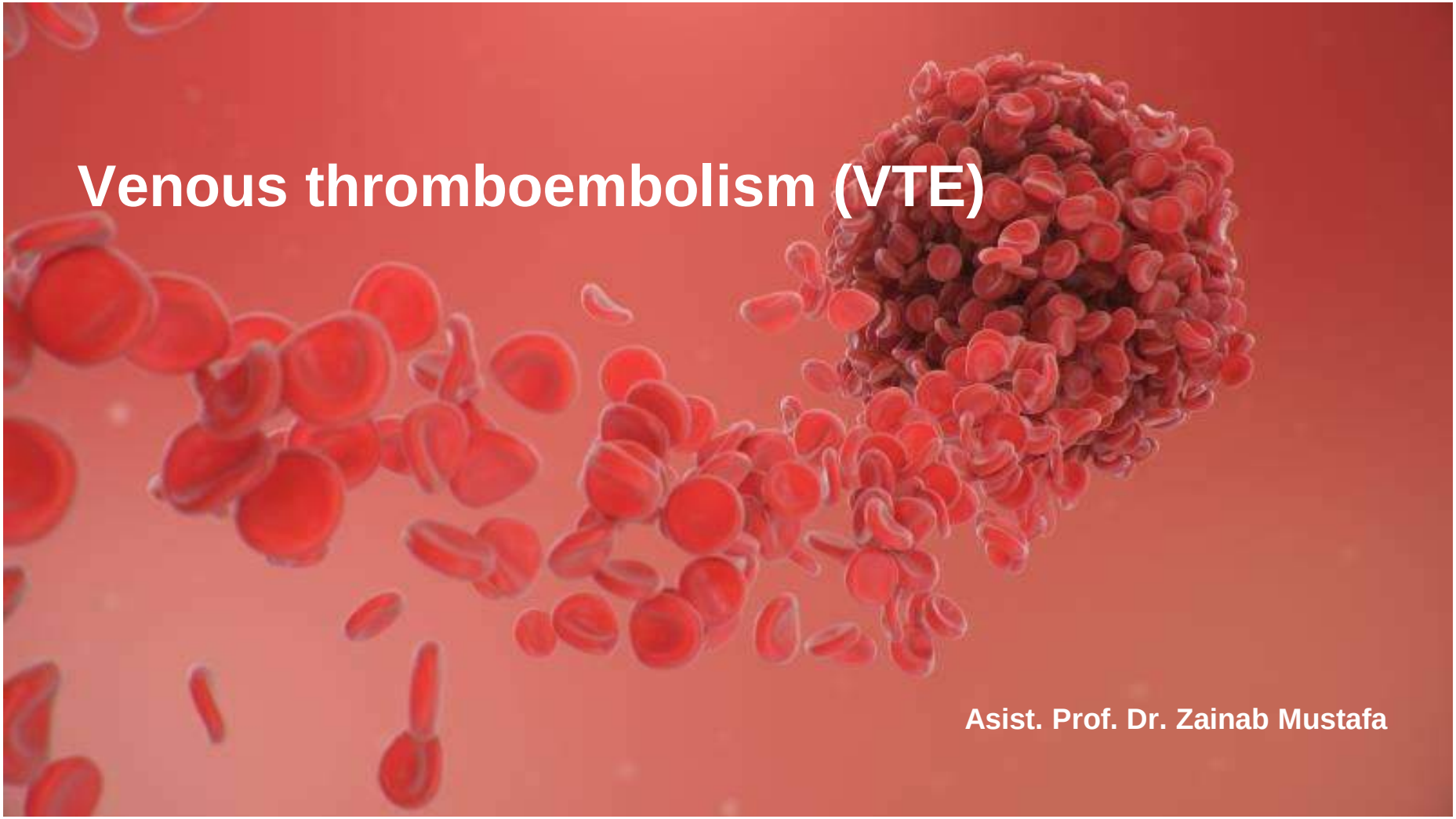
Venous thromboembolism (VTE)



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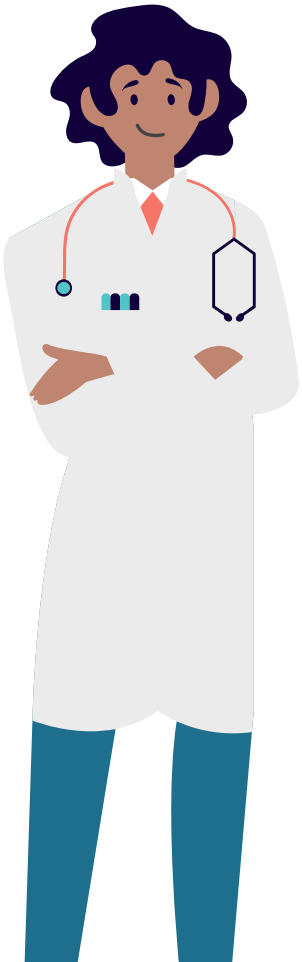
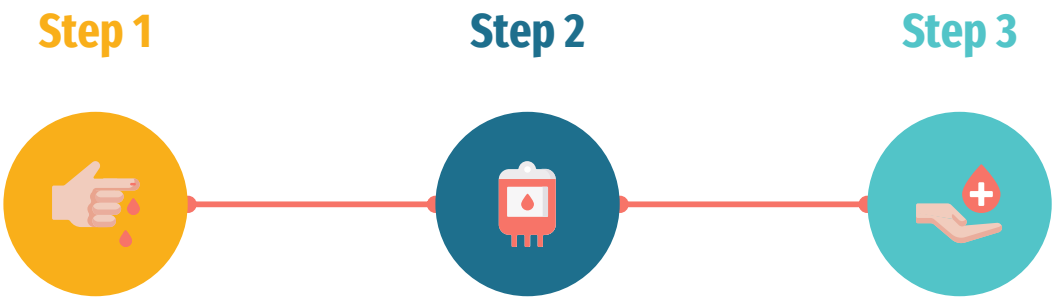


Venous thromboembolism (VTE)

results from clot formation in the venous circulation and is manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE)

PATHOPHYSIOLOGY

1.Risk factors for VTE include increasing age, history of VTE, and aspects related to Virchow's triad



blood stasis (eg, immobility and obesity)

vascular injury (eg, surgery, trauma, venous catheters)

hypercoagulability (eg, malignancy, coagulation factor abnormalities, antiphospholipid antibodies, certain drugs).

2.The most common inherited hypercoagulability disorder is activated protein C (aPC) resistance ,the risk of VTE three fold.

3.The prothrombin mutation is the second most frequent inherited hypercoagulability disorder and imparts a three fold increased risk of VTE.

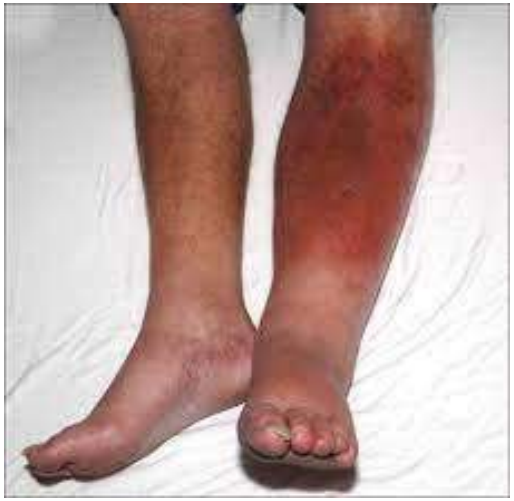
4.Inherited deficiencies of protein C, protein S, and antithrombin.

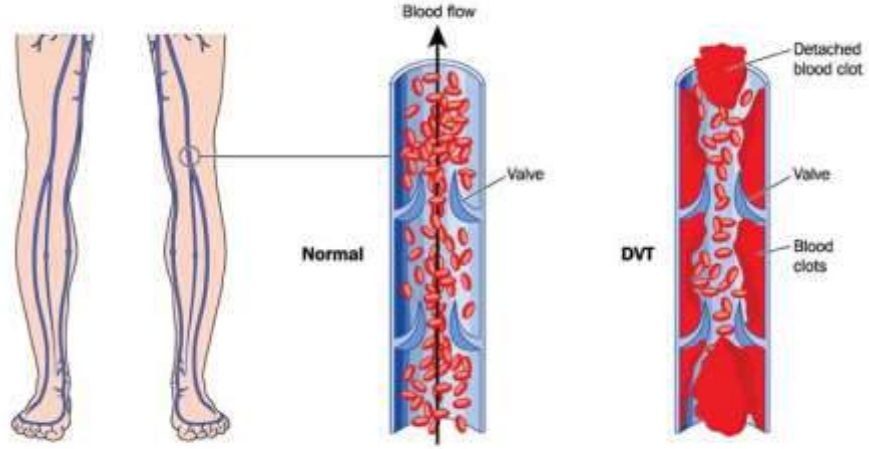
5.Normal hemostasis maintains circulatory system integrity after blood vessel damage.

6.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.

CLINICAL PRESENTATION

1.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.





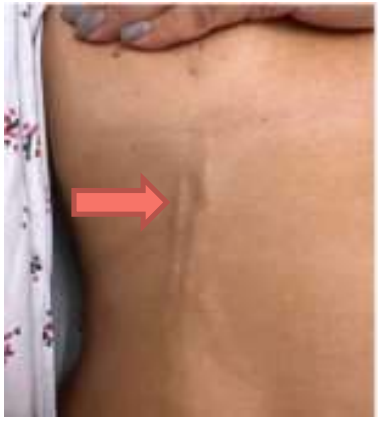
BACKGROUND

* CLINICAL FINDING of PAIN BEHIND KNEE upon FORCED DORSIFLEXION of FOOT
  - DESCRIBED by AMERICAN SURGEON JOHN HOMANS in 1994
  - POSITIVE SIGN TRADITIONALLY THOUGHT to be CLINICAL SIGN of DEEP VEIN THROMBOSIS (DVT)

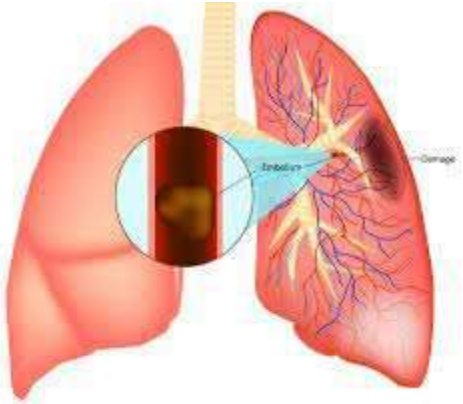
1. POSITION CLIENT'S KNEE in FLEXED POSITION

2. FORCIBLY & ABRUPTLY DORSIFLEX CLIENT'S ANKLE & OBSERVE for **PAIN BEHIND KNEE**

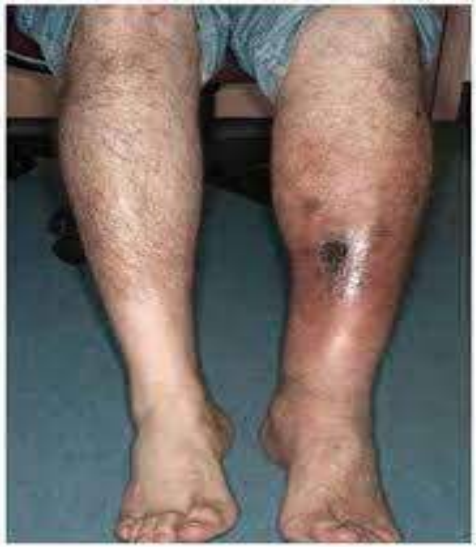
POSITIVE HOMAN SIGN



2.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.



3.Postthrombotic syndrome may produce chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration.



DIAGNOSIS

1. Assessment should focus on identifying risk factors .
2. Compression ultrasound (CUS) and computed tomography pulmonary angiography (CTPA) are used most often for initial evaluation of suspected VTE.
3. Radiographic contrast studies (venography, pulmonary angiography) are the most accurate and reliable diagnostic methods but are expensive, invasive, and difficult to perform and evaluate.
4. 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.
5. 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

General Approach to Treatment of VTE

- Anticoagulation is the primary treatment for VTE; DVT and PE
- After VTE is confirmed objectively, therapy with a rapid-acting anticoagulant should be instituted as soon as possible.
- 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.
- 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.

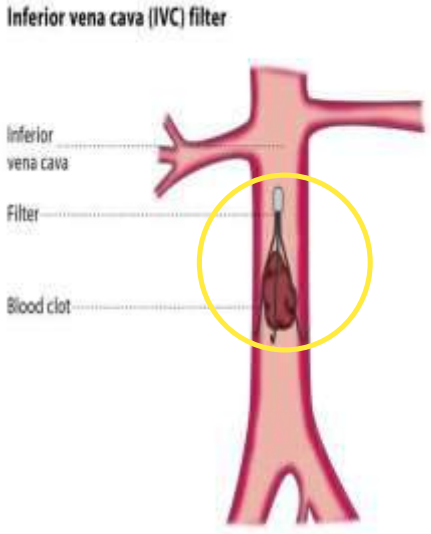
Nonpharmacologic Therapy

•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 bed rest 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

1.Direct Oral Anticoagulants (DOACs) :

Rivaroxaban, apixaban, edoxaban, and betrixaban are oral selective inhibitors of both free and clot-bound factor Xa.

Dabigatran is an oral selective, reversible, direct factor IIa inhibitor.

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.

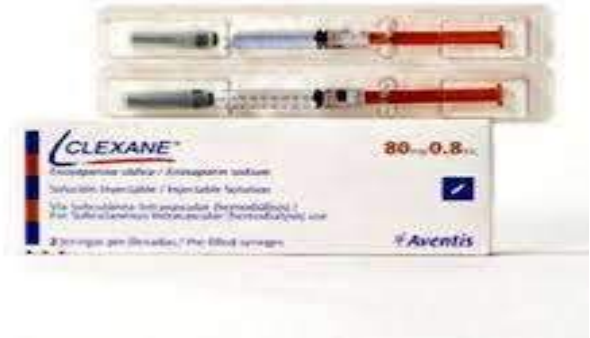
Recombinant coagulation factor Xa (also known as andexanet alfa; Andexxa) can reverse life-threatening bleeding in patients taking rivaroxaban or apixaban.

Adding **aspirin** to DOAC therapy nearly **doubles bleeding rates** and should be avoided in most patients with VTE. All DOACs are P-gp substrates an 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.

2. 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:

predictable anticoagulation dose response

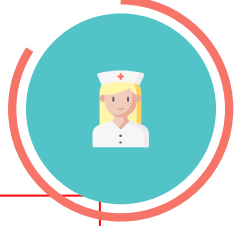
longer biologic half-life

improved SC bioavailability

lower incidence of thrombocytopenia

dose-independent clearance

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.

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
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.

3.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.

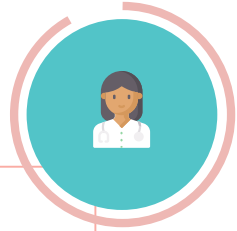
Patients receiving fondaparinux do not require routine coagulation testing. Determine baseline kidney function before starting therapy because fondaparinux is contraindicated if CrCl is <30 mL/min (0.5 mL/s).

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.

4.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 . 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.
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.

5. 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.

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.

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 perse, but it exacerbates bleeding from existing lesions and enables massive bleeding from ordinarily minor sources

The likely hood 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.

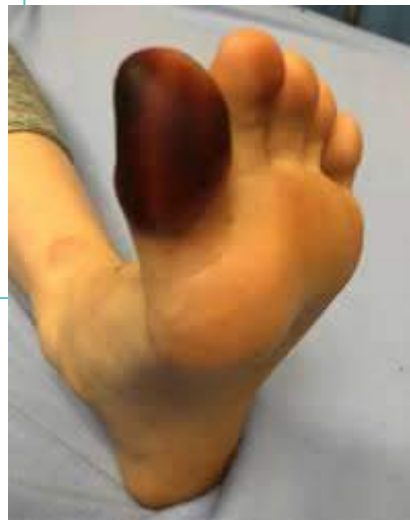
✓ If the INR is between 5 and 10 and no bleeding is present, routine vitamin K use is not recommended because it has not been shown to affect the risk of developing subsequent bleeding or thromboembolism compared to simply withholding warfarin alone.

✓ 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 or fresh frozon plasma.

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.



6. 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.

T.G. (weight 125 kg) is admitted for the treatment of a DVT with a PE. He is given a 10,000-unit bolus of UFH and initiated on an infusion of 2250 units/ hour. Twelve hours into the infusion, he begins to vomit blood. Which is the most appropriate protamine dose for T.G.?

A. 1 mg\100 mg max dose 50 mg.
B. 2 mg\100 mg max dose 50 mg
C. 1 mg\200 mg max dose 50 mg
D. 1 mg\100 mg max dose 100 mg