Chapter 38: Venous Thromboembolism

Daniel M. Witt; Nathan P. Clark; Sara R. Vazquez

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 14, Venous Thromboembolism.

KEY CONCEPTS

KEY CONCEPTS

1. Venous thromboembolism (VTE) is often associated with identifiable risk factors.
2. The diagnosis of suspected VTE should be confirmed by objective testing.
3. During hospitalization, patients should receive VTE prophylaxis based on the VTE risk factors present and the anticipated duration of risk.
4. Initial VTE treatment should include a rapid-acting anticoagulant.
5. For VTE treatment, injectable anticoagulants should be overlapped with warfarin for at least 5 days and until the patient's international normalized ratio is ≥2.0 for at least 24 hours.
6. Direct oral anticoagulants (DOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban are significant advancements in VTE prevention and treatment.
7. Most patients with uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) can be safely treated as outpatients.
8. Most patients with VTE should receive 3 months of anticoagulation therapy; treatment beyond 3 months should be based on the risk of VTE recurrence and bleeding as well as patient preferences.
9. Optimal anticoagulant therapy management requires knowledge of pharmacologic and pharmacokinetic characteristics as well as a systematic management approach with ongoing patient education.

BEYOND THE BOOK

BEYOND THE BOOK

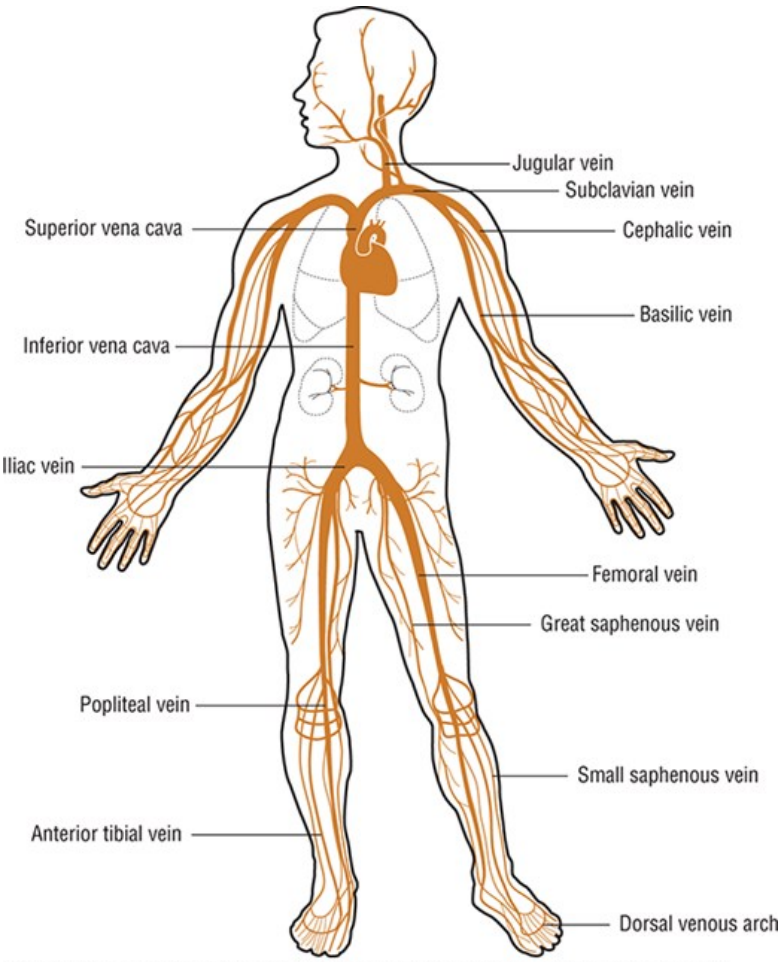
Visit the **National Blood Clot Alliance: Stop The Clot** website and read the stories of at least five different patients (https://www.stoptheclot.org/patient-stories/). These stories are useful to enhance student understanding regarding the impact of VTE and its treatment on the lives of patients and their families.

INTRODUCTION

Venous thromboembolism (VTE) is a potentially fatal disorder and a significant health problem in our aging society.[1] VTE results from clot formation within the venous circulation and manifests as deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (Fig. 38-1).[1] DVT is rarely fatal, but PE can result in death within minutes of symptom onset before effective treatment can be given. Late VTE complications, such as the postthrombotic syndrome and chronic thromboembolic pulmonary hypertension (CTPH), also cause substantial morbidity.[1] Identifying VTE risk factors is important for targeting patients at high risk for VTE who would most benefit from VTE prevention strategies.[2,3]

FIGURE 38-1

Venous circulation.



Rapid and accurate diagnosis is critical to making appropriate treatment decisions when VTE is suspected.[4] Optimal prevention and treatment of VTE using anticoagulant drugs requires an in-depth knowledge of their pharmacology and pharmacokinetic properties, and a comprehensive approach to patient management.[5] Bleeding is a common and serious complication of anticoagulant therapy.[5]

EPIDEMIOLOGY

VTE is associated with a significant global disease burden.[6] The incidence rate of symptomatic first VTE is estimated at 132 per 100,000 patient-years and occurs more frequently in women (55.6%).[7] When standardized by age, Asian patients appear to have the lowest VTE incidence (122 per 100,000

patient-years) followed by White (191) and Black (203) patients.[7] Recurrent VTE rates are highest in the 180 days following the initial event and decline slowly over the next 4 to 10 years. In the absence of secondary prevention, the 10-year cumulative recurrent VTE risk is approximately 25.0%.[7]

ETIOLOGY

1 A number of identifiable factors increase VTE risk (Table 38-1). Many risk factors fall into categories constituting what is known as Virchow's triad: blood stasis, vascular injury, and hypercoagulability.

TABLE 38-1

Risk Factors for VTE

Risk Factor	Comments/Examples
Age	Incidence of VTE in adults age 75 and older is seven to ten times higher than adults younger than 55 years, with risk increasing even more over age 85
Prior VTE History	Potent risk factor for recurrence; risk is highest during the first 180 days after VTE
Blood stasis	• Acute medical illness requiring hospitalization • Surgery (especially general anesthesia >30 minutes) • Paralysis (eg, status post-stroke, spinal cord injury) • Immobility (eg, plaster casts, status post-stroke, or spinal cord injury) • Polycythemia vera • Obesity
Vascular injury	• Major orthopedic surgery (eg, knee or hip replacement) • Trauma (especially fractures of the pelvis, hip, or leg) • Indwelling venous catheters

Hypercoagulability	• Malignancy
	• Factor V Leiden (homozygous >>heterozygous)
	• Prothrombin (G20210A) gene mutation
	• Protein C deficiency
	• Protein S deficiency
	• Antithrombin deficiency
	• Factor VIII excess (>90th percentile)
	• Factor XI excess (>90th percentile)
	• Antiphospholipid antibodies
	  ◦ Lupus anticoagulant
	  ◦ Anticardiolipin antibodies (IgG and/or IgM >99th percentile)
	  ◦ Anti–β_2-glycoprotein I antibodies (IgG and/or IgM >99th percentile)
	• Inflammatory bowel disease
	• Nephrotic syndrome
	• Paroxysmal nocturnal hemoglobinuria
	• Pregnancy or up to 6 weeks postpartum
	• Drug therapy (eg, estrogen-containing contraceptives, estrogen replacement therapy, tamoxifen, raloxifene, cancer therapy, heparin-induced thrombocytopenia)

Data from References 2, 3, and 8-10.

Blood Stasis

Blood stasis favors clotting in part through concentrating the elements responsible for blood clot formation.[11] Contraction of the calf and thigh

muscles coupled with one-way valves in leg veins facilitate blood flow back to the heart and lungs. Thus, damage to venous valves and prolonged immobility result in venous stasis, which partly explains why numerous medical conditions and surgical procedures are associated with increased VTE risk (Table 38-1).[12]

Vascular Injury

An intact vascular endothelium separates flowing blood from subendothelial vessel wall components responsible for preventing blood loss through clot formation (see detailed description in section "Pathophysiology"). Vascular injury (eg, surgery, trauma) disrupts this protective barrier initiating blood clot formation.[13]

Hypercoagulability

Several inherited and acquired disorders as well as drugs have been linked to blood hypercoagulability (Table 38-1). Estrogen-containing contraception, estrogen replacement therapy, and selective estrogen receptor modulators are all linked to VTE risk.[8] Women with inherited hypercoagulability disorders are at particularly high risk of developing VTE during pregnancy and while taking estrogen.[8]

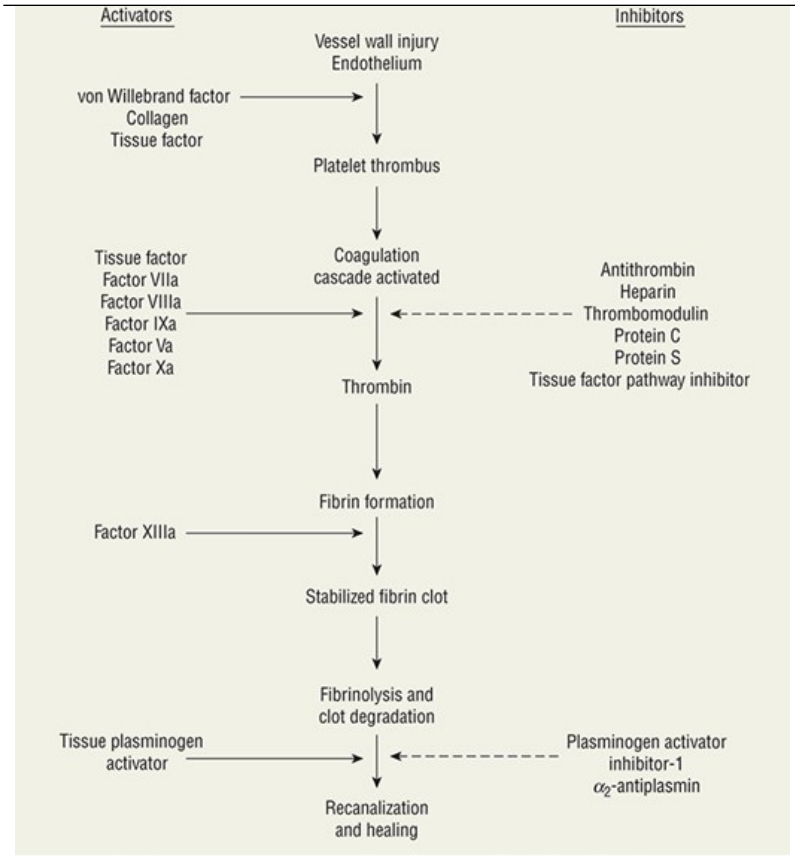
In many cases, VTE results from combinations of inherited and acquired thrombotic risk factors. Thus, an individual with inherited hypercoagulability may experience VTE only after being placed in high-risk situations such as surgery, immobilization, the use of estrogen-containing oral contraceptives, or pregnancy. Approximately a third of VTEs are provoked by identifiable risk factors.[7]

PATHOPHYSIOLOGY

Hemostasis is the process responsible for maintaining circulatory system integrity following blood vessel damage (Fig. 38-2).[13] Hemostatic clots are formed rapidly and remain localized to the vessel wall without significantly impairing blood flow. In contrast, pathologic clots like those causing VTE form slowly, impair blood flow, and often cause complete vessel occlusion.[13]

FIGURE 38-2

Overview of hemostasis.

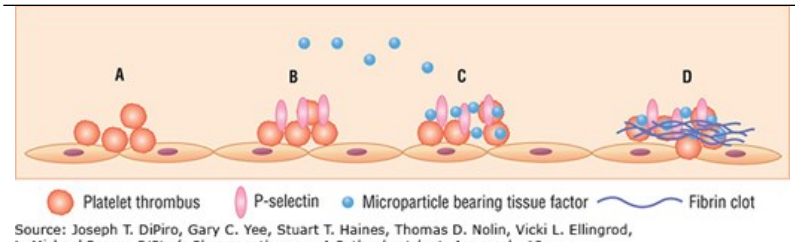


Collagen and tissue factor (TF) form a subendothelial hemostatic barrier around blood vessels and organs. Under normal circumstances, endothelial cells lining the vessel wall physically separate collagen and TF from circulating platelets and clotting factors (namely, activated factor VII [VIIa]). Vessel injury results in platelet activation and TF-mediated clotting factor cascade initiation that culminates in thrombin formation. Ultimately, a fibrin clot forms and seals the breach (Fig. 38-2).[13] In contrast to physiologic hemostasis, pathologic VTE often occurs without gross vessel wall damage and may be triggered by TF brought to the growing thrombus by circulating microparticles. Venous clots are mainly composed of fibrin, platelets, and trapped red blood cells and often occur in areas of disturbed blood flow, like deep leg vein valve cusps.[13]

Platelet and coagulation cascade activation occur nearly simultaneously. Platelets become actively involved in thrombus formation after binding to adhesion proteins like von Willebrand factor and collagen when blood is exposed to damaged vessel endothelium.[13] A platelet thrombus grows as activated platelets recruit and activate additional platelets. Activated platelets change shape and release components critical for sustaining further thrombus formation into the environment surrounding the developing clot.[13] Activated platelets accumulating in the thrombus also express P-selectin, an adhesion molecule that facilitates the capture of blood-borne TF bearing microparticles resulting in fibrin clot formation via the coagulation cascade (Fig. 38-3).[13] Activated platelets provide phospholipid-rich surfaces necessary for coagulation cascade reactions.[13]

FIGURE 38-3

Model of pathologic thrombus formation: (A) activated platelets adhere to vascular endothelium; (B) activated platelets express P-selectin; (C) pathologic microparticles express active tissue factor and are present at a high concentration in the circulation—these microparticles accumulate, perhaps by binding to activated platelets expressing P-selectin; (D) tissue factor can lead to thrombin and fibrin generation. *(Adapted from De Caterina R, et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;109:569–579.)*



The conceptual coagulation cascade model has evolved from the classic depiction of extrinsic, intrinsic, and common pathways (Fig. 38-4) to one in which highly regulated reactions take place on cell surfaces in three overlapping phases: initiation, amplification, and propagation. The cascade starts on TF-bearing cells and continues on the surfaces of activated platelets (Fig. 38-5).[13]

FIGURE 38-4

Classic depiction of the coagulation cascade. (HMK, high-molecular-weight kininogen; PK, prekallikrein.)

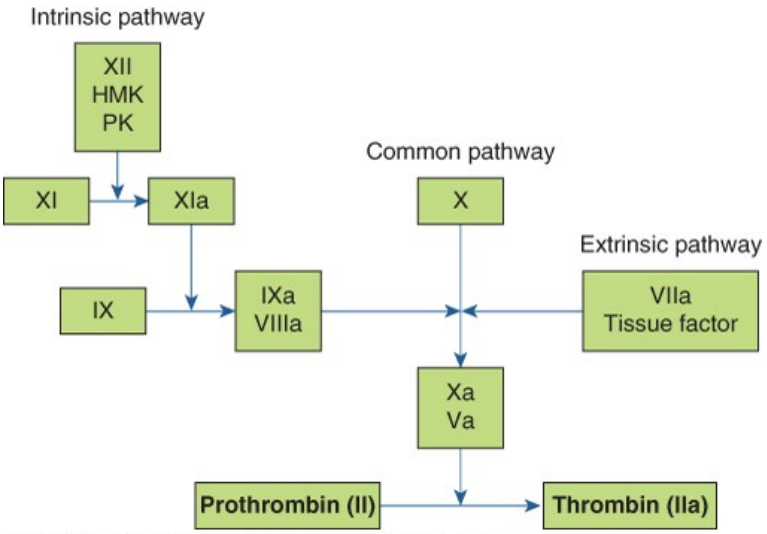
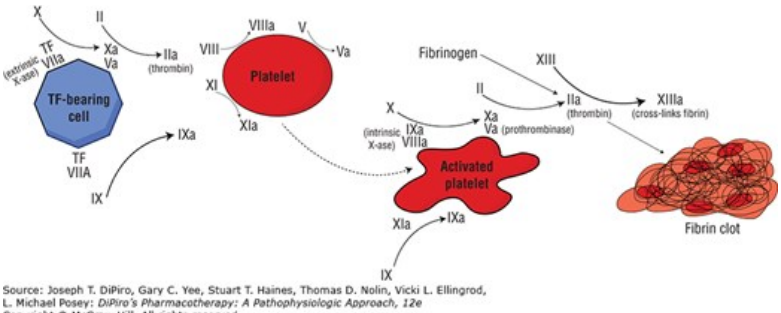


FIGURE 38-5

Cellular coagulation cascade model. *(Adapted from De Caterina R, et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;109:569-579.)*



The initiation phase takes place on TF-bearing cells exposed after vessel injury or captured via P-selectin (Fig. 38-3). The TF/VIIa complex (known as extrinsic tenase) activates limited amounts of factors IX and X. Factor Xa then associates with factor Va to form the prothrombinase complex, which cleaves prothrombin (factor II) to generate a small (picomolar) amount of thrombin (factor IIa) which activates factors V, VIII, and XI on platelet surfaces

(Fig. 38-5). Factor IXa moves from TF-bearing cells to the surface of activated platelets in the growing platelet thrombus. Tissue factor pathway inhibitor (TFPI), an important regulator of TF/FVIIa-induced coagulation, rapidly terminates the initiation phase.[13]

The propagation phase is characterized by a burst of thrombin generation as VIIIa/IXa (known as "intrinsic tenase") promotes factor Xa formation and prothrombinase complexes assemble on the surface of activated platelets accelerating thrombin generation. Thrombin generation is further supported by factor XIa bound to the platelet surface, which activates factor IX to form an additional intrinsic tenase.[13]

Thrombin generated during the propagation phase converts fibrinogen to fibrin monomers that precipitate and polymerize to form fibrin strands. Factor XIIIa, which is also activated by thrombin, covalently bonds these strands together (Fig. 38-5) to form an extensive meshwork that surrounds and encases the aggregating platelet thrombus and red blood cells to form a stabilized fibrin clot.[13] Clot formation eventually terminates when the expanding meshwork of platelets and fibrin "paves over" the initiation site preventing activated factors from diffusing through the overlying clot layer.

A number of tempering mechanisms control coagulation (Fig. 38-2). Without effective self-regulation, thrombus formation results in vascular occlusion. Intact endothelium adjacent to the growing thrombus actively produces several antithrombotic substances.[11] Thrombomodulin modulates thrombin activity by converting protein C to its active form (aPC). With its cofactor protein S, aPC inactivates factors Va and VIIIa regulating the functionality of the prothrombinase and tenase complexes, respectively.[11] aPC and protein S prevent coagulation reactions from spreading to healthy, uninjured vessel walls. Circulating antithrombin inhibits thrombin and factor Xa. Heparan sulfate, a heparin-like compound secreted by endothelial cells, exponentially accelerates antithrombin activity.[11] As described previously, TFPI plays an important role by regulating the initiation phase.[13] When these self-regulatory mechanisms are intact, the fibrin clot is limited to the vessel injury zone. However, disruptions in the system can result in hypercoagulability and thrombotic complications.[14]

The fibrinolytic system is responsible for blood clot dissolution.[15] Inactive plasminogen is converted by tissue plasminogen activator (tPA) to active plasmin, an enzyme that degrades fibrin mesh into soluble end products. Collectively, these soluble products are known as fibrin degradation products and include D-dimer, which is a marker of thrombosis used when diagnosing VTE.[15] The fibrinolytic system is regulated by a series of stimulatory and inhibitory substances (Fig. 38-2). Plasminogen activator inhibitor-1 inhibits tPA and α_2-antiplasmin inhibits plasmin activity. Impaired functioning of the fibrinolytic system has also been linked to hypercoagulability and thrombotic complications.[15]

Most venous thrombi begin in the leg(s). Thrombus isolated in calf veins is unlikely to break loose (embolize). Thrombus involving the popliteal and larger veins above the knee is more likely to embolize and travel through the right side of the heart and lodge in the pulmonary artery or one of its branches, causing PE, occlusion of blood flow to the lung, and impaired gas exchange. Without treatment, the affected lung becomes necrotic and oxygen delivery to other vital organs decreases, potentially resulting in fatal circulatory collapse.[1]

Inherited and Acquired Hypercoagulability Disorders

Disturbances in hemostatic regulation may result in inherited or acquired hypercoagulability.[14] aPC resistance increases the risk of VTE approximately threefold and is the most common inherited hypercoagulability disorder with a prevalence rate of 2.0% to 7.0% in White individuals.[14] aPC resistance most often results from a gene mutation that renders factor V resistant to degradation by aPC. This mutation is known as factor V Leiden.[14]

The prothrombin G20210A mutation also imparts about a threefold increased VTE risk and is the second most frequent inherited hypercoagulability disorder, occurring in about 2.0% to 4.0% of White individuals.[14] This mutation increases circulating prothrombin, enhancing thrombin generation potential.[10] Some patients inherit both factor V Leiden and prothrombin G20210A mutations, significantly increasing their lifetime VTE risk.[14]

Experts believe the lifetime risk associated with inherited protein C, protein S, and antithrombin deficiencies (present in <1% of the population) is high, perhaps sevenfold higher than patients without such disorders. Many patients with protein C, protein S, or antithrombin deficiency suffer VTE prior to age 60.[10]

Acquired disorders of hypercoagulability may result from cancer, the presence of antiphospholipid antibodies, or estrogen use. A strong link between cancer and thrombosis has long been recognized.[16] Tumor cells secrete procoagulant substances that activate the coagulation cascade, and patients with cancer often have suppressed protein C, protein S, and antithrombin levels. Cancer cells use thrombotic mechanisms to recruit a blood supply,

metastasize, and create barriers against host defense mechanisms.[16]

Antiphospholipid antibodies are a heterogeneous group of antibodies targeting proteins that bind phospholipids.[10] These include antibodies that prolong phospholipid-based clotting assays, known as lupus anticoagulants, as well as anticardiolipin and β_2-glycoprotein (β_2-gp) I antibodies.

Antiphospholipid antibodies are more common among patients with autoimmune disorders (eg, systemic lupus erythematosus and inflammatory bowel disease) compared to healthy individuals. The precise mechanism by which antiphospholipid antibodies provoke thrombosis remains uncertain. Contributing factors include complement activation, protein C and fibrinolysis inhibition, platelet activation, and increased TF expression.[10]

CLINICAL PRESENTATION (INCLUDING DIAGNOSTIC CONSIDERATIONS)

2 The symptoms of DVT or PE are nonspecific and objective tests are required to confirm or exclude the diagnosis. Patients with DVT frequently present with unilateral leg pain and swelling. Postthrombotic syndrome, a long-term complication of DVT caused by damage to the venous valves, may also result in chronic lower extremity swelling, pain, tenderness, skin discoloration, and, in the most severe cases, ulceration. PE typically presents with chest pain, shortness of breath, tachypnea, and tachycardia, which in some cases may result in cardiopulmonary collapse.[17,18]

Because VTE can be debilitating or fatal, it is important to treat it quickly and aggressively. Conversely, because major bleeding induced by anticoagulant drugs can be equally harmful, it is important to avoid treatment when the diagnosis is not a reasonable certainty. Assessment of the patient's status should focus on the search for risk factors in the patient's medical history (Table 38-1). Even in the presence of mild, seemingly inconsequential symptoms, VTE should be strongly suspected in those with multiple risk factors.[17]

Clinical assessment significantly improves the diagnostic accuracy of noninvasive tests such as compression ultrasound (CUS), computed tomography pulmonary angiography (CTPA), and D-dimer. Simple clinical assessment checklists such as the Wells score for DVT or PE or the revised Geneva score for PE can be used to determine if a patient is "likely" or "unlikely" to have DVT or PE (Figs. 38-6 and 38-7).[19] Patients with a likely probability of VTE have a >60% chance of VTE, compared with a <10% chance for patients with an unlikely probability.[20] In general, patients with an unlikely probability of VTE should first have their D-dimer tested. If the D-dimer result is below the defined cutoff point or reported as "negative," VTE is ruled out. D-dimer results above the cutoff point warrant appropriate diagnostic imaging (CUS for suspected DVT, or CTPA or ventilation/perfusion [V/Q] scanning for suspected PE).

FIGURE 38-6

Deep vein thrombosis diagnostic algorithm. Wells score: 1 pt each for: active cancer, paralysis, or recent plaster cast, immobilization >3 days or surgery in previous 12 weeks, tenderness along the venous system, entire leg swollen, calf swelling >3 cm, pitting edema, collateral superficial veins, history of DVT. Alternate diagnosis as likely as DVT, subtract 2 pts. Surveillance, follow-up CUS in 7-14 days to assess for proximal DVT. *(Data from References 19-21.)*

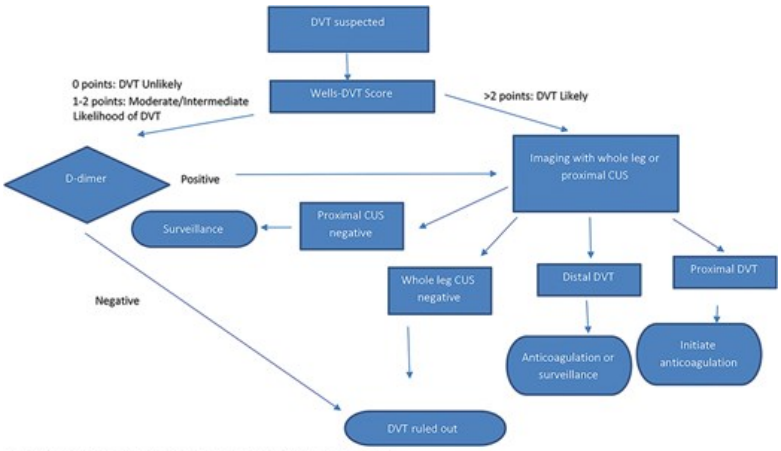
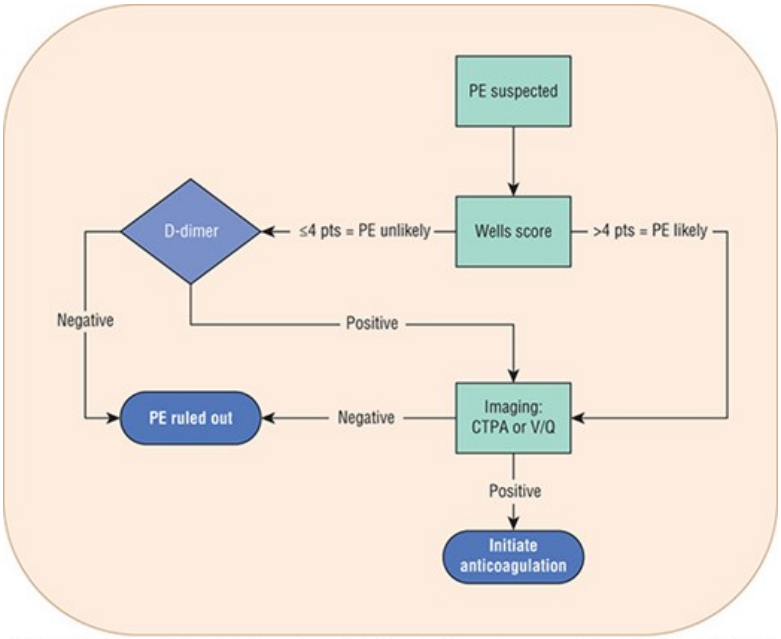


FIGURE 38-7

Pulmonary embolism diagnostic algorithm. (Simplified Wells PE Score, signs/symptoms of DVT, alternative diagnosis less likely than PE [3 pts each], HR >100 bpm, immobile >3 days in past 4 weeks, history of DVT/PE [1.5 pts each], hemoptysis or malignancy [1 pt each]). *(Data from References 17 and 22.)*



D-dimer is a fibrin clot degradation product and levels are significantly elevated in patients with acute thrombosis. A variety of conditions other than VTE are associated with D-dimer elevations, including recent surgery or trauma, pregnancy, advanced age, and cancer; therefore, a positive D-dimer test is not conclusive evidence of VTE diagnosis. However, a *negative* D-dimer, for most assays defined as <500 ng/mL (mcg/L), can be useful in ruling out the diagnosis of VTE.[20] Appropriate use of D-dimer should include initial risk stratification using a validated clinical assessment tool.[20]

All patients with a likely probability of DVT should receive either proximal (popliteal, femoral, and iliac veins) or whole leg CUS. A normal whole leg ultrasound rules out DVT, whereas a normal proximal ultrasound requires whole leg ultrasound or repeat proximal ultrasound surveillance in 1 week. Patients with CUS indicating proximal DVT should receive anticoagulant treatment. Evidence of distal DVT (anterior and posterior tibial, peroneal, gastrocnemius veins) after whole leg ultrasound may be managed with anticoagulants or repeated ultrasound surveillance in 1 to 2 weeks to assess for propagation into the proximal deep veins of the leg (Fig. 38-6). Patients with a likely probability of PE should receive imaging with either CTPA or V/Q scan. A negative imaging result rules out PE, whereas a positive imaging result indicates need for anticoagulant treatment (Fig. 38-7).[17,19,20]

CLINICAL PRESENTATION: Deep Vein Thrombosis

General

DVT most commonly develops in patients with identifiable risk factors (see Table 38-1). Some may have asymptomatic disease.

Symptoms

The patient may complain of leg swelling, pain, or warmth. Symptoms are nonspecific and objective testing must be performed to establish the diagnosis

Signs

The patient's superficial veins may be dilated and a "palpable cord" may be felt in the affected leg. The patient may experience pain in the back of the knee when the examiner dorsiflexes the foot of the affected leg (Homan's sign).

Laboratory Tests

Serum concentration of D-dimer, a by-product of fibrin degradation, is nearly always elevated. A negative D-dimer (values <500 ng/mL [mcg/L]) combined with clinical decision rules are useful in ruling out the diagnosis of DVT.

Diagnostic Tests

Compression ultrasound is the most commonly used test to diagnose DVT. It is a noninvasive test that can visualize clot formation in veins of the legs. Coupled with a careful clinical assessment, it can rule in or out the diagnosis in the majority of cases. Venography is the gold standard for the diagnosis of DVT. However, it is an invasive test that involves the injection of radiopaque contrast dye into a foot vein. It is expensive and can cause anaphylaxis and nephrotoxicity.

CLINICAL PRESENTATION: Pulmonary Embolism

General

PE most commonly develops in patients with risk factors for VTE (see Table 38-1). Although many patients develop a symptomatic DVT prior to developing a PE, some do not. Patients may die suddenly from cardiogenic shock and circulatory collapse before effective treatment can be initiated.

Symptoms

The patient may complain of cough, chest pain, chest tightness, shortness of breath, or palpitation. The patient may spit or cough up blood (hemoptysis). When PE is massive, the patient may complain of dizziness or light-headedness. Symptoms may be confused with myocardial infarction, requiring objective testing to establish the diagnosis.

Signs

The patient may have tachypnea, tachycardia, and appear diaphoretic. The patient's neck veins may be distended. In massive PE, the patient may appear cyanotic and become hypotensive. In such cases, oxygen saturation by pulse oximetry or arterial blood gas will likely indicate that the patient is hypoxic. In the worse cases, the patient may go into cardiogenic shock and die within minutes.

Laboratory Tests

Serum concentration of D-dimer, a by-product of fibrin degradation, is nearly always elevated. D-dimer values <500 ng/mL (mcg/L) combined with clinical decision rules are useful in ruling out the diagnosis of PE.

Diagnostic Tests

Computerized tomography pulmonary angiography (CTPA) is the most commonly used test to diagnose PE, but some centers still use the V/Q scan. A V/Q scan measures the distribution of blood and airflow in the lungs. When there is a large mismatch between blood and airflow in one area of the lung, there is a PE.

Pulmonary angiography is the gold standard for the diagnosis of PE. However, it is an invasive test that involves the injection of radiopaque contrast dye into the pulmonary artery. The test is expensive and associated with a significant risk of mortality.

PREVENTION OF VENOUS THROMBOEMBOLISM

Unfortunately, public awareness of the life-threatening nature of DVT and PE is lacking with many patients having little or no awareness of VTE symptoms or risk factors.[23] VTE awareness is substantially lower than for other disease states like stroke, heart attack, and breast cancer and there is a need to increase knowledge of the risks, signs, and symptoms of VTE.

Desired Outcomes

Prevention strategies in at-risk populations positively impact patient outcomes because VTE is potentially fatal and costly to treat.[26] Treatment of VTE is aimed at preventing thrombus extension and embolization, reducing recurrence risk, and preventing long-term complications such as the postthrombotic syndrome and CTPH. Carefully managed anticoagulant drug use is important to reduce the risk of bleeding associated with these agents.

General Approach to the Prevention of Venous Thromboembolism

Effective prophylaxis can reduce the risk of fatal PE in high-risk medical and surgical populations. Early ambulation is often sufficient for those at low risk of VTE.[27] Educational programs and clinical decision support systems have been shown to improve the appropriate use of VTE prevention

methods.[28]

3 VTE continues to be a major risk for patient morbidity and mortality in hospitalized patients. Approximately half of all VTE occurs secondary to hospital admission or surgery, often occurring after hospital discharge. Effective VTE prophylaxis can prevent as much as 70% of VTE events related to hospitalization or surgery.[29-31] Safe and effective prophylaxis strategies must balance the risks for thromboembolism and bleeding. There is evidence that VTE prophylaxis is both underused in patients at high risk for VTE and overused in low-risk populations.[32] It is essential that patients are assessed for risks of VTE and bleeding (Table 38-2) prior to deciding whether VTE prophylaxis is appropriate. Distinct populations to consider for VTE prophylaxis include the medically ill and those undergoing surgery (Table 38-3). Each group has unique risk factors for VTE and bleeding to consider in determining an approach to VTE prophylaxis (Fig. 38-8).

TABLE 38-2

VTE and Bleeding Risk Assessment for Medically Ill Patients

VTE Risk Assessment		**Bleeding Risk Assessment**	
Characteristic	Points	Characteristic	Points
Reduced mobility	3	Renal failure (GFR 30-59 mL/min/1.73 m^2)	1
Active cancer	3	Male	1
Previous VTE (excluding superficial thrombophlebitis)	3	Age 40-80	1.5
Known thrombophelia	3	Current cancer	2
Recent trauma or surgery (within 1 month)	2	Rheumatic disease	2
Age >70 years	1	Central venous catheter	2
Heart or respiratory failure	1	Intensive or critical care unit stay	2.5
Acute myocardial infarction or ischemic stroke	1	Renal failure (GFR <30 mL/min/1.73 m^2)	2.5
Ongoing hormonal treatment	1	Hepatic failure (INR >1.5)	2.5
Obesity (BMI >30 kg/m^2)	1	Age ≥85	3.5
Active infection or rhematologic disorder	1	Platelet count <50,000/mm^3 (50 × 10^9/L)	4
		Bleeding in previous 3 months	4
		Active gastroduodenal ulcer	4.5
4 points or greater is high risk for VTE		7 points or greater is high risk for major bleeding	

BMI, body mass index; GFR, glomerular filtration rate; INR, international normalized ratio. GFR expressed in units of mL/min/1.73 m^2 is converted to SI units of mL/s/m^2 by multiplying by 0.0096. *Data from References 39 and 40.*

TABLE 38-3

Summary of Guideline Recommended Therapies Indicated for VTE Prophylaxis

		Orthopedic Surgery		
Indication	**Medically ill**	**TKA/THA**	**Hip fracture repair**	**Other major surgeries[a]**
Preferred agents	LMWH or fondaparinux	Aspirin or anticoagulants (DOACs favored; LMWH also supported)	LMWH or UFH	LMWH or UFH
Combined pharmacological and mechanical prophylaxis[b]	No	Yes	Yes	Yes
Extended duration pharmacological prophylaxis	No	Yes	Yes	Yes
Alternative pharmacologic agents	UFH or rivaroxaban	Fondaparinux, low-dose UFH, or warfarin	Fondaparinux or warfarin	n/a
Alternative mechanical prophylaxis in high bleeding risk	IPC	IPC and/or compression stockings	IPC and/or compression stockings	IPC and/or compression stockings

THA, total hip arthroplasty; TKA, total knee arthroplasty; LMWH, low-molecular weight heparin; DOACs, direct-acting oral anticoagulants; UFH, unfractionated heparin; IPC, intermittent pneumatic compression.

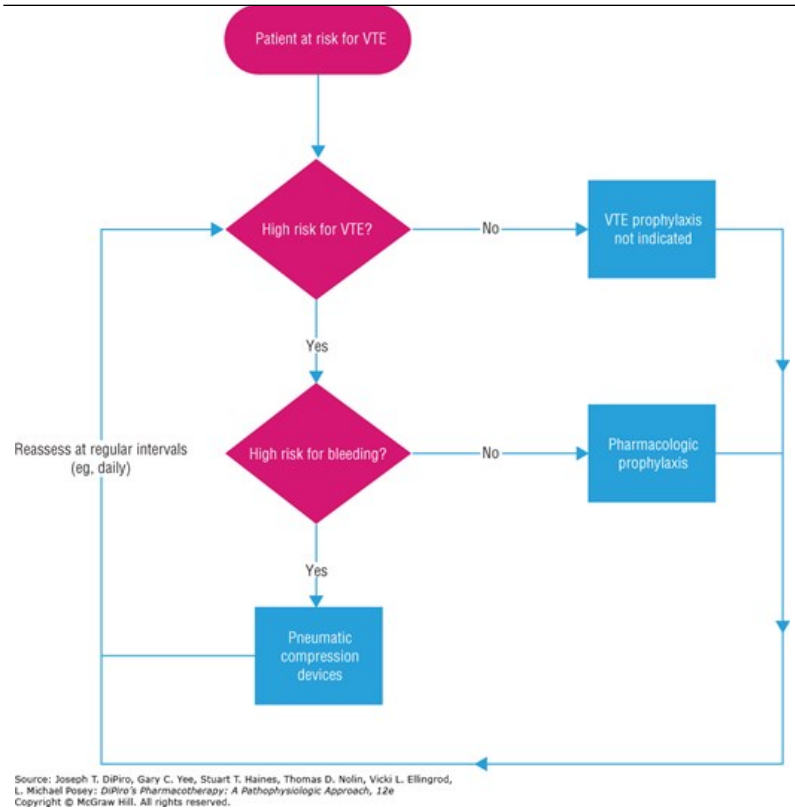
[a]Excludes prostate resection, prostatectomy, and neurosurgery.

[b]Combination of aspirin or anticoagulation plus IPC or graduated compression stockings.

Data from References 2, 3, 34, and 37.

FIGURE 38-8

General approach to VTE prophylaxis. *(Data from References 2 and 3.)*



Nonpharmacologic Therapy

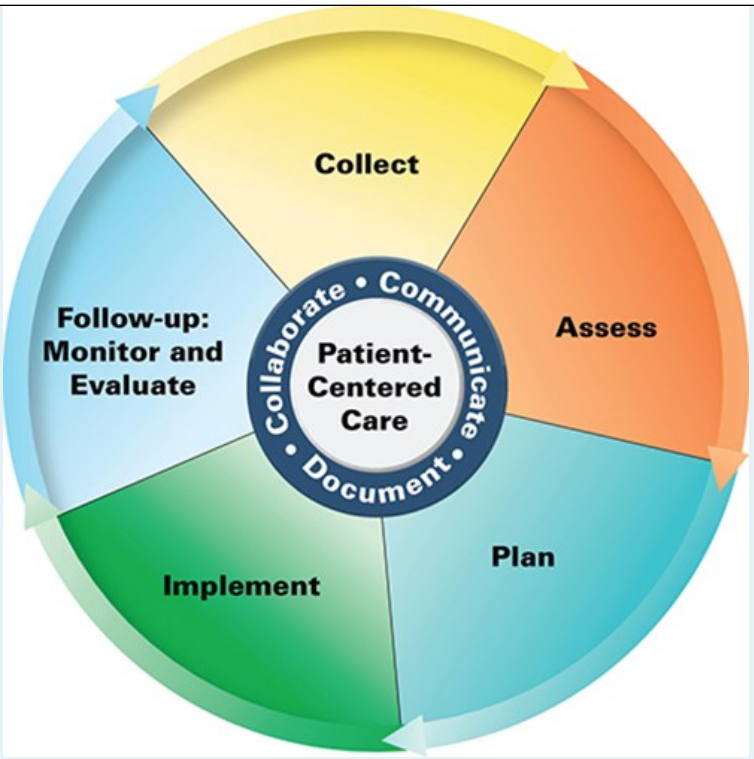
Graduated compression stockings and intermittent pneumatic compression (IPC) devices prevent VTE by increasing the velocity of lower extremity venous blood flow through graded pressure application. IPC devices utilize a series of cuffs wrapped around the patient's legs that inflate in continuous 1- to 2-minute cycles from the ankles to the knees or thighs. IPC devices should be worn at least 18 hr/day for optimal effectiveness.

Graduated compression stockings do not reliably reduce VTE in medically ill patients.[33] However, they reduce the incidence of VTE (including asymptomatic and distal DVT) by approximately 65% when used after orthopedic surgery, cardiac surgery, gynecologic surgery, or neurosurgery.[34] IPC reduces the risk of VTE by more than 60% following general surgery, neurosurgery, and orthopedic surgery.[34] Both modalities can be used in combination with anticoagulation in appropriate settings (see below) to maximize VTE prevention.[35]

Mechanical methods do not increase bleeding risk, which makes them attractive for VTE prophylaxis following surgery, especially in patients with contraindications to anticoagulation. However, they are not risk-free, as discomfort, skin breakdown, and ulceration can occur.[33]

Inferior vena cava (IVC) filters can provide short-term protection against PE in very high-risk patients by blocking embolization of thrombus formed below the filter.[36] Percutaneous insertion of an IVC filter is a minimally invasive procedure performed using fluoroscopic imaging to verify placement. Frequently "retrievable" IVC filters are never retrieved, increasing the risk for long-term complications such as DVT, filter migration, IVC occlusion, and insertion site thrombosis.[34] Therefore, IVC filters should be reserved for patients at the highest VTE risk in whom other prophylactic strategies cannot be used. The data supporting the use of IVC filters for primary VTE prophylaxis in patients at high risk of bleeding is very weak.[2] Routine use of IVC filters is not recommended and their potential role in high bleeding risk patients remains to be determined.[2] IVC filters should be removed when VTE risk has passed or when anticoagulation is no longer contraindicated.[36]

Patient Care Process for the Prevention of VTE



Collect

- Patient characteristics (eg, age, sex, active cancer, pregnant)
- Patient history (past medical [eg, bleeding history], family, social—dietary habits including intake of vitamin K-containing foods [see Table 38-12], tobacco/ethanol use)
- Current medications including over-the-counter aspirin and NSAID use; prior anticoagulant medication use
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), O_2-saturation, height, weight
  - Labs (eg, hemoglobin [Hgb], serum creatinine [Scr], platelets, activated partial thromboplastin time [aPTT], prothrombin time [PT])

Assess

- Presence of VTE risk factors (see Table 38-1); consider using risk stratification tools appropriate for medical or surgical patients (see Table 38-2)
- Presence of active bleeding and/or bleeding risk factors (see Table 38-10)
- Presence of medications that increase VTE risk (eg, estrogen)
- Presence of contraindications to anticoagulation therapy
- Ability/willingness to self-inject LMWH or fondaparinux if extended parenteral therapy is being considered
- Ability/willingness to pay for various anticoagulation therapy options if extended therapy is being considered
- Ability/willingness to obtain appropriate laboratory monitoring if extended therapy is being considered (eg, INR [international normalized ratio] for warfarin)

Plan*

- Drug therapy regimen including specific anticoagulant(s) or reversal agent(s), dose, route, frequency, and duration (see Fig. 38-9)
- Monitoring parameters including effectiveness (eg, INR results, signs and symptoms of VTE), safety (bleeding, platelet count [heparin]), and timing of assessments
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy; see Table 38-5)
- Self-monitoring for VTE symptoms, occurrence of bleeding, when to seek emergency medical attention

Implement

- Ensure appropriate VTE prevention is initiated based on patient-specific VTE/bleeding risk
- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence if extended therapy being considered
- Schedule follow-up (eg, INR tests [warfarin], bleeding assessment, duration of therapy assessment)

Follow-up: Monitor and Evaluate

- Occurrence of VTE symptoms (eg, shortness of breath, chest pain, leg or arm swelling, redness, pain)
- Presence of adverse drug reactions (eg, bleeding, gastrointestinal upset [dabigatran only], HIT [heparin-induced thrombocytopenia])
- INR results (adjust warfarin dose as needed to keep within target range)
- Patient adherence to the treatment plan if extended therapy
- Inquire whether the patient is ambulatory and/or weight-bearing (following orthopedic surgery)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Pharmacologic Therapy

Pharmacologic options for preventing VTE have been extensively evaluated in randomized clinical trials and significantly reduce the risk of VTE following hip and knee replacement, hip fracture repair, general surgery, myocardial infarction, ischemic stroke, and in selected hospitalized medical patients.[33,34,37] The optimal agent and dose for VTE prevention must be based on an assessment of VTE and bleeding risk, as well as cost and availability. In general, pharmacologic therapy is preferred over mechanical interventions in patients without active bleeding or high risk for bleeding. Pharmacologic prophylaxis options include UFH, LMWH, DOACs, aspirin, and warfarin. Each can be used safely and effectively given the appropriate clinical scenario.

Medical Patients

Low-dose UFH, LMWH, and fondaparinux all reduce symptomatic VTE and fatal PE among high-risk medical patients.[2] Rivaroxaban is as effective as enoxaparin for VTE prophylaxis during hospitalization and is approved for VTE prophylaxis in medically ill patients including after hospital discharge for a total duration of 39 days.[38] However, routine use of extended duration prophylaxis beyond hospital discharge is not supported by guidelines.[3]

Hospitalized and acutely ill medical patients at high VTE risk and low bleeding risk should receive pharmacologic prophylaxis with low-dose UFH, LMWH, fondaparinux, or rivaroxaban during hospitalization or until fully ambulatory. The use of extended prophylaxis beyond hospital discharge reduces the risk of VTE but with a comparable increase in bleeding and is not recommended in the medically ill population.[3] LMWH or fondaparinux are preferred to low-dose UFH or DOACs for VTE prophylaxis in medically ill inpatients. Routine pharmacologic prophylaxis is not warranted in low-

VTE-risk medical patients.

Several risk assessment models have been developed to identify hospitalized and critically ill patients at high VTE risk likely to benefit from thromboprophylaxis. The Padua Prediction Score is a prospectively validated VTE risk assessment tool for hospitalized medical patients.[39] Among high-risk patients (score ≥4 points) not receiving prophylaxis, VTE occurred in 11.0% within 90 days compared with just 0.3% of low-risk patients. Bleeding risk can be estimated using various risk stratification tools such as the IMPROVE bleeding score.[40] An IMPROVE score of ≥7 points was associated with a major bleeding risk of 4.1%. Mechanical prophylaxis is preferred over anticoagulation therapy in medical patients at high bleeding risk.[2] Patients with severe hepatic insufficiency are not adequately protected from VTE even if baseline INR is elevated. This population is particularly challenging as they are at risk for VTE without prophylaxis and bleeding with pharmacologic prophylaxis.[41,42]

Table 38-2 summarizes a scoring system for VTE risk and bleeding assessment in medically ill patients. Figure 38-8 outlines a general approach to deciding on VTE prophylaxis once VTE and bleeding risk scores have been estimated.

Surgical Patients

General recommendations for reducing perioperative VTE risk include using regional rather than general anesthesia, whenever possible, and having patients ambulate as soon as it is safe to do so.[17]

Risk stratification tools (eg, Caprini score) also exist for estimating VTE risk in surgical populations. However, current guidelines provide recommendations according to the type of surgery rather than based on specific risk assessment models.[2] Most patients having general, gynecologic, cardiac, and vascular surgery should receive pharmacologic prophylaxis with LMWH or low-dose UFH to prevent VTE. Patients unable to receive pharmacologic prophylaxis should use IPCs or compression stockings.[2] Combination of pharmacologic and mechanical VTE prevention methods have the potential to reduce the risk for VTE as well as mortality compared to pharmacologic prophylaxis alone. The addition of mechanical prophylaxis is generally well tolerated and should be particularly advantageous to patients with additional risk factors for VTE.[2]

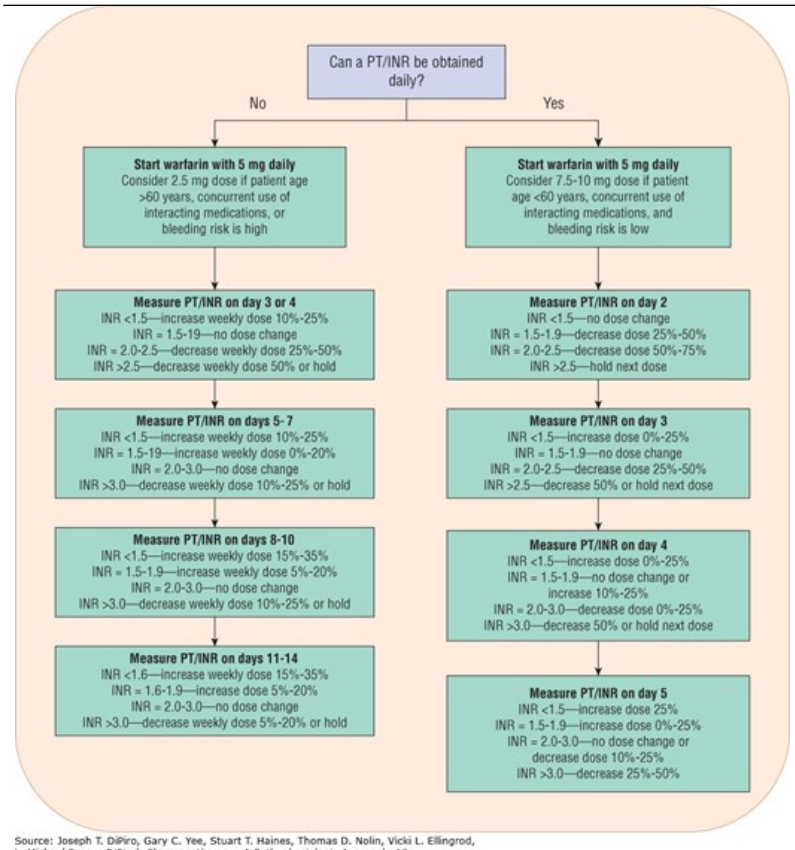
There are a few surgery types excluded from the general recommendations above. Uncomplicated laparoscopic cholecystectomy does not routinely require VTE prophylaxis unless the patient has additional VTE risk factors, such as a history of VTE, hypercoagulability, or active cancer. Patients undergoing surgery that involves high bleeding risk (eg, urologic procedures) or where small amounts of bleeding can result is substantial morbidity (eg, intracranial or spinal surgery) are typically managed with IPCs rather than pharmacologic prophylaxis.[2]

Total joint arthroplasty has historically been associated with very high postoperative VTE risk.[37] Pharmacologic agents for VTE prevention following joint replacement surgery include aspirin, adjusted-dose warfarin, low-dose UFH, LMWH, fondaparinux, dabigatran, apixaban, and rivaroxaban for a minimum of 10 days postsurgery.[37] Optimal timing of anticoagulation initiation is between 6 and 12 hours postop. Earlier initiation increases bleeding risk up to fivefold.[37] Extended duration prophylaxis is also recommended to prevent delayed VTE up to 35 days postoperatively.

Warfarin remains a commonly prescribed agent for VTE prevention after total joint arthroplasty due to low acquisition cost, oral administration, and delayed onset, potentially reducing the risk of early postoperative bleeding (see Fig. 38-9).[43] The optimal target INR during warfarin prophylaxis is not clear. It is common for INR targets lower than the standard range of 2 to 3 to be employed as the American Academy of Orthopaedic Surgery guidelines do not recommend a specific INR target.[37,44]

FIGURE 38-9

Initiation of warfarin therapy.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

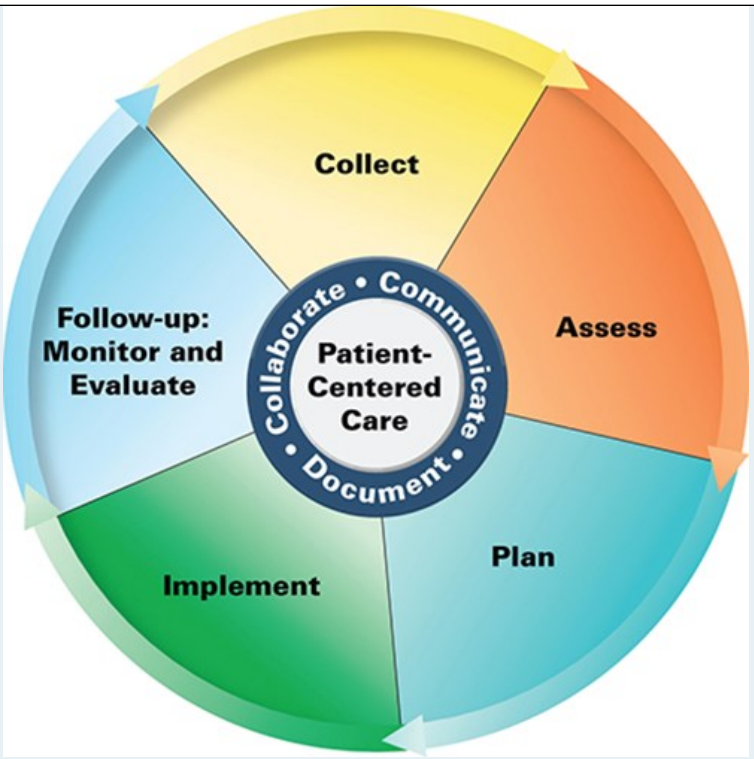
DOACs offer convenient oral administration and fixed dosing without the need for routine coagulation testing. The safety and efficacy of DOACs are similar to enoxaparin after total joint replacement, but studies after hip fracture surgery are lacking.[37] The American Society of Hematology recommends DOACs over other anticoagulants for VTE prophylaxis after total joint replacement.[2] If a DOAC is not available or contraindicated, LMWHs are generally preferred over UFH or warfarin (see Table 38-3 for VTE prophylaxis summary). If aspirin is used, a two-tiered approach might be considered where aspirin is the default option for patients who have no additional VTE risk factors and DOACs, warfarin, or LMWH reserved for patients with additional VTE risk factors (eg, obesity, active cancer, history of VTE). Finally, a short course (eg, 5 days) of DOAC therapy followed by aspirin provides an early anticoagulant effect and may optimally balance the use of an anticoagulant to prevent early postoperative thrombosis when the risk is highest, and a low-cost oral option (aspirin) that can be easily administered after hospital discharge.[45]

Duration of Therapy

VTE incidence is relatively high in the month following hospital discharge among patients undergoing lower extremity orthopedic procedures; therefore, extended prophylaxis appears to be beneficial.[2] Most clinical trials support the use of antithrombotic prophylaxis for 15 to 42 days following total knee or hip replacement surgery.[2] Optimal VTE prophylaxis duration following other major surgeries is not well established. Prophylaxis should be given throughout the period of increased VTE risk. Guidelines support extended VTE prophylaxis for up to 42 days after major surgery.[2] However, it may be reasonable to forego extended prophylaxis after less extensive procedures where patients are ambulatory and other risk factors are no longer present.

PATIENT CARE PROCESS

Patient Care Process for the Treatment of VTE



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient history (past medical, family, social—dietary habits including intake of vitamin K-containing foods (see Table 38-12), tobacco/ethanol use
- Current medications including over-the-counter aspirin/NSAID use; prior anticoagulant medication use
- Objective data
  - BP, HR, RR, O_2-saturation, height, weight
  - Labs (eg, Hgb, Scr, platelets, aPTT, PT)
  - Do NOT order hypercoagulability tests
  - Objective confirmation of VTE (see Figs. 38-6 and 38-7)

Assess

- For PE, hemodynamic instability (eg, SBP <90 mm Hg, HR >110 bpm, O_2-sat <90% [0.90])
- Presence of active bleeding and/or bleeding risk factors (see Table 38-10)
- Presence of VTE provoking factors (eg, recent surgery, plaster casting of lower extremity, indwelling catheter, cancer, pregnancy, estrogen use, prolonged immobility, recent hospitalization)
- Ability/willingness to self-inject LMWH/fondaparinux
- Ability/willingness to pay for various anticoagulation therapy options

- Ability/willingness to obtain appropriate laboratory monitoring (eg, INR for warfarin)
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen including specific anticoagulant(s), dose, route, frequency, and duration (see Figs. 38-8 to 38-11, Tables 38-4 to 38-6)
- Monitoring parameters including effectiveness (eg, INR results, pain control, limb swelling, shortness of breath), safety (bleeding, VTE recurrence), and timing of assessments
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, invasive procedures, drug therapy; see Table 38-5)
- Self-monitoring for resolution of VTE symptoms, the occurrence of bleeding, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, thrombosis specialist, behavioral health, dietician)

Implement

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, INR tests [warfarin], Scr [DOACs], adherence assessment, bleeding risk assessment, duration of therapy assessment)

Follow-up: Monitor and Evaluate

- Resolution of VTE symptoms (eg, shortness of breath, chest pain, swelling, redness, pain)
- Presence of adverse drug reactions (eg, bleeding, GI upset [dabigatran])
- INR results (adjust warfarin dose as needed to keep between 2 and 3)
- Patient adherence to treatment plan using multiple sources of information
- Duration of therapy after 90 days

**Collaborate with patient, caregivers, and other healthcare professionals.*

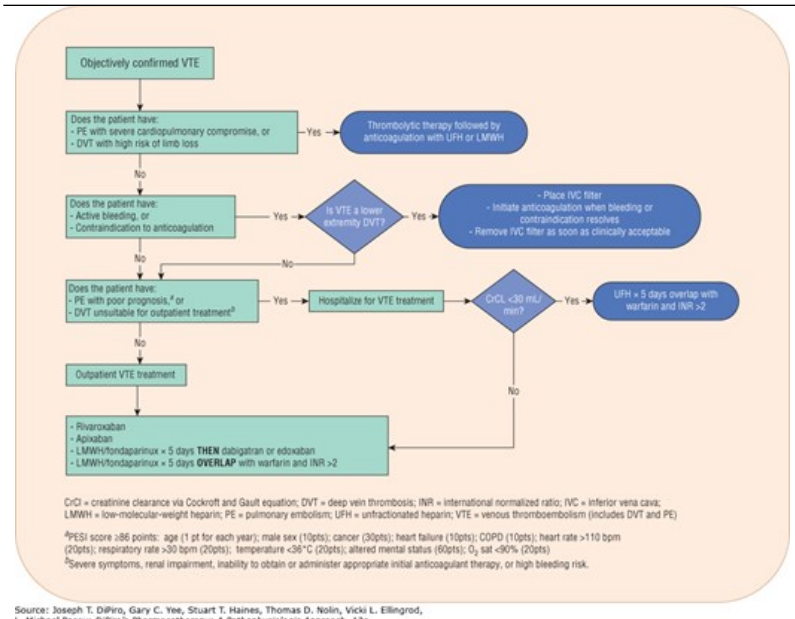
TREATMENT OF VENOUS THROMBOEMBOLISM

General Approach to the Treatment of Venous Thromboembolism

Anticoagulation therapies remain the mainstay of VTE treatment. DVT and PE are manifestations of the same disease process and are treated similarly (Figs. 38-10 and 38-11). Before prescribing anticoagulation therapy for VTE treatment, establishing an accurate diagnosis is imperative to prevent unnecessary bleeding risk and expense to the patient.[18] Patients with a likely VTE probability (Figs. 38-6 and 38-7) may need rapid-onset anticoagulation therapy while awaiting diagnostic testing results. However, patients with unlikely VTE probability may only need rapid-onset anticoagulation in the setting of a positive D-dimer with anticipated delays in diagnostic testing exceeding 4 hours.[17]

FIGURE 38-10

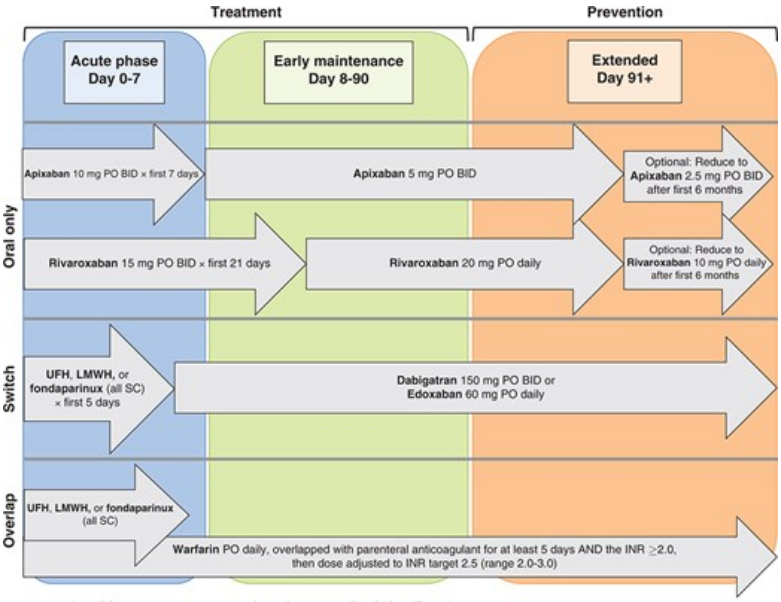
Decision algorithm: Acute treatment of VTE. (CrCl, creatinine clearance via Cockroft and Gault equation; VTE, venous thromboembolism [includes DVT and PE].) *(Data from References 37 and 39.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

FIGURE 38-11

Overview of VTE treatment strategies: Acute, early maintenance, and extended treatment phases.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Strict bed rest was traditionally recommended following acute DVT based on the assumption that leg movement would dislodge the clot, resulting in PE. However, ambulation in conjunction with graduated compression stockings results in a faster reduction of pain and swelling with no apparent increase in embolization rate. Patients should be encouraged to ambulate as much as symptoms permit. If ambulation increases pain and swelling, the patient should be instructed to lie down and elevate the affected leg until symptoms subside.

IVC filters have a limited role in the management of acute VTE and should only be used when anticoagulants are contraindicated due to active bleeding.[21] As soon as the bleeding resolves, patients should receive a conventional course of anticoagulant therapy and have the filter removed within 90 to 120 days of implantation.[17,18,36] In life- or limb-threatening circumstances, elimination of the obstructing thrombus may be warranted and the use of thrombolysis or thrombectomy considered.[18,46]

[4] [7] Once the diagnosis of VTE has been objectively confirmed (see details regarding Clinical Presentation and Diagnosis above), anticoagulant therapy with a rapid-acting anticoagulant should be instituted as soon as possible. Available anticoagulants can be administered in the outpatient setting in most patients with DVT and in carefully selected hemodynamically stable patients with PE. Given the predictable response and reduced need for laboratory monitoring with LMWH and DOACs, stable patients with DVT or PE who have normal vital signs, low bleeding risk, and no other uncontrolled comorbid conditions requiring hospitalization can be discharged early or treated entirely on an outpatient basis (Table 38-4).[47] Not all patients are appropriate candidates for outpatient VTE treatment. At a minimum, patients must be reliable or have adequate caregiver support and be willing and active participants in outpatient VTE management. Important patient education aspects for outpatient VTE treatment are summarized in Table 38-5. Hemodynamically unstable patients with PE should be admitted for anticoagulation therapy initiation. The decision to initiate outpatient therapy should be based on institutional resources and patient-specific variables.[46,48]

TABLE 38-4

Outpatient Treatment Suggestions for DVT and PE

- Inclusion: Patients with objectively diagnosed VTE
- Exclusion: Hemodynamically unstable, arterial thromboembolism or patients currently receiving dialysis, actively bleeding, recent (within 2 weeks) major surgery/trauma, or other severe uncompensated comorbid conditions
- Suggested procedure may vary depending on the patient's clinical condition
- Confirm diagnosis of VTE by objective testing

Day 1

- Baseline laboratory evaluation
  - INR—if use of warfarin anticipated
  - SCr
  - Complete blood count (CBC) with platelets
- Medication—see Fig. 38-11
- Patient education
  - Clinical pharmacy/nursing
    - Educate patient regarding the importance of proper monitoring of anticoagulation therapy (if applicable) and warning signs that should prompt additional medical evaluation; document activities in the medical record
    - If applicable, teach patient how to self-administer LMWH/fondaparinux (if patient or family member unwilling or unable to self-administer injection, visiting nurse services should be arranged or consider single oral anticoagulant approach); initial injection should be administered in the medical office or hospital
    - Instruct patient regarding local therapy: elevation of affected extremity, localized heat, anti-embolic exercises (flexion–extension of ankle for lower extremity VTE, or hand squeezing–relaxation for upper extremity VTE)
  - Dispensing pharmacy
    - Reinforce patient education regarding indication, use, monitoring, adverse drug reactions, and drug interactions with antithrombotic therapy
    - Screen patient's pharmacy profile for potential drug-drug interactions with anticoagulation therapy
    - Dispense anticoagulant therapy
    - Verify anticoagulation service enrollment

Days 3-4

- Laboratory evaluation if on warfarin: check INR
- Assess for symptoms of pulmonary embolism or bleeding
- Medications: continue anticoagulant medication(s) as directed
- Anticoagulation service

- If on warfarin interpret results of INR and adjust dose of warfarin to achieve an INR of 2 to 3
- Patient activity: continue reduced activity as long as pain persists (when possible, elevate extremity); increase activity as tolerated
- Document activities in medical record

Day 5

- Laboratory evaluation if on warfarin: check INR
- Assess for symptoms of bleeding or pulmonary embolism
- Medications: continue anticoagulant medication(s) as directed
- Anticoagulation service
  - If on warfarin interpret results of INR and adjust dose of warfarin to achieve an INR of 2 to 3 (stop LMWH if INR ≥2.0)
  - Patient activity: no restriction; if pain increases, contact primary care provider
  - Document activities in medical record

Day 6 (Dabigatran or Edoxaban)

- Medications: transition from parenteral to oral medication
- Assess for symptoms of bleeding or pulmonary embolism
- Anticoagulation service
  - Verify adherence, affordability, and tolerability of oral medication
  - Patient activity: no restriction; if pain increases, contact primary care provider
  - Review key education points (eg, keep in original container [dabigatran])
  - Document activities in medical record

Day 8 (Apixaban)

- Medications: decrease apixaban dose
- Anticoagulation service
  - Patient activity: no restrictions; if pain increases contact primary care provider
  - Verify adherence, affordability, and tolerability of oral medication
  - Document activities in medical record

Day 22 (Rivaroxaban)

- Medications: decrease rivaroxaban dose
- Anticoagulation service
  - Verify adherence, affordability, and tolerability of oral medication
  - Patient activity: no restriction; if pain increases, contact primary care provider
  - Review key education points (eg, take with food [rivaroxaban])
  - Document activities in medical record

TABLE 38-5

Patient Education for Outpatient VTE Therapy

General Information Regarding VTE and the Goals of Treatment

- Anticoagulant medications (injections and warfarin tablets, injections and dabigatran or edoxaban, or rivaroxaban or apixaban) have been prescribed

to prevent your blood clot from growing larger so that the body can begin to dissolve the clot.

- Your body may be able to completely dissolve the clot, but in some cases, the clot never goes completely away; even with adequate anticoagulation therapy, some people will have chronic pain and swelling in the affected limb; people who have had one clot are at increased risk of having future clots.
- Warfarin tablets take several days to begin to work, so at first, LMWH or fondaparinux injections and warfarin tablets are used together.
- When the warfarin has become effective, you will be able to stop the LMWH or fondaparinux injections; you will continue to take warfarin tablets for 3 months or longer to prevent blood clots from returning.
- It is important for you to administer your LMWH or fondaparinux and warfarin exactly as directed.
- It is important not to use LMWH at the same time as dabigatran or edoxaban—first use LMWH then switch to dabigatran or edoxaban.

Subcutaneous Injection Technique (If Needed)

- You must learn to give yourself an injection of LMWH or fondaparinux under the skin; alternatively, you may have a family member or visiting nurse give it to you.
- If your LMWH or fondaparinux syringes were filled by the manufacturer, they can be stored at room temperature; if your syringes were filled by the pharmacy, they should be stored in the refrigerator; if you were instructed to fill your own syringes, you should prepare the syringe immediately prior to injecting its contents.
- If you see a bubble in the syringe, do not try to get it out; you may accidentally squirt out part of your dose.
- Choose an injection site on your abdomen; clean the area with alcohol, and then position an uncapped syringe at a 90° angle; pinch the skin, stick the needle in as far as it will go, and gently but firmly push the plunger down; this will inject the medicine into the skin; when all the medication has been injected, remove the needle and dispose of it in an appropriate container.
- You will likely experience a burning sensation when the medication is injected; this will go away after a few minutes.
- Rotate injection sites from side to side; do not inject into the same site more than once; avoid the area around your navel; do not inject into any bruises.

Blood Test Monitoring

- If you are taking warfarin, regular blood tests are required to make sure your medication is working properly.
- The PT tells how quickly your blood forms a clot; it is used to tell how well warfarin is working.
- The INR is a way to standardize the PT between laboratories; your goal INR range is between 2 and 3; if your INR is less than 2, you are at higher risk for clotting; if your INR is greater than 3, you are at higher risk for bleeding; your dose of warfarin will be adjusted based on the results of this test.
- If you are taking LMWH, fondaparinux, dabigatran, edoxaban, rivaroxaban, or apixaban, you need to have a blood test to determine how well your kidneys are working.

Warfarin Information

- Each strength of warfarin has a unique color; each time you refill your prescription, make sure your new tablets are the same color as the ones you have been taking; if not, ask your pharmacist why.
- Warfarin should be taken at approximately the same time each day.
- The most common and serious adverse drug reaction of warfarin is bleeding; you should be careful to avoid situations or activities that increase your risk of injury; apply direct pressure to control bleeding from superficial cuts.
- Warfarin has many drug interactions; always check with your provider before taking any new medications (including nonprescription medications and dietary supplements).
- Foods rich in vitamin K (dark green leafy vegetables, etc.) may interfere with warfarin; do not avoid foods rich in vitamin K, but try to maintain consistent dietary habits.
- Alcohol can increase your risk for bleeding and interfere with warfarin therapy; drink alcohol in moderation (one to two drinks per day); avoid binge drinking.
- If you need to have a surgery or diagnostic procedure, talk to your provider to make a plan for how to take your anticoagulant medication before and after the procedure. Do not stop taking your anticoagulant medication without first talking to your provider.

Dabigatran, Edoxaban, Rivaroxaban, and Apixaban Information

- Take rivaroxaban 15- or 20-mg doses with food to make sure the medication is well absorbed from your stomach.
- It is very important that you take each dose of your medication. These medications leave your body within hours; so missing a dose of medication may place you at a higher risk of blood clots.
- If you need to have a surgery or procedure, talk to your provider to make a plan for how to take your anticoagulant medication before and after the procedure. Do not stop taking your anticoagulant medication without first talking to your provider.
- There are a few drug interactions with dabigatran, edoxaban, rivaroxaban, and apixaban; always check with your provider before taking any new medications (including nonprescription medications and dietary supplements).

Contact Your Provider If You Experience

- Prolonged bleeding from a cut or scrape
- Blood in your urine
- Blood in your stool
- Prolonged nose bleeding (longer than 30 minutes)
- Increased swelling or pain where the blood clot was

Go to the Emergency Department If You Experience

- Sudden onset of shortness of breath
- Chest pain
- Coughing up blood
- Black tarry-appearing stool
- Severe headache of sudden onset
- Drooping of one side of your face
- Weakness in one of your arms
- Slurred speech

8 The appropriate initial duration of anticoagulation therapy to effectively treat an acute first episode of VTE for all patients is 3 months.[47] To prevent new VTE episodes not directly related to the preceding episode, continuing anticoagulation therapy may be required.[1] Individually tailoring anticoagulation therapy duration therapy beyond 3 months requires careful consideration of the circumstances surrounding the initial thromboembolic event, the presence of ongoing thromboembolic risk factors, bleeding risk, and patient preference.[47]

The most important considerations in determining recurrent VTE risk are whether the initial thrombotic event was associated with a major transient or reversible risk factor (eg, surgery, plaster cast leg immobilization, or hospitalization in the month prior to VTE) and the presence of active cancer.[47] The estimated cumulative risk of recurrent VTE after stopping anticoagulant therapy for VTE provoked by surgery is 1% after 1 year and 3% after 5 years. The cumulative risk of recurrent VTE provoked by a nonsurgical reversible risk factor is higher, 5% and 15% after 1 and 5 years, respectively. Three months of anticoagulation therapy is recommended in these situations.[18] Patients with a first unprovoked (idiopathic) VTE have approximately 10% recurrence risk in the first year and approximately 30% and 50% over 5 and 10 years, respectively. These patients should be considered for extended anticoagulation therapy when feasible.[47] With extended therapy, anticoagulation continues beyond 3 months, stopping only if bleeding risk increases substantially or change in patient preference for anticoagulation changes.[47] For patients with a second idiopathic VTE episode, extended anticoagulation is recommended.[47] Anticoagulation is rarely stopped in patients with VTE and active cancer because of the high recurrence risk.[47] Factors that may lead to the decision to stop anticoagulation therapy after 3 months include nonadherence with therapy, initial clot isolated in calf veins (even if idiopathic), moderate-to-high bleeding risk, or patient preference.[47]

Important risk factors for bleeding include age >75 years, previous noncardioembolic stroke, history of gastrointestinal bleeding, renal or hepatic impairment, anemia, thrombocytopenia, concurrent antiplatelet use (avoid if possible), nonadherence, poor anticoagulant control (for patients on warfarin), serious acute or chronic illness, and the presence of structural lesions (eg, tumor, recent surgery) that could bleed. One to two bleeding risk

factors suggest moderate bleeding risk while three or more suggest high bleeding risk.[18]

Various risk prediction rules aimed at identifying patients with very low recurrence risk after a first idiopathic VTE have evaluated whether the safe withdrawal of anticoagulation therapy may be possible after 3 months. Some factors that may predict lower recurrence risk include female sex, low D-dimer levels 1 month after stopping anticoagulation therapy, absence of residual clot on ultrasound, absence of hereditary and acquired thrombophilia, and absence of the postthrombotic syndrome. Risk assessment derived from combining several independent recurrence risk factors has also been investigated.[18] Further validation is needed before any one factor or prediction rule using a combination of factors can justify stopping anticoagulation. The decision to continue extended anticoagulation therapy should be reassessed periodically. Patients should be involved in any decision to continue therapy with consideration given to long-term prognosis, risk of bleeding, ability to adhere to anticoagulation therapy instructions, financial resources, lifestyle, and quality of life.[18] When anticoagulation therapy is stopped, there is a similar risk of recurrence whether patients have been treated for 3 months or longer.[47]

Patients with VTE are often tested for hereditary and acquired hypercoagulable states (thrombophilia). The available evidence does not support a strong association between genetically transmitted thrombophilia (especially factor V Leiden and prothrombin G20210A) and higher recurrent VTE rates.[10] For this reason, routine testing for thrombophilia is not recommended.[17]

For patients with proximal DVT, wearing graduated compression stockings does not reduce the risk of developing the postthrombotic syndrome.[49] However, for patients with persistent leg pain and swelling, graduated compression stockings can be suggested for symptomatic relief.

Pharmacologic Therapy

The anticoagulant drugs used to treat VTE are the same as those used for VTE prevention. However, there are important differences in the approach to VTE treatment regarding the doses used and duration of therapy.

Direct Oral Anticoagulants

Clinical trials have demonstrated that single-drug therapy with rivaroxaban or apixaban produces similar rates of recurrent VTE when compared to the traditional approach of initiating warfarin overlapped with enoxaparin for both acute DVT and PE.[50-52] The rate of major bleeding was lower with rivaroxaban in the PE trial,[51] but not in the DVT trial.[52] Apixaban was associated with significantly fewer major bleeding episodes than traditional therapy.[50] Both drugs are initiated with a higher dose and subsequently reduced to a maintenance dose (Fig. 38-11). Patients with CrCl <25 to 30 mL/min (0.42-0.5 mL/s), active cancer, and those requiring thrombolytic therapy were excluded from these clinical trials.[50-52] Subsequent studies have shown that edoxaban and rivaroxaban can be used in cancer patients with VTE and prescribing information for apixaban contains no restrictions based on creatinine clearance.[53,54] Replacing the effective but cumbersome combination warfarin overlapped with an injectable anticoagulant with a single-drug regimen simplifies VTE treatment. However, the higher acquisition cost of rivaroxaban and apixaban may be a barrier for some patients.

6 Oral dabigatran 150 mg twice daily and oral edoxaban 60 mg once daily have each been compared with traditional therapy in randomized, double-blind, noninferiority trials involving patients with acute VTE.[55,56] In these trials, all patients were initially given at least 5 days of parenteral anticoagulation therapy (UFH or LMWH) and then randomized to study treatment. Both dabigatran and edoxaban were noninferior to warfarin following the use of a parenteral anticoagulant. Dabigatran caused similar rate of major bleeding[55] and edoxaban significantly fewer major bleeding events when compared to warfarin.[56] The requirement for parenteral anticoagulation prior to initiation of dabigatran or edoxaban therapy is a disadvantage compared with single-drug approaches to VTE treatment. DOACs are preferred over traditional anticoagulation therapy approaches for the treatment of VTE in consensus guidelines.[57,58] Edoxaban and rivaroxaban may be reasonable alternatives to LMWH monotherapy for patients with cancer-associated VTE.[47,59]

Low-Molecular-Weight Heparin

LMWH given subcutaneously in fixed, weight-based doses (enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily) is at least as effective as UFH given intravenously for the treatment of VTE.[60] UFH is preferred as the initial anticoagulant for unstable patients in case thrombolytic therapy or embolectomy is needed.[61] Among patients without cancer treated initially with LMWH, acute treatment with LMWH is generally transitioned to long-

term warfarin therapy after at least 5 days of overlap with warfarin and an INR of 2.0 or greater.

Fondaparinux

Fondaparinux is a safe and effective option for acute VTE treatment.[18] Compared with weight-based LMWH dosing, fondaparinux's more flexible dosing scheme may be particularly useful with obese patients and those whose weight falls between commercially available prefilled LMWH syringes. Fondaparinux may be used to overlap with warfarin during initiation or for at least 5 days of parenteral anticoagulation prior to edoxaban or dabigatran initiation for acute VTE. Careful attention should be paid to renal function as fondaparinux is contraindicated if CrCl is <30 mL/min (0.5 mL/s).[62]

Unfractionated Heparin

UFH may be administered subcutaneously (SQ) or by continuous intravenous (IV) infusion (Table 38-6). The anticoagulant response to UFH is highly variable when given intravenously and it is standard practice to adjust the dose according to coagulation test results. The aPTT and antifactor Xa concentration are the two most commonly used tests to monitor the UFH anticoagulant effect. The therapeutic aPTT range at each institution should be adapted to the responsiveness of the reagent and instrument used.[60] Weight-based UFH dosing by IV infusion is preferred. However, failure to give a sufficient IV UFH dose increases VTE recurrence risk.[60] IV UFH requires hospitalization with frequent aPTT monitoring and dose adjustment. Failure to achieve an adequate response to UFH therapy is common despite close monitoring.[60] Consequently, UFH has largely been replaced by LMWH, fondaparinux, and DOACs for the management of acute VTE. However, because the clearance of LMWH, fondaparinux, and DOACs is dependent on renal function, UFH continues to have a role in acute VTE treatment in patients with CrCl <30 mL/min (0.5 mL/s).[18,63] UFH should also be used in unstable patients potentially requiring invasive interventions or thrombolytic therapy.[18,63]

TABLE 38-6

Weight-Based[a] Dosing for UFH Administered by Continuous IV Infusion for Acute VTE

Initial Bolus Dose	**Initial Infusion Rate**
80 units/kg (maximum = 10,000 units)	18 units/kg/hr (maximum = 2,300 units/hr)
Maintenance Infusion Rate	
Activated Partial Thromboplastin Time (seconds)	**Dose Adjustment**
<37 (or antifactor Xa <0.20 unit/mL [kU/L])	80 units/kg bolus, and then increase infusion by 4 units/kg/hr
37-47 (or antifactor Xa 0.20-0.29 unit/mL [kU/L])	40 units/kg bolus, and then increase infusion by 2 units/kg/hr
48-71 (or antifactor Xa 0.30-0.70 unit/mL [kU/L])	No change
72-93 (or antifactor Xa 0.71-1 unit/mL [kU/L])	Decrease infusion by 1-2 units/kg/hr
>93 (or antifactor Xa >1 unit/mL [kU/L])	Hold infusion for 1 hr, and then decrease by 3 units/kg/hr

[a]Use actual body weight for all calculations. Adjusted body weight may be used for obese patients (>130% of ideal body weight).

Data from Reference 60.

Warfarin

5 Warfarin monotherapy is unacceptable for acute VTE treatment because of the slow onset of effect. However, warfarin is effective for long-term VTE management provided it is started concurrently with rapid-acting injectable anticoagulant therapy.[58] Injectable anticoagulation should overlap with warfarin therapy for at least 5 days and until an INR ≥2 has been achieved for at least 24 hours.[58] The initial dose of warfarin should be 5 to 10 mg for most patients with subsequent adjustments to achieve and maintain an INR between 2 and 3 (Fig. 38-9).

Thrombolysis and Thrombectomy

Most VTE cases require only anticoagulation therapy. In select cases, removing the occluding thrombus by pharmacologic or surgical means may be warranted.[58] Thrombolytic agents are proteolytic enzymes that enhance the conversion of plasminogen to plasmin. Thrombolytic therapy for DVT improves early venous patency, but this does not necessarily translate into improved long-term outcomes.[58] If thrombolytic therapy is pursued, catheter-directed thrombolysis is suggested over systemic thrombolysis as the latter is not considered appropriate for DVT treatment in the United States.[58] Patients with extensive proximal DVT presenting within 14 days of symptom onset, with good functional status, low bleeding risk, and a life expectancy of a year or more are thrombolysis candidates (Table 38-7). Patients with DVT involving the iliac and common femoral veins are at the highest risk for postthrombotic syndrome and may derive the most benefit from thrombus removal strategies.

TABLE 38-7

Thrombolysis for the Treatment of VTE

- The majority of patients with VTE do not require thrombolytic therapy
- Thrombolytic therapy for DVT should be reserved for patients who present with extensive proximal DVT (eg, ileofemoral) within 14 days of symptom onset, have good functional status, and are at low risk of bleeding
- Thrombolytic therapy should be administered to patients with massive PE with evidence of hemodynamic compromise (hypotension or shock) unless contraindicated by bleeding risk
- Routine use of thrombolytic therapy is not recommended for PE without hypotension or shock but might be appropriate for selected high-risk patients (see below) provided the risk of bleeding is acceptable
- Factors associated with high risk for adverse PE outcomes include:
  - Ill-appearing patients with marked dyspnea, anxiety, and low oxygen saturation
  - Elevated troponin levels
  - Right ventricular dysfunction on echocardiography
  - Right ventricular enlargement on chest CT
- Factors that increase the risk of bleeding must be evaluated before thrombolytic therapy is initiated (ie, recent surgery, trauma or internal bleeding, uncontrolled hypertension, recent stroke or intracranial hemorrhage)
- Baseline labs should include CBC and blood typing in case transfusion is needed
- Alteplase 100 mg infused via peripheral vein over 2 hours is the most commonly used thrombolytic for patients with PE
- Before thrombolytic therapy for PE, IV UFH should be administered in full therapeutic doses
- During thrombolytic therapy, it is acceptable to either continue or suspend IV UFH (suspending UFH is the most common practice in the United States)
- aPTT should be measured following the completion of thrombolytic therapy
  - If aPTT is <80 seconds, UFH infusion should be started and adjusted to maintain aPTT in the therapeutic range
  - If aPTT is >80 seconds, measure every 2-4 hours and start UFH infusion when aPTT is <80 seconds
- Avoid phlebotomy, arterial puncture, and other invasive procedures during thrombolytic therapy to minimize the risk of bleeding

CBC, complete blood cell count; CT, computed tomography.

Data from References 1 and 58.

In acute PE, successful clot dissolution with thrombolytic therapy reduces elevated pulmonary artery pressure and normalizes right ventricular dysfunction. However, the risk of death from PE should outweigh the risk of serious bleeding associated with thrombolytic therapy. Therefore, patients being considered for thrombolytic therapy should be screened carefully for contraindications relating to bleeding risk (Table 38-7).[58,64] Thrombolytic therapy is considered necessary in addition to aggressive interventions such as volume expansion, vasopressor therapy, intubation, and mechanical ventilation for patients with massive PE accompanied by shock and cardiovascular collapse (about 5% of patients with PE).[58,64] Thrombolytic therapy in these patients should be administered without delay to reduce risk of progression to multisystem organ failure and death.

The benefit of thrombolytic therapy in patients with PE without hemodynamic compromise is less clear and requires rapid risk stratification to determine the initial treatment intensity.[61] Low-risk patients can be discharged early or managed as outpatients, and high-risk patients should be admitted to an intensive care unit for surveillance and/or advanced therapies such as thrombolysis.[65] The Pulmonary Embolism Severity Index (PESI) is a prognostic tool utilizing 11 routinely available clinical parameters: demographics (age and gender), comorbid illnesses (cancer, heart failure, and chronic lung disease), and clinical findings (pulse, systolic blood pressure, respiratory rate, temperature, mental status, and arterial oxygen saturation). PESI stratifies patients into five risk classes with classes I and II considered low risk.[65] Patients with acute PE and evidence of hemodynamic compromise, right ventricular strain by echocardiography, or elevated cardiac biomarker levels have higher mortality risk than patients without these findings, but the risk of death is much less than patients with hemodynamic compromise. Therefore, routine use of thrombolytic therapy is not recommended in these patients, but this decision needs to be individualized (Table 38-7).[58]

In rare circumstances, surgical thrombectomy for extensive ileofemoral DVT may be necessary, but catheter-directed thrombolysis is preferred if bleeding risk is acceptable.[21] For acute PE treatment, catheter-based embolectomy might be suitable in settings where the necessary expertise and resources are available for patients who have contraindications to thrombolytic therapy, have failed thrombolytic therapy, or in whom death is likely before thrombolytic onset.[21] Surgical embolectomy is reserved for patients experiencing massive PE with hemodynamic instability when thrombolysis is either contraindicated or failed, or when insufficient time exists for thrombolysis to take effect.[18] In chronic PE cases—where persistent emboli produce CTPH, hypoxemia, and right-sided heart failure—surgical pulmonary thromboendarterectomy offers greater benefit than anticoagulants and may be the treatment of choice if performed by an experienced surgical team.[21] A permanent IVC filter is usually inserted before or during the procedure and long-term anticoagulation therapy is needed.[18]

Special Populations

Some patient populations with VTE require special consideration due to increased risk for recurrence, adverse events, or altered anticoagulant pharmacokinetics.

Pregnancy

Anticoagulation therapy is commonly used for the prevention and treatment of VTE during pregnancy.[8] UFH and LMWH do not cross the placenta and are preferred during pregnancy (Table 38-8).[8] Warfarin crosses the placenta and can result in fetal bleeding, central nervous system abnormalities, and embryopathy and should not be used for VTE treatment during pregnancy.[8] Women of childbearing age taking warfarin must be counseled regarding fetal risks and the need for effective contraception. DOACs should be avoided in pregnancy until more information regarding their safety is available.[66-69] Fondaparinux has not been extensively studied in pregnancy and may cross the placenta.[62] However, fondaparinux may be considered in pregnant patients intolerant to LMWH or those with a history of HIT.[70]

TABLE 38-8

Anticoagulant Use During Pregnancy and Delivery

Acute treatment[a]	LMWH • Enoxaparin 1 mg/kg SC q 12 hr or 1.5 mg/kg q 24 hr *Or* • Dalteparin 100 units/kg SC q 12 hr *Or* UFH • Initiate using weight-based IV therapy and adjust dose to achieve therapeutic anti-Xa level for at least 5 days • Transition to SC adjusted-dose UFH administered q 8-12 hr with mid-interval anti-Xa activity adjusted to achieve an anti-Xa level of 0.3-0.7 unit/mL [kU/L][b]
Long-term treatment[c]	LMWH • Maintain initial LMWH dose regimen throughout pregnancy *Or* • Alter LMWH dose in proportion to any weight change (usually gain) *Or* UFH • Obtain anti-Xa level at the midpoint of the dosing interval and adjust UFH dose to achieve an anti-Xa level of 0.3-0.7 unit/mL (kU/L)
Issues at the time of delivery	Elective induction of labor • Discontinue UFH or LMWH 24 hr prior to induction • Initiate therapeutic doses of UFH by IV infusion and discontinue 4-6 hr prior to the expected time of delivery if the risk of recurrent VTE is deemed high Spontaneous labor • For LMWH, if there is a reasonable expectation that significant anticoagulant effect will be present at the time of delivery: (a) epidural should be avoided and (b) reversal with protamine sulfate may be considered • For UFH, monitor the aPTT and reverse with protamine sulfate if aPTT is prolonged near the time of delivery Postpartum • Commence UFH or LMWH as soon as safely possible (usually 12 hr following delivery) • Concurrently initiate warfarin therapy and discontinue UFH or LMWH when the INR is 2 or greater • Continue anticoagulants for at least 6 weeks following delivery • Warfarin can be safely used by women who are breast-feeding

[a]Twice-daily LMWH preferred during pregnancy due to increased clearance.

[b]Anti-Xa monitoring preferred as the relationship between aPTT and heparin levels differs in pregnant compared with nonpregnant patients.

[c]As pregnancy progresses the volume of distribution of LMWH changes, glomerular filtration rate increases, and most women gain weight.

SC, subcutaneously.

Data from Reference 8.

Pregnant women with a history of VTE should receive VTE prophylaxis for 6 weeks after delivery.[71] Antenatal prophylaxis may also be indicated in women with a history of multiple VTE, VTE associated with pregnancy or estrogen therapy, or known thrombophilia. Anticoagulation for acute VTE during pregnancy should continue for at least 6 weeks postpartum and a minimum total duration of 3 months.[8] Warfarin, UFH, and LMWH are safe during breastfeeding.[60,72] It is not known if DOACs are excreted in human milk and breastfeeding is not recommended.[66-69]

Pediatric Patients

VTE in pediatric patients is increasing secondary to prematurity, cancer, trauma, surgery, congenital heart disease, and systemic lupus erythematosus. Pediatric patients rarely experience unprovoked VTE, but often develop DVTs associated with indwelling central venous catheters.[73] In many cases, recommendations for anticoagulant therapy in pediatric patients are largely extrapolated from data from clinical trials in adults. However, in recent years, the available information, knowledge, and expertise in relation to appropriate diagnosis, prevention, and clinical management of VTE in neonates and children have increased dramatically.[73] When possible, a pediatric hematologist with experience treating VTE should manage pediatric patients.[74]

Anticoagulation with LMWH and warfarin remains the most frequently used approach for VTE treatment in pediatric patients. The decision between LMWH and warfarin should depend on patient values and preferences, health services resources, infrastructure and support, indication for anticoagulation, comorbidities, and other medications. The recommended target INR range, as well as the duration of therapy, is the same as for adults.[73] Frequent INR monitoring and warfarin dose adjustments are typically required. Obtaining blood for coagulation monitoring tests in pediatric patients is challenging because many have poor venous access. Using finger-stick blood samples with point-of-care INR monitors is an option in this situation. Despite the need for daily injections, LMWH is an attractive alternative for pediatric patients due to the low potential for drug-drug interactions and less frequent laboratory testing. Most experts recommend anti-Xa activity monitoring with goal antifactor Xa levels between 0.5 and 1.0 unit/mL (kU/L) 4 to 6 hours following subcutaneous injection. Warfarin should be initiated concurrently with UFH or LMWH therapy. Similar to adults, therapy should be overlapped for a minimum of 5 days and until the INR is therapeutic. Anticoagulation should be continued for up to 3 months for provoked VTE and 6 to 12 months for unprovoked VTE.[73] DOACs are attractive alternatives in pediatric patients due to oral administration and no need for routine coagulation monitoring; however, safety, effectiveness, and dosing in this population have not been established.[66-69] Thrombolysis has been used in pediatric patients, but published data are very limited—routine use is not recommended with the exception of PE associated with hemodynamic compromise.[73]

Patients with Cancer

Cancer-related VTE is associated with threefold higher rates of recurrent VTE and up to sixfold higher rates of bleeding. In addition, increased rates of recurrent VTE have been associated with warfarin-based approaches to VTE treatment in patients with active cancer.[75] Warfarin therapy in cancer patients is often complicated by drug interactions (eg, chemotherapy and antibiotics) and the need to interrupt therapy for invasive procedures. Maintaining stable INR control is also more difficult in this patient population because of nausea, anorexia, and vomiting.[18]

Long-term LMWH monotherapy (dalteparin 200 units/kg every 24 hr for 30 days, followed by 150 units every 24 hr, or enoxaparin as described above) is a preferred option for patients with cancer-associated VTE. Treatment of cancer-related VTE with LMWH monotherapy rather than traditional warfarin-based therapy decreases recurrent VTE rates without increasing bleeding risk but does not affect overall mortality.[16,18,76,77] Advantages of LMWH over warfarin for VTE treatment in cancer are expected to be greatest in those with one or more of the following: metastatic disease, treatment with aggressive chemotherapy, extensive VTE at presentation, liver dysfunction, poor or unstable nutritional status, or desire to avoid frequent blood draws for coagulation monitoring.[18]

For patients with cancer and VTE receiving LMWH, therapy should continue for 3 to 6 months after which the LMWH can be continued or warfarin or DOAC therapy substituted. Anticoagulation therapy should continue for as long as the cancer is “active” and while the patient is receiving antitumor therapy.[18] A risk-to-benefit assessment should be performed on a regular basis considering overall clinical status, bleeding risk, quality of life, and life expectancy.[18] For patients with cancer who experience a VTE recurrence despite receiving anticoagulant therapy, LMWH appears to be more effective than warfarin-based therapy in preventing further recurrences, and increasing the anticoagulant intensity may not be necessary for this situation.[75]

Edoxaban and rivaroxaban have been compared to dalteparin monotherapy for the treatment of cancer-related VTE and were as effective as dalteparin for preventing VTE recurrence but caused more bleeding.[53,54] Excess DOAC-related bleeding often occurred in the gastrointestinal tract in patients with gastrointestinal malignancy.[53] Thus, DOACs may be an important alternative to LMWH for cancer-related VTE given the limited tolerability of long-term LMWH but should be used with caution in patients with tumors involving the gastrointestinal lumen.

Patients with Renal Insufficiency

Patients with acute or chronic kidney disease often require anticoagulation for VTE prevention or treatment. With the exception of warfarin and UFH, most anticoagulants require adequate renal function for their elimination. Accumulation of drug is possible during treatment with LMWH, fondaparinux, and most DOACs.[60,72] In addition, patients with chronic kidney disease are at increased risk of bleeding, regardless of anticoagulant choice.[25]

LMWHs are renally eliminated and should be used with caution in patients with severe renal impairment.[78] Enoxaparin has specific labeling for patients with CrCl <30 mL/min (0.5 mL/s), but supporting evidence is limited to pharmacokinetic modeling analyses.[79] Bleeding and recurrent VTE outcomes for patients with CrCl <30 mL/min (0.5 mL/s) receiving enoxaparin 1 mg/kg once daily for acute VTE treatment was comparable to patients with normal renal function in one retrospective study.[63] However, UFH remains preferred for acute VTE treatment in this setting until further evidence becomes available.[18] Fondaparinux is contraindicated in patients with CrCl <30 mL/min (0.5 mL/s).

DOACs are eliminated to varying[80] degrees through the kidney and require dose adjustment for renal impairment.[66-69] Periodic renal function assessment is important during long-term DOAC therapy, especially for patients with CrCl <50 mL/min (0.83 mL/s). The use of dabigatran and rivaroxaban in patients with CrCl <30 mL/min (0.5 mL/s) should be avoided.[67,68] Edoxaban dosing is reduced to 30 mg once daily in patients with CrCl 15 to 50 mL/min (0.25-0.83 mL/s).[69] Product labeling for apixaban permits its use in patients with end-stage kidney disease and emerging data suggest that apixaban may be an option for these patients.[66,80]

Patients Undergoing Invasive Procedures

Patients scheduled to undergo invasive procedures often require temporary discontinuation of anticoagulation therapy.[81] The decision to withhold anticoagulation therapy should be based on the bleeding risk associated with the procedure and the patient's underlying thromboembolic risk. Anticoagulation therapy is typically continued in patients undergoing minimally invasive procedures such as dental work, cataract surgery, or minor dermatologic procedures.[82] If the bleeding risk from the procedure is considerable, near-normal hemostasis should be achieved prior to the procedure. For DOACs the time required for the restoration of normal hemostasis after interrupting therapy is dependent on renal function and medication half-life. Stopping DOACs 2 days prior to invasive procedures is usually sufficient to restore near-normal hemostasis for patients with normal renal function. Additional days off therapy may be required for patients with impaired renal function.[66-69] The anticoagulant effect of dabigatran can be rapidly reversed with idarucizumab and andexanet can be used to reverse the effect of rivaroxaban and apixaban for patients requiring urgent surgical interventions.[83,84] Up to 5 days may be required for the restoration of normal hemostasis after warfarin discontinuation. Patients at high thromboembolic risk (ie, DVT or PE in the previous month) may be considered for so-called "bridge therapy" with UFH or an LMWH given before and after the procedure.[82] Bridge therapy has been associated with increased major bleeding without offering additional recurrent VTE risk reduction in low-to-moderate risk patients. Therefore, most patients with VTE can safely interrupt warfarin for invasive procedures without using bridge therapy.[81] Resumption of anticoagulation following an invasive procedure is based on post-procedure bleeding risk and drug-specific time to onset of the anticoagulant effect (Table 38-9).

TABLE 38-9

Anticoagulant Interruption and Resumption Around High Bleeding-Risk Invasive Procedures

Anticoagulant	Timing of Anticoagulant Interruption Prior to Procedure	Day of Procedure	Timing of Anticoagulant Resumption After Procedure[a]
UFH	• IV: hold infusion 6-8 hours prior to the procedure • SC: last dose 12 hours prior to the procedure	No anticoagulation	24-48 hours after the procedure
LMWH	Last dose 24 hours prior to the procedure		
Fondaparinux	Last dose 2 days prior to the procedure		
Apixaban	Last dose 2 days prior to the procedure		
Dabigatran • CrCl <50 mL/min (0.83 mL/s) • CrCl ≥50 mL/min (0.83 mL/s)	• Last dose 3-4 days prior to the procedure • Last dose 2 days prior to the procedure		
Edoxaban	Last dose 2 days prior to the procedure		
Rivaroxaban	Last dose 2 days prior to the procedure		
Warfarin[b]	Last dose 4-5 days prior to the procedure		Day of or 1 day after the procedure

[a]Assumes hemostasis has been achieved.

[b]Warfarin hold time is dependent on the INR prior to beginning the interruption and the target INR for the day of the procedure (eg, patients beginning with elevated INR may require a longer holding period to achieve target INR for the day of procedure)

DRUG CLASS INFORMATION

Optimal use of anticoagulant therapies requires knowledge of pharmacologic and pharmacokinetic characteristics as well as systematic management and ongoing patient education (Table 38-5) to reduce the risks of bleeding and therapeutic failure (Table 38-10).

TABLE 38-10

Risk Factors for Major Bleeding While Taking Anticoagulation Therapy

Higher anticoagulation intensity
Initiation of therapy (first few days and weeks)
Unstable anticoagulation response
Age >65 years
Concurrent aspirin or other antiplatelet therapy
Concurrent nonsteroidal anti-inflammatory drug use
History of gastrointestinal tract bleeding
Recent surgery or trauma
High risk for fall/trauma
Heavy alcohol use
Renal failure
Cerebrovascular disease
Malignancy

Data from Reference 25.

Direct Oral Anticoagulants

Shortcomings with warfarin, LMWH, fondaparinux, and UFH have driven the search for replacements with rapid anticoagulant onset and oral administration without the need for monitoring. The DOACs have provided a major advance in VTE prevention and treatment.

Pharmacology/Mechanism of Action

Rivaroxaban, apixaban, and edoxaban are potent and selective inhibitors of both free and clot-bound factor Xa that do not require antithrombin to exert their anticoagulant effect.[58] Dabigatran is a selective, reversible, direct factor IIa (thrombin) inhibitor.[67]

Pharmacokinetics

Rivaroxaban, apixaban, and edoxaban have good oral bioavailability (greater than 60%), whereas dabigatran is formulated as a prodrug (dabigatran etexilate) to overcome poor oral bioavailability.[66-69] All DOACs reach peak plasma concentrations in less than 4 hours. Each drug is renally eliminated to a variable extent, as low as 27% for apixaban and as high as 80% for dabigatran.[66-69] Terminal half-lives range from 9 to 12 hours for rivaroxaban, apixaban, and edoxaban, and 14 to 17 hours for dabigatran.[66-69] DOACs should be used with caution in patients with renal dysfunction.[85] Rivaroxaban and apixaban are substrates of cytochrome p450 (CYP) 3A4 and the P-glycoprotein (P-gp) transporter.[66] Edoxaban and dabigatran do not undergo

significant CYP 3A4 metabolism, but all are P-gp substrates. Strong inhibitors and inducers of CYP 3A4 enzymes or P-gp may cause changes in DOAC exposure and increase the risk of bleeding or VTE events.[66-69]

Efficacy

DOACs are noninferior to warfarin therapy overlapped with LMWH for VTE treatment.[66-69] For patients who are at high risk of VTE recurrence who require extended anticoagulant therapy beyond 6 months, rivaroxaban and apixaban at either the treatment or prophylactic doses were superior to low-dose aspirin or placebo, respectively.[86,87] Similarly, when compared to LMWH, rivaroxaban and apixaban are noninferior for preventing VTE following hip or knee replacement surgery.[66-68,88]

Adverse Drug Reactions

The most common adverse drug reaction associated with DOAC therapy is bleeding.[66-69] The International Society for Thrombosis and Haemostasis defines major bleeding as fatal bleeding, any bleeding into a critical anatomic space (eg, intracranial bleeding, hemarthrosis, pericardial bleeding, or intraocular bleeding), bleeding that requires transfusion of two or more units of whole blood or red cells, or bleeding that leads to a greater than 2 g/dL (20 g/L; 1.24 mmol/L) drop in hemoglobin concentration. Bleeding that does not meet the major bleeding criteria but requires medical intervention or alteration of therapy is sometimes termed clinically relevant nonmajor bleeding. All other bleeding is considered minor and is common during anticoagulation therapy even in the most expertly managed patients. The most frequent nonbleeding adverse events in clinical trials of DOACs were gastrointestinal complaints.[66-69]

Patients presenting with significant bleeding during DOAC therapy should receive routine supportive care (fluid resuscitation, blood transfusion, maintenance of renal function, bleeding source identification, and surgical intervention if needed), and discontinuation of anticoagulation therapy.[89] Because DOACs have relatively short half-lives, these measures may control bleeding in many patients, especially those with normal renal function.[89] Activated charcoal may provide some benefit if drug intake occurred within the previous 2 hours.[89]

Idarucizumab is a humanized monoclonal antibody fragment that rapidly reverses dabigatran's anticoagulant effect following IV administration.[83] Idarucizumab can be used during emergency situations such as life-threatening bleeding and when there is a need for urgent surgical intervention. Andexanet is a recombinant Factor Xa molecule that binds the Factor Xa inhibitors rivaroxaban and apixaban without having intrinsic antithrombotic activity. It can be used for the reversal of life-threatening bleeding in patients taking rivaroxaban or apixaban (Table 38-11). If traditional hemostatic measures fail or drug-specific reversal agents are not available in a life-threatening bleeding situation, it may be reasonable to consider the use of 4-factor prothrombin complex concentrates (PCCs) while weighing the associated risk for thrombotic events. Animal, in vitro, and healthy volunteer studies have shown that these agents reverse coagulation laboratory parameters, but controlled studies of these agents in bleeding patients taking DOACs are not available. Fresh-frozen plasma (FFP) is unlikely to provide clinical benefit.[89]

TABLE 38-11

Reversal Agents for the DOACs

Reversal Agent	Target	Outcomes and Current Status
Idarucizumab (monoclonal antibody fragment)	Dabigatran	• Reversed anticoagulant effect of dabigatran in patients with serious bleeding or needing urgent reversal for a procedure • Approved by the FDA in October 2015
Andexanet (modified recombinant Factor Xa)	Rivaroxaban, Apixaban	• Reversed anticoagulant effect of rivaroxaban and apixaban in patients with intracranial hemorrhage • Approved by the FDA in May 2018

Data from References 83 and 90-92.

Drug-Drug and Drug-Food Interactions

Adding aspirin to DOAC therapy nearly doubles bleeding rates and should be avoided in most patients with VTE. Although the DOACs have far fewer drug interactions than warfarin, all DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with strong P-gp inhibitors or inducers. Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP 3A4.[66-69] Which drug interactions must be avoided is a matter of debate. Strong inducers of P-gp and CYP 3A4 enzymes such as carbamazepine and rifampin should be avoided. Caution should be used with concurrent use of strong P-gp or combination P-gp/CYP 3A4 inhibitors with a DOAC, particularly in the setting of renal insufficiency.[66-69] When interacting drugs cannot be avoided it may be best to switch to warfarin for dose adjustment guided by INR monitoring.

Dosing and Administration

Rivaroxaban and apixaban can be used in a single-drug approach for acute VTE treatment, whereas at least 5 days of parenteral anticoagulant therapy is required prior to initiating edoxaban or dabigatran for acute VTE (Fig. 38-11). The 15- and 20-mg doses of rivaroxaban should be taken with food to enhance oral absorption, but all other DOACs can be taken irrespective of food.[66-69]

Low-Molecular-Weight Heparin

LMWH fragments produced by either chemical or enzymatic depolymerization of UFH are heterogeneous mixtures of sulfated glycosaminoglycans with approximately one-third the mean molecular weight of UFH.[60] Advantages of LMWH over UFH include predictable anticoagulation dose-response, improved subcutaneous bioavailability, dose-independent clearance, longer biologic half-life, lower incidence of thrombocytopenia, and reduced need for routine laboratory monitoring.[60]

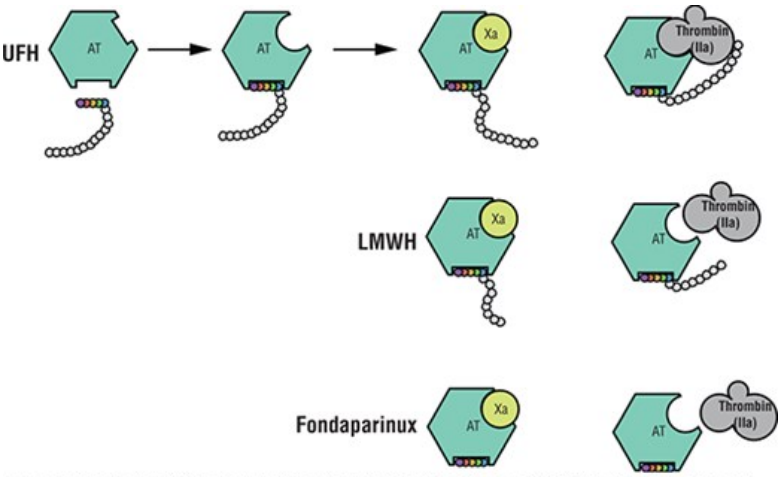
Pharmacology/Mechanism of Action

LMWH prevents thrombus growth and propagation by enhancing and accelerating the activity of antithrombin.[60] The anticoagulant effect of LMWH (and UFH) is mediated through a specific pentasaccharide sequence that binds to antithrombin, provoking a conformational change (Fig. 38-12). To inactivate thrombin, the heparin molecule must form a ternary complex bridging between antithrombin and thrombin.[60] Only molecules containing more than 18 saccharides are able to bind to both antithrombin and thrombin simultaneously. Smaller heparin molecules cannot facilitate the interaction between antithrombin and thrombin. In contrast, the inactivation of factor Xa does not require the formation of a bridge with antithrombin but requires only heparin binding to antithrombin via the specific pentasaccharide sequence. Heparin molecules with as few as five saccharide units are able to catalyze the inhibition of factor Xa. The principal difference in the pharmacologic activity of LMWH and UFH is their relative inhibition of factor Xa and thrombin. Because of smaller chain lengths, LMWH has limited activity against thrombin (Fig. 38-12). The ratio of antifactor Xa:IIa activity

varies between 4:1 and 2:1.

FIGURE 38-12

Pharmacologic activity of UFH, LMWHs, and fondaparinux. (AT, antithrombin.)



Pharmacokinetics

Compared with UFH, LMWH has a more predictable anticoagulation response. The improved pharmacokinetic profile of LMWH is the result of reduced binding to proteins and cells.[60] The bioavailability of LMWH is about 90% when administered subcutaneously. The peak anticoagulation effect is seen within 3 to 5 hours of subcutaneous LMWH injection and the predominant mode of elimination for LMWH is renal. Consequently, the biologic half-life may be prolonged in patients with renal impairment.[60] The plasma half-life of LMWH preparations is 3 to 6 hours. Unlike UFH, the clearance of LMWH is independent of dose.[60]

Efficacy

The efficacy of LMWH for the prevention of VTE was established in clinical trials in comparison to low-dose UFH and placebo. For the treatment of VTE, the efficacy of fixed weight-based LMWH was compared to aPTT-adjusted IV UFH; all patients were transitioned to warfarin for long-term therapy.[79,93]

Adverse Drug Reactions

As with other anticoagulants, bleeding is the most common LMWH adverse drug reaction.[25] The frequency of major bleeding may be less with LMWH than with UFH, but this has not been consistently demonstrated in clinical trials.[25] Although there is no proven method for reversing LMWH anticoagulation if major bleeding occurs, IV protamine sulfate can be administered. However, because of limited binding to the shorter LMWH chains, protamine sulfate neutralizes only around 60% to 75% of LMWH anticoagulant activity.[60] The recommended dose of protamine sulfate is 1 mg/1 mg of enoxaparin or 1 mg/100 antifactor Xa units of dalteparin administered in the previous 8 hours. A second protamine sulfate dose of 0.5 mg/1 mg or 100 antifactor Xa units can be given if bleeding continues. Smaller doses of protamine sulfate can be used if the LMWH dose was given in the previous 8 to 12 hours. The use of protamine sulfate is not recommended if LMWH was administered more than 12 hours earlier.[60]

Although thrombocytopenia can occur with LMWH use, the incidence of HIT is one-third of that observed with UFH, perhaps due to the reduced propensity of LMWH to bind to platelets.[60] However, LMWH exhibits nearly 100% cross-reactivity with UFH antibodies in vitro, and thus LHWH should be avoided in patients with an established diagnosis or history of HIT.[60] The risk of osteoporosis appears to be lower with LMWH than with UFH.[60]

Drug-Drug Interactions

The concurrent use of drugs that enhance bleeding risk should be avoided during LMWH therapy if possible. This includes aspirin or other antiplatelet agents, nonsteroidal anti-inflammatory drugs, dipyridamole, or sulfinpyrazone.[79,93]

Dosing and Administration

LMWH is given in fixed or weight-based doses based on the product and indication. Doses should be based on actual body weight and dose capping (ie, a fixed, maximum daily dose) is not recommended.[78] The dose for enoxaparin is expressed in milligrams, whereas dalteparin doses are expressed in units of antifactor Xa activity. LMWH is given by subcutaneous injection.

Significant LMWH accumulation is possible in patients with severe renal impairment.[60] The enoxaparin dose should be reduced or the dosing interval extended to once daily in patients with CrCl <30 mL/min (0.5 mL/s).[79] Dalteparin is less reliant upon renal elimination than enoxaparin; however, its pharmacokinetics are insufficiently characterized in renal insufficiency.[94] LMWH use in patients with end-stage renal disease receiving hemodialysis is poorly understood; thus, UFH is preferred for these patients.[60] Some experts recommend measuring antifactor Xa activity if LMWH therapy is continued for more than a few days in patients with severe renal disease.[60] For patients with CrCl <30 mL/min (0.5 mL/s) who require VTE prophylaxis, enoxaparin 30 mg once daily is recommended.[60]

Fondaparinux

Fondaparinux is a synthetic molecule consisting of the five critical saccharide units that bind specifically, but reversibly, to antithrombin. Unlike UFH or LMWH, fondaparinux inhibits only factor Xa activity.[60]

Pharmacology/Mechanism of Action

Fondaparinux prevents thrombus generation and clot formation by indirectly inhibiting factor Xa activity through its interaction with antithrombin (Fig. 38-12). Fondaparinux is not destroyed during this process and is released to bind to other antithrombin molecules.[60]

Pharmacokinetics

Fondaparinux is rapidly and completely absorbed following subcutaneous administration achieving peak plasma concentrations approximately 2 hours after a single dose and 3 hours with repeated once-daily dosing. At therapeutic concentrations, fondaparinux does not bind to red blood cells or other plasma proteins.[60] Fondaparinux is primarily eliminated unchanged in the urine and its terminal elimination half-life is 17 to 21 hours.[60] The anticoagulant effect of fondaparinux persists for 2 to 4 days following discontinuation of the drug in patients with normal renal function.

Efficacy

The efficacy of fondaparinux for the prevention of VTE was established in several clinical trials in comparison to LMWH. For the treatment of VTE, the efficacy of fixed weight-based dosing of fondaparinux was compared to weight-based dosing of LMWH; all patients were transitioned to warfarin for long-term therapy.[62]

Adverse Drug Reactions

The primary adverse drug reaction associated with fondaparinux therapy is bleeding.[62] Fondaparinux should be used with extreme caution with neuraxial anesthesia or following spinal puncture because of the risk for spinal or epidural hematoma formation.[62] Some case reports have implicated fondaparinux as a cause of HIT, while others have documented successful HIT treatment with fondaparinux.[95] A specific antidote to reverse the antithrombotic activity of fondaparinux is not currently available.[60]

Drug-Drug Interactions

Fondaparinux has no known pharmacokinetic drug interactions; other drugs with anticoagulant, fibrinolytic, or antiplatelet activity increase the risk of

bleeding.[62]

Dosing and Administration

The dose of fondaparinux for VTE prevention is 2.5 mg injected subcutaneously once daily following surgery if hemostasis has been established. It is important to avoid initiating fondaparinux too soon because there is a significant relationship between first dose timing and major bleeding risk.[60] Patients weighing less than 50 kg should not receive VTE prophylaxis with fondaparinux.[62] The usual duration of prophylaxis is 5 to 9 days, but extended prophylaxis for up to 35 days following a lower extremity orthopedic procedure may be used.[37] For the treatment of DVT or PE, the dose of fondaparinux is 5 mg for patients up to 50 kg, 7.5 mg for 50 to 100 kg, and 10 mg for >100 kg.[62]

Unfractionated Heparin

UFH has been used for VTE prevention and treatment for decades. Commercially available UFH preparations are derived from bovine lung or porcine intestinal mucosa. Although some differences exist between the two sources, no differences in antithrombotic activity have been demonstrated.[60]

Pharmacology/Mechanism of Action

UFH is a heterogeneous mixture of sulfated mucopolysaccharides of variable lengths and pharmacologic properties.[60]

Only one-third of the UFH molecules possess the unique pentasaccharide sequence with an affinity for antithrombin. Antithrombin inhibits factor IXa, Xa, XIIa, and IIa activity. Thrombin and Xa are most sensitive to UFH–antithrombin complex inhibition. UFH has an antifactor Xa:IIa activity ratio of 1:1 (Fig. 38-12).[60] UFH prevents thrombus growth and propagation allowing endogenous thrombolytic systems to lyse the clot.[60]

After it has produced its effect UFH uncouples from antithrombin and quickly recouples with another antithrombin molecule.[60]

Pharmacokinetics

UFH is not reliably orally absorbed because of its large molecular size and anionic structure. The bioavailability and biologic activity of UFH are limited by a propensity to bind plasma proteins, platelet factor-4, macrophages, fibrinogen, lipoproteins, and endothelial cells. This may explain the substantial interpatient and intrapatient variability observed in the anticoagulation response to UFH.[60]

The onset of anticoagulant effect after subcutaneous injection is 1 to 2 hours, peaking at 3 hours.[60] Continuous infusion is preferred for IV UFH administration.[18] Intramuscular administration is discouraged because of the risk of large hematoma formation.

UFH has a dose-dependent half-life of approximately 30 to 90 minutes.[60] There are two primary mechanisms for UFH elimination, a rapid, but saturable zero-order process involving enzymatic inactivation of heparin molecules bound to endothelial cells and macrophages, and renal elimination via a slower, nonsaturable first-order process. With typical therapeutic UFH regimens, the zero-order process predominates.[60]

Efficacy

UFH has demonstrated clinical effectiveness for the prevention and treatment of VTE over many years of clinical use.

Adverse Drug Reactions

Low-dose subcutaneous UFH is associated with a minimal risk of major bleeding. Bleeding rates for patients receiving therapeutic UFH doses range from 0% to 2%.[25] Close monitoring for bleeding signs and symptoms during UFH therapy is crucial.[25,60] When major bleeding occurs, UFH should be discontinued and the underlying bleeding source should be identified and treated. Protamine sulfate in a dose of 1 mg per 100 units of UFH (maximum of 50 mg) can be administered via slow IV infusion to reverse the anticoagulant effects of UFH.[60] Protamine sulfate neutralizes UFH in 5 minutes and persists for 2 hours. Multiple doses or prolonged infusion of protamine sulfate may be necessary if bleeding continues.[60]

HIT is a rare drug-induced immunologic reaction requiring immediate intervention.[96] The most common complication of HIT is VTE; arterial thromboembolic events occur less frequently. Approximately 5% to 10% of patients with HIT die, usually from thrombotic complications.[96] Thrombocytopenia (defined as a platelet count <150 × 10^3/mm^3 [150 × 10^9/L]) is the most common clinical HIT manifestation. HIT should be suspected if platelet counts decrease by 30% to 50% but remain above 150 × 10^3/mm^3 (150 × 10^9/L).[96] The characteristic onset of falling platelet count occurs in the first 5 to 10 days after initiation of UFH (Day 0 being the first day of UFH), particularly when administered perioperatively.[96] Thrombocytopenia alone is not sufficient for diagnosing HIT; serologic confirmation of heparin antibodies using an assay available only in a few specialty laboratories is required.[96] Falsely diagnosing HIT can have serious consequences including unnecessary anxiety, unnecessary UFH withdrawal, and the use of alternative anticoagulants with higher bleeding risk. The use of a clinical prediction rule, such as the 4Ts score (thrombocytopenia, timing of platelet count fall or thrombosis, thrombosis, other explanations for thrombocytopenia) can improve the predictive value of platelet count monitoring and heparin antibody testing.[96,97] A 4Ts score should be calculated when HIT is suspected in patients receiving heparin (UFH or LMWH). If the 4Ts score is low (3 or less), no further workup is needed, whereas a moderate (4 to 5) or high (6 to 8) 4Ts score requires further HIT workup including serologic testing.[98] In the setting of new thrombosis occurring in conjunction with falling platelets and a moderate or high 4Ts score, all sources of heparin should be discontinued. Alternative anticoagulation with a direct thrombin inhibitor or fondaparinux should then be initiated. If warfarin therapy is being used, it should be discontinued and reversed with vitamin K. Once platelet counts have recovered, warfarin can be resumed so long as it is overlapped with a direct thrombin inhibitor or fondaparinux until the INR is ≥2.0.[96]

Using UFH in doses ≥20,000 units/day for more than 6 months, especially during pregnancy, is associated with significant bone loss and may lead to osteoporosis.[60]

Drug-Drug and Drug-Food Interactions

Few drug interactions are reported with UFH, but concurrent use with other anticoagulants, thrombolytics, and antiplatelet agents increases bleeding risk.[60]

Dosing and Administration

UFH dose is expressed in units of activity. For VTE prevention, UFH is given by subcutaneous injection in the abdominal fat layer. The typical prophylaxis dose is 5,000 units every 8 to 12 hours. When immediate and full anticoagulation is required, an IV bolus dose followed by a continuous infusion is preferred (Table 38-6).[60] Subcutaneous UFH (initial dose of 333 units/kg followed by 250 units/kg every 12 hours) also provides adequate therapeutic anticoagulation for the treatment of acute VTE and does not require aPTT or anti-Xa monitoring.[60]

Warfarin

Because of its narrow therapeutic index, predisposition to drug and food interactions, and propensity to exacerbate bleeding, warfarin requires frequent monitoring and extensive patient education to achieve optimal outcomes.[72]

Pharmacology/Mechanism of Action

Warfarin exerts its anticoagulation effect by inhibiting the enzymes responsible for the cyclic vitamin K interconversion in the liver.[72] Vitamin K in its reduced form is a required cofactor for vitamin K-dependent carboxylation of factors II, VII, IX, and X, as well as the endogenous anticoagulant proteins C and S. Hepatic carboxylation of the N-terminal region of these proteins is required for biologic activity. By inhibiting the reduced vitamin K supply used in the production of these proteins, warfarin therapy produces partially carboxylated and decarboxylated coagulation proteins with reduced activity.[72] Warfarin has no direct effect on previously circulating clotting factors or previously formed thrombus. The time required for warfarin to achieve its pharmacologic effect is dependent on coagulation protein elimination half-lives (6 hours for factor VII and 72 hours for prothrombin).[72] Full antithrombotic effect is not achieved for at least 6 days after warfarin therapy initiation. By suppressing fully functional clotting factor production, warfarin prevents initial thrombus formation and propagation.[72]

Pharmacokinetics

Warfarin is a racemic mixture of *R* and *S* isomers, with *S*-warfarin being 2.7 to 3.8 times more potent than *R*-warfarin.[72] Warfarin is rapidly and extensively absorbed from the gastrointestinal tract (bioavailability >90%) and reaches peak plasma concentration within 4 hours of oral administration. Warfarin is 99% bound to plasma proteins and undergoes stereoselective metabolism via CYP 1A2, 2C9, 2C19, 2C8, 2C18, and 3A4 isoenzymes in the liver, with 2C9 being the main enzyme to modulate the elimination of *S*-warfarin.[99] Warfarin pharmacokinetics varies substantially between individuals leading to large interpatient differences in dose requirements. Genetic variations in the 2C9 isoenzyme and vitamin K epoxide reductase (VKOR) have been shown to correlate with warfarin dose requirements.[72] Given the greater potency of *S*-warfarin, coadministration of drugs that induce or inhibit the CYP 2C9 isoenzyme is more likely to cause clinically significant interactions.[72]

Efficacy

Warfarin has demonstrated clinical effectiveness for the prevention and treatment of VTE over many years of clinical use.

Adverse Drug Reactions

Warfarin's primary adverse drug reaction is bleeding that can range from mild to life-threatening.[72] Although warfarin does not cause bleeding per se, it exacerbates bleeding from existing lesions and can enable massive bleeding from ordinarily minor sources.[72] Anticoagulation therapy intensity is an important bleeding risk factor; the likelihood of bleeding rises with increasing INR values.[72] Therefore, maintaining the INR within the target range is important to reduce bleeding risk. Most patients with asymptomatic INR elevations between 4.5 and 10 can be safely managed by withholding warfarin alone.[5] For an INR >10 without evidence of bleeding, oral vitamin K 2.5 mg is recommended but does not improve clinical outcomes compared to withholding warfarin alone.[100] Vitamin K can be administered subcutaneously, IV, or orally; the oral route is preferred in the absence of serious bleeding. Vitamin K should be used cautiously in patients at high thromboembolism risk due to the possibility of INR overcorrection. Conversely, simply withholding warfarin therapy may not lower high INRs quickly enough in patients at high bleeding risk or in situations associated with prolonged INR elevations such as drug interactions and intentional overdoses.

Patients with warfarin-associated life-threatening bleeding require supportive care and rapid reversal of anticoagulation with both 4-factor PCC (rather than FFP) and 5 to 10 mg of vitamin K (administered via slow IV injection).[5]

Other adverse drug reactions associated with warfarin are uncommon but can be serious.[72] The etiology of the "purple toe syndrome" is unknown, but is thought to be the result of cholesterol microembolization into the arterial circulation of the toes.[72] If recognized early, complete resolution can be achieved by simply substituting a different anticoagulant for warfarin.[101] Warfarin-induced skin necrosis is a serious dermatologic reaction usually manifesting in the first week of therapy as a painful maculopapular rash and ecchymosis or purpura that subsequently progresses to necrotic gangrene. Areas of the body rich in subcutaneous fat, such as the breasts, thighs, buttocks, and abdomen are most commonly affected.[72] If skin necrosis is suspected, warfarin therapy should be discontinued immediately, reversed with vitamin K and either FFP or PCC, and full-dose UFH or LMWH therapy initiated. Patients with a history of skin necrosis should restart warfarin with extreme caution, if at all, using small doses and gradual titration under full-dose unfractionated heparin or LMWH coverage until a therapeutic INR is achieved.[72]

Drug-Food and Drug-Drug Interactions

The pharmacokinetic and pharmacodynamic properties of warfarin predispose patients to numerous clinically important food and drug interactions.[102] Vitamin K can reverse warfarin's pharmacologic activity; many foods contain sufficient vitamin K to reduce the anticoagulation effect if consumed in large portions or repetitively within a short period of time.[72] Patients should be instructed to maintain a relatively consistent intake of vitamin K–rich foods (Table 38-12). It is important to stress consistency rather than abstinence.

TABLE 38-12

Vitamin K Content of Select Foods[a]

Very High (>200 mcg)	High (100-200 mcg)	Medium (50-100 mcg)	Low (<50 mcg)
Brussel sprouts	Basil	Apple, green	Apple, red
Chickpeas	Broccoli	Asparagus	Avocado
Collard greens	Chive	Cabbage	Beans
Coriander	Coleslaw	Cauliflower	Breads, grains
Endive	Cucumber (with peel)	Mayonnaise	Carrot
Kale	Canola oil	Nuts, pistachio	Cereal
Lettuce, red leaf	Green onion/scallion	Squash, summer	Celery
Parsley	Lettuce, butterhead		Coffee
Spinach	Mustard greens		Corn
Swiss chard	Soybean oil		Cucumber (without peel)
Tea, green			Dairy products
Tea, black			Eggs
Turnip greens			Fruit (varies)
Watercress			Lettuce, iceberg
			Meats, fish, poultry
			Pasta
			Peanuts
			Peas
			Potato
			Rice
			Tomato

[a]Approximate amount of vitamin K per 100 g (3.5 oz) serving.

Data from Reference 24.

Pharmacokinetic drug interactions with warfarin primarily result from alterations in hepatic metabolism. Drugs inhibiting or inducing CYP 2C9, 1A2, and 3A4 isoenzymes have the greatest potential to significantly alter warfarin therapy response.[72] Drugs altering hemostasis or platelet function (eg, aspirin, clopidogrel) can increase bleeding risk without altering warfarin pharmacokinetics or impacting the INR.[72] Clinicians should advise patients on warfarin to report potential interactions to their anticoagulation provider whenever a drug product, dietary supplement, or herbal product is initiated or stopped, whether prescribed or available over the counter. If there is a known drug interaction or doubt about the potential to alter the warfarin response, more frequent INR testing is recommended with warfarin dose adjustments as needed to maintain INRs in the target range.[102]

Dosing and Administration

The dose of warfarin is individualized based on the desired target INR range and anticoagulant response by periodically measuring the PT and calculating the INR.[72] The pharmacodynamic response and pharmacokinetic disposition of warfarin between and within patients are highly variable. Therefore, the dose of warfarin must be individualized based on frequent clinical and laboratory monitoring.[72] The average weekly warfarin dose is between 25 and 55 mg. Some patients require lower than usual dose requirements, including patients who are of advanced age (>65 years), have an elevated baseline INR, poor nutritional status, liver disease, genetic polymorphisms in CYP 2C9 and VKOR, and concurrent use of medications known to enhance the effect of warfarin.[72] Higher than usual dose requirements are also necessary in some patients, including concurrent use of medications known to induce the metabolism of warfarin such as rifampin and carbamazepine, high dietary vitamin K intake, and genetic polymorphisms in CYP 2C9. It is important to collect a complete medication history, including the use of herbal and nutritional products as these can influence warfarin's metabolism, dose requirements, and the risk of bleeding.[72]

Initiating warfarin therapy with 5 to 10 mg daily and adjusting the dose based on the INR response will produce therapeutic INRs in 5 to 7 days for most patients (Fig. 38-9). Lower starting doses may be acceptable based on patient-related factors such as advanced age, malnutrition, liver disease, or heart failure. Starting doses >10 mg should be avoided.[72] When warfarin therapy is initiated in the outpatient setting, the INR should be measured every 3 to 4 days until stabilized. For patients with acute VTE, a parenteral, rapid-acting anticoagulant such as UFH, LMWH, or fondaparinux should be overlapped with warfarin therapy for at least 5 days regardless of whether the target INR has been achieved earlier.[18,72]

It is important to allow sufficient time for changes in the INR to occur when adjusting warfarin doses. In general, maintenance dose changes should not be made more frequently than every 3 days. When adjusting maintenance warfarin doses, the weekly dosage should be reduced or increased by 5% to 25%; the full effect of dose changes may not become evident for 5 to 7 days or longer.[72] Patients demonstrating a stable response to warfarin as evidenced by consistently therapeutic INR results on the same warfarin dose can have INRs checked as infrequently as every 8 to 12 weeks, although most stable patients are tested approximately every 4 to 6 weeks.[5]

Therapeutic Considerations

Prevention Versus Treatment of Venous Thromboembolism

Lower doses of LMWH and DOACs are used for VTE prevention than during VTE treatment. Warfarin may be targeted to a traditional INR range (2.0 to 3.0) or reduced-intensity (1.5 to 2.5) for VTE prophylaxis. Orthopedic surgeons frequently prefer the lower INR range due to perceived lower bleeding risk. VTE prophylaxis in high-risk hospitalized patients is typically discontinued at discharge. In contrast, after certain surgeries (eg, major orthopedic surgery), VTE prophylaxis continues following hospital discharge for up to 35 days.

VTE treatment requires full therapeutic anticoagulant doses for at least 3 months. Patients unwilling to self-administer LMWH or fondaparinux injections may prefer apixaban or rivaroxaban. The duration of anticoagulant therapy after acute VTE is principally determined by whether the clot was provoked, unprovoked, or recurrent. Three months of therapeutic anticoagulation is sufficient following a first episode of VTE provoked by major transient risk factors such as surgery, pregnancy, or trauma. Most patients with unprovoked or recurrent VTE should receive long-term anticoagulation for secondary VTE prevention. Patients selected for long-term secondary anticoagulation traditionally receive standard therapeutic doses. In patients for whom there is clinical equipoise regarding anticoagulation continuation, prophylactic doses of apixaban and rivaroxaban are as effective as full therapeutic doses after 6 months of treatment has been completed.[86,87] However, prophylactic doses were not safer than therapeutic doses as the risk of major bleeding was low for both options. Switching to aspirin for long-term secondary VTE prevention is also an option but is less effective than continuing anticoagulation therapy.[103,104]

Weight

Patients at extremes of body weight were underrepresented in DOAC VTE treatment trials. There is speculation regarding whether very obese or very small patients receive equivalent anticoagulant effects with DOAC when compared to other patients. The International Society of Thrombosis and Haemostasis suggests that standard doses of rivaroxaban or apixaban, without monitoring of peak and trough concentrations, are among the appropriate anticoagulant options for VTE treatment or prevention regardless of high BMI and weight.[105] They suggest avoiding dabigatran and edoxaban for VTE treatment and prevention in patients with BMI >40 kg/m^2 or weight >120 kg, given that data are either unconvincing (dabigatran) or lacking (edoxaban). DOACs should be avoided for both prevention and treatment of VTE in the acute setting following bariatric surgery because of concerns of decreased absorption.[105] Switching to a DOAC after at least 4 weeks following surgery may be reasonable but obtaining a DOAC trough level to check for drug absorption and bioavailability is suggested (see Evaluation of Therapeutic Outcomes section).[105]

LMWH dosing in obesity frequently causes concern. Patients weighing more than 90 kg would exceed the maximum dose specified in the approved labeling for dalteparin (18,000 units).[93] However, evidence supports similar anti-Xa exposure to LMWH and no increase in bleeding risk compared to nonobese patients when doses based on actual body weight without capping are administered.[106] Fondaparinux is a convenient option for obese patients as the 10 mg dose is suitable for acute VTE treatment in patients >100 kg.[62] Obese patients requiring VTE prophylaxis may need higher than normal LMWH doses. For example, enoxaparin 40 mg subcutaneously twice daily may be more effective than usual VTE prophylaxis doses for patients undergoing bariatric surgery.[107]

Response to Previous Therapy

Other than bleeding, anticoagulants are generally well tolerated. However, adverse reactions, treatment failure, or allergies during previous therapy may necessitate preferential use of one anticoagulant over another.

Warfarin allergy is rare and often related to dyes or tablet excipients rather than the active ingredient. Warfarin 10 mg tablets contain no dye and can be considered when an allergy is suspected. Patients experiencing dabigatran-related dyspepsia can try taking the dose with a full glass of water or food. Transitioning to another DOAC or warfarin may be necessary.

Cost is an important aspect of personalizing anticoagulant therapy for VTE prevention and treatment. For patients unable to afford DOACs, warfarin remains a cost-effective option.

Patients suspected of having a recurrent VTE during anticoagulant therapy should have their adherence to therapy assessed and imaging compared to historical data to ensure the clot is new. Determining and correcting the causes of poor medication adherence to anticoagulation therapy should occur before switching anticoagulants. Malignancy should be considered when anticoagulant adherence is verified. Switching to an LMWH is recommended for breakthrough VTE occurring during oral anticoagulation therapy.[21] Patients having breakthrough VTE during LMWH should be switched to twice daily injections (if receiving once-daily LMWH) and considered for dose escalation of 25% to 33%.[21] Switching to an oral factor Xa inhibitor may also be an option given the comparable efficacy of edoxaban and dalteparin for the treatment of cancer-related VTE; however, less is known regarding their use in breakthrough VTE.

Pharmacogenomics

CYP2C9 is the hepatic microsomal enzyme responsible for the metabolism of the more potent S-enantiomer of warfarin. Polymorphisms in CYP 2C9 and the gene coding for VKOR (known as vitamin K epoxide reductase complex 1) explain a substantial proportion of warfarin dose variability between patients. Dosing algorithms using CYP 2C9 and VKOR pharmacogenomics, as well as clinical and drug interaction information, have been developed to assist providers more accurately select initial warfarin doses based upon a predicted maintenance warfarin dose for an individual patient (see www.warfarindosing.org). The Food and Drug Administration (FDA) updated the warfarin package label to include the use of pharmacogenetic testing in 2007.[99]

There are several barriers to the widespread application of pharmacogenomic testing for warfarin. First, and most important, is the INR. The ability to rapidly assess a patient's physiologic response to warfarin using an inexpensive and widely available test limits the need for pharmacogenomic

information. Second is the timeliness of receiving pharmacogenomic test results. Pharmacogenomic information is most valuable when selecting the first 3 or 4 warfarin doses. However, pharmacogenomic testing outside of clinical trials may require several days or longer before results become available. Delaying warfarin initiation is rarely safe, thus pharmacogenomic test results are only meaningful if they are available in the first 2 to 3 days after treatment initiation. Although poor metabolizing CYP2C9 subtypes have been associated with increased risk of bleeding compared to the wild-type, clinical trials have not demonstrated improved bleeding or thromboembolic outcomes with the routine use of pharmacogenomic information to guide warfarin dosing when compared to usual care.[108,109] As a result, the clinical utility and cost-effectiveness of warfarin pharmacogenomics remains ill-defined and the American College of Chest Physicians guidelines does not recommend routine use.[110]

EVALUATION OF THERAPEUTIC OUTCOMES

Warfarin dose titration based on INR monitoring and UFH dose titration based on aPTT or anti-Xa monitoring allows a degree of personalized therapy not available with other anticoagulants. The intensity of warfarin or UFH therapy can be easily titrated in high-risk situations such as invasive procedures, accidental or intentional overdose, suspected nonadherence, or concomitant therapy with interacting drugs. Titrating DOAC therapy cannot be accomplished due to lack of readily available quantitative coagulation assays and dosing guidelines in these clinical scenarios.[111] In rare circumstances, such as patients who have previously had bariatric surgery, measuring trough levels of rivaroxaban or apixaban has been suggested.[105] This should be accomplished using an anti-Xa level specific to rivaroxaban or apixaban.

While laboratory coagulation monitoring is unnecessary during DOAC therapy, clinical surveillance is likely beneficial. In clinical trials comparing DOACs to warfarin, patients receiving DOAC therapy had regular contact with healthcare providers who screened for bleeding, changes in renal or hepatic function, drug adherence, potential drug interactions, and plans for invasive procedures.

Adherence is essential to preventing recurrent VTE during DOAC therapy due to their short half-lives. A study performed in patients with atrial fibrillation taking dabigatran found that pharmacist involvement during initial drug selection, patient education, and follow-up contacts improved drug adherence.[112] Pharmacist involvement during DOAC initiation may be especially important to ensure proper transitions from LMWH to dabigatran or edoxaban or from initiation to maintenance dosing with rivaroxaban or apixaban. An ABCDEF checklist may be helpful when monitoring patients on DOACs: A—Adherence with therapy, B—Bleeding risk assessment, C—Creatinine clearance/renal function monitoring, D—Drug interaction evaluation, E—Examination for adverse events and therapeutic effectiveness, and F—Final assessment and recommendations regarding the need for ongoing DOAC therapy.[113] What remains unclear is how frequently patient monitoring should be performed for patients on DOACs and whether it should be performed for all patients taking DOACs or only those at highest risk.

Because LMWH anticoagulant response is predictable when given subcutaneously, routine laboratory monitoring is unnecessary.[60] Prior to LMWH initiation, baseline complete blood cell counts with platelets and SCr should be obtained. If neuraxial anesthesia has been used, patients should be closely monitored for signs and symptoms of neurologic impairment.[79]

Antifactor Xa activity is the most widely used test to monitor the anticoagulant effect of LMWH in clinical practice. Routine antifactor Xa activity measurement is unnecessary in uncomplicated patients who are stable.[60] Measuring antifactor Xa activity may be considered in patients who are morbidly obese, pregnant, or have a significant renal impairment (eg, CrCl <30 mL/min [0.5 mL/s]).[60] However, many laboratories do not standardize the measurement of anti-factor Xa levels for specific LMWH products. For this reason and because the correlation between antifactor Xa levels and adverse outcomes is uncertain, guidelines recommend against measuring antifactor Xa activity in these situations.[5,114]

When antifactor Xa activity is used to monitor LMWH therapy, the sample should be drawn during the peak antifactor Xa activity—once a steady state has been achieved (after the second or third dose) and approximately 4 hours after the subcutaneous injection.[60] The antifactor Xa activity therapeutic range is not well-defined and has not been clearly correlated with efficacy or the risk of bleeding. For the treatment of VTE, an acceptable target range for the peak anti-Xa level for twice-daily enoxaparin dosing is 0.6 to 1 unit/mL (kU/L). For once-daily dosing, peak targets >1 unit/mL (kU/L) for enoxaparin and 1.05 units/mL (kU/L) for dalteparin have been suggested.[60] The target range for peak anti-Xa concentrations during cancer-associated VTE treatment with dalteparin is 0.5 to 1.5 units/mL (kU/L).[93]

Prior to initiating fondaparinux, baseline kidney function should be determined as fondaparinux is contraindicated when CrCL is <30 mL/min (0.5 mL/s).[62] Signs and symptoms of bleeding should be monitored daily, particularly in patients with a baseline CrCl between 30 and 50 mL/min (0.5 and

0.83 mL/s). If neuraxial anesthesia has been used, patients should be closely monitored for signs and symptoms of neurologic impairment.[62] The role of antifactor Xa monitoring during fondaparinux is not well-defined, but routine coagulation testing is not required.[62]

Administration of UFH requires close monitoring because each patient's anticoagulant response is unpredictable.[60] Although the aPTT has several limitations, most experts advocate using the aPTT to monitor UFH provided that institution-specific therapeutic ranges are defined.[60] The aPTT should be measured prior to the initiation of therapy to determine the patient's baseline. With IV infusion, the aPTT response to UFH therapy should be measured 6 hours after initiation or dose changes. UFH doses should be adjusted based on patient response and the institution-specific aPTT therapeutic range (Table 38-6).[60]

The PT measures the biologic activity of factors II, VII, and X and has been used for decades to monitor the anticoagulation effects of warfarin. The PT is performed by measuring the time required for clot formation after adding calcium and thromboplastin to citrated plasma.[72] Interpreting the PT is problematic because thromboplastins of differing sensitivity produce substantially different results, some of which could lead to inappropriate dosing decisions. The World Health Organization (WHO) addressed the need for standardization in the late 1970s by developing a reference thromboplastin and recommending the use of the INR to monitor warfarin therapy.[72] The INR attempts to correct for differences in thromboplastin reagents through the following formula:

$$\text{INR} = \left(\frac{\text{PT}^{\text{patient}}}{\text{PT}^{\text{control}}}\right)^{\text{ISI}}$$ INR=(PTpatientPTcontrol)ISI

The International Sensitivity Index (ISI) is a measure of thromboplastin responsiveness compared with the WHO reference standard.[72] Although the INR system has a number of limitations, it remains the preferred method for monitoring warfarin therapy.[72]

Referring patients with VTE to anticoagulation therapy management services is recommended to optimize the care of patients who take warfarin therapy by providing structured care, comprehensive patient education, and evaluation of outcomes.[5] When anticoagulation management services are not available, individual clinicians should strive to implement similar structured care processes.[110]

Portable finger-stick INR devices are available for monitoring warfarin therapy. These devices permit clinicians to do "real-time" therapeutic INR monitoring and enable patients to engage in self-testing at home.[5] Patients who engage in INR self-testing and warfarin self-management have fewer thromboembolic complications, report high levels of satisfaction with care, and maintain INRs within the therapeutic range slightly more frequently than those managed by "usual care." However, home INR testing and self-management is not for everyone and requires careful patient selection and considerable patient education.[110] Finger-stick INR devices are relatively expensive, but some patients qualify for insurance coverage for the monitor and testing supplies.

CONCLUSION

VTE is a significant public health issue, yet there is little public awareness of the life-threatening nature of this commonly occurring condition. Given the number and variety of clinical circumstances that place individuals at risk for VTE, improvements in VTE prevention and care have the potential to benefit many patients. Over the past decade, the focus on quality healthcare has included systematic measures to improve the use of effective VTE prophylaxis and evidence-based VTE treatments. The concerted efforts of government and accrediting agencies working with hospitals and other healthcare institutions will hopefully reduce VTE rates. Systematic approaches to this problem are needed at every level, starting with increased public and health practitioner awareness, continuing with the uniform use of effective prophylactic strategies in patients at risk, and concluding with the application of high-quality VTE treatment strategies.

ABBREVIATIONS

aPC	activated protein C
aPTT	activated partial thromboplastin time
β_2-gp	β_2-glycoprotein

BMI	body mass index
CrCl	creatinine clearance
CTPA	computed tomography pulmonary angiography
CTPH	chronic thromboembolic pulmonary hypertension
CUS	compression ultrasound
CYP	cytochrome P450
DOAC	direct-acting oral anticoagulant
DVT	deep vein thrombosis
FFP	fresh-frozen plasma
HIT	heparin-induced thrombocytopenia
INR	international normalized ratio
IPC	intermittent pneumatic compression
ISI	International Sensitivity Index
IVC	inferior vena cava
LMWH	low-molecular-weight heparin
NICE	National Institute for Health and Care Excellence
PCCs	prothrombin complex concentrates
PE	pulmonary embolism
PESI	Pulmonary Embolism Severity Index
P-gp	P-glycoprotein
PT	prothrombin time
SBP	systolic blood pressure
TF	tissue factor
TFPI	tissue factor pathway inhibitor
tPA	tissue plasminogen activator
UFH	unfractionated heparin

V/Q	ventilation/perfusion
VKOR	vitamin K epoxide reductase
VTE	venous thromboembolism
WHO	World Health Organization

REFERENCES

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012;379:1835–1846. [PubMed: 22494827]

2. Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: Prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv.* 2019;3:3898–3944. doi: 10.1182/bloodadvances.2019000975.

3. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv.* 2018;2:3198–3225. doi: 10.1182/bloodadvances.2018022954.

4. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Diagnosis of venous thromboembolism. *Blood Adv.* 2018;2:3226–3256. doi: 10.1182/bloodadvances.2018024828.

5. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Optimal management of anticoagulation therapy. *Blood Adv.* 2018;2:3257–3291. doi: 10.1182/bloodadvances.2018024893.

6. ISTH Steering Committee for World Thrombosis Day. Thrombosis: A major contributor to the global disease burden. *J Thromb Haemost.* 2014;12:1580–1590. [PubMed: 25302663]

7. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: A population-based cohort study in patients without active cancer. *Thromb Haemost.* 2014;112:255–263. [PubMed: 24695909]

8. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Venous thromboembolism in the context of pregnancy. *Blood Adv.* 2018;2:3317–3359. doi: 10.1182/bloodadvances.2018024802.

9. Johnson SA, Eleazer GP, Rondina MT. Pathogenesis, diagnosis, and treatment of venous thromboembolism in older adults. *J Am Geriatr Soc.* 2016;64:1869–1878. [PubMed: 27556937]

10. Anderson JA, Weitz JI. Hypercoagulable states. *Crit Care Clin.* 2011;27:933–952,vii. [PubMed: 22082521]

11. Turpie AG, Esmon C. Venous and arterial thrombosis: Pathogenesis and the rationale for anticoagulation. *Thromb Haemost.* 2011;105:586–596. [PubMed: 21225099]

12. Reitsma PH, Versteeg HH, Middeldorp S. Mechanistic view of risk factors for venous thromboembolism. *Arterioscler Thromb Vasc Biol.* 2012;32:563–568. [PubMed: 22345594]

13. De Caterina R, Husted S, Wallentin L, et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis: Task Force on Anticoagulants in Heart Disease. *Thromb Haemost.* 2013;109:569–579. [PubMed: 23447024]

14. Margaglione M, Grandone E. Population genetics of venous thromboembolism. A narrative review. *Thromb Haemost.* 2011;105:221–231. [PubMed: 20941456]

15. Rijken DC, Lijnen HR. New insights into the molecular mechanisms of the fibrinolytic system. *J Thromb Haemost.* 2009;7:4–13. [PubMed: 19017261]

16. Khorana AA. Cancer and coagulation. *Am J Hematol.* 2012;87(Suppl 1):S82–S87. [PubMed: 22389165]

17. Chong LY, Fenu E, Stansby G, Hodgkinson S, Guideline Development G. Management of venous thromboembolic diseases and the role of thrombophilia testing: Summary of NICE guidance. *BMJ.* 2012;344:e3979. [PubMed: 22740565]

18. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e419S–e494S. [PubMed: 22315268]

19. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e351S–e418S. [PubMed: 22315267]

20. Le Gal G, Righini M. Controversies in the diagnosis of venous thromboembolism. *J Thromb Haemost.* 2015;13(Suppl 1):S259–S265. [PubMed: 26149033]

21. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149:315–352. [PubMed: 26867832]

22. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: Increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost.* 2000;83:416–420. [PubMed: 10744147]

23. Wendelboe AM, McCumber M, Hylek EM, et al. Global public awareness of venous thromboembolism. *J Thromb Haemost.* 2015;13:1365–1371. [PubMed: 26084415]

24. Booth SL, Centurelli MA. Vitamin K: A practical guide to the dietary management of patients on warfarin. *Nutr Rev.* 1999;57:288–296. [PubMed: 10568341]

25. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:257S–298S. [PubMed: 18574268]

26. Mahan CE, Holdsworth MT, Welch SM, Borrego M, Spyropoulos AC. Deep-vein thrombosis: A United States cost model for a preventable and costly adverse event. *Thromb Haemost.* 2011;106:405–415. [PubMed: 21833446]

27. Guyatt GH, Eikelboom JW, Gould MK, et al. Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e185S–e194S. [PubMed: 22315260]

28. Gray J, Razmus I. Improving venous thromboembolism prevention processes and outcomes at a community hospital. *Jt Comm J Qual Patient Saf.* 2012;38:61–66. [PubMed: 22372252]

29. Zeidan AM, Streiff MB, Lau BD, et al. Impact of a venous thromboembolism prophylaxis “smart order set”: Improved compliance, fewer events. *Am J Hemat.* 2013;88:545–549. doi: 10.1002/ajh.23450.

30. Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. *J Thromb Thrombolysis*. 2016;41:32–67. doi: 10.1007/s11239-015-1317-0.

31. Streiff MB, Brady JP, Grant AM, et al. CDC Grand Rounds: Preventing hospital-associated venous thromboembolism. *MMWR Morb Mortal Wkly Rep.* 2014;63(9):190–3.

[PubMed: 24598595] .

32. Grant PJ, Conlon A, Chopra V, et al. Use of venous thromboembolism prophylaxis in hospitalized patients. *JAMA Intern Med.* 2018;178:1122. doi: 10.1001/jamainternmed.2018.2022.

33. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e195S–e226S. [PubMed: 22315261]

34. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e227S–e277S. [PubMed: 22315263]

35. Zareba P, Wu C, Agzarian J, Rodriguez D, Kearon C. Meta-analysis of randomized trials comparing combined compression and anticoagulation with either modality alone for prevention of venous thromboembolism after surgery. *Br J Surg.* 2014;101:1053–1062. [PubMed: 24916118]

36. Rajasekhar A, Streiff MB. Vena cava filters for management of venous thromboembolism: A clinical review. *Blood Rev.* 2013;27:225–241. [PubMed: 23932118]

37. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e278S–e325S. [PubMed: 22315265]

38. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med.* 2013;368:513–523. doi: 10.1056/nejmoa1111096.

39. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: The Padua Prediction Score. *J Thromb Haemost.* 2010;8:2450–2457. doi: 10.1111/j.1538-7836.2010.04044.x.

40. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients. *Chest*. 2011;139:69–79. doi: 10.1378/chest.09-3081.

41. Reichert JA, Hlavinka PF, Stolzfus JC. Risk of hemorrhage in patients with chronic liver disease and coagulopathy receiving pharmacologic venous thromboembolism prophylaxis. *Pharmacotherapy.* 2014;34:1043–1049. [PubMed: 25052037]

42. Ali M, Ananthakrishnan AN, McGinley EL, Saeian K. Deep vein thrombosis and pulmonary embolism in hospitalized patients with cirrhosis: A nationwide analysis. *Dig Dis Sci.* 2011;56:2152–2159. [PubMed: 21279685]

43. Anderson FA Jr., Huang W, Friedman RJ, et al. Prevention of venous thromboembolism after hip or knee arthroplasty: Findings from a 2008 survey of US orthopedic surgeons. *J Arthroplasty.* 2012;27:659–666. e5. [PubMed: 22035977]

44. Mont MA, Jacobs JJ, Boggio LN, et al. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Am Acad Orthop Surg.* 2011;19:768–776. [PubMed: 22134209]

45. Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or Rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. *N Engl J Med.* 2018;378:699–707. [PubMed: 29466159]

46. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. *JAMA.* 2014;311:717–728. [PubMed: 24549552]

47. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). *J Clin Oncol.* 10, 2018;36(20):2017–2023. doi: 10.1200/JCO.2018.78.8034.

48. Meyer G, Planquette B, Sanchez O. Pulmonary embolism: Whom to discharge and whom to thrombolyze? *J Thromb Haemost.* 2015;13(Suppl 1):S252–S258. [PubMed: 26149032]

49. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: A randomised placebo-controlled trial. *Lancet*. 2014;383:880–888. [PubMed: 24315521]

50. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369:799–808. [PubMed: 23808982]

51. Investigators E-P, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366:1287–1297. [PubMed: 22449293]

52. Investigators E, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363:2499–2510. [PubMed: 21128814]

53. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 2018;378:615–624. [PubMed: 29231094]

54. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). *J Clin Oncol.* 2018;36(20):2017–2023. [PubMed: 29746227]

55. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129:764–772. [PubMed: 24344086]

56. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369:1406–1415. [PubMed: 23991658]

57. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315–352. doi: 10.1016/j.chest.2015.11.026
[PubMed: 26867832] .

58. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020;4:4693–4738. doi: 10.1182/bloodadvances.2020001830.

59. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 15 , 2018;378(7):615–624. doi: 10.1056/NEJMoa1711948.

60. Garcia DA, Baglin TP, Weitz JI, Samama MM, American College of Chest P. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e24S–e43S. [PubMed: 22315264]

61. Goldhaber SZ. Advanced treatment strategies for acute pulmonary embolism, including thrombolysis and embolectomy. *J Thromb Haemost.* 2009;7(Suppl 1):322–327. [PubMed: 19630826]

62. GlaxoSmithKline. Arixtra Prescribing Information 2018.

63. Martinez K, Kosirog E, Billups SJ, Clark NP, Delate T, Witt DM. Clinical outcomes and adherence to guideline recommendations during the initial treatment of acute venous thromboembolism. *Ann Pharmacother.* 2015;49:869–875. [PubMed: 25931575]

64. Wang TF, Squizzato A, Dentali F, Ageno W. The role of thrombolytic therapy in pulmonary embolism. *Blood*. 2015;125:2191–2199. [PubMed: 25631770]

65. Aujesky D, Hughes R, Jimenez D. Short-term prognosis of pulmonary embolism. *J Thromb Haemost.* 2009;7(Suppl 1):318–321. [PubMed: 19630825]

66. Bristol Myers Squibb C. Eliquis Prescribing Information. 2021. Available at: https://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed October 20, 2021.

67. Boehringer-Ingelheim. Pradaxa Prescribing Information. 2021. Available at: https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. Accessed October 30, 2021.

68. Janssen Pharmaceuticals I. Xarelto Prescribing Information. 2021. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/XARELTO-pi.pdf. Accessed October 30, 2021.

69. Daiichi Sankyo I. Savaysa Prescribing Information. 2021. Available at: https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true. Accessed October 30, 2021.

70. Knol HM, Schultinge L, Erwich JJ, Meijer K. Fondaparinux as an alternative anticoagulant therapy during pregnancy. *J Thromb Haemost.* 2010;8:1876–1879. [PubMed: 20492464]

71. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med.* 2014;370:1307–1315. [PubMed: 24524551]

72. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e44S–e88S. [PubMed: 22315269]

73. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Treatment of pediatric venous thromboembolism. *Blood Adv.* 2018;2:3292–3316. doi: 10.1182/bloodadvances.2018024786.

74. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e737S–e801S. [PubMed: 22315277]

75. Schulman S, Zondag M, Linkins L, et al. Recurrent venous thromboembolism in anticoagulated patients with cancer: Management and short-term prognosis. *J Thromb Haemost.* 2015;13:1010–1018. [PubMed: 25851122]

76. Easaw JC, Shea-Budgell MA, Wu CM, et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: Treatment. *Curr Oncol.* 2015;22:144–155. [PubMed: 25908913]

77. Farge D, Debourdeau P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemost.* 2013;11:56–70. [PubMed: 23217107]

78. Clark NP. Low-molecular-weight heparin use in the obese, elderly, and in renal insufficiency. *Thromb Res.* 2008;123(Suppl 1):S58–S61. [PubMed: 18809206]

79. Sanofi-Aventis. Lovenox Prescribing Information. 2018. Available at: http://products.sanofi.us/lovenox/lovenox.html. Accessed May 29, 2018.

80. Hanni Claudia, Petrovitch Elizabeth, Ali Mona, et al. Outcomes associated with apixaban vs warfarin in patients with renal dysfunction. *Blood Adv.* 2020;4:2366–2371. doi: 10.1182/bloodadvances.2019000972.

81. Clark NP, Witt DM, Davies LE, et al. Bleeding, recurrent venous thromboembolism, and mortality risks during warfarin interruption for invasive procedures. *JAMA Intern Med.* 2015;175:1163–1168. [PubMed: 26010033]

82. Douketis JD, Spyropoulos AC, Spencer FA, et al. 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:e326S–e350S. [PubMed: 22315266]

83. Pollack CV Jr., Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med.* 2015;373:511–520. [PubMed: 26095746]

84. Alexion Pharmaceuticals, Inc. Andexxa (coagulation factor Xa (recombinant), inactivated-zhzo) prescribing information. 2021. Available at: https://alexion.com/Documents/andexxa_uspi.pdf. Accessed October 30, 2021.

85. Yeh CH, Gross PL, Weitz JI. Evolving use of new oral anticoagulants for treatment of venous thromboembolism. *Blood*. 2014;124:1020–1028. [PubMed: 24923298]

86. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368:699–708. [PubMed: 23216615]

87. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med.* 2017;376:1211–1222. [PubMed: 28316279]

88. Portola Pharmaceuticals I. Betrixaban prescribing information. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208383s000lbl.pdf. Accessed May 19, 2018.

89. Weitz JI, Pollack CV Jr. Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. *Thromb Haemost.* 2015;114.

90. Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: An overview of current developments. *Thromb Haemost.* 2015;113:931–942. [PubMed: 25832311]

91. Tornkvist M, Smith JG, Labaf A. Current evidence of oral anticoagulant reversal: A systematic review. *Thromb Res.* 2018;162:22–31. [PubMed: 29258056]

92. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med.* 2014;371:2141–2142. [PubMed: 25371966]

93. PfizerLabs. Fragmin Prescribing Information. 2018. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=2293. Accessed May 19, 2018.

94. Park D, Southern W, Calvo M, et al. Treatment with dalteparin is associated with a lower risk of bleeding compared to treatment with unfractionated heparin in patients with renal insufficiency. *J Gen Intern Med.* 2016;31(12):182–187. [PubMed: 26209179]

95. Blackmer AB, Oertel MD, Valgus JM. Fondaparinux and the management of heparin-induced thrombocytopenia: The journey continues. *Ann Pharmacother.* 2009;43:1636–1646. [PubMed: 19737996]

96. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e495S–e530S. [PubMed: 22315270]

97. Crowther MA, Cook DJ, Albert M, et al. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. *J Crit Care*. 2010;25:287–293. [PubMed: 20149589]

98. Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: A systematic review and meta-analysis. *Blood*. 2012;120:4160–4167. [PubMed: 22990018]

99. Bristol Myers Squibb C. Coumadin Prescribing Information. 2018. Available at: http://packageinserts.bms.com/pi/pi_coumadin.pdf. Accessed May 19, 2018.

100. Farrow GS, Delate T, McNeil K, et al. Vitamin K versus warfarin interruption alone in patients without bleeding and an international normalized ratio >10. *J Thromb Haemost.* 2020;18(5):1133–1140. doi: 10.1111/jth.14772 [PubMed: 32073738] .

101. Cakebread HE, Knight HM, Gajendragadkar PR, Cooper JP. Warfarin-induced purple toe syndrome successfully treated with apixaban. *BMJ Case Rep.* 2014;2014doi: 10.1136/bcr-2014-205320.

102. Clark NP, Delate T, Riggs CS, et al. Warfarin interactions with antibiotics in the ambulatory care setting. *JAMA Inter Med.* 2014;174:409–416.

103. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med.* 2012;367:1979–1987. [PubMed: 23121403]

104. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med.* 2012;366:1959–1967. [PubMed: 22621626]

105. Martin KA, Beyer-Westendorf J, Davidson BL, et al. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost.* 2021;19:1874–1882. 10.1111/jth.15358.

106. Al-Yaseen E, Wells PS, Anderson J, Martin J, Kovacs MJ. The safety of dosing dalteparin based on actual body weight for the treatment of acute venous thromboembolism in obese patients. *J Thromb Haemost.* 2005;3:100–102. [PubMed: 15634272]

107. Parker SG, McGlone ER, Knight WR, Sufi P, Khan OA. Enoxaparin venous thromboembolism prophylaxis in bariatric surgery: A best evidence topic. *Int J Surg.* 2015;23:52–56. [PubMed: 26394187]

108. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med.* 2013;369:2294–2303. [PubMed: 24251363]

109. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med.* 2013;369:2283–2293. [PubMed: 24251361]

110. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e152S–e184S. [PubMed: 22315259]

111. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol.* 2014;64:1128–1139. [PubMed: 25212648]

112. Shore S, Ho PM, Lambert-Kerzner A, et al. Site-level variation in and practices associated with dabigatran adherence. *JAMA.* 2015;313:1443–1450. [PubMed: 25871670]

113. Gladstone DJ, Geerts WH, Douketis J, Ivers N, Healey JS, Leblanc K. How to Monitor Patients Receiving Direct Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation: A Practice Tool Endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. *Ann Intern Med.* 2015;163:382–385. [PubMed: 26121536]

114. Baglin T. What happens after venous thromboembolism? *J Thromb Haemost.* 2009;7(Suppl 1):287–290. [PubMed: 19630818]

SELF-ASSESSMENT QUESTIONS

1. XT is a 55-year-old male (height = 63 in. [160 cm], weight = 80 kg) who presents to the Emergency Department (ED) and is diagnosed with a new unprovoked left lower extremity deep vein thrombosis (DVT) and pulmonary embolism (PE). The patient has no significant past medical history and takes no other medications. All baseline labs are within normal limits and the patient is hemodynamically stable. Which of the following is the best initial treatment regimen for XT upon discharge from the ED?

   A. Enoxaparin 80 mg subcutaneously BID × 5 days + edoxaban 60 mg PO daily

   B. Enoxaparin 80 mg subcutaneously BID × 5 days then edoxaban 60 mg PO daily

   C. Enoxaparin 120 mg subcutaneously BID × 5 days + warfarin 5 mg PO daily

   D. Enoxaparin 120 mg subcutaneously daily × 5 days then warfarin 5 mg PO daily

2. Which of the following is a factor when considering a direct oral anticoagulant (DOAC) for the treatment of venous thromboembolism (VTE)?

   A. History of hypertension requiring losartan therapy

   B. History of epilepsy requiring carbamazepine therapy

   C. History of heart failure requiring furosemide therapy

   D. History of hypothyroidism requiring levothyroxine therapy

3. A 70-year-old male patient with DVT and a baseline international normalized ratio (INR) of 1.1 is started on warfarin 5 mg daily on day 1 and day 2 as well as enoxaparin 80 mg SC BID. The patient has no history of malignancy, malnutrition, heart failure, alcohol abuse, or liver dysfunction. INR today (day 3) is 1.5. Which of the following reflects the best warfarin dose for day 3?

   A. 10 mg

   B. 5 mg

   C. 1 mg

   D. HOLD warfarin today

4. Which one of the following statements best describes how a patient should interpret their INR results?

   A. When the INR is below 2.0 she is at increased risk for bleeding.

   B. When the INR is between 2 and 3 she needs to eat less vitamin K-containing food in her diet.

   C. When the INR is below 2.0 her dose of warfarin may need to be adjusted.

   D. When the INR is higher than 3.0 she is at increased risk for having another VTE.

5. NB is a 57-year-old 5’8” (173 cm) female weighing 60 kg admitted to the hospital for elective total knee replacement surgery. Past medical history includes anxiety and hypertension. Prescription medications include lisinopril 20 mg daily and paroxetine 20 mg daily. Preoperative labs include: BUN 28 mg/dL (10.0 mmol/L) and SCr 1.1 mg/dL (97 µmol/L). Which of the following is the best recommendation for pharmacological VTE prophylaxis to reduce NB’s VTE risk following her knee replacement surgery?

   A. Enoxaparin 60 mg subcutaneously BID

   B. Dabigatran 150 mg twice daily

   C. Rivaroxaban 10 mg PO daily

D. Edoxaban 30 mg PO QD

6. Which of the following is the most appropriate duration of apixaban therapy for a patient who experienced a first DVT following knee replacement surgery?

   A. 6 weeks

   B. 3 months

   C. 6 months

   D. Indefinite

7. Which of the following is the most appropriate drug to administer for bleeding due to an accidental warfarin overdose?

   A. Vitamin K

   B. Protamine

   C. Idarucizumab

   D. Andexanet

8. SJ is a 76-year-old male (height = 69 in. [175 cm], weight = 105 kg) who is diagnosed with PE. Current medications include: lisinopril 40 mg PO daily, hydrochlorothiazide 25 mg PO daily, atorvastatin 40 mg PO daily. Labs include BUN 26 mg/dL (9.3 mmol/L) and serum creatinine (SCr) 2.3 mg/dL (203 µmol/L). What is the best recommendation for initial parenteral anticoagulant treatment for SJ's acute PE?

   A. Fondaparinux 10 mg subcutaneously daily

   B. Dalteparin 5,000 units subcutaneously daily

   C. Enoxaparin 100 mg subcutaneously twice daily

   D. Unfractionated heparin (UFH) 10,000 unit bolus with 2,000 units/hr continuous infusion

9. A patient's INR is 1.6 following a significant dietary change. Which of the following is the most likely explanation for today's lab result?

   A. Eating more dark green leafy vegetables than usual

   B. Eating fewer dark green leafy vegetables than usual

   C. Drinking grapefruit juice

   D. Drinking cranberry juice

10. Which of the following is the most appropriate anticoagulant to treat VTE during pregnancy?

    A. Warfarin

    B. Dabigatran

    C. Enoxaparin

    D. UFH

11. A 66-year-old male presents with unilateral leg pain, redness, and swelling. Past medical history is significant for hypertension. D-dimer is elevated. Which of the following is the most appropriate next step?

A. UFH

B. Apixaban

C. Compression ultrasound

D. Computed tomography pulmonary angiography

12. In which of the following clinical scenarios would anti-Xa monitoring be recommended during low-molecular-weight heparin (LMWH) treatment?

A. Initial DVT treatment for a patient weighing 120 kg

B. Initial PE treatment in an 80-year-old female with renal dysfunction

C. VTE prophylaxis in a patient with cancer

D. Long-term PE treatment in a pregnant patient

13. Which of the following is not a risk factor for DVT in hospitalized patients?

A. Cancer

B. Hypertension

C. Age >70 years

D. Estrogen therapy

14. Which of the following should be included in patient education for outpatient DVT treatment with enoxaparin and warfarin?

A. Avoiding vitamin K-rich foods

B. Interpreting INR results

C. Discontinuing enoxaparin therapy in 3 days

D. Injecting enoxaparin with the needle at a 45° angle to the skin

15. Which of the following is the most appropriate VTE prophylaxis strategy for a general surgery patient at high risk of VTE with ongoing bleeding?

A. Aspirin

B. Edoxaban

C. Inferior vena cava filter

D. Intermittent pneumatic compression devices

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** is the correct answer because the dose of enoxaparin is appropriate based on the patient's weight and is followed by the appropriate dose of edoxaban. Answer A is incorrect because edoxaban and enoxaparin should not be overlapped. Answer C is incorrect because the enoxaparin dose is too high. Answer D is incorrect because warfarin and enoxaparin should be overlapped for at least 5 days and until the INR is above 2.

2. **B.** is the correct answer because carbamazepine is a strong inducer of CYP 3A4 and P-gp and could potentially result in subtherapeutic DOAC concentrations and therapeutic failure. None of the medications or medical conditions in Answers A, C, or D are known to influence DOAC concentrations. See subsection "Direct Oral Anticoagulants" under section "Drug Class Information" for additional information.

3. **B.** is the correct answer because the patient's INR is beginning to increase but not too rapidly. The INR is not expected to reach the therapeutic range until 5 to 7 days on an appropriate warfarin dose so this response seems reasonable. Answer A is incorrect because increasing the warfarin dose may result in an INR>3 in a few days. Answers C and D are incorrect because lowering or holding the warfarin dose will prolong the time required to reach an INR of 2 and hence the duration of enoxaparin injections. See subsection "Warfarin" under section "Drug Class Information" for additional details.

4. **C.** is the correct answer because INRs outside the usual therapeutic range of 2.0 to 3.0 indicate the possible need for warfarin dose adjustment. Answer A is incorrect because an INR below 2.0 indicates an increased risk for recurrent VTE. Answer B is incorrect because an INR in the therapeutic INR range indicates that the patient should make no changes to the amount of vitamin K-containing food she is eating. Answer D is incorrect because an INR above 3.0 indicates increased bleeding risk. See subsection "Warfarin" under section "Drug Class Information" for additional details.

5. **C.** is the correct answer because the rivaroxaban dose for VTE prophylaxis is correctly identified. Answer A is incorrect because the enoxaparin dose for VTE prophylaxis following orthopedic surgery is 30 mg subcutaneously BID. Answer B is incorrect because the dose listed is for stroke prevention in atrial fibrillation. Answer D is incorrect because edoxaban is not indicated for surgical VTE prophylaxis.

6. **B.** is the correct answer because it correctly identifies the duration of therapy recommended by consensus guideline panels following a surgically provoked DVT. Answer A is incorrect because the duration of therapy is too short. Answers C and D are incorrect because the duration of therapy is too long. See section "General Approach to the Treatment of Venous Thromboembolism" for additional details.

7. **A.** is the correct answer because vitamin K will bypass the inhibition of clotting factor synthesis produced by warfarin and restore clotting factor function. Answer B is incorrect because protamine reverses the effects of UFH, not warfarin. Answer C is incorrect because idarucizumab reverses the effects of dabigatran, not warfarin. Answer D is incorrect because andexanet reverses the effect of direct Xa inhibitors, not warfarin. See Table 38-12 and subsection on warfarin under section "Drug Class Information" for additional details.

8. **D.** is the correct answer because UFH is not reliant on the patient's kidney function for elimination and this patient has a creatinine clearance below 30 mL/min (0.5 mL/s). Answer A is incorrect because fondaparinux is contraindicated when creatinine clearance is <30 mL/min (0.5 mL/s). Answer B is incorrect because dalteparin is cleared by the kidneys and the dose listed is for VTE prophylaxis, not treatment. Answer C is incorrect because the enoxaparin dose has not been adjusted for creatinine clearance <30 mL/min (0.5 mL/s). See subsections on fondaparinux, LMWH, and UFH under section "Drug Class Information" for additional details.

9. **A.** is the correct answer because dark green leafy vegetables are a rich source of vitamin K, which can lower the INR. Answer B is incorrect because eating LESS dietary vitamin K would result in the INR going higher, not lower. Answer C is incorrect because drinking grapefruit juice will probably have no effect on the INR but is a CYP enzyme inhibitor and would therefore be expected to increase the INR if there was an effect on the INR. Answer D is incorrect because cranberry juice is unlikely to have any appreciable effect on the INR. See subsection on warfarin in "Drug Class Information" for additional details.

10. **C.** is the correct answer because enoxaparin does not cross the placenta and has been shown to be safe during pregnancy. Answer A is incorrect because warfarin is a known teratogen. Answer B is incorrect because DOACs are not recommended in pregnancy because they cross the placenta and also have not been well studied in pregnancy. Answer D is incorrect because although UFH doesn't cross the placenta, it can cause osteoporosis when used for prolonged periods of time at therapeutic doses as would likely be required during pregnancy-related VTE treatment. See subsection "Pregnancy" under section "Special Populations" and Table 38-10 for additional detail.

11. **C.** is the correct answer because elevated D-dimer cannot reliably be used to confirm DVT diagnosis, it is most appropriately used to rule out DVT—compression ultrasound is the correct imaging test to diagnose DVT. Answers A and B are incorrect because anticoagulation should not be initiated until DVT is objectively confirmed. Answer D is incorrect because computed tomography scanning is generally used to diagnose PE, not DVT.

12. **D.** is the correct answer; measuring antifactor Xa activity may be considered in patients who are pregnant. Answer A and B are incorrect because current guidelines recommend against the routine use of anti-Xa monitoring in obesity (answer A) and renal dysfunction (answer B). Routine antifactor Xa monitoring is not necessary in patients with cancer (answer C). See section "Evaluation of Therapeutic Outcomes" for additional detail.

13. **B.** is the correct answer because of the available choices it is the only one that is NOT a recognized risk factor for DVT in hospitalized patients. See Table 38-1 for additional detail.

14. **B.** is the correct answer because it is important that patients are aware of what their INR results mean. Answer A is incorrect because dietary vitamin K intake should be consistent, not avoided. Answer C is incorrect because enoxaparin must be overlapped with warfarin for at least 5 days and only if the INR is above 2.0. Answer D is incorrect because enoxaparin should be injected at a 90-degree angle to the skin.

15. **D.** is correct because it has the lowest associated bleeding risk. Answers A and B are incorrect because they would affect the hemostatic system and further increase bleeding risk in this patient. Answer C is incorrect because inferior vena cava filters are associated with increased DVT risk long-term and a safer, less invasive option is available.