Chapter 14: Venous Thromboembolism

INTRODUCTION

- *Venous thromboembolism* (VTE) results from clot formation in the venous circulation and is manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE).

PATHOPHYSIOLOGY

- Risk factors for VTE include increasing age, history of VTE, and aspects related to Virchow's triad: (1) blood stasis (eg, immobility and obesity); (2) vascular injury (eg, surgery, trauma, venous catheters); and (3) hypercoagulability (eg, malignancy, coagulation factor abnormalities, antiphospholipid antibodies, certain drugs).
- The most common inherited hypercoagulability disorder is activated protein C (aPC) resistance (Caucasian prevalence 2%–7%), which increases the risk of VTE threefold. Most aPC resistance results from a factor V gene mutation (known as factor V Leiden) that renders it resistant to degradation by aPC.
- The prothrombin G20210A mutation is the second most frequent inherited hypercoagulability disorder (Caucasian prevalence 2%–4%) and imparts a threefold increased risk of VTE. The mutation increases circulating prothrombin and may enhance thrombin generation.
- Inherited deficiencies of protein C, protein S, and antithrombin occur in <1% of the population and may increase the lifetime VTE risk by as much as sevenfold.
- Normal hemostasis maintains circulatory system integrity after blood vessel damage. Disruption of the endothelial cell lining with injury results in platelet activation and tissue-factor–mediated clotting factor cascade initiation, culminating in thrombin formation and ultimately a fibrin clot. In contrast to physiologic hemostasis, pathologic VTE often occurs without gross vessel wall damage and may be triggered by tissue factor (TF) brought to the growing thrombus by circulating microparticles. Clots causing VTE impair blood flow and often cause complete vessel occlusion.
- Exposure of blood to damaged vessel endothelium causes platelets to become activated after binding to adhesion proteins (eg, von Willebrand factor, collagen). Activated platelets recruit additional platelets, causing growth of the platelet thrombus. Activated platelets change shape and release components that sustain further thrombus formation at the site. Activated platelets express the adhesion molecule P-selectin, which facilitates capture of TF-bearing microparticles, resulting in fibrin clot formation via the coagulation cascade.
- The conceptual model for the coagulation cascade involves reactions that occur on cell surfaces in three overlapping phases (**Fig. 14-1**):

  ✔ *Initiation*: A TF/VIIa complex (known as extrinsic tenase or X-ase) on cells bearing TF that have been exposed after vessel injury or captured via P-selectin 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 amount of thrombin (factor IIa). Factor IXa moves to the surface of activated platelets in the growing platelet thrombus. Tissue factor pathway inhibitor (TFPI) regulates TF/VIIa-induced coagulation, rapidly terminating the initiation phase.

  ✔ *Amplification:* Thrombin produced during the initiation phase activates factors V and VIII, which bind to platelet surfaces and support the large-scale thrombin generation occurring during the propagation phase. Platelet-bound factor XI is also activated by thrombin during amplification.

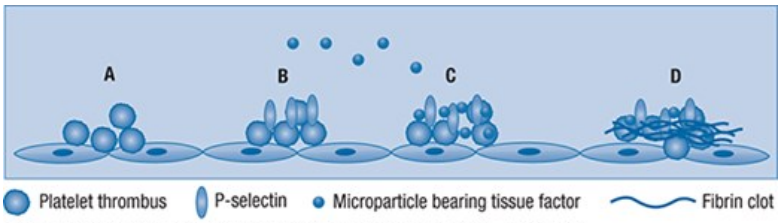
  ✔ *Propagation:* A burst of thrombin generation occurs as factor VIIIa/IXa complex (known as intrinsic tenase) promotes factor Xa formation and prothrombinase complexes assemble on the surface of activated platelets, accelerating thrombin generation. Thrombin generation is

further supported by factor XIa bound to platelet surfaces, which activates factor IX to form additional intrinsic tenase.

- Thrombin then converts fibrinogen to fibrin monomers that precipitate and polymerize to form fibrin strands. Factor XIIIa (also activated by thrombin) covalently bonds these strands to form an extensive meshwork that encases the aggregating platelet thrombus and red cells to form a stabilized fibrin clot.
- Hemostasis is controlled by antithrombotic substances produced by intact endothelium adjacent to damaged tissue. Thrombomodulin modulates thrombin activity by converting protein C to its activated form (aPC), which joins with protein S to inactivate factors Va and VIIIa. This prevents coagulation reactions from spreading to uninjured vessel walls. In addition, circulating antithrombin inhibits thrombin and factor Xa. Heparan sulfate is secreted by endothelial cells and accelerates antithrombin activity. These self-regulatory mechanisms limit fibrin clot formation to the zone of vessel injury.
- The fibrinolytic system dissolves formed blood clots; inactive plasminogen is converted to plasmin by tissue plasminogen activator (tPA). Plasmin is an enzyme that degrades the fibrin mesh into soluble end products (known as fibrin degradation products including D-dimer).
- Thrombi can form in any part of the venous circulation but usually begin in the leg(s). Isolated calf vein thrombi seldom embolize; those involving the popliteal and larger veins above it are more likely to embolize and lodge in the pulmonary artery or one of its branches, occluding blood flow to the lung and impairing gas exchange. Without treatment, the affected lung area becomes necrotic and oxygen delivery to other vital organs may decrease, potentially resulting in fatal circulatory collapse.

FIGURE 14-1

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; and (*D*) tissue factor can lead to thrombin generation, and thrombin generation leads to platelet thrombus formation and fibrin generation.



CLINICAL PRESENTATION

- Some patients with DVT are asymptomatic. Symptoms may include unilateral leg swelling, pain, tenderness, erythema, and warmth. Physical signs may include a palpable cord and a positive Homan sign.
- Symptoms of PE may include cough, chest pain or tightness, shortness of breath, palpitations, hemoptysis, dizziness, or lightheadedness. Signs of PE include tachypnea, tachycardia, diaphoresis, cyanosis, hypotension, shock, and cardiovascular collapse.
- Postthrombotic syndrome may produce chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration.

DIAGNOSIS

- Assessment should focus on identifying risk factors (see section Pathophysiology).
- Compression ultrasound (CUS) and computed tomography pulmonary angiography (CTPA) are used most often for initial evaluation of suspected VTE.

- Radiographic contrast studies (venography, pulmonary angiography) are the most accurate and reliable diagnostic methods but are expensive, invasive, and difficult to perform and evaluate. The ventilation-perfusion (V/Q) scan is an alternative PE diagnostic test.
- Serum concentration of D-dimer is nearly always elevated; values <500 ng/mL (mcg/L) combined with clinical probability scores are useful in ruling out VTE.
- Clinical assessment checklists (eg, Wells score) can be used to determine whether a patient is likely or unlikely to have DVT or PE.

TREATMENT

- Goals of Treatment: The initial goal is to prevent VTE in at-risk populations. Treatment of VTE is aimed at preventing thrombus extension and embolization, reducing recurrence risk, and preventing long-term complications (eg, postthrombotic syndrome, chronic thromboembolic pulmonary hypertension).

Prevention of VTE

- Nonpharmacologic methods improve venous blood flow by mechanical means and include early ambulation, graduated compression stockings, intermittent pneumatic compression (IPC) devices, and inferior vena cava filters.
- Hospitalized and acutely ill medical patients at high VTE risk and low bleeding risk should receive pharmacologic prophylaxis with **low-dose unfractionated heparin** (**LDUH**), **low-molecular-weight heparin** (**LMWH**), **fondaparinux**, or **betrixaban** during hospitalization or until fully ambulatory. Routine pharmacologic prophylaxis is not warranted in low-risk medical patients.
- In general, nonorthopedic surgery patients at high VTE risk but low bleeding risk should receive **LDUH** or **LMWH** prophylaxis plus graduated compression stockings or IPC. Low-risk patients able to ambulate early after surgery do not routinely require VTE prophylaxis.
- Recommended VTE prophylaxis following joint replacement surgery may include **aspirin**, adjusted-dose **warfarin**, **LDUH**, **LMWH**, **fondaparinux**, **dabigatran**, **apixaban**, or **rivaroxaban** for at least 10 days postsurgery.
- VTE prophylaxis after surgery should be given throughout the period of increased VTE risk. For general surgical procedures, prophylaxis can be discontinued when patients are able to ambulate and have no other VTE risk factors. Extended prophylaxis may be beneficial for patients undergoing lower extremity orthopedic procedures; most clinical trials support use of prophylaxis for 15–42 days after total knee or hip replacement surgery.
- Refer to *Antithrombotic Therapy and Prevention of Thrombosis, 9th edition: Evidence-Based Clinical Practice Guidelines* published by the American College of Chest Physicians for information on prophylaxis strategies based on clinical situation and risk level for VTE.

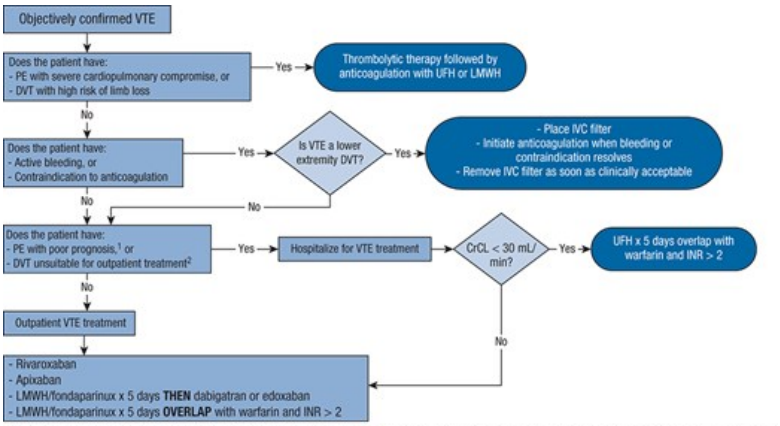
General Approach to Treatment of VTE

- Anticoagulation is the primary treatment for VTE; DVT and PE are treated similarly (**Fig. 14-2**).
- After VTE is confirmed objectively, therapy with a rapid-acting anticoagulant should be instituted as soon as possible. Anticoagulants can be administered in the outpatient setting in most patients with DVT and in carefully selected hemodynamically stable patients with PE.
- 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 (if considered appropriate candidates). Hemodynamically unstable patients with PE should be admitted for initiation of anticoagulation therapy.
- Three months is the appropriate initial duration of anticoagulation therapy for the acute first episode of VTE for all patients. This duration is also recommended when the initial thrombotic event was associated with a major transient or reversible risk factor (eg, surgery, hospitalization).
- Continuing anticoagulation is required to prevent new VTE episodes not directly related to the preceding episode. Consider extended therapy beyond 3 months for patients with a first unprovoked (idiopathic) VTE when feasible because of a relatively high recurrence rate. In patients with VTE and active cancer, extended therapy is rarely stopped because of a high recurrence risk.

[1]PESI score ≥86 points: age (1 pt for each year); male sex (10 pts); cancer (30 pts); heart failure (10 pts); COPD (10 pts); heart rate >110 bpm (20 pts); respiratory rate >30/min (20 pts); temperature <36°C (20 pts); altered mental status (60 pts); O_2 sat <90% (20 pts). [2]Severe symptoms, renal impairment, inability to obtain or administer appropriate initial anticoagulant therapy, or high bleeding risk. (CrCl, creatinine clearance via Cockcroft and Gault equation; DVT, deep vein thrombosis; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism [includes DVT and PE].)

FIGURE 14-2

Acute treatment of venous thromboembolism (VTE).



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[2]Severe symptoms, renal impairment, inability to obtain or administer appropriate initial anticoagulant therapy, or high bleeding risk.

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Nonpharmacologic Therapy

- Encourage patients to ambulate as much as symptoms permit.
- Ambulation in conjunction with graduated compression stockings results in faster reduction in pain and swelling than strict bedrest with no increase in embolization rate.
- Inferior vena cava filters should only be used when anticoagulants are contraindicated due to active bleeding.
- Elimination of the obstructing thrombus via thrombolysis or thrombectomy may be warranted in life- or limb-threatening DVT.

Pharmacologic Therapy

Direct Oral Anticoagulants (DOACs)

- **Rivaroxaban**, **apixaban**, **edoxaban**, and **betrixaban** are oral selective inhibitors of both free and clot-bound factor Xa and do not require antithrombin to exert their anticoagulant effect. **Dabigatran** is an oral selective, reversible, direct factor IIa inhibitor.
- See **Table 14-1** for DOAC indications and dosing. Use DOACs with caution in patients with renal dysfunction.
- Single-drug oral therapy with rivaroxaban or apixaban produces similar rates of recurrent VTE compared to traditional therapy with warfarin overlapped with enoxaparin and perhaps less major bleeding. Both drugs are initiated with a higher dose and subsequently reduced to a maintenance dose. Until further data are available, these drugs should not be used in patients with creatinine clearance (CrCl) <25 mL/min (0.42 mL/s), active cancer, and patients requiring thrombolytic therapy. Neither drug requires routine anticoagulation monitoring, but the high acquisition cost may be a barrier for some patients.
- Edoxaban and dabigatran must be given only after at least 5 days of subcutaneous (SC) anticoagulation with UFH, LMWH, or fondaparinux. These

regimens were noninferior to warfarin in patients with acute VTE for the outcome of recurrent VTE. Compared to warfarin, dabigatran caused similar major bleeding and edoxaban caused significantly less bleeding. Until further data are available, these agents should not be given to patients with hemodynamically unstable PE or at high bleeding risk.

- Bleeding is the most common adverse effect with DOAC therapy. Patients experiencing significant bleeding should receive routine supportive care and discontinuation of anticoagulant therapy. **Idarucizumab** (Praxbind) 5 g IV rapidly reverses the dabigatran anticoagulant effect when needed during emergency situations (eg, life-threatening bleeding) and when there is need for urgent surgical intervention. **Recombinant coagulation factor Xa** (also known as **andexanet alfa**; Andexxa) can reverse life-threatening bleeding in patients taking rivaroxaban or apixaban. Adding aspirin to DOAC therapy nearly doubles bleeding rates and should be avoided in most patients with VTE. All DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with P-gp inhibitors or inducers. Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP 3A4.

TABLE 14-1

Approved Indications and Dosing for the Direct Oral Anticoagulants

Generic (Brand) Name	VTE Prophylaxis	Acute VTE Treatment	Reduction in Risk of Recurrent VTE in Patients at Continued Risk
Dabigatran (Pradaxa)	Hip replacement surgery: CrCl >30 mL/min: 110 mg the first day beginning 1–4 hours after surgery once hemostasis is achieved, then 220 mg once daily for 28–35 days CrCl ≤30 mL/min or on dialysis: Dosing recommendations cannot be provided	150 mg PO twice daily with or without food FOLLOWING at least 5 days of parenteral anticoagulant therapy	150 mg PO twice daily with or without food
Rivaroxaban (Xarelto)	Hip or knee replacement surgery: 10 mg PO once daily with or without food beginning 6–10 hours after surgery once hemostasis is achieved and continuing for 12 (knee) to 35 (hip) days	15 mg PO twice daily with food for days 1–21, then 20 mg PO once daily with food beginning on day 22	10 mg PO once daily with or without food
Apixaban (Eliquis)	Hip or knee replacement surgery: 2.5 mg PO twice daily with or without food beginning 12–24 hours after surgery and continuing for 12 (knee) or 35 (hip) days	10 mg PO twice daily with or without food on days 1–7, then 5 mg PO twice daily beginning on day 8	2.5 mg PO twice daily with or without food
Edoxaban (Savaysa)	Not approved for use	60 mg PO once daily with or without food FOLLOWING at least 5 days of parenteral anticoagulant therapy; 30 mg once daily with CrCl 15–50 mL/min (0.25–0.83 mL/sec) or body weight ≤60 kg or who use certain P-gp inhibitors	Not approved for use
Betrixaban (Bevyxxa)	Adults hospitalized for acute medical illness: Initial single dose of 160 mg PO with food, followed by 80 mg once daily with food for 35–42 days	Not approved for use	Not approved for use

PO, by mouth; CrCl, creatinine clearance; P-gp, P-glycoprotein; VTE, venous thromboembolism.

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 UFH molecular weight. LMWH prevents thrombus propagation by accelerating the activity of antithrombin similar to UFH.
- LMWH given SC in fixed, weight-based doses is at least as effective as UFH given IV for VTE treatment. LMWH has largely replaced UFH for initial VTE treatment due to improved pharmacokinetic and pharmacodynamic profiles and ease of use. Advantages of LMWH over UFH include: (1) predictable anticoagulation dose response; (2) improved SC bioavailability; (3) dose-independent clearance; (4) longer biologic half-life; (5) lower

incidence of thrombocytopenia; and (6) less need for routine laboratory monitoring.

- Recommended doses (based on actual body weight) include:

  ✔ **Enoxaparin** (Lovenox): For acute DVT treatment with or without PE, 1 mg/kg SC every 12 hours or 1.5 mg/kg every 24 hours;

  ✔ **Dalteparin** (Fragmin): For acute DVT treatment, 200 units/kg SC once daily or 100 units/kg SC twice daily (not FDA approved in the United States for this indication). For VTE in patients with cancer, 200 units/kg SC every 24 hours for 30 days, followed by 150 units SC every 24 hours. The maximum total daily dose is 18,000 units.

- In patients without cancer, acute LMWH treatment is generally transitioned to long-term warfarin therapy after 5–10 days.

- Routine laboratory monitoring is unnecessary because LMWH anticoagulant response is predictable when given SC. Prior to initiating therapy, obtain a baseline complete blood cell count (CBC) with platelet count and serum creatinine. Check the CBC every 5–10 days during the first 2 weeks of LMWH therapy and every 2–4 weeks thereafter to monitor for occult bleeding. Measuring anti–factor Xa activity is the most widely used method to monitor LMWH; routine measurement is unnecessary in stable, uncomplicated patients. Monitoring may be considered in patients who have significant renal impairment, are morbidly obese, or are pregnant.

- As with other anticoagulants, bleeding is the most common adverse effect of LMWH therapy, but major bleeding may be less common than with UFH. If major bleeding occurs, IV **protamine sulfate** can be administered, but it cannot neutralize the anticoagulant effect completely. The recommended protamine sulfate dose is 1 mg per 1 mg of enoxaparin or 1 mg per 100 anti–factor Xa units of dalteparin administered in the previous 8 hours. A second dose of 0.5 mg per 1 mg or 100 anti–factor Xa units can be given if bleeding continues. Smaller protamine doses can be used if the LMWH dose was given in the previous 8–12 hours. Protamine sulfate is not recommended if the LMWH was given more than 12 hours earlier.

- Thrombocytopenia can occur with LMWHs, but the incidence of heparin-induced thrombocytopenia (HIT) is one-third that of UFH. LMWH has been associated with osteopenia, but the risk of osteoporosis appears to be lower with LMWH than with UFH.

Fondaparinux

- **Fondaparinux** (Arixtra) prevents thrombus generation and clot formation by indirectly inhibiting factor Xa activity through its interaction with antithrombin. Unlike UFH or LMWH, fondaparinux inhibits only factor Xa activity.

- Fondaparinux is a safe and effective alternative to LMWH for acute VTE treatment and is likewise followed by long-term warfarin therapy.

- Fondaparinux is dosed once daily via weight-based SC injection: 5 mg if <50 kg, 7.5 mg if 50–100 kg, and 10 mg if >100 kg.

- Patients receiving fondaparinux do not require routine coagulation testing. Determine baseline kidney function before starting therapy because fondaparinux is contraindicated if CrCl is <30 mL/min (0.5 mL/s).

- Bleeding is the primary adverse effect associated with fondaparinux therapy. Measure CBC at baseline and periodically thereafter to detect occult bleeding. Monitor for signs and symptoms of bleeding daily. There is no specific antidote to reverse the antithrombotic activity of fondaparinux.

Unfractionated Heparin

- **Unfractionated heparin** binds to antithrombin, provoking a conformation change that makes it much more potent in inhibiting the activity of factors IXa, Xa, XIIa, and IIa. This prevents thrombus growth and propagation allowing endogenous thrombolytic systems to lyse the clot. Because some patients fail to achieve an adequate response, IV UFH has largely been replaced by LMWH, fondaparinux, and DOACs. UFH continues to have a role in patients with CrCl <30 mL/min (0.5 mL/s) and unstable patients.

- When immediate and full anticoagulation is required, a weight-based IV loading dose followed by a continuous IV infusion is preferred (**Table 14-2**). Subcutaneous UFH (initial dose 333 units/kg followed by 250 units/kg every 12 hours) also provides adequate anticoagulation for treatment of acute VTE.

- The activated partial thromboplastin time (aPTT) is generally recommended for monitoring UFH, provided that institution-specific therapeutic ranges are defined. Measure aPTT prior to initiation of therapy and 6 hours after the start of therapy or a dose change. Adjust the UFH dose based on patient response and the institution-specific aPTT therapeutic range.
- Monitor patients closely for bleeding signs and symptoms during UFH therapy. If major bleeding occurs, discontinue UFH immediately, identify and treat the underlying bleeding source, and give **protamine sulfate** by slow IV infusion over 10 minutes (1 mg/100 units of UFH infused during the previous 4 hours; maximum 50 mg).
- HIT is a rare immunologic reaction requiring immediate intervention and that may be fatal. The most common complication of HIT is VTE; arterial thrombosis occurs less frequently. Thrombocytopenia is the most common clinical manifestation, but serologic confirmation of heparin antibodies is required to diagnose HIT. Use of a clinical prediction rule, such as the 4Ts score (*T*hrombocytopenia, *T*iming of platelet count fall or thrombosis, *T*hrombosis, o*T*her explanation for thrombocytopenia), can improve the predictive value of platelet count monitoring and heparin antibody testing. Discontinue all heparin if new thrombosis occurs in the setting of falling platelets in conjunction with a moderate or high 4Ts score. Alternative anticoagulation with a direct thrombin inhibitor should then be initiated.
- Using UFH doses of 20,000 units/day or more for longer than 6 months, especially during pregnancy, is associated with significant bone loss and may lead to osteoporosis.

TABLE 14-2

Weight-Based[a] Dosing for Unfractionated Heparin Administered by Continuous IV Infusion

Indication	Initial Loading Dose	Initial Infusion Rate
Deep venous thrombosis/pulmonary embolism	80–100 units/kg Maximum = 10,000 units	17–20 units/kg/hr Maximum = 2300 units/hr
Activated Partial Thromboplastin Time (seconds)	Maintenance Infusion Rate	
	Dose Adjustment	
<37 (or anti–factor Xa <0.20 unit/mL [kU/L])	80 units/kg bolus, and then increase infusion by 4 units/kg/hr	
37–47 (or anti–factor 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 anti–factor Xa 0.30–0.70 unit/mL [kU/L])	No change	
72–93 (or anti–factor Xa 0.71–1 unit/mL [kU/L])	Decrease infusion by 1–2 units/kg/hr	
>93 (or anti–factor Xa >1 unit/mL [kU/L])	Hold infusion for 1 hour, 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).

Warfarin

- **Warfarin** inhibits enzymes responsible for cyclic interconversion of vitamin K in the liver. Reduced vitamin K is a cofactor required for carboxylation of the vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X and the endogenous anticoagulant proteins C and S. By inhibiting the reduced vitamin K supply needed for production of these proteins, warfarin therapy produces coagulation proteins with less activity. By suppressing clotting factor production, warfarin prevents initial thrombus formation and propagation. The time required to achieve its anticoagulant effect depends on the elimination half-lives of the coagulation proteins (6 hours for factor VII and 72 hours for prothrombin). Full antithrombotic effect is not achieved for at least 6 days after warfarin therapy initiation.

- Because of its slow onset of effect, warfarin must be started concurrently with rapid-acting injectable anticoagulant therapy with an overlap of at least 5 days and until an international normalized ratio (INR) of 2 or greater has been achieved for at least 24 hours.
- Guidelines for initiating warfarin therapy are given in **Figure 14-3**. The initial dose should be 5–10 mg for most patients. Lower starting doses may be acceptable in patients with advanced age, malnutrition, liver disease, or heart failure. Starting doses more than 10 mg should be avoided.
- Monitor warfarin therapy by the INR; the recommended target INR for VTE treatment is 2.5, with an acceptable range of 2–3. After an acute thromboembolic event, obtain a baseline INR and CBC prior to initiating warfarin and every 1–3 days until stabilized. Once the patient's dose response is established, obtain an INR every 7–14 days until it stabilizes, then ideally every 4–12 weeks thereafter.
- In general, maintenance dose changes should not be made more frequently than every 3 days. Adjust maintenance doses by calculating the weekly dose and reducing or increasing it by 5%–25%. The full effect of a dose changes may not become evident for 5–7 days.
- Warfarin's primary adverse effect is bleeding that can range from mild to life threatening. It does not cause bleeding per se, but it exacerbates bleeding from existing lesions and enables massive bleeding from ordinarily minor sources. The likelihood of bleeding rises with increasing INR values; therefore, maintaining the INR within the target range is important to reduce bleeding risk:

  ✔ When the INR is >4.5 without evidence of bleeding, the INR can be lowered by withholding warfarin, adjusting the warfarin dose, and/or providing a small dose of vitamin K to shorten the time to return to normal INR. Although vitamin K can be given parenterally or orally, the oral route is preferred in the absence of serious bleeding.

  ✔ If the INR is between 5 and 10 and no bleeding is present, routine vitamin K use is not recommended because it has not been shown to affect the risk of developing subsequent bleeding or thromboembolism compared to simply withholding warfarin alone.

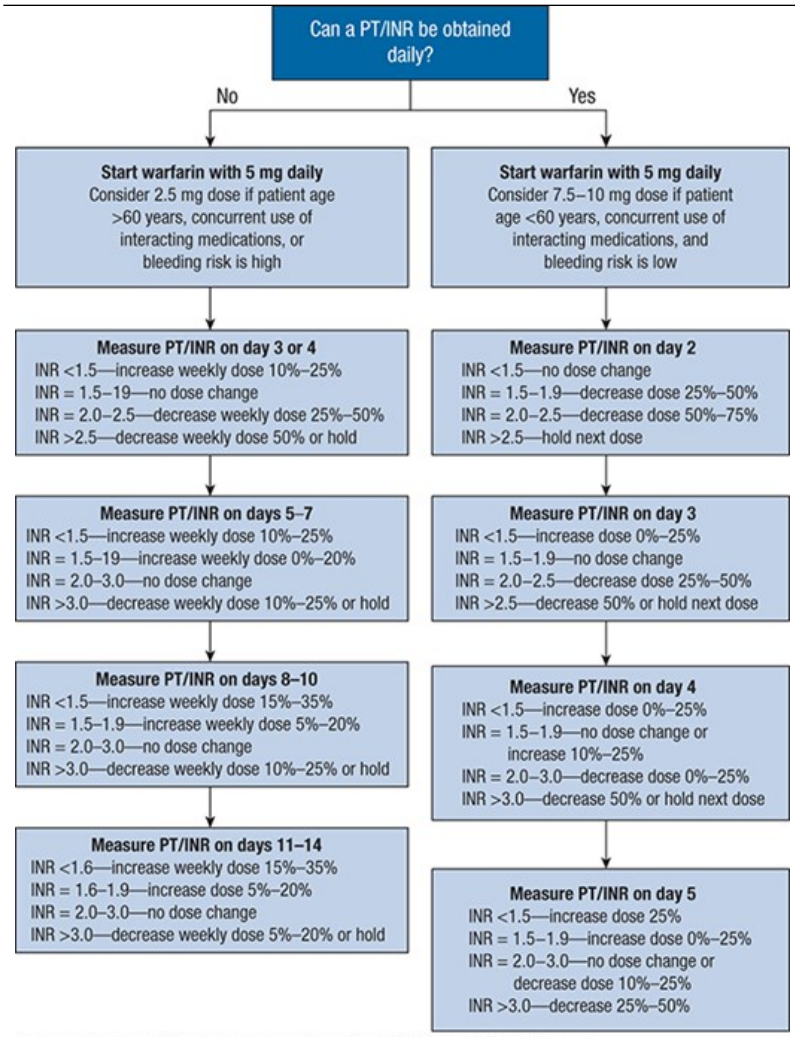
  ✔ For INR >10 without evidence of bleeding, oral vitamin K (**phytonadione** 2.5 mg) is suggested. Use vitamin K with caution in patients at high risk of recurrent thromboembolism because of the possibility of INR overcorrection.
- Patients with warfarin-associated major bleeding require supportive care. Rapid reversal of anticoagulation with a four-factor prothrombin complex concentrate and 5–10 mg of vitamin K given by slow IV injection are also recommended.
- Nonhemorrhagic adverse effects of warfarin include the rare “purple toe” syndrome and skin necrosis.
- Because of the large number of food–drug and drug–drug interactions with warfarin, close monitoring and additional INR determinations may be indicated when other medications are initiated or discontinued or a change in consumption of vitamin K–containing foods occurs.

(INR, international normalized ratio; PT, prothrombin time.)

FIGURE 14-3

Initiation of warfarin therapy.

(INR, international normalized ratio; PT, prothrombin time.)



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Thrombolytics

- Thrombolytic agents are proteolytic enzymes that enhance conversion of plasminogen to plasmin, which subsequently degrades the fibrin matrix.
- Most patients with VTE do not require thrombolytic therapy. Treatment should be reserved for patients who present with extensive proximal (eg, ileofemoral) DVT within 14 days of symptom onset, have good functional status, and are at low risk of bleeding.
- Patients with massive PE and evidence of hemodynamic compromise (hypotension or shock) should receive thrombolytic therapy unless contraindicated by bleeding risk.
- The same duration and intensity of anticoagulation therapy is recommended as for DVT patients not receiving thrombolysis. Patients with DVT involving the iliac and common femoral veins are at highest risk for postthrombotic syndrome and may receive the greatest benefit from thrombus removal strategies.
- For patients with massive PE manifested by shock and cardiovascular collapse (~5% of patients with PE), thrombolytic therapy is considered necessary in addition to aggressive interventions such as volume expansion, vasopressor therapy, intubation, and mechanical ventilation. Administer thrombolytic therapy in these patients without delay to reduce the risk of progression to multisystem organ failure and death. However, the risk of death from PE should outweigh the risk of serious bleeding associated with thrombolytic therapy.
- **Alteplase** (Activase) 100 mg by IV infusion over 2 hours is the most commonly used thrombolytic therapy for patients with PE.

- Before giving thrombolytic therapy for PE, IV UFH should be administered in full therapeutic doses. During thrombolytic therapy, IV UFH may be either continued or suspended; the most common practice in the United States is to suspend UFH.
- Measure the aPTT after completion of thrombolytic therapy. If the aPTT is <80 seconds, start UFH infusion and adjust to maintain the aPTT in the therapeutic range. If the posttreatment aPTT is >80 seconds, remeasure it every 2–4 hours and start UFH infusion when the aPTT is <80 seconds.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients for resolution of symptoms, development of recurrent thrombosis, symptoms of postthrombotic syndrome, and adverse anticoagulant effects.
- Monitor hemoglobin, hematocrit, and blood pressure carefully to detect bleeding from anticoagulant therapy.
- Perform coagulation tests (aPTT, PT, INR) prior to initiating therapy to establish the patient's baseline values and guide later anticoagulation.
- Ask outpatients taking warfarin about medication adherence to prior dosing instructions, other medication use, changes in health status, and symptoms related to bleeding and thromboembolic complications. Any changes in concurrent medications should be carefully explored, and dietary intake of vitamin K-rich foods should be assessed.

See Chapter 37, Venous Thromboembolism, authored by Daniel M. Witt, Nathan P. Clark, and Sara R. Vazquez, for a more detailed discussion of this topic.