Thrombosis

Thrombosis is the formation of a blood clot inside a blood vessel. It can be classified into:

- Arterial thrombosis
  - Stroke (*Ischemic stroke*)
  - Myocardial infarction (STEMI & NSTEMI)
- Venous thrombosis, for example:
  - Deep vein thrombosis
  - Renal vein thrombosis
  - Portal vein thrombosis

Venous thromboembolism

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

Deep venous thrombosis

Deep venous thrombosis (DVT) is a manifestation of venous thromboembolism (VTE). Although most DVT is occult and resolves spontaneously without complication. DVT-associated massive pulmonary embolism (PE) causes death.

Symptoms of DVT include unilateral leg swelling, pain, tenderness, erythema, and warmth. Physical signs may include a palpable cord and a positive Homan sign (dorsiflexion sign).

Pulmonary embolism

Pulmonary emboli (PE) usually arise from thrombi that originate in the deep venous system of the lower extremities; however, they rarely also originate in the pelvic, renal, upper extremity veins, or the right heart chamber. After traveling to the lung, large thrombi can lodge at the bifurcation of the main pulmonary artery or the lobar branches and cause hemodynamic compromise.

Symptoms of pulmonary embolism include cough, chest pain or tightness, shortness of breath palpitations, hemoptysis, dizziness, or lightheadedness.
Signs of pulmonary embolism include tachypnea, tachycardia, diaphoresis, cyanosis, hypotension, shock, and cardiovascular collapse.

Postthrombotic syndrome

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

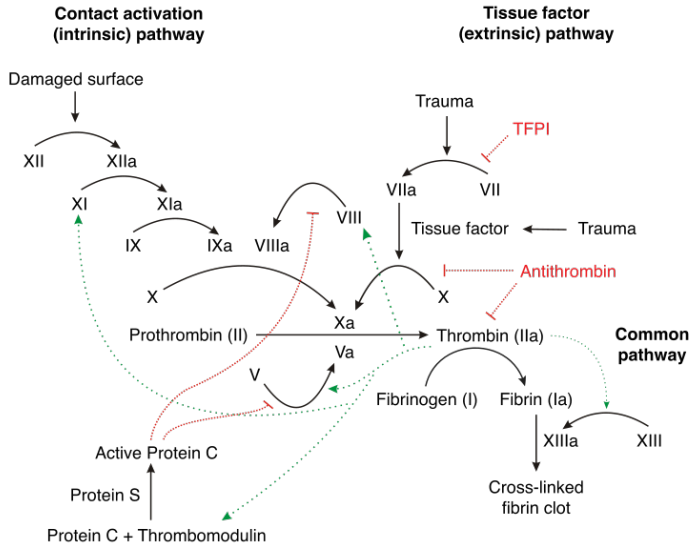
Causes and Risk factors

VTE occurs primarily due to a combination of stagnation of blood low and hypercoagulability.

1. Sluggishness of blood low may be related to bed rest, surgery or reduced cardiac output, for example, in heart failure.
2. Factors increasing the risk of hypercoagulability include surgery, pregnancy, estrogen administration, malignancy, myocardial infarction and several acquired or inherited disorders of coagulation (such as: protein C deficiency, protein S deficiency, factor V Leiden, antithrombin III deficiency, etc.)

Other risk factors of venous thromboembolism include:

- Increased age
- Major surgery
- Previous VTE
- Trauma
- Drug therapy



Diagnosis

- Clinical assessment
- Identifying risk factors
- Radiographic contrast studies
  - Venography
  - Pulmonary angiography
- Noninvasive tests
  - Compression ultrasound
  - Computed tomography scan
  - Ventilation-perfusion scan
  - Magnetic resonance imaging (MRI)
    - Magnetic resonance imaging with direct thrombus imaging (MRI DTI)
  - Computed tomography pulmonary angiogram (CTPA)
  - Ventilation–perfusion scanning
    - Ventilation/perfusion single-photon emission computed tomography (V/Q SPECT) scan
    - V/Q planar scan
- Elevated D-dimer blood level
  - It occurs in acute thrombosis but also with other conditions (e.g., recent surgery or trauma, pregnancy, cancer). Therefore, a negative test can help exclude VTE, but a positive test is not conclusive evidence of the diagnosis.
  - It is also elevated in COVID-19.

Non-pharmacological treatment

- Graduated compression stockings
- Intermittent pneumatic compression (IPC)
- Inferior vena cava filters
- Thrombectomy or embolectomy

Anticoagulant therapy

- Anticoagulation is the primary treatment for VTE; DVT and PE are treated similarly.
- The acute phase (~7 days) requires rapidly-acting anticoagulants to prevent thrombus extension and embolization.
- The early maintenance phase (7 days to 3 months) to reduce risk of long-term sequelae (e.g., postthrombotic syndrome).
- Anticoagulation beyond 3 months for long-term secondary prevention of recurrent VTE.

Anticoagulants

- ***Unfractionated heparin***

Unfractionated heparin (UFH) prevents growth and propagation of a formed thrombus and allows endogenous thrombolytic systems to degrade the clot. It can be given by IV infusion, IV bolus dose or SC injection.

The activated partial thromboplastin time (aPTT) with a therapeutic range of 1.5 to 2.5 times the mean normal control value is generally used to determine the degree of therapeutic anticoagulation.

Protamine sulfate is the antidote.

- ***Low molecular weight heparins (LMWH)***

Advantages of LMWHs (including enoxaparin, bemiparin, dalteparin, tinzaparin, etc.) over UFH include:

- Predictable anticoagulation dose response
- Improved SC bioavailability
- Dose-independent clearance
- Longer biologic half-life
- Lower incidence of thrombocytopenia
- Less need for routine laboratory monitoring.

- ***Factor Xda inhibitor (Fondaparinux)***

Fondaparinux is a safe and effective alternative to LMWH for treatment of DVT or PE. It prevents thrombus generation and clot formation by indirectly inhibiting factor Xa activity through its interaction with antithrombin.

- ***Direct thrombin inhibitor (Hirudins)***

Lepirudin and bivalirudin are indicated to be used in patient with, or at risk of, heparin-induced thrombocytopenia (HIT) or thrombosis syndrome, undergoing percutaneous coronary intervention (PCI).

- **Heparinoids**

Danaparoid is a heparinoid that is licensed for prophylaxis of DVT in patients undergoing general or orthopedic surgery.

Oral anticoagulants:

- ***Coumarins***

Warfarin is to be started concurrently with UFH or LMWH therapy. Because prothrombin has a 2- to 3-day half-life, warfarin's full antithrombotic effect is not achieved for 8 to 15 days after initiation of therapy. Warfarin therapy is monitored by the INR. Vitamin K is the antidote.

- ***Direct acting oral anticoagulants (DOACs):***
  - ***Direct Xa Inhibitors*** *(Rivaroxaban, apixaban, edoxaban and betrixaban)*

Rivaroxaban and apixaban are selective inhibitors of both free and clot-bound factor Xa that do not require antithrombin to exert their anticoagulant effect.
They are not approved by FDA for VTE, but rivaroxaban is approved for prevention of VTE following hip or knee replacement surgery.

Andexanet alfa is an antidote for patients treated with direct Xa Inhibitors who require anticoagulation reversal due to uncontrolled or life-threatening bleeding.

  - ***Direct factor IIa inhibitor*** *(Dabigatran)*

Dabigatran is oral selective reversible direct factor IIa inhibitor. It is indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days. Also, it is Indicated for the prophylaxis of DVT and PE following hip replacement surgery.

Idarucizumab rapidly reverses the dabigatran anticoagulant effect when needed during emergency situations (e.g. life-threatening bleeding) and needed for urgent surgical interventions.

Thrombolytics:

Thrombolytic agents or fibrinolytic agents (alteplase, streptokinase, urokinase, reteplase and tenecteplase) degrade the fibrin matrix. Removal of the occluding thrombus by fibrinolytic therapy (or surgical means) is rarely warranted.

	DVT	PE	AIS	AMI	Notes
Alteplase	✓	✓	✓	✓	The most widely used.
Streptokinase	✓	✓		✓	Limited use.
Urokinase	(✓)	✓			It is also licensed to restore patency in intravenous catheters and cannulas blocked by fibrin thrombi.
Reteplase				✓	Heparin is required to prevent rebound thrombosis.
Tenecteplase				✓	Heparin is required to prevent rebound thrombosis. It may be used to restore function to hemodialysis catheters.

Defibrotide is an thrombolytic agents indicated for adults and children with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem cell transplantation (HSCT).

The international normalized ratio (INR)

In healthy people an INR of 1.1 or below is considered normal. An INR range of 2.0 to 3.0 is generally an effective therapeutic range for people taking warfarin for most conditions related to venous thromboembolism.

		Standard Targets	Notes
PE		2.5 (2.0-3.0)	Unprovoked, infrequent INR checks: 1.5-1.9 after 3 months of standard therapy
DVT	lower extremity	2.5 (2.0-3.0)	
	upper extremity	2.5 (2.0-3.0)	
	children	2.5 (2.0-3.0)	CVC related: 1.5-1.9 after 3 months of standard therapy

$$\text{INR} = \left(\frac{\text{PT of patient}}{\text{PT of normal range mean}}\right)^{\text{ISI}}$$

PT = Prothrombin time
ISI = International Sensitivity Index

Antidotes for anticoagulants

Anticoagulants	***Antidotes***
Unfractionated heparin (UFH)	Protamine sulfate
Low molecular weight heparins (LMWH)	Protamine sulfate (rarely used)
Fondaparinux	N/A
Hirudins	N/A
Warfarin	Vitamin K
Direct Xa Inhibitors	Andexanet alfa
Dabigatran	Idarucizumab