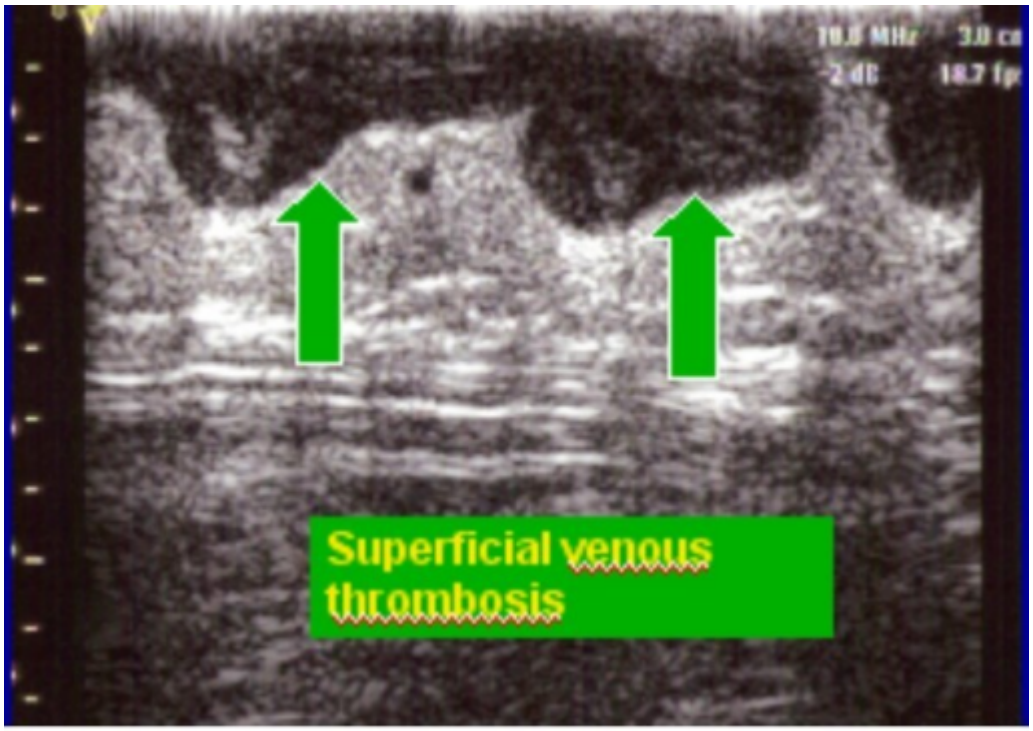
Thrombosis

See online here



Introduction

Blood must be maintained in a fluid state to allow for the transport of oxygen and nutrients all over the body. This is achieved by striking a balance between hemostasis and blood loss.

Definition of Hemostasis

Hemostasis is the ability of blood to solidify and form a clot in the event of a vascular injury to prevent further blood loss.

Under normal circumstances, successful hemostasis should be:

- Localized to the area of injury
- Followed by the removal of the clot and tissue repair

The process progresses in stages that begin with a pre-injury condition where the **blood vessel is intact and ready to release nitric oxide, heparans, and prostacyclins upon damage** or any form of injury.

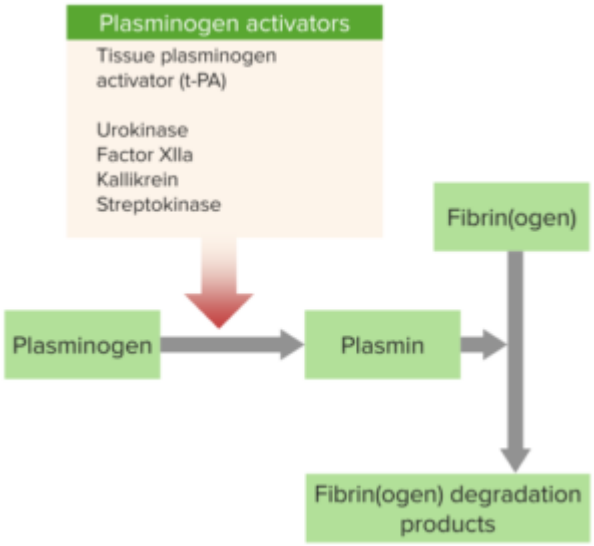
This sets in for the hemostatic response stage where there is an **aggregation of platelets following the interaction of Gp Ia and Gp Ib platelet receptors with**

collagen and von Willebrand factor respectively that are in the vessel.

Furthermore, the **platelets degranulate leading to a release of adenosine diphosphatase (ADP) and thromboxane A2 (TXA2)** which facilitate further aggregation of platelets to each other via fibrin polymers that attach to the platelet receptors Gp IIb and Gp IIIa and hence act as a bridge.

Fibrin clot formation may take the:

- Longer intrinsic pathway that begins with collagen and high molecular weight kininogen being exposed to activate factor XII (Hageman factor) which, in turn, activates factor XI and the resultant activates Christmas factor (Factor IX) that ends up activating factor X to start off the common pathway.
- The shorter extrinsic pathway that is activated by tissue injury that leads to activation of factor VII which, in turn, activates factor X of the common pathway.



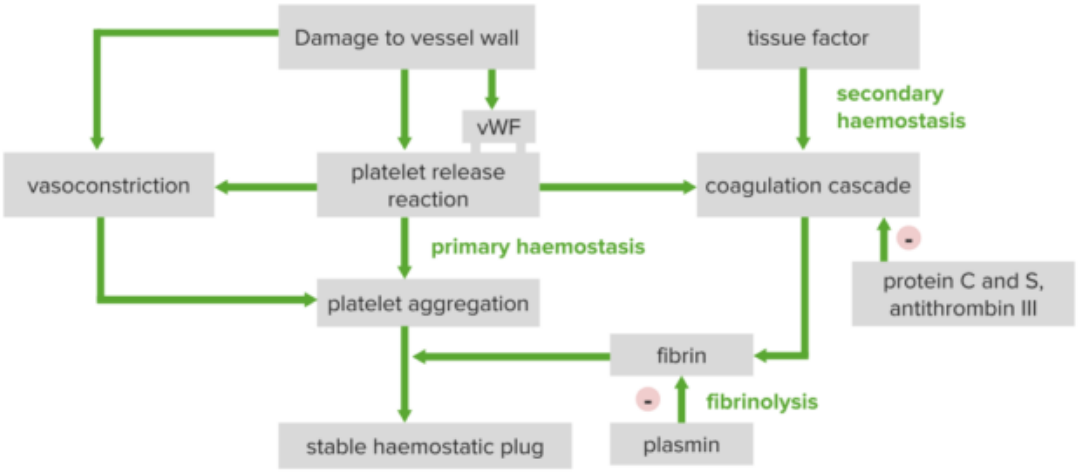
"Fibrinolysis" by Lecturio.

Activated factor X leads to **conversion of prothrombin to thrombin**. The thrombin will convert fibrinogen to fibrin which is converted to a more insoluble fibrin clot by activated factor XIII.

Limiting clot formation to avoid excessive and prolonged formation of the clot is carried out by the breaking down of the fibrin clot into fibrin degranulation products by plasmin derived from plasminogen by plasminogen activators. This is also known as **fibrinolysis**.

Dysfunction in the hemostasis mechanism may lead to:

- Hemorrhage
- Thrombosis
- Embolism



"Overview of Hemostasis" by Lecturio.

Definition of Thrombosis

Thrombosis is the formation of a **blood clot inside the vessel leading to obstruction of the flow of blood**.

Embolus, on the other hand, is a **clot or a piece of it that breaks free and travels throughout the body's vascular system**. Thrombus may be classified based on the vessel involved.

Venous thrombosis

Further classified into:

- Deep venous thrombosis
- Paget Schroetter disease
- Cerebral venous sinus thrombosis

This refers to the formation of a **clot in the venous system of blood**. It results into congestion of the affected parts of the body that, if not treated, leads to obstruction of the arterial supply and ultimately leads to ischemia and death of a part of the body.

Some common forms of venous thrombosis include:

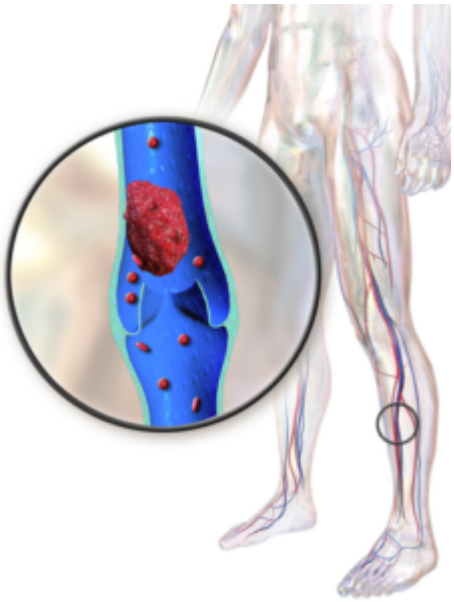


Image: “Deep Vein Thrombosis.” by BruceBlaus.
License: CC BY 3.0

Deep venous thrombosis

This is the formation of a clot in the deep veins, mostly of the lower limbs, i.e., the femoral, popliteal, and tibial vein.

Paget Schroetter disease

This is formation of a blood clot in the smaller veins of the upper extremity (axillary vein and subclavian vein). It is commonly seen in young males who were previously healthy, but developed a clot after a period of heavy exercising.

Cavernous sinus and cerebral venous sinus thrombosis (CVST)

These entities involve the formation of a thrombus in the dural venous sinuses. The cavernous sinus thrombosis is a unique entity of cavernous sinus involvement and different clinical presentation. They are medically important due to their association with retrograde spread of infection and resulting inflammation that leads to clot formation.

They present with:

- Double vision or squint
- Meningitis
- Headache
- Abnormal vision
- Signs of stroke such as focal neurological deficits and seizures

The main way of investigating for these diseases is by **MRI and CT scans of the head**.

Arterial thrombus

- Mesenteric ischemia
- Acute limb ischemia
- Myocardial infarction

It begins with the formation of a **thrombus within an artery that mostly results from rupture of an atheroma;** hence, the name atherothrombotic. It may also occur when an embolus arises from a smaller artery, the venous system or the heart and

travels to affect the smaller artery. Such examples include cardiogenic emboli seen in atrial fibrillation and **lead to the formation of thrombus in the arteries of the brain**.

Arterial thrombus can be classified based on the involved vessel.

Stroke

It is the formation of a **clot in the arteries of the brain leading to ischemic injury of the brain**.

It is the third leading cause of death in the developed world after cancer and ischemic heart disease.

It may involve large vessels, such as the internal carotid and the vertebral-basilar systems, or it may involve small vessels such as the branches of the circle of Willis.

The patients present with rapid appearance of focal deficit of the brain with/without higher cerebral dysfunction such as aphasia, hemisensory loss, visual field defects and brain stem deficit.

Myocardial infarction

It arises when the **myocardial oxygen supply is outweighed by demand leading to ischemia and infarction of the cardiac muscles**. It may arise from several mechanisms, but formation of an atheroma that ruptures to trigger coagulation and formation of a thrombus is the most common cause.

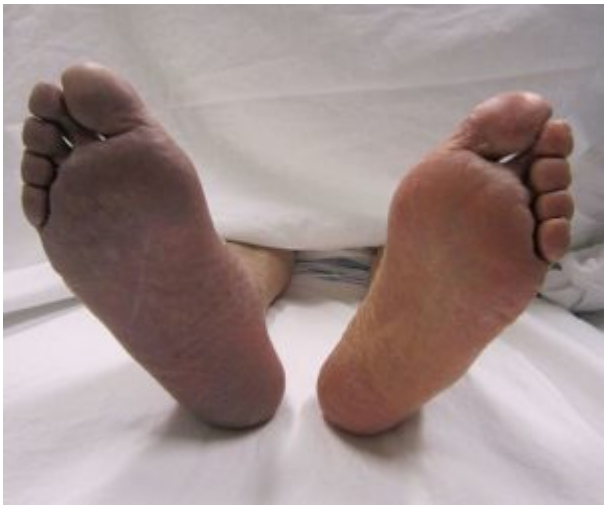


Image: “Cyanosis of the right foot distal to an occlusion caused by acute arterial thrombosis of the right leg” by James Heilman, MD.

Acute limb ischemia

It results from a **sudden formation of a clot in the arteries supplying the limb**. If the clot is not removed immediately, ischemic injury ensues and the limb dies.

Etiology & Pathogenesis of Thrombosis

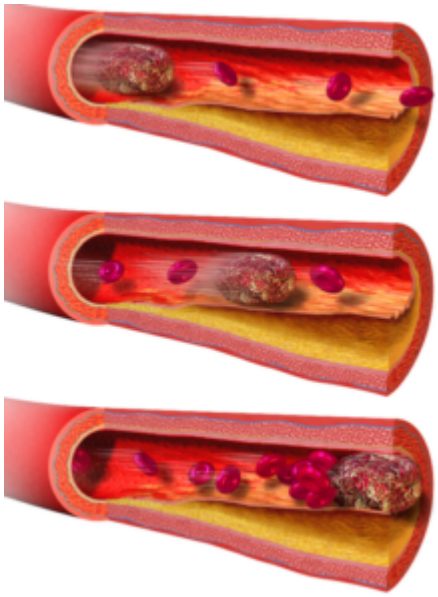


Image: “Blood clot motion.” by BruceBlaus.
License: CC BY 3.0

Thrombosis results from an **imbalance in the normal hemostatic mechanisms of clotting** leading to a favorable environment for clotting.

The risk factors that increase the risk of clotting are grouped into three subjects which make up the Virchow’s triad. These include:

- Stasis of blood within the vessel.
- Vessel wall injury.
- Hypercoagulability states of blood.

Some factors are known to increase the venous clotting more than arterial clotting and vice versa. Thrombosis is a multifactorial disease with etiology being either acquired or they are congenital risk factors.

Acquired risk factors for thrombosis

Events leading to stasis of blood

Pregnancy

The state leads to an increased risk of coagulation due to several factors:

- It is a hypercoagulable state due to an increase in procoagulant hormones, such as estrogen.
- Mechanical pressure of the gravid uterus on the deep veins of the lower limbs against the spine posteriorly.
- Immobilization associated with pregnancy.

Prolonged bedrest

This leads to stasis of blood within the vessels and clot formation. It may arise from events such as following trauma or incapacitating disease such as one leading to severed weakness, immobilization after cast or limb fixation.

Immobility due to paralysis following spinal injury or limb injury, paresis due to nerve injury or immobility due to medical contraindication such as upon application of traction, plaster of Paris etc.

Long flights and train rides

Obesity

Malignancies with high cell production leads to leukostasis within the vessel.

Events leading to endothelial injury:

- Trauma
- Surgery
- Vascular diseases such as HIV associated vasculitis.

Events leading to hypercoagulable states:

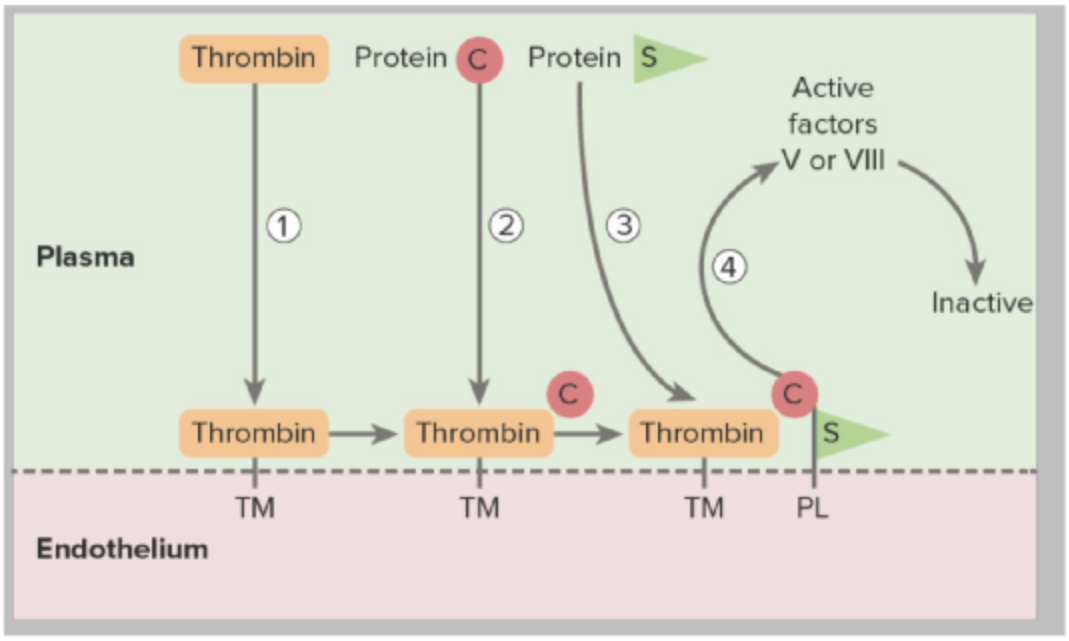
- **Increased levels of estrogen,** as seen with hormonal replacement therapy and oral estrogen-only contraceptive pills.
- **Presence of a malignancy** that leads to an increase in inflammatory mediators and thus favors the development of a hypercoagulable state.
- **Sepsis may lead to vessel injury or activation of inflammatory mediators.**
- **Nephrotic syndrome** that leads to a loss of smaller anticoagulant factors and retention, coupled with a compensatory increase in the production of the larger procoagulant factors leading to the development of clots.
- **Myeloproliferative diseases.**
- **Hyperviscosity syndromes** such as multiple myeloma and Waldenstrom macroglobulinemia.

The congenital risk factors for hypercoagulability

Factor V Leiden mutation leads to resistance against protein C that acts as a factor V and VIII inhibitor; thus, mutation in the gene encoding for factor V leads to increased prothrombin activity and procoagulant states in blood.

Prothrombin gene mutation leads to abnormally formed prothrombin and increased activation of the thrombotic process.

Protein C, protein S and Antithrombin III deficiencies which are proteins necessary to halt the coagulation pathway. Antithrombin III is a thrombin inhibitor; thus, deficiency of the protein leads to increased thrombus formation.



"Inherited Thrombophilia" by Lecturio.

Diagnosis of Thrombosis

The diagnosis of a thrombus begins with **history taking and a physical examination** to try and establish the likely cause of the thrombus formation and the available risk factors for the same.

Tests that should be done include:

Complete blood count (CBC)

It forms the basic form of investigation to **characterize the nature of the clotting disorder**. The parameters are likely to be normal or elevated in most cases. Platelet count and hemoglobin levels are the most important parameters in patient management.

Coagulation profile

It includes:

1. **Prothrombin time** that signifies adequacy of the extrinsic pathway,
2. **International normalized ratio (INR)** compares the prothrombin time to the average of normal, and
3. **Activated partial thromboplastin time** that signifies the adequacy of the intrinsic pathway.

Fibrin D dimer

It measures the **degranulation products of cross-linked fibrin molecules** that increase in the acute thrombotic period. It is a sensitive, but a non-specific marker of deep venous thrombosis. It has a **better negative predictive value** in that if it is negative, it rules out the possibility of having a thrombus with a higher accuracy, while a positive result is non-specific for thrombosis and could represent other processes, such as disseminated intravascular coagulopathy, inflammation, infection, and malignancy.

Duplex ultrasound

It is a form of ultrasonography that inculcates the ultrasound B mode to offer a non-invasive analysis for thrombus by eliciting for compressibility and detection of thrombosis. Vessels with clots within them are not compressible and there is reduction in flow quality.

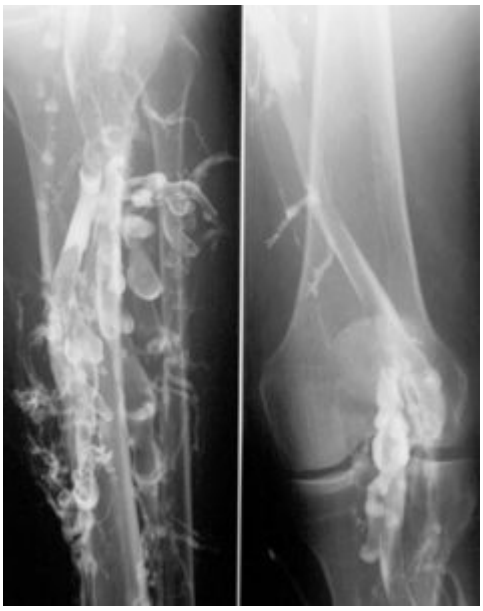


Image: “Phlebography in deep vein thrombosis (Venography for DVT)” by Hellerhoff. License: CC BY-SA 3.0

Venography

It involves **invasive introduction of contrast into the vein and taking of an X-ray of the limb**. It is the **gold standard** for diagnosis of deep vein thrombosis.

However, it is rarely done due to the **risk of infection, allergic reaction to the contrast and the risk of dislodging the clot**.

I 125 labelled fibrinogen scintigraphy

It is a new method of detecting fresh thrombi by analyzing for uptake of the radioactive material.

Impendence plethysmography

It is a technique where a tourniquet is applied around the involved vein and released after some minutes. The **change in the size of the limb is measured to indicate obstruction in the flow** of blood within the limb.

Magnetic resonance venography (MRV)

It is a newer technique where the MRI image replaces the X-ray image to show a new or old clot.

Computed tomography

This is the method of choice in the investigation for pulmonary system thrombus, mesenteric ischemia, and stroke among others. The clot is visualized as a hypodense lesion within the vessel containing blood light up with contrast.

For a stroke, contrast is not advised and the effect of the clot helps in diagnosis as a

triangular region of hypodense brain tissue is seen depicting the distribution of the blood vessel.

Genetic screening

It is also done for patients who are likely to have congenital bleeding disorders, such as protein C and S levels.

Treatment of Thrombosis

Definitive/medical/anticoagulant treatment

Heparins

Intravenous unfractionated heparin that is administered as an infusion of -80 units/kg bolus then 18 units/kg/hr. Continuous infusion.

Subcutaneous unfractionated heparin that is administered at a dose of 333 units/kg loading dose and a maintenance dose of 250 units/kg every 12 hours.

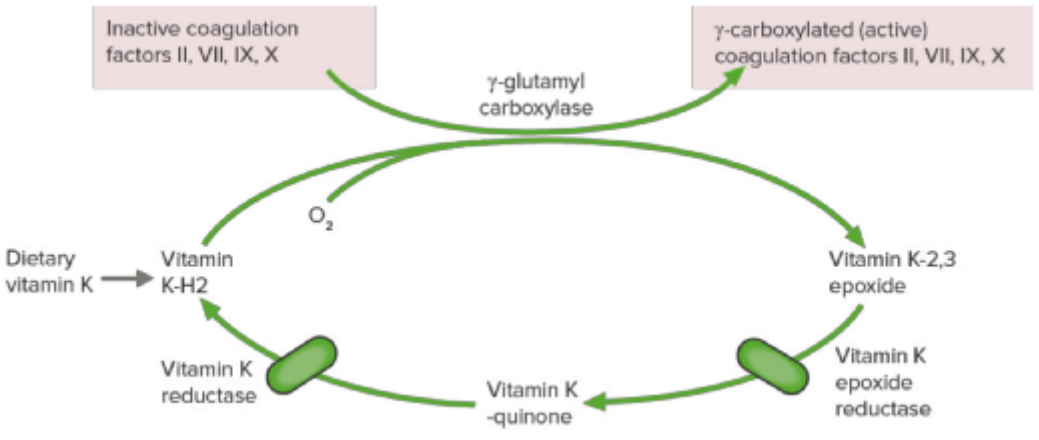
Low molecular weight heparin, such as enoxaparin (clexane), that is administered at a dose of 1 mg/kg BD or 1.5 mg/kg OD. Other low molecular weight heparins include dalteparin, nadroparin, and tinzaparin.

Monitoring if heparin is done using the activated partial thromboplastin time which signifies the adequacy of the intrinsic pathway where heparin works. The target aPTT is two times the upper limit of normal/baseline.

Common side effects of heparin that should be monitored include **heparin-induced thrombocytopenia (HIT) and intracerebral hemorrhage**.

Warfarin

It is started at 5 mg OD dosage and monitored via INR since its main pathway of action is the extrinsic pathway that is assessed by prothrombin time. Some **rare adverse effects of warfarin include warfarin-induced skin necrosis, embryopathies, and hemorrhage**.



"Warfarin" by Lecturio.

Administration of heparin is done simultaneously with warfarin for at least 5 days before the patient is allowed home on warfarin. Since **heparin is fast acting and warfarin**

requires at least 72 hours to achieve antithrombotic effects, warfarin administration is initially procoagulant and thus requires a bridge with heparin.

Finally, warfarin is available in forms that can be taken at home, while heparin is limited to hospital use for its agents act mostly on parenteral routes.

Hence, administer heparin and warfarin simultaneously and do INR on day 3, then titrate the doses accordingly.

Once INR is therapeutic, stop heparin and consider discharging the patient on warfarin.

New oral anticoagulant drugs (NOAC)

Anticoagulant therapy is ever-changing since the inception of older anticoagulants that are now considered to have a rather unsafe profile. The new oral anticoagulant drugs do **not require frequent monitoring due to their predictable dose-response relationships** and they come in forms that can be used for outpatient care; thus, they are gaining widespread use.

They include:

- **Direct thrombin inhibitors,** such as hirudin, lepirudin, argatroban and dabigatran.
- **Activated factor X inhibitors,** such as apixaban and rivaroxaban.

Fondaparinux

It is a newer agent that is **used as a replacement for heparin and warfarin**. It is a synthetic polysaccharide from the antithrombin binding region of heparin and catalyzes the inactivation of activated factor X.

Supportive/physical treatment

This involves the use of a **compression stocking to encourage venous return**. The stockings are usually pneumatic with variation in pressures at various levels of the legs.

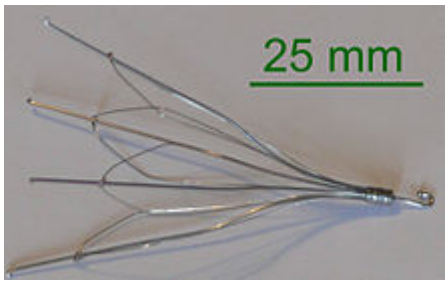


Image: “An IVC filter” by BozMo. License: CC BY-SA 3.0

The use of **IVC filters** in patients with deep venous thrombosis prevents the dislodgement of the clot and formation of pulmonary embolism. They are associated with an increase in the risk of thrombosis or failure of the mesh altogether and thus they are **rarely used**.

Elevation of the involved limb is done in conjunction with definitive treatment and encourages venous return to reduce the amount of swelling in the limbs.

The supportive forms of therapy are considered in patients who have a serious

contraindication to anticoagulant use, such as in patients with an intracerebral bleed. Other supportive measures, such as **pain control** and **partial ambulation,** help in increasing the adherence rate of these patients and in improving the quality of life in the patients.

References

Barrett, K. E., & Ganong, W. F. (2012). Ganong’s review of medical physiology. New York: McGraw Hill Medical.

Boon, N. A., Walker, B. R., Colledge, N. R., & Davidson, S. (2010). Davidson’s principles and practice of medicine. Edinburg: Churchill Livingstone.

Harrison, T. R., Fauci, S. A., Kasper, L. D., Longo, L. D., Hauser, S. L., & Jameson, J. L. (2012). Harrison’s Principles of Internal Medicine.18th edition. New York: McGraw Hill.

Orkin , S. H., Fisher, D. E., Ginsburg, D., Look, A. T., Lux, S. E., & Nathan, D. G. (2015). Nathan and Oski’s Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: Elsevier Saundres.

Notes