, high concentrations of factor in an effort to eliminate a coagulation inhibitor.

Platelet Disorders

Both decreased platelet numbers (thrombocytopenia) and qualitative platelet disorders can result in severe bleeding. Inherited platelet disorders are rare congenital diseases that typically affect qualitative function of platelets. In addition to inherited disorders, a multitude of acquired disorders can affect platelet number, platelet function, or both. Both inherited and acquired disorders of platelet function are characterized by prolonged bleeding time and abnormal platelet function tests.

Thrombocytopenia

Low platelet counts can be the result of decreased platelet production, increased destruction, or sequestration. Decreased platelet production in the bone marrow occurs in myelodysplastic syndromes, infections (especially in the setting of sepsis), and nutrient deficiencies. Patients with these disorders typically present with pancytopenia because production of all cell lines in the bone marrow is impaired. Other causes of impaired production of platelets include immune thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) and drug-induced bone marrow suppression. Peripheral platelet destruction by antiplatelet antibodies can be induced by certain medications or ingested substances, as well as in the setting of specific autoimmune diseases. Heparin-induced thrombocytopenia (HIT) occurs in less than 5% of patients exposed to heparin. Antibodies to platelet factor 4 can cause thrombocytopenia and platelet activation, potentially leading to life-threatening arterial and venous thrombosis. Increased platelet consumption within thrombi is seen in disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura/hemolytic uremic syndromes (TTP-HUS). Diseases that cause splenomegaly or splenic congestion through portal hypertension (e.g., cirrhosis) lead to sequestration of platelets in the spleen, inhibiting their release into circulation.

Multiple disorders of pregnancy result in thrombocytopenia including gestational thrombocytopenia, preeclampsia, and pregnancy-associated hypertensive disorders (also see Chapter 33). The most severe of these disorders is the HELLP syndrome (hemolysis, elevated liver function test results, low platelet counts), which necessitates emergent delivery before life-threatening maternal complications occur.

Qualitative Platelet Disorders

Even with adequate platelet numbers, poor function can increase bleeding risk and affect measures of platelet aggregation. Several common drugs impair platelet function including aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), alcohol, dipyridamole, and clopidogrel. Uremia, when severe, is associated with increased clinical bleeding. Proposed pathophysiologic mechanisms include intrinsic platelet metabolic defects, impaired platelet granule release, and impaired platelet–endothelial cell interactions. Normal platelet function is also impaired in conditions with high levels of abnormal circulating proteins (multiple myeloma, dysproteinemia, transfused dextran solutions). Many rare conditions involve inherited disorders of platelet function. Glanzmann thrombasthenia is an autosomal recessive disorder characterized by defective GPIIb/IIIa receptors on platelets leading to impaired platelet aggregation. Giant platelet disorders include platelet glycoprotein abnormalities, as in Bernard-Soulier syndrome. Wiskott-Aldrich syndrome is an X-liked recessive disorder in which patients have immunodeficiency, severely dysfunctional platelets, and thrombocytopenia. This syndrome is an example of a storage pool disorder, in which granule deficiencies lead to impaired platelet aggregation.

Treatment of Platelet Disorders (Also See Chapter 24)

In the nonbleeding patient, treatment of thrombocytopenia in the form of platelet transfusion is usually withheld until the platelet count is less than 10,000 cells/μL. In the patient who is actively bleeding or requires surgical intervention, platelet transfusion is recommended to a goal of 50,000 cells/μL, or in some cases, such as intracranial hemorrhage or neurosurgery, 100,000 cells/μL. A major concern with the transfusion of platelets is the potential for human leukocyte antigen (HLA) or human platelet antigen antibodies to form. If multiple platelet transfusions are expected, platelets should be HLA-matched whenever possible. For patients with normal platelet counts but suspected dysfunctional platelets, administration of platelets is often ineffective because the patient's underlying condition causes transfused platelets to function abnormally. In these cases, DDAVP may be effective.

DISEASES ASSOCIATED WITH THROMBOSIS

Development of venous thrombosis (most commonly deep venous thrombosis [DVT] or pulmonary embolus) is a common occurrence in the surgical population and leads to increased morbidity and mortality rates. The classic teaching for the pathogenesis of venous thromboembolism (VTE), often referred to as Virchow triad, proposes that VTE occurs as a result of (1) stasis of blood flow, (2) endothelial injury, and (3) a hypercoagulable state (inherited or acquired).

Patients with inherited thrombophilia (deficiencies of protein C, protein S, and AT; factor V Leiden and prothrombin gene mutations) have an increased tendency for VTE. Numerous other conditions such as malignancy, pregnancy, immobilization, trauma, DIC, antiphosholipid syndrome, infection, drugs (e.g., oral contraceptives), and recent surgery also predispose patients to VTE.

Hereditary Hypercoagulable States

Factor V Leiden and Prothrombin Gene Mutation

The most common inherited thrombophilias are the factor V Leiden mutation and the prothrombin gene mutation, accounting for 50% to 60% of cases. Individuals with factor V Leiden have an abnormal mutation of factor V that is resistant to the action of aPC. aPC regulates the coagulation process by inhibiting factor V from forming excessive fibrin in normal individuals. The prothrombin gene mutation (prothrombin 20210) leads to overproduction of prothrombin (factor II) and makes the blood more likely to clot. Individuals with factor V Leiden or the prothrombin gene mutation are at increased risk of developing DVTs, with homozygotes having the highest risk. Despite the increased relative risk, the absolute risk of blood clots in these patients remains low in the absence of other risk factors for hypercoagulability.

Protein C and Protein S Deficiencies

Under normal physiologic conditions, aPC inactivates factors Va and VIIIa (enhanced by protein S). In addition, aPC acts directly on cells to protect the endothelial barrier function and also has antiinflammatory activities. Protein C deficiency is an autosomal dominant trait affecting approximately 1 in 500 individuals in the general population. Clinical manifestations of the deficiency include VTE, neonatal purpura (in homozygous neonates), fetal loss, and warfarin-induced skin necrosis. Protein S is a cofactor for aPC and is synthesized by hepatocytes, endothelial cells, and megakaryocytes. Forty to 50% of protein S circulates as the free form, the only form with aPC cofactor activity. In the presence of protein S, aPC inactivates factors Va and VIIIa at an accelerated rate. Protein S also serves as a cofactor for protein C enhancement of fibrinolysis and can directly inhibit prothrombin activation. Individuals with protein S deficiency present similarly to those with other inherited thrombophilias and are at increased risk of VTE, superficial thrombophlebitis, and pulmonary embolism (PE).

Both protein C and protein S deficiencies can be acquired secondary to underlying disease. Acquired protein C deficiency can be seen in liver disease, severe infection (especially meningococcemia), septic shock, and DIC. Acquired protein S deficiency has been associated with pregnancy, use of oral contraceptives, DIC, human immunodeficiency virus (HIV) infection, nephrotic syndrome, and liver disease.

Acquired Hypercoagulable States

Antiphospholipid Syndrome

The antiphospholipid (antibody) syndrome (APS) is a condition characterized by both venous and arterial thromboses or recurrent pregnancy complications (also see Chapter 33). Patients with this syndrome have persistent circulating antiphospholipid antibodies (aPLs), which include lupus anticoagulant, anticardiolipin antibody, or anti-β2GPI antibodies. It is one of the few prothrombotic states in which arterial and venous thromboses occur. Most cases of APS are sporadic or acquired. Rarely, the condition runs in families; yet it does not exhibit a clear pattern of inheritance.

DVT is the most common venous thrombosis and stroke is the most common arterial thrombosis. Diagnosis is made by clinical criteria (arterial/venous thromboses, recurrent pregnancy complications) and by the presence of one or more of the three aPLs detected on two or more occasions at least 12 weeks apart. Patients who have persistently positive aPLs (especially those with multiple differing aPLs), who present with arterial thromboses, or who have recurrent thromboses in the setting of anticoagulation are most likely at risk for thrombosis. The lupus anticoagulant, although often found in patients with systemic lupus erythematosus, can also be associated with medications (phenothiazines, phenytoin, hydralazine, quinine, and antibiotics), inflammatory bowel disease (Crohn disease and ulcerative colitis), infections, and certain kinds of tumors. Catastrophic APS (CAPS) is a rare accelerated form of APS in which patients present with coagulopathy, ischemic necrosis of the extremities, and multiorgan failure in the setting of positive circulating aPLs and histopathologic evidence of small vessel occlusion. Although CAPS occurs in less than 1% of patients with APS, mortality rate is approximately 30%.[6] Early recognition and treatment with anticoagulation and immunosuppressant therapy are paramount to survival.

Disseminated Intravascular Coagulation

DIC is an acquired disorder caused by an underlying condition (most commonly, sepsis) that is characterized by widespread systemic activation of coagulation (also see Chapter 24). This results in uncontrolled intravascular thrombin generation and fibrin deposition in small blood vessels. The formation of microvascular thrombi ultimately leads to end-organ dysfunction and multiorgan failure. Excessive consumption of circulating coagulation factors, platelets, and fibrinogen occurs simultaneously with microvascular thrombi formation, which can result in life-threatening bleeding. A patient with DIC may present with both thrombotic and hemorrhagic complications.

No single laboratory test identifies DIC; however, a combination of laboratory tests in the setting of a condition known to cause DIC can be sufficient for diagnosis (Table 22.2). The most common laboratory abnormalities

Table 22.2 Conditions Associated With Disseminated Intravascular Coagulation

Category	Conditions
Infections	Bacterial (gram-negative bacilli, gram-positive cocci) Viral (CMV, EBV, HIV, VZV, hepatitis) Fungal (histoplasma) Parasites (malaria)
Malignancy	Hematologic (AML) Solid tumors (prostate cancer, pancreatic cancer) Malignant tumors (mucin-secreting adenocarcinoma)
Obstetric causes	Amniotic fluid embolism Preeclampsia/eclampsia Placental abruption Acute fatty liver of pregnancy Intrauterine fetal demise
Massive inflammation	Severe trauma Burns Traumatic brain injury Crush injury Severe pancreatitis
Toxic/ immunologic	Snake envenomation Massive transfusion ABO blood type incompatibility Graft versus host disease
Other	Liver disease/fulminant hepatic failure Vascular disease (aortic aneurysms, giant hemangiomas) Ventricular assist devices

AML, Acute myelogenous leukemia; *CMV*, cytomegalovirus; *EBV*, Epstein-Barr virus; *HIV*, human immunodeficiency virus; *VZV*, varicella zoster virus.

associated with DIC are thrombocytopenia, elevated fibrin degradation products (D-dimers), prolonged PT and aPTT, and low fibrinogen. Because laboratory abnormalities in DIC can be seen in other conditions such as massive blood loss, liver failure, HIT, and thrombotic microangiopathy, a scoring system has been developed by the International Society on Thrombosis and Hemostasis (ISTH). The ISTH scoring system uses simple laboratory tests (platelet count, PT, aPTT, fibrinogen, D-dimer) plus the presence of a triggering underlying condition to diagnose DIC. It has a high sensitivity and specificity (91% and 97%, respectively) and is an independent predictor of mortality risk.[7]

Treatment of Hypercoagulable States

Inherited thrombophilias are relatively rare in the general population, and screening for the presence of these diseases in the absence of VTE is not recommended. In patients with a known thrombophilia but no history of VTE (or pregnancy complications), primary prophylaxis with anticoagulation is not recommended. Patients who present with VTE and test positive for an inherited thrombophilia are anticoagulated for their acute presentation. Continuation of anticoagulation after resolution of acute VTE is determined by severity of presentation, presence of more than one thrombophilia, and homozygosity or heterozygosity for thrombophilia.[8] In the case of pregnant patients with known thrombophilia, anticoagulation is often recommended in the antepartum and postpartum setting (also see Chapter 33). The necessary duration and type of anticoagulation therapy are not clear because of the rarity of these diseases; a hematologist should manage all patients. Patients with antiphospholipid syndrome (APS) have an increased risk of recurrent thrombosis and are most often treated with long-term anticoagulation. The specific treatment and targets for optimal anticoagulation therapy remain controversial.

For DIC, the mainstay of therapy is to treat the underlying cause. Supportive care for actively bleeding patients is guided by laboratory tests to ensure appropriate transfusion therapy (also see Chapter 24). In patients with active bleeding and suspected fibrinolysis, antifibrinolytics, such as TXA, may be used. Transfusions for nonbleeding patients are typically withheld unless platelets, fibrinogen, or coagulation factors are severely low, or if patients undergo an invasive procedure. Anticoagulation in patients with DIC remains controversial, and therapy with heparin is rarely initiated unless severe thrombosis is present.

LABORATORY EVALUATION OF HEMOSTASIS

Currently, the coagulation tests that are commonly performed in the laboratory have limited clinical value and are poor at predicting surgical bleeding (Table 22.3; also see Chapter 24). Although routine coagulation tests have been standardized to guide heparin and warfarin therapy and certainly play a role in the diagnosis and management of factor deficiencies (e.g., hemophilia), they were not developed with the intent to manage the actively bleeding patient. Newer global coagulation assays (thromboelastography, rotational thromboelastometry) may provide a more detailed picture of complex hemostasis and help guide therapy toward specific abnormalities of coagulation or fibrinolysis.

Tests of Coagulation

Prothrombin Time

PT can be used to assess what was traditionally thought of as the extrinsic pathway of clotting. Prolonged PT will occur with low levels of TF, factor VII, factor II, factor

Table 22.3 Common Laboratory Tests of Hemostasis and Normal Ranges

Platelet Tests	Coagulation Tests	Fibrinolysis Tests
Platelet count: 140,000-450,000 cells/μL	Prothrombin time: 11.5-14.5 sec[a]	Thrombin time: 22.1-31.2 sec
Bleeding time: <11 min	Partial thromboplastin time: 24.5-35.2 sec[a]	Fibrinogen-fibrin degradation products: >5 μg/dL
Platelet function analysis	Thrombin time: 22.1-31.2 sec[a]	Fibrin D-dimer assay: <250 μg/mL
Collagen/epinephrine: 94-193 sec	Fibrinogen: 175-433 mg/dL	
Collagen/adenosine diphosphate: 71-118 sec	Activated coagulation time: 70-180 sec	
Platelet aggregation (response to aggregating agents: collagen, adenosine diphosphate, epinephrine, and ristocetin)		

[a]The normal range varies with reagent lots.
From Stratmann G. Hemostasis. In Miller RD, Pardo MC, eds. *Basics of Anesthesia*. 6th ed. Philadelphia: Elsevier; 2011.

V, factor X, and fibrinogen. For the test, citrated patient plasma is recalcified in the presence of thromboplastin (which activates factor X in the presence of factor VII). The end point of the test is the time to formation of fibrin clot, as measured by visual, optical, or electromechanical means. Because the PT can measure reduced activity of the vitamin K–dependent factors, it is used to monitor warfarin therapy. Heparin, low-molecular-weight heparin (LMWH), and fondaparinux inhibit thrombin and therefore should prolong the PT. However, most PT reagents contain heparin-binding chemicals that block this effect and thus PT remains normal in the setting of these therapies. Because PT reagents can vary widely between laboratories and lead to differing values, the international normalized ratio (INR) was developed by the World Health Organization to standardize PT and allow the values to be directly compared between laboratories.

Activated Partial Thromboplastin Time

The aPTT is used to assess the integrity of the intrinsic and common coagulation pathways. It can detect low levels of prekallikrein; high-molecular-weight kininogen; factors XII, XI, IX, and VIII (intrinsic pathway); as well as low levels of factors II, V, and X and fibrinogen (final common pathway). Citrated plasma is recalcified in the presence of a thromboplastic material that does not have TF activity. A negatively charged substance such as kaolin, celite, ellagic acid, or silica provides a surface for contact activation of factor and speeds up the reaction. As with the PT, the end point of the aPTT is formation of fibrin clot. Both hemophilias A and B as well as vWD (because of potentially low levels of factor VIII) will prolong aPTT. Unfractionated heparin (UFH) therapy and therapy with parenteral direct thrombin inhibitors (DTIs) (argatroban) are monitored with aPTT levels.

Thrombin Time

The thrombin time measures the conversion of fibrinogen to fibrin, which is the final step in the clotting pathway. The test is performed by recalcifying citrated plasma and adding thrombin. Time to clot formation is measured in seconds. Conditions that prolong the thrombin time include therapy with anticoagulants (including heparin and DTIs), hypofibrinogenemia (<100 mg/dL), the presence of abnormal fibrinogen or fibrinogen degradation products, high concentrations of serum proteins (multiple myeloma, amyloidosis), and circulating bovine thrombus antibodies (after exposure during surgery).

Fibrinogen Level

A number of methods are available for measuring fibrinogen. The most common method uses the Clauss assay, in which diluted plasma is exposed to a high concentration of thrombin. The time to clot formation is compared to a standard calibration curve, and the fibrinogen concentration is deduced. Immunologic fibrinogen assays are used when clotting-based fibrinogen assays suggest reduced fibrinogen for no obvious clinical reason, or when dysfibrinogenemia is suspected.

Activated Clotting Time

The activated clotting time (ACT) measures the time in seconds for formation of a clot after an activating agent (e.g., celite, kaolin) is added to a sample of freshly drawn whole blood. The aPTT has replaced this test in many clinical situations, except in the operating room. In the setting of high heparin concentrations (>1 unit/mL), the aPTT becomes infinitely prolonged; therefore, for procedures that require high heparin doses such as coronary artery bypass surgery or percutaneous coronary interventions (PCIs), the ACT is still used for heparin monitoring.

Tests of Fibrinolysis

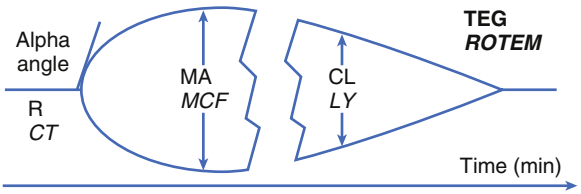
Laboratory analysis of fibrinolysis is difficult because of the complexity of the fibrinolytic system and the interchange between hemostasis and fibrinolysis proteins. Current assays in clinical studies are poor predictors of thrombosis or bleeding. Furthermore, other inflammatory states can increase the concentrations of fibrin degradation products in the absence of fibrinolysis. Global tests of fibrinolysis, including clot lysis time and thromboelastography, have shown promise in the perioperative setting in predicting bleeding and allowing for targeted treatment of fibrinolysis with antifibrinolytics and cryoprecipitate. These global assays allow for fast, real-time analysis of hemostasis, and are especially useful in cases with increased risk of hemorrhage such as trauma (also see Chapter 42), liver transplant (also see Chapter 36), postpartum hemorrhage (also see Chapter 33), cardiac surgery (also see Chapter 25), or multiple blood transfusions (also see Chapter 24).

Fibrin Degradation Products

Elevated levels of different fibrin degradation products result from the action of plasmin on fibrin and fibrinogen during fibrinolysis. D-dimer is formed when plasmin cleaves cross-linked fibrin polymers at the D fragment site and has been used as a marker of fibrinolytic states. Increased D-dimer concentrations have predictive and prognostic value in states of fibrinolysis, such as DIC, and in thrombotic disorders such as pulmonary embolus or DVT. Although an increased D-dimer level is nearly 90% sensitive (in the case of DIC), it is not very specific and therefore is not often used to detect fibrinolysis.

Global Coagulation Assays

There are currently two available semiautomated devices that use viscoelastic measures to analyze time to blood clot formation, maximal clot stability, and resolution of clot due to fibrinolysis (Fig. 22.2). Thromboelastography (TEG) uses fresh whole blood placed in a cup that continuously rotates around a pin. As clot forms, there is increased resistance to rotation of the cup, which is transmitted to the sensor pin and displayed graphically. In rotational thromboelastometry (ROTEM), a similar rotational method and graphic display are used; however, in this case, the cup with fresh whole blood is fixed while the pin rotates. Since the advent of viscoelastic measurements of coagulation in 1948, improvements in technique have led to easier use and the ability to perform point-of-care testing with rapid results. The addition of various trigger reagents provides further information on the extrinsic pathway, levels of fibrinogen, effects or presence of heparin, and resistance to lysis.[9] Although viscoelastic measurements can assess platelet aggregation, these tests do not measure platelet dysfunction (either inherited or drug induced). In addition, they are unable to detect the effects of vWF. Other concerns include difficulty with quality control and the ability to standardize these measurements across different centers. Despite these limitations, TEG and ROTEM clearly can help detect coagulopathy, guide transfusion therapy, and even decrease the need for some blood transfusions (Fig. 22.3) (also see Chapter 24).



Variable	TEG	ROTEM
From start to 2-mm amplitude (clot initiation)	R (reaction time)	CT (clotting time)
From 2-mm to 20-mm amplitude (clot kinetics)	K (kinetics)	CFT (clot formation time)
Alpha angle	Slope between R and K	Angle of tangent at 2-mm amplitude
Maximum strength (clot strength)	MA (maximum amplitude)	MCF (maximum clotting time)
Clot lysis (at minutes)	CL 30, CL 60	LY 30, LY 60

Fig. 22.2 Comparison of common variables for the global coagulation assays TEG (thromboelastography) and ROTEM (rotational thromboelastometry). *CL*, Clot lysis; *LY*, lysis.

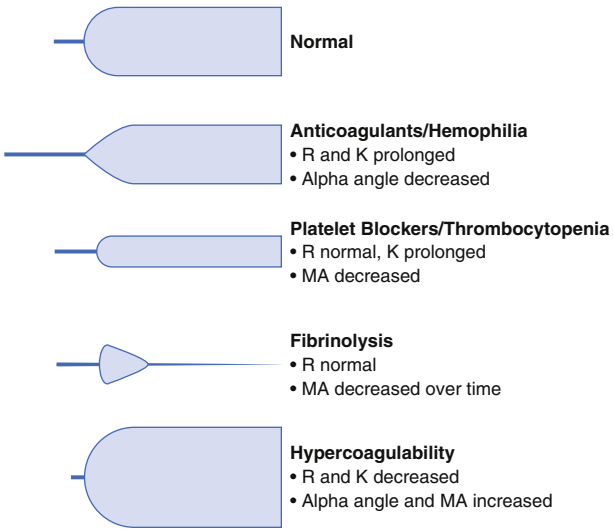


Fig. 22.3 Common thromboelastography examples with analysis. *K*, Kinetics; *MA*, maximum amplitude; *R*, reaction time.

Tests of Platelet Function

Platelet Count

Platelet count is determined as part of the complete blood count and is performed by automated machines that use optical, impedance, or flow cytometry methods. Platelet clumping (that results from minimal platelet activation) and the presence of giant platelets can lead to artificially decreased platelet counts. Conversely, if samples contain cellular debris (thalassemias, leukemias, TTP), the platelet count may be overestimated by some methods.

Bleeding Time

The bleeding time has been used as a screening test for platelet function in the past, however, because of the difficulty in performing an accurate test, it is rarely used in clinical practice today. To perform the test, a blood pressure cuff is inflated on the upper part of the arm to 40 mm Hg and a standardized 9-mm long and 1-mm deep incision is made on the volar surface of the forearm. Blood is blotted away every 30 seconds with filter paper and a prolonged bleeding time (>11 minutes) can signify either platelet dysfunction or platelet count of less than 100,000 cells/μL.

Platelet Aggregation Studies

Platelet aggregation studies are not commonly used in the perioperative setting, but they may be useful in the preoperative evaluation of patients with potential platelet disorders. A platelet agonist (e.g., collagen, ADP, epinephrine, or ristocetin) is added to platelet rich plasma, and then platelet aggregration is measured by decreased light scatter. These studies can help differentiate between inherited disorders of platelet dysfunction (e.g., Glanzmann thrombasthenia, Bernard-Soulier syndrome, vWD) as well as monitor antiplatelet therapy with aspirin or clopidogrel.

Platelet Function Analysis

Platelets within citrated blood are exposed to a membrane coated with collagen and either ADP or epinephrine to initiate adhesion. The test measures the time to instrument aperture occlusion as a result of platelet thrombus. Abnormal closure times indicate platelet dysfunction; however, the result is not specific for any disorder. Because the test is simple, rapid, and does not require special training, it may be useful as a screening tool to assess for platelet dysfunction.

ANTITHROMBOTICS AND PROCOAGULANTS

Antithrombotic drugs are usually used to treat cardiovascular disease, stroke, and DVT or PE. They can be further subdivided into antiplatelet agents, anticoagulants (Table 22.4), and thrombolytics.

Antiplatelet Drugs

Platelets are involved in the formation of pathologic thrombus leading to coronary artery disease. Antiplatelet drugs can be divided into three classes: (1) cyclooxygenase (COX) inhibitors, (2) P2Y12 receptor antagonists, and (3) platelet GPIIb/IIIa antagonists.

Cyclooxygenase Inhibitors

There are two primary COX isozymes: COX-1 and COX-2. COX-1 maintains the integrity of the gastric lining and renal blood flow and initiates the formation of TxA_2, which is important for platelet aggregation. COX-2 is responsible for synthesizing the prostaglandin mediators in pain and inflammation.

Table 22.4 Common Anticoagulants with the Required Monitoring and Possible Reversal Drugs for Emergencies

Anticoagulants	Drug Name	Monitoring	Reversal Agents
Vitamin K antagonists	Warfarin	PT, INR	PCC, FFP, vitamin K
Heparins	Unfractionated heparin (UFH)	aPTT	Protamine
	Low-molecular-weight heparin (LMWH)	None required, but anti-factor Xa assay can monitor levels	Partially reversed by protamine
Pentasaccharide	Fondaparinux	None required, but anti-factor Xa assay can monitor levels	None
Direct thrombin inhibitors	Hirudin, argatroban, bivalirudin	aPTT or ACT	None
	Dabigatran	None required	Idarucizumab, dialysis may remove drug
Factor Xa inhibitors	Rivaroxaban, apixaban	None required	None

ACT, Activated clotting time; *aPTT,* activated partial thromboplastin time; *FFP,* fresh frozen plasma; *INR,* international normalized ratio; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time.

Small doses of aspirin irreversibly inhibit COX-1. Large doses of aspirin irreversibly inhibit both COX-1 and COX-2, which leads to antiinflammatory and analgesic effects. Because platelets have no deoxyribonucleic acid (DNA), they are unable to synthesize new COX-1 once aspirin has irreversibly inhibited the enzyme, which means despite its short half-life (15 to 20 minutes), aspirin works for 7 to 10 days, the expected lifetime of anucleated platelets. The recovery of platelet function after aspirin depends on platelet turnover. Generally, megakaryocytes generate 10% to 12% of platelets daily, so near normal hemostasis is expected in 2 to 3 days after the last dose of aspirin, assuming platelet turnover is normal. Otherwise, immediate reversal can only be achieved with platelet transfusions.

Most NSAIDs are nonselective reversible COX inhibitors (also see Chapters 40 and 44). Platelet function returns to normal 3 days after discontinuing the use of NSAIDs. Selective COX-2 antagonists such as celecoxib were developed to provide pain relief without the gastrointestinal bleeding complications, but recent clinical trials with selective COX-2 antagonists have reported increased risks for cardiovascular complications.[10] COX-2 specific inhibitors do not affect platelet function because platelets do not express COX-2. The increased cardiovascular risk is likely due to inhibition of prostacyclin (PGI_2) without inhibition of TxA_2, thus tipping the balance toward thrombosis. Current recommendations are to use COX-2 inhibitors only when necessary and then with the smallest effective dose possible along with low-dose aspirin.

P2Y12 Receptor Antagonists

These drugs (ticlopidine, clopidogrel, prasugrel, ticagrelor) interfere with platelet function by inhibiting the P2Y12 receptor, which prevents the expression of GPIIb/IIIa on the surface of activated platelets and inhibits platelet adhesion and aggregation. Clopidogrel (Plavix) is the most commonly prescribed drug in this class. Platelet functions normalize 7 days after discontinuing clopidogrel and 14 to 21 days after discontinuing ticlopidine.

Clopidogrel, a noncompetitive and irreversible antagonist, is a prodrug that requires CYP2C19 for activation. It has wide interindividual variability in inhibiting ADP-induced platelet function. Although many factors may be involved, genetic factors deserve consideration. Patients treated with clopidogrel who have decreased CYP2C19 activity were shown to have significantly increased risk of major cardiovascular events. The Food and Drug Administration (FDA) put a black box warning on clopidogrel to make patients and health care providers aware that patients who are CYP2C19-poor metabolizers, which represents up to 14% of patients, are at high risk of treatment failure and that genotype testing may be helpful.

Ticagrelor has much lower interindividual variability because it binds to a separate site on the P2Y12 receptor to inhibit G-protein activation and signaling, and ticagrelor is not a prodrug. Because it is much shorter acting than clopidogrel, ticagrelor must be dosed twice daily.

Glycoprotein IIb/IIIa Antagonists

The GPIIb/IIIa receptor mediates platelet aggregation by binding fibrinogen and vWF. Available drugs that block the receptor are abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat). They are given intravenously in order to (1) stop ongoing arterial thrombosis and (2) eliminate excessive platelet reactivity in diseased vessels so that occlusive thrombi and restenosis do not occur. Abciximab is a noncompetitive irreversible inhibitor of GPIIb/IIIa, whereas eptifibatide and tirofiban are competitive, reversible GPIIb/IIIa antagonists. The inhibition provided by abciximab continues at various levels for several days after the infusion has stopped. Platelet aggregation normalizes 24 to 48 hours after discontinuing abciximab and 8 hours after discontinuing eptifibatide and tirofiban. All of these drugs cause thrombocytopenia, but the effect is strongest with abciximab (incidence of about 2.5%).

Anticoagulants

Vitamin K Antagonists

Warfarin, the most frequently used oral vitamin K antagonist (VKA), disrupts the formation of factors II, VII, IX, and X and proteins C and S. Without vitamin K, these proteins do not undergo carboxylation and therefore cannot actively bind to the phospholipid membrane of platelets during hemostasis (Fig. 22.4).

Warfarin has a long half-life (40 hours), and the complete anticoagulant effects take 48 to 72 hours to develop after administration because of the half-lives of the preexisting coagulation factors. Prothrombin (factor II) has the longest half-life (~60 hours). Factor VII and protein C have the shortest half-lives (3 to 6

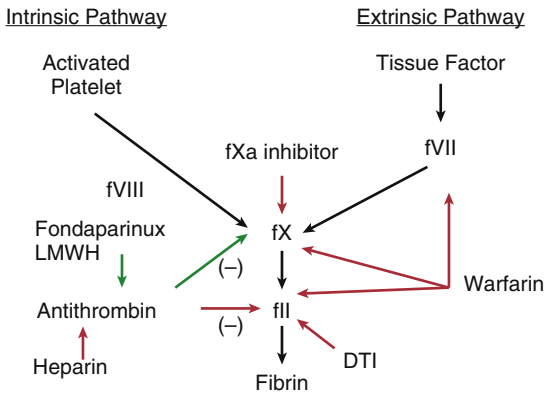


Fig. 22.4 Sites of action for common anticoagulants. *DTI*, Direct thrombin inhibitor; *f*, factor; *LMWH*, low-molecular-weight heparin.

hours). Early reductions in the anticoagulant protein C can cause an imbalance toward a hypercoagulable state during the initiation of warfarin therapy, resulting in thrombosis or warfarin-induced skin necrosis. Patients at high risk for thromboembolism must be bridged with another anticoagulant (usually heparin) until the target INR is achieved.

The therapeutic range for warfarin anticoagulation is generally an INR of 2.0 to 3.0, except for patients with mechanical heart valves, in whom higher values are necessary (INR 2.5 to 3.5). The INR is not calibrated to evaluate coagulation deficiencies in liver disease and should not be used to evaluate therapeutic effects of other anticoagulants. Warfarin is difficult to manage because of a very narrow therapeutic window. Drugs, foods, and alcohol can profoundly alter the pharmacokinetic profile of warfarin, making frequent laboratory monitoring a necessity. Warfarin is contraindicated in pregnancy because fetal exposure can lead to embryopathy.

Warfarin's pharmacology is also affected by genetic variations in the metabolism of the drug (cytochrome P450, CYP2C9). Pharmacogenetic testing for polymorphisms that affect the metabolism of warfarin may be considered when there is difficulty achieving a target INR.

Unfractionated Heparin

UFH indirectly inhibits thrombin and factor Xa by binding to AT (see Fig. 22.1). Heparin therapy is monitored with the aPTT or ACT. Benefits of heparin are its short half-life and ability to be fully reversed with protamine, a positively charged protein isolated from salmon. Patients may be resistant to UFH if they have hereditary insufficiency of AT or an acquired deficiency of AT from prolonged heparin administration. Treatment should be with FFP transfusions, which will replenish AT levels.

Full-dose heparin for cardiac surgery is administered as an intravenous bolus of 300 to 400 U/kg. An ACT greater than 400 seconds is usually considered safe for initiation of cardiopulmonary bypass. One mg protamine to 100 units of heparin is the reversal dose used at the conclusion of cardiopulmonary bypass.

The main complication of heparin, aside from bleeding risk, is HIT. UFH and to a lesser degree LMWH can stimulate the production of antibodies against the heparin–platelet factor 4 (PF4) complex. HIT is the most feared nonhemorrhagic complication of heparin and has a mortality rate of 20% to 30%. These antibodies can activate platelets to induce thrombosis and cause HIT. HIT should be suspected if the platelet count decreases to less than 100,000 cells/μL or less than 50% of baseline 5 to 10 days after the initiation of heparin therapy. If thrombocytopenia or thrombosis develops in a patient on heparin, HIT antibodies testing should be undertaken to confirm the diagnosis. The enzyme-linked immunosorbent assay (ELISA) is sensitive but not as specific as the serotonin release assay, which is currently the gold standard. Patients with suspected HIT must be started on an alternate anticoagulant (not UFH or LMWH) immediately, while test results are pending. The most commonly used agents are the parenteral DTIs such as bivalirudin, argatroban, and lepirudin. Warfarin is contraindicated for HIT treatment because the initial decreased synthesis of proteins C and S enhances the patient's prothrombotic state. Platelet transfusions should also be held unless the patient is severely thrombocytopenic (<20,000 cells/μL) with signs of bleeding.

A difficult decision about anticoagulation arises when patients with a history of HIT require cardiopulmonary bypass. If time allows, antibody titers to heparin–PF4 complex should be measured. If titers are low, then a single dose of heparin can be considered for cardiac bypass. Otherwise, bivalirudin, the shortest acting DTI, is the alternative agent for anticoagulation while on bypass. Presurgical treatment with plasmapheresis for rapid antibody clearance is an alternative plan, but risks and benefits should be discussed with a hematologist.

Low-Molecular-Weight Heparin and Fondaparinux

LMWH, produced by cleaving heparin into shorter fragments, and fondaparinux, a synthetic pentasaccharide, act more specifically to inhibit factor Xa via AT. LMWH and fondaparinux do not affect the aPTT assay, and coagulation testing is usually not needed. However, if necessary, the drugs' plasma activity levels can be assessed with factor Xa levels. This may be helpful in patients with renal failure, which affects drug excretion, or in pregnant women, obese patients, and neonates for whom drug levels are less certain after subcutaneous injection. LMWH and fondaparinux have longer half-lives than heparin and can be administered subcutaneously either once or twice daily. Protamine is only partially effective in reversing LMWH and not effective for fondaparinux. LMWH is contraindicated in HIT. Although the incidence of HIT is relatively rare for fondaparinux, cases have been reported, and it is not approved for use in HIT.

Direct Thrombin Inhibitors

All DTIs inhibit thrombin in its free and fibrin-bound states, unlike heparin, which only has an effect on free thrombin. Clinical effects can be monitored with aPTT or ACT in the operating room. Hirudin is a naturally occurring anticoagulant found in leeches. Lepirudin is recombinant hirudin derived from yeast cells, whereas argatroban and bivalirudin are synthetic agents. Argatroban, which has a half-life of 45 minutes, is the preferred DTI in patients with renal insufficiency because it is hepatically eliminated. Bivalirudin is a reversible DTI and is metabolized by plasma proteases and renally excreted.

It has the shortest half-life and is the drug of choice for patients with both renal and hepatic dysfunction. There are no antidotes for any of the DTIs, so reversal depends upon their clearance. All DTIs will interfere with the INR, but argatroban will prolong the INR the most, which can complicate transition to warfarin therapy for long-term anticoagulation.

New Oral Anticoagulants

During the past few years, several direct oral anticoagulants (DOACs) have been introduced into the market. These new drugs have more predictable pharmacokinetics and pharmacodynamics and fewer interactions with foods and other drugs. The predictability allows for fixed daily dosing without the need for monitoring, but the drawback is the lack of specific antidotes for anticoagulation reversal and a paucity of evidence to guide placement of neuraxial/peripheral blocks (also see Chapter 40).

The DOACs have a shorter half-life than warfarin and have demonstrated noninferior efficacy to warfarin. A meta-analysis of phase II and phase III randomized clinical trials comparing DOACs with VKAs in patients with atrial fibrillation showed that use of DOACs was associated with a significant reduction in major bleeding (relative risk [RR] 0.86, 95% confidence interval [CI] 0.72-1.02) and significantly decreased the risk of intracranial hemorrhage (RR 0.46, 95% CI 0.39 to 0.56).[11] Comparison of apixaban, a factor Xa inhibitor, versus warfarin in patients with atrial fibrillation showed a reduction of stroke along with a significant reduction in major bleeding.[12]

Dabigatran (Pradaxa), an oral DTI, is approved for the prevention of ischemic stroke in patients with nonvalvular atrial fibrillation and the treatment of VTE. Direct factor Xa inhibitors, rivaroxaban (Xarelto) and apixaban (Eliquis), are new drugs whose activity is directed against the active site of factor Xa. These drugs are approved for use in DVT/PE prophylaxis, stroke prophylaxis in patients with atrial fibrillation, and VTE treatment.

Although monitoring is not routine, it would be useful in patients presenting with relatively high or low body weight, renal insufficiency (dabigatran), patients taking other medications that alter P-glycoprotein and cytochrome P450 metabolism, overdoses, life-threatening bleeding, or need for emergent surgery. The perfect laboratory test would be the dilute thrombin time or ecarin clotting time for DTI and an anti–factor Xa assay calibrated for the specific direct factor Xa inhibitor; however, these tests are currently not widely available.

There are limited data regarding the use of these new anticoagulants with regional anesthesia, which includes neuraxial techniques. Most recommendations are based exclusively on the pharmacokinetics and pharmacodynamics of these drugs.[13]

In the event of an emergency, antidotes are becoming available. Idarucizumab, a specific antidote for dabigatran, is a humanized antibody fragment that binds to dabigatran with an affinity 350 times greater than thrombin. Andexanet alfa, a recombinant factor Xa, was developed to reverse the factor Xa inhibitors. Lastly, ciraparantag (PER977), a small, synthetic, water-soluble, cationic molecule, binds and neutralizes UFH, LMWH, fondaparinux, dabigatran, and the new factor Xa inhibitors through hydrogen bonding and charge-charge interactions. Idarucizumab has been approved by the FDA whereas andexanet alfa and ciraparantag are still undergoing clinical trials.

Because dabigatran and rivaroxiban/apixaban are competitive inhibitors of thrombin and factor Xa, respectively, in theory, it would make physiologic sense to attempt reversal with a PCC, but randomized controlled in vivo studies are lacking. There are some case reports that hemodialysis can eliminate dabigatran. Further research is needed to document the best method for reversing the clinical effects of these NOACs. Fortunately, their half-lives are relatively short, so time and supportive medical care are often enough to manage the acute clinical situation.

Thrombolytics

Thrombolytic therapy is used to break up or dissolve blood clots during acute myocardial infarctions (within 12 hours), strokes (within 3 hours), or massive pulmonary embolus. Thrombolysis may be given through an intravenous line systemically or directly to the site of the blockage. Most thrombolytic agents are serine proteases that work by converting plasminogen to plasmin, which then lyses the clot by breaking down fibrinogen and fibrin.

Fibrinolytic drugs are divided into two categories: (1) fibrin-specific drugs and (2) non–fibrin-specific drugs. Recombinant tPAs (e.g., alteplase, reteplase, and tenecteplase) are fibrin-specific drugs that theoretically produce less plasminogen conversion in the absence of fibrin. Non–fibrin-specific drugs (e.g., streptokinase) catalyze systemic fibrinolysis. Streptokinase, produced by β-hemolytic streptococci, is highly antigenic and can cause immunologic sensitization and allergic reactions, particularly with repeat administration. Streptokinase is not widely used in the United States but is still used elsewhere because of its lower cost.

tPAs are both thrombolytics and anticoagulants because fibrinolysis generates increased amounts of circulating fibrin degradation products, which inhibit platelet aggregation by binding to platelet surfaces. Surgery or puncture of noncompressible vessels is contraindicated within a 10-day period after the use of thrombolytic drugs.

Procoagulants

There are really only two main causes of perioperative bleeding. The first and most common is surgical bleeding,

which will not be discussed here (see Chapter 24). The second is nonsurgical bleeding, or failure of the hemostatic pathways. Causes for this failure include massive blood transfusion (leading to thrombocytopenia, low fibrinogen, and coagulopathy) (also see Chapter 24), fibrinolysis (induced by the surgical procedure such as prostatectomy, orthotopic liver transplant [also see Chapter 36], or exposure to a foreign graft material), DIC (from sepsis, cardiopulmonary bypass [also see Chapter 25]), or transfusion reactions [also see Chapter 24]), an undetected preexisting bleeding disorder, or a combination of the foregoing possibilities.

The mainstays of massive blood loss management include replacement of red blood cells, platelets, clotting factors, and fibrinogen. The patient needs to be kept warm and frequent laboratory reports are necessary to help guide transfusions and electrolyte replacements. A basic laboratory profile in the operating room should include hematocrit, platelet count, PT, aPTT, and fibrinogen level. Although blood products and transfusion thresholds are discussed separately in Chapter 24, some other procoagulants exist that could be helpful to the anesthesia provider when the patient is bleeding at a rapid rate.

Antifibrinolytics

There are two types of antifibrinolytics: (1) the lysine analogs, EACA and TXA, and (2) a serine protease inhibitor, aprotinin. Aprotinin was removed from the U.S. market and is now only available in Europe and Canada. The lysine analogs work by competitively inhibiting the binding site on plasminogen and preventing its cleavage to plasmin. TXA and EACA likely have equivalent efficacy and decrease perioperative blood loss in cardiac surgery, liver transplantation, and orthopedic surgery.

In trauma patients (also see Chapter 42), TXA administration may reduce mortality rate (14.5% vs. 16%, $p = 0.0035$), including the risk of death due to bleeding (4.9% vs. 5.8%, $p = 0.0077$), without an increase in fatal or nonfatal vascular occlusive events.[14] Early treatment (≤1 hour) after traumatic injury significantly reduced the risk of death due to bleeding events in the tranexamic acid group (5.3%) versus placebo group (7.7%). Overall, the lysine analogs (TXA and EACA) likely should be considered for use in major surgery or critical bleeding.

Recombinant Factor VIIa

rFVIIa increases the generation of thrombin (factor II), which enhances hemostasis. The drug was originally FDA approved for use in hemophiliac patients. It works by having an effect on both pathways of the coagulation system. In the TF dependent or extrinsic system, rFVIIa binds to TF at the site of vessel injury, causing activation of factor X. In the TF independent or intrinsic system, rFVIIa binds to the surface of the activated platelet, activating factor X. Both mechanisms result in a "burst" of thrombin and fibrin generation, which leads to clot formation. The half-life of rFVIIa is only 2 to 2.5 hours, so the initial dose may require repeating until the bleeding is controlled.

rFVIIa has generated a great deal of interest because of its ability to enhance hemostasis in patients with severe bleeding. The off-label uses of rFVIIa have been quite varied and include intracranial hemorrhage, cardiac surgery, trauma, traumatic brain injury, and liver transplantation. If all trials are analyzed together, there is a slight reduction in the number of patients who need packed red blood cell transfusions, but there is no evidence that the use of rFVIIa changed overall survival rate.

Because of concern for arterial and venous thrombosis, prophylactic use of rFVIIa is questionable. Considering that no randomized controlled trial has been able to demonstrate a significant benefit in terms of intensive care unit (ICU) stay, hospital stay, or mortality rate, each clinician will have to weigh the risk of thromboembolic events against the benefit of clotting for the individual patient.

Prothrombin Complex Concentrate

PCCs are commercially available formulations containing varying amounts of coagulation factors (factors II, VII, IX, and X) as well as one or more types of anticoagulants (protein C or S). Three-factor PCCs differ from four-factor PCCs in that they do not contain significant amounts of factor VII. Most of the factors are administered in the inactive state, which is supposed to decrease the thrombogenic risks. PCCs are now the drug of choice for emergent reversal of VKAs in place of rFVIIa or FFP. Although PCCs are derived from human plasma, they are treated with at least one viral reduction process, which reduces the risk for infectious and noninfectious transfusion reactions.

PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION

The perioperative management of patients who require chronic anticoagulation or antiplatelet therapy involves two major risk determinations: (1) the risk of a thrombotic complication for that patient and (2) the risk of a major bleeding complication from the procedure being performed. A multidisciplinary team should evaluate patients a few weeks prior to elective surgery to perform these necessary risk assessments and make management decisions regarding continuation, stoppage, and reinstitution of anticoagulation or antiplatelet therapy.

For those patients taking VKAs, the current recommendation is to stop VKAs 5 days prior to surgery for

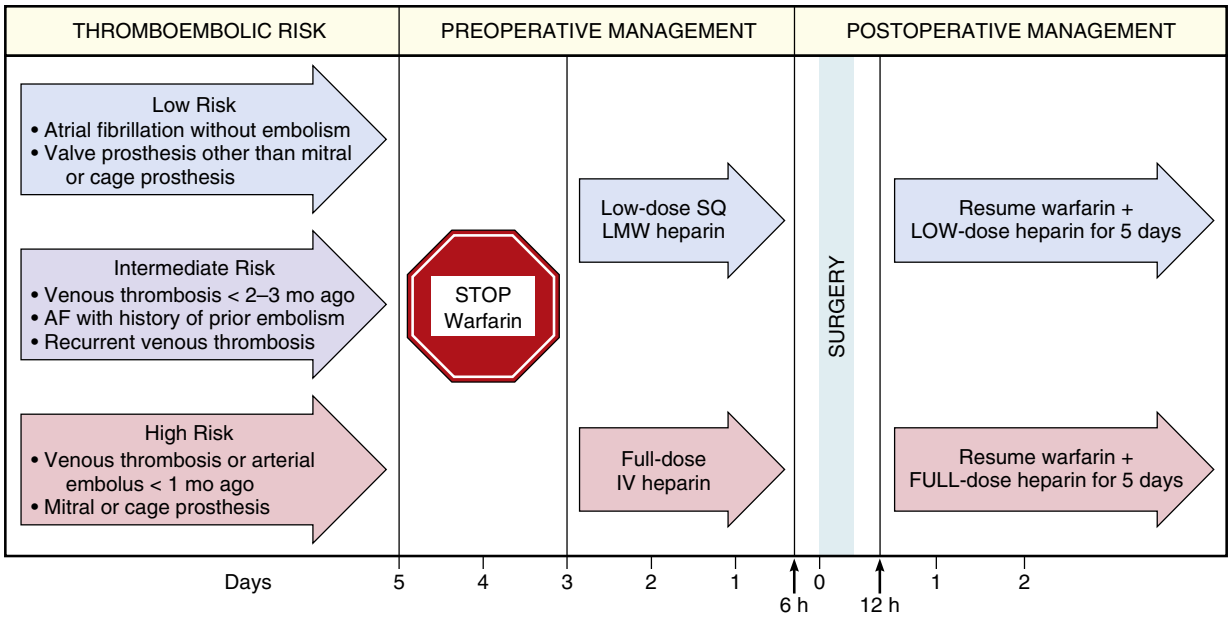


Fig. 22.5 Perioperative management of an anticoagulated patient. *AF,* Atrial fibrillation; *IV,* intravenous; *LMW,* low-molecular-weight; *SQ,* subcutaneous. (From Stratmann G. Hemostasis. In Miller RD, Pardo MC, eds. *Basics of Anesthesia.* 6th ed. Philadelphia: Elsevier; 2011.)

those patients who are at low risk for perioperative VTE. VKAs should be restarted 12 to 24 hours postoperatively. For patients at high risk of VTE, the current recommendation is bridging with heparin or LMWH after discontinuation of VKAs prior to surgery. No clear evidence exists for patients who are at moderate risk for VTE with regard to discontinuation of VKAs and bridging, so the approach chosen is based on the individual patient and surgical risk factors. For those patients receiving bridging therapy with UFH, the infusion should be stopped 4 to 6 hours prior to surgery and resumed without a bolus dose no sooner than 12 hours postoperatively. In surgeries with increased postoperative bleeding risk, resumption of UFH should be delayed 48 to 72 hours. In patients receiving bridging therapy with LMWH, the last dose of LMWH should be administered 24 hours prior to surgery and dosing should be resumed 24 hours postoperatively (or delayed until 48 to 72 hours postoperatively for surgeries with high bleeding risk)[15] (Fig. 22.5).

For patients receiving antiplatelet therapy, risk assessment is based on the patient's risk of a perioperative cardiovascular event, whether the surgery is a minor procedure, noncardiac major procedure, or cardiac procedure, and the timing and type of stent placement for those patients who have undergone recent PCI. Many studies have examined management of aspirin therapy perioperatively, but there are fewer data for management of clopidogrel in the perioperative setting. For patients undergoing minor procedures who are receiving acetylsalicylic acid (ASA) or aspirin for the secondary prevention of cardiovascular events, ASA should be continued throughout the perioperative period. In addition, patients who are at high or moderate risk for cardiovascular events, as well as those undergoing cardiac or vascular surgery, should continue ASA throughout the perioperative period. Patients who are at low risk for cardiovascular events and who are undergoing noncardiac surgery should discontinue ASA therapy 7 to 10 days prior to surgery. Patients on dual antiplatelet therapy (ASA and clopidogrel) should discontinue clopidogrel 5 days prior to cardiac or noncardiac surgery.

Lastly, for patients who have undergone recent PCI with coronary stent placement, surgery should be delayed for at least 6 weeks after placement of a bare-metal stent (BMS) and for at least 6 months after placement of a drug-eluting stent (DES). If surgery is required before this time has passed, dual antiplatelet therapy should be continued unless the risk of bleeding outweighs the risk of stent thrombosis.

In addition to surgical bleeding risk assessment, many patients who are receiving anticoagulant or antiplatelet therapy can potentially benefit from neuraxial

Table 22.5 University of California San Francisco Guidelines for the Use of Antithrombotic Drugs in the Setting of Neuraxial Procedures

Anticoagulant	Minimum Time Between the Last Dose and When Neuraxial Catheter Can Occur	Minimum Time After Catheter Placement to Drug Start	Minimum Time Between Last Dose and Catheter Removal	Minimum Time Between Neuraxial Catheter Removal and When Next Dose Can Be Given
NSAIDs/ASA	No restrictions for catheter placement or removal			
Heparin SQ bid	No restrictions for catheter placement or removal			
Heparin SQ tid	4 hours	2 hours	4 hours	2 hours
Lovenox qd	12 hours	6 hours	12 hours	4 hours
Clopidogrel	7 days	Contraindicated while catheter in place		2 hours
Ticlodipine	14 days	Contraindicated while catheter in place		2 hours
Dabigatran	5 days	Contraindicated while catheter in place		6 hours
Rivaroxaban	3 days	Contraindicated while catheter in place		6 hours
Apixaban	3 days	Contraindicated while catheter in place		6 hours
Abciximab	48 hours	Contraindicated while catheter in place		2 hours
Eptifibatide	8 hours	Contraindicated while catheter in place		2 hours
Alteplase	10 days	Contraindicated while catheter in place		10 days

ASA, Acetylsalicylic acid; *bid*, twice a day; *NSAIDs*, nonsteroidal antiinflammatory drugs; *qd*, every day; *SQ*, subcutaneous; *tid*, three times a day.

anesthesia procedures. Given the abundance of different antithrombotic medications being used in the perioperative setting to treat thrombosis and prevent postoperative thrombotic events, anesthesia providers must be aware of the risks of bleeding and neurologic injury associated with each therapy. These guidelines and recommendations will continue to be updated as evidence emerges on the bleeding risk and pharmacologic profiles of the newer anticoagulants. In the absence of concrete data, many hospital committees are setting local practice guidelines (Table 22.5).

Management of perioperative anticoagulation is becoming increasingly more complex with the advent of the DOACs and the number of patients who are now receiving chronic anticoagulation. Continued research on thromboembolic events and bleeding risk in the setting of these novel therapies is needed before official recommendations can be made regarding management. Early preoperative assessment of patients receiving anticoagulation and a multidisciplinary team approach between the patient, primary care physician, surgeon, anesthesia provider, and hematologist is essential to ensure the perioperative safety of these patients.

QUESTIONS OF THE DAY

1. What are the steps in the coagulation cascade after the initial formation of a platelet plug at the site of vascular endothelial injury?
2. Which regulatory molecules facilitate termination of the coagulation cascade?
3. A patient presents with a history of von Willebrand disease (vWD). What are the different types of vWD?
4. What are the two most common hereditary hypercoagulable states? What is the mechanism of the prothrombotic state in each?
5. What are the clinical manifestations of heparin-induced thrombocytopenia (HIT)? What diagnostic tests can be used to confirm the diagnosis? If a patient with HIT requires ongoing anticoagulation, what medications can be used as an alternative?
6. A patient develops diffuse bleeding during surgery. How can thromboelastography be used to assess coagulation status?
7. What coagulation factors are present in prothrombin complex concentrate (PCC)? What are the indications for administration of this concentrate?

REFERENCES

1. Stalker TJ, Welsh JD, Brass LF. Shaping the platelet response to vascular injury. *Curr Opin Hematol*. 2014;21(5):410–417.
2. Berndt MC, Metharom P, Andrews RK. Primary haemostasis: newer insights. *Haemophilia*. 2014;20(suppl 4):15–22.
3. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev*. 2015;29(1):17–24.
4. Mensah PK, Gooding R. Surgery in patients with inherited bleeding disorders. *Anaesthesia*. 2015;70(suppl 1):112–120. e39–e40.
5. Kempton CL, Meeks SL. Toward optimal therapy for inhibitors in hemophilia. *Blood*. 2014;124(23):3365–3372.
6. Lim W. Antiphospholipid syndrome. *Hematology Am Soc Hematol Educ Program*. 2013;2013:675–680.
7. Venugopal A. Disseminated intravascular coagulation. *Indian J Anaesth*. 2014;58(5):603–608.
8. De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. A review of the Guidelines from Scientific Societies and Working Groups. *Thromb Haemost*. 2013;110(4):697–705.
9. Lancé MD. A general review of major global coagulation assays: thrombelastography, thrombin generation test and clot waveform analysis. *Thromb J*. 2015;13:1–6.
10. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382:769–779.
11. Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation*. 2012;126:2381–2391.
12. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
13. Horlocker T, Wedel D, Rowlingson J, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (third edition). *Reg Anesth Pain Med*. 2010;35:64–101.
14. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH2): a randomized, placebo controlled trial. *Lancet*. 2010;376(9734):23–32.
15. Douketis JD, Spyropoulos AC, Spencer FA, et al. American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2): e326S–e350S.