Anticoagulants, Thrombolytics, and Antiplatelets

Hemostasis (Bleeding Control)

Hemostasis refers to the stoppage of bleeding, when blood vessels are damaged and bleeding begins. Three processes occur in hemostasis:

(1) **blood vessel spasm**, When a blood vessel breaks, the smooth muscle at the site of the damage in its wall contracts and causes the blood vessel to spasm. This spasm reduces the amount of blood lost through the vessel

(2) **platelet plug formation**, Platelets also begin to stick to the broken area and to each other to form a platelet plug. The platelet plug stops the bleeding temporarily

(3) **blood coagulation**, a blood clot eventually replaces the platelet plug. In this process, the plasma protein fibrinogen is converted to fibrin. Once fibrin forms, it sticks to the damaged area of the blood vessel, creating a meshwork that entraps blood cells and platelets. The resulting mass, the blood clot, stops bleeding until the vessel has repaired itself.

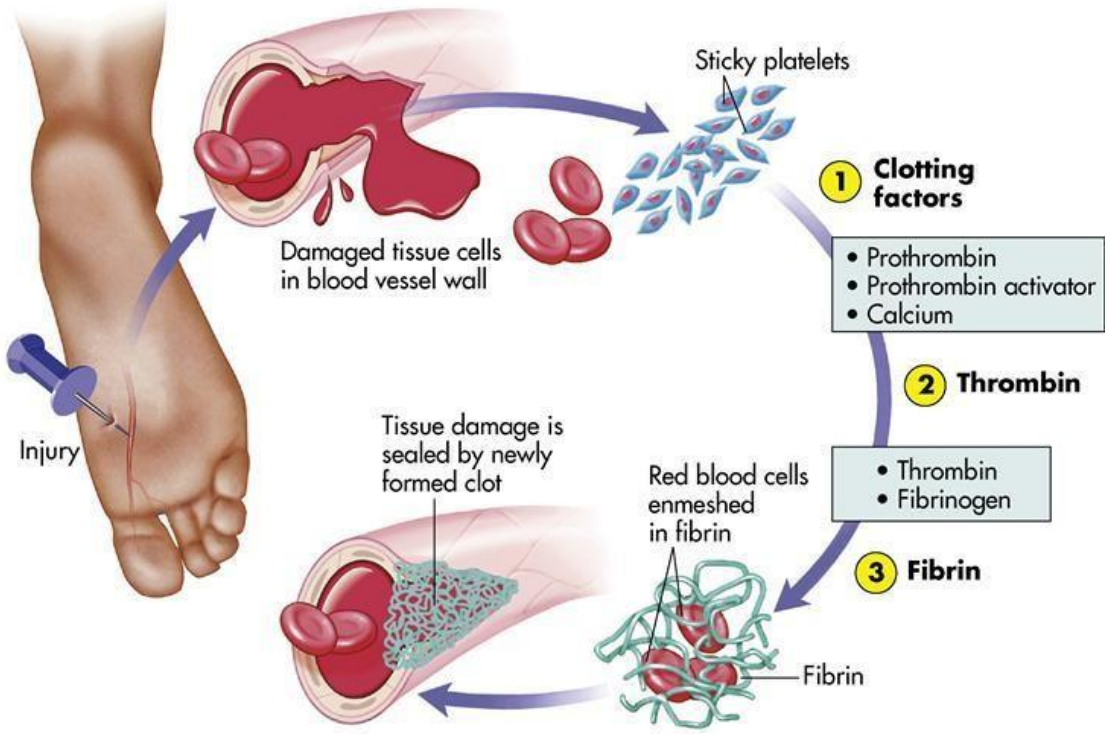


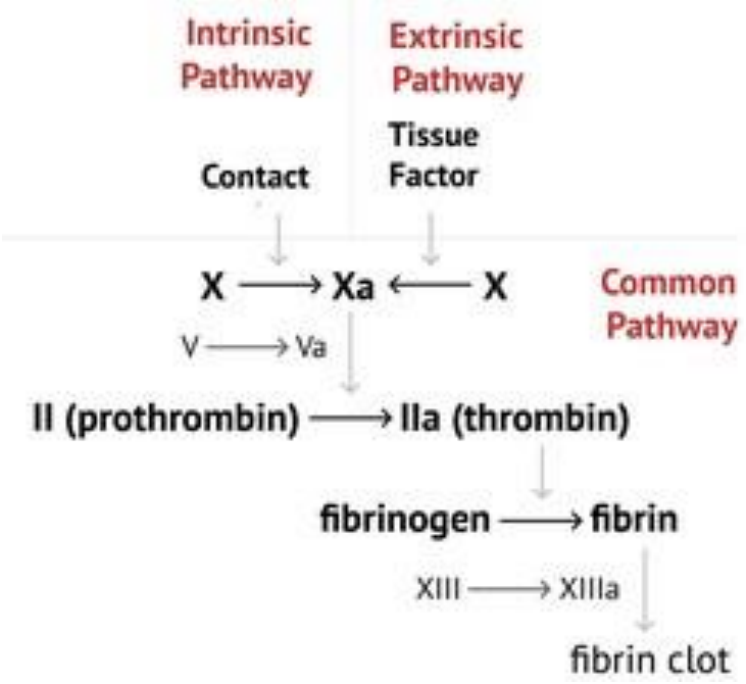
Figure: Hemostasis (stoppage of bleeding)

COAGULATION

Coagulation is the formation of a blood clot, and is essential to haemostasias. The process of clot(الخترة) formation occurs via two pathways:

- The extrinsic pathway: This is triggered by external trauma which causes blood to escape the circulation.
- The intrinsic pathway: This is triggered by internal damage to the vessel wall

Both intrinsic and extrinsic pathways converge to give rise to **activated factor X. Activated factor X** convert the inactive enzyme **prothrombin** (also called factor II) to its active form thrombin (factor IIa). **Thrombin** then converts soluble fibrinogen (also referred to as factor I) into insoluble fibrin strands. The fibrin strands which comprise the clot are further stabilized by factor XIII.



some of the important factors in process of clot formation are:

I Fibrinogen.
II Prothrombin.
III Tissue factor.
IV Calcium.
VIII Antihemophilic factor.
IX Christmas factor.
X Stuart-Prowers factor.
XIII Fibrin-stabilizing factor.

ANTICOAGULANT, ANTI-PLATELET DRUGS , and THROMBOLYTIC.

- (anticoagulants) Inhibit clotting mechanism
  GOAL: prevent progression of thrombosis
- (antiplatelet drugs) Interfere either with platelet adhesion and/or aggregation.
  GOAL: prevent initial clot formation
- (thrombolytic, or fibrinolytic agents) Degrade fibrinogen/fibrin
  GOAL: eliminate formed clots.

ANTICOAGULANTS

An anticoagulant is a substance that prevents coagulation; that is, it stops blood from clotting by two mechanisms:

1. interfere with synthesis of clotting factors.
2. decrease the activity of clotting factors.

Indications

Anticoagulants are used in the following conditions:

1. Deep vein thrombosis, and pulmonary and cerebral embolism.
2. Unstable angina, and heart attack
3. Atrial fibrillation.
4. Disseminated intravascular coagulation – In disseminated intravascular coagulation, a number of small clots are formed in the blood. Heparin is useful in this condition.
5. Anticoagulants are also useful to prevent emboli in other condition like dialysis, prosthetic heart valves and vascular surgery such as angioplasty and stent placement.

I. Oral anticoagulants

Oral anticoagulants can be classified as follows:

1. Vitamin K antagonists: Inhibit the activation of the vitamin K-dependent clotting factors, like **warfarin.** The usual dose of warfarin is 5 mg/day which can be changed depending on International **Normalized Ration (INR)** values.

Note:

The **International Normalized Ratio (INR)** is derived from prothrombin time (PT) which is calculated as a ratio of the patient's PT to a control PT using the following formula:

INR = Patient PT ÷ Control PT.

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 disorders such as atrial fibrillation or a blood clot in the leg or lung.

The reference range for prothrombin time is 11.0-12.5 seconds.

2. Direct thrombin inhibitors (DTIs): Bind with thrombin which is the central effector of coagulation to inactivate thrombin. Example includes **dabigatran** etexilate.

3. Direct factor Xa inhibitors: Bind to clotting factor Xa specifically to block its activity. Examples include **apixaban and rivaroxaban**

What are the side effects of Anticoagulant?

- Severe bleeding.
- Red or brown urine.
- Black or bloody stool.
- Severe headache or stomach pain.
- Joint pain, discomfort or swelling, especially after an injury.
- Vomiting of blood or material that looks like coffee grounds.
- Coughing up blood.

II.Parentral anticoagulants

Heparin, is a Glycosaminoglycan chains attached to a protein core proteoglycan. it is derived from mucosal tissues of slaughtered meat animals (sheep, cows, and pigs). Also, it is secreted form mast cells at the site of tissue injury. Heparin works by inhibiting the three major clotting factors (thrombin, thromboplastin, and prothrombin). The following dosing guidelines based on clinical experience:

-Initial dose: 5000 units by IV injection

-Maintenance dose: 20,000 to 40,000 units per 24 hours by continuous IV infusion. The dose is monitored by activated partial thromboplastin times (aPTTs).

Goal: Therapeutic range based on body weight-based dosage aPTT between 1.5 – 2.5 times normal control level. Effects reversed by protamine sulfate.

Note: The reference range of the aPTT is 30-40 seconds.

Note: Activated partial thromboplastin time(aPTT)

activated partial thromboplastin time (aPTT) are used to test used to measure how long it takes your blood to form a clot. It is used to monitor the patient's response to heparin therapy. The reference range of the aPTT is 30-40 seconds

Low-molecular weight heparin

Low-molecular weight heparin is gradually replacing heparin for treatment of most patients with venous thromboembolism and acute coronary syndromes because it has more convenient and cost-effective. It has similar results to heparin, Administered by subcutaneous injection

LOVENOX® is an example.

Side effects of Anticoagulants

The main side effect of anticoagulants is bleeding. Others include reduced platelet counts, allergic reactions, and skin necrosis .

ANTIPLATELET DRUGS

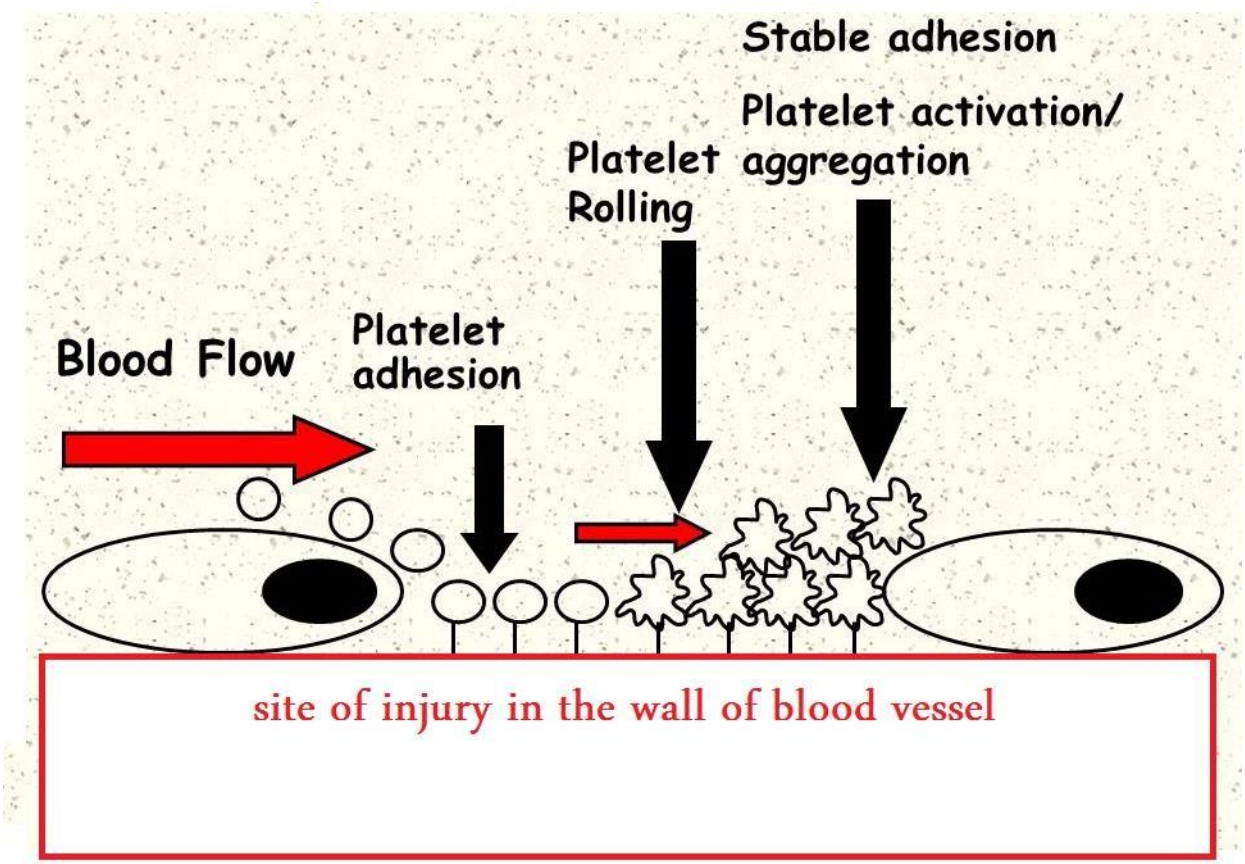
Antiplatelet drugs describe agents which decrease platelet aggregation and inhibit thrombus (clot) formation.

platelet aggregation

when a blood vessel injury take place, there is platelet activation. The process of platelet activation involves the production of several platelet activation agonists including

- thrombin,
- thromboxane A2 (TXA2)
- adenosine diphosphate (ADP)

these factors amplify the platelet response and stimulate platelet aggregation. Oral antiplatelet drugs decrease platelet aggregation.



Antiplatelet drugs classification:

Antiplatelet drugs can be classified as follows:

1. **COX-1 inhibitor:** Potent antiplatelet which inhibits platelet cyclooxygenase (COX), a key enzyme in the generation of TXA2 which is responsible for platelet activation and aggregation. The main member of this class is **aspirin**,its main side effect is bleeding.

2.Thienopyridine(P2Y12 receptor antagonists): Act by inhibiting the ADP-dependent pathway of platelet activation. Examples include **ticlopidine, clopidogrel and prasugrel.**

3. Adenosine triphosphate analogue: Reversibly interact with the P2Y12 receptor to inhibit the receptor to prevent ADP-induced platelet aggregation. Example includes **ticagrelor**.

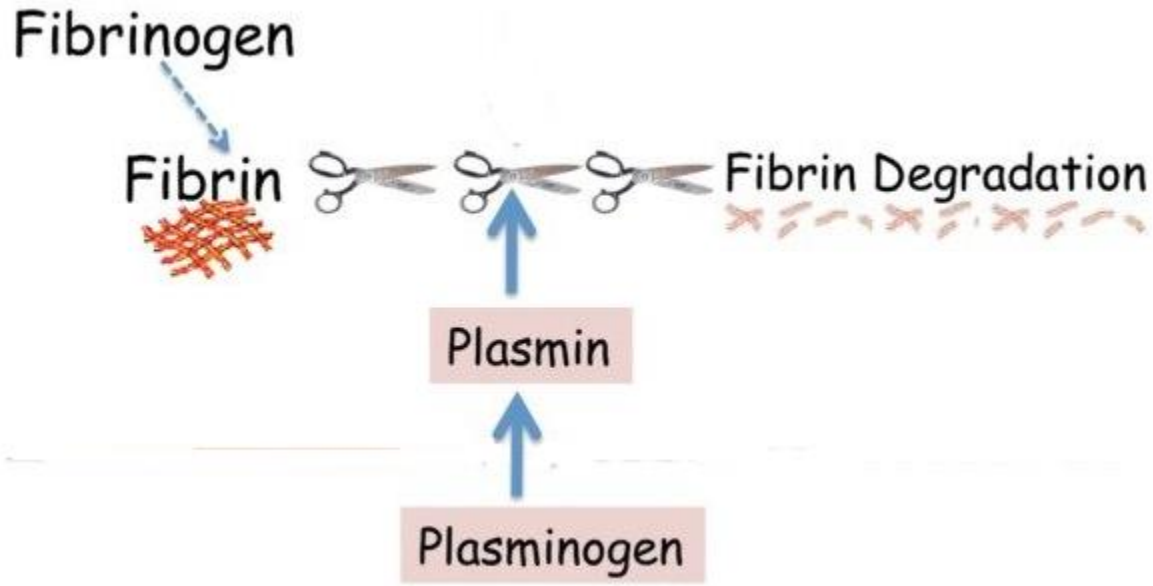
4. Phosphodiesterase inhibitors: Inhibit adenosine uptake and cyclic GMP phosphodiesterase activity, thus decreases platelet aggregability.. Example includes **dipyridamole**.

Newer Anticoagulants

1. Parenteral factor (Xa) inhibitor like Fondaparinux .
2. Oral factor (Xa) inhibitors, like Rivaroxaban and Apixaban

FIBRINOLYTIC DRUG

fibrinolytic drug, also called **thrombolytic drug**, any agent that is capable of stimulating the dissolution of a blood clot (thrombus). Fibrinolytic drugs work by activating the so-called fibrinolytic pathway. The fibrinolytic pathway comprises a proenzyme, plasminogen, which can be activated to the active enzyme plasmin, that will degrade fibrin.



Indication

- Acute trans-mural MI
- Ischaemic stroke
- Massive PE
- Peripheral arterial thrombus
- Massive DVT
- Thrombosed prosthetic valves
- pulmonary embolism.

Tissue Plasminogen Activators

This family of thrombolytic drugs is used in acute myocardial infarction, cerebrovascular thrombotic stroke and pulmonary embolism and include:

- Alteplase (Activase®; rtPA) is a recombinant form of human tissue plasminogen activator . It has a short half-life (~5 min) and therefore is usually administered as an intravenous bolus followed by an infusion.

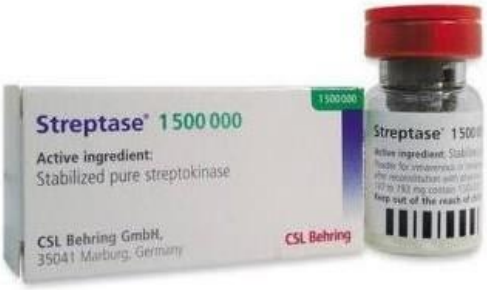
- Retaplase (Retavase®) is a genetically engineered, smaller derivative of recombinant tPA that has increased potency and is faster acting than rtPA. It is usually administered as IV bolus injections. It is used for acute myocardial infarction and pulmonary embolism.
- Tenecteplase (TNK-tPA) has a longer half-life and greater binding affinity for fibrin than rtPA. Because of its longer half-life, it can be administered by IV bolus. It is only approved for use in acute myocardial infarction.

Streptokinase

Streptokinase and anistreplase are used in acute myocardial infarction, arterial and venous thrombosis, and pulmonary embolism. These compounds are antigenic because they are derived from streptococci bacteria.

- Natural streptokinase (SK) is isolated and purified from streptococci bacteria. Its lack of fibrin specificity makes it a less desirable thrombolytic drug than tPA compounds because it produces more fibrinogenolysis.

- Anistreplase (Eminase®) is a complex of SK and plasminogen. It has more fibrin specificity and has a longer activity than natural SK; however, it causes considerable fibrinogenolysis.



Urokinase

Urokinase (Abbokinase®; UK) is sometimes referred to as urinary-type plasminogen activator (uPA) because it is formed by kidneys and is found in urine. It has limited clinical use because, like SK, it produces considerable fibrinogenolysis.

Adverse Effects

Common adverse effects of all the thrombolytic drugs is bleeding complications. The bleeding is often noted at a catheterization site, although gastrointestinal and cerebral hemorrhages may occur.