Antiplatelets
Anticoagulants Drugs
Thrombolytics
1. **Resting platelets**

- Healthy, intact endothelial cells
- Sub-endothelium
- Collagen fibers

2. **Inactive GP IIb/IIIa receptors**

- $Ca^{2+}$ sequestered
- $Ca^{2+}$
- $Ca^{2+}$
- $Ca^{2+}$

- ATP
- cAMP
- 5'-AMP

- Prostacyclin
- Nitric oxide
- Endothelial cells

- Healthy, intact endothelium releases prostacyclin into plasma.
- Prostacyclin binds to platelet membrane receptors, causing synthesis of cAMP.
- cAMP stabilizes inactive GP IIb/IIIa receptors and inhibits release of granules containing platelet aggregation agents or $Ca^{2+}$.

3. **Platelet adhesion**

- Activated platelets cover and adhere to exposed subendothelial surface of damaged endothelium.
4 Platelet activation

Activated platelets release chemical mediators.

Chemical mediators released by platelets:
- Thromboxane A₂
- ADP
- Serotonin
- PAF

5 Platelet aggregation

Platelets are recruited into the platelet plug.

Platelet aggregating agents:
- Thromboxane A₂
- ADP
- Serotonin
- PAF
Thrombin, thromboxane A₂, ADP, and other mediators released from activated platelets bound to collagen from the sub-endothelium cause an increase in Ca²⁺ levels.

7 Elevated Ca²⁺ causes:
- Release of platelet granules
- Activation of thromboxane A₂ synthesis
- Activation of the GP IIb/IIIa receptors

Active GP IIb/IIIa receptors
**Fibrinolysis**

Tissue plasminogen activator

Plasminogen → Plasmin

Fibrin peptides

**Formation of platelet-fibrin plug**

Prothrombin

Thrombin

Activation of coagulation factors in plasma

Heparin

Platelet-fibrin clot
Platelet Aggregation Inhibitors (Antiplateletes)

• Decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation.

• Inhibit cyclooxygenase-1 (COX-1) or block GP IIb/IIIa or ADP receptors, thereby interfering with the signals that promote platelet aggregation.

• Because these agents have different mechanisms of actions, synergistic or additive effects may be achieved when agents from different classes are combined.

• These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.
Aspirin irreversibly inhibits platelet cyclooxygenase-1.
Aspirin

- The recommended dose of aspirin ranges from 50 to 325 mg daily.
- Complete inactivation of platelets occurs with 75 mg of aspirin given daily.
- Aspirin is used in the prophylactic treatment of transient cerebral ischemia.
- To reduce the incidence of recurrent MI.
- Decrease mortality in the setting of primary and secondary prevention of MI.

- The inhibitory effect is rapid, and aspirin-induced suppression of Thromboxane A2 and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days.
Adverse effects

- Higher doses of aspirin increase drug-related toxicities as well as the probability that aspirin may also inhibit prostacyclin production.
- Bleeding time is prolonged by aspirin treatment, causing complications that include an increased incidence of hemorrhagic stroke and gastrointestinal (GI) bleeding.
- Nonsteroidal anti-inflammatory drugs, such as ibuprofen, inhibit COX-1 by transiently competing at the catalytic site.
- Ibuprofen, if taken within the 2 hours prior to aspirin, can obstruct the access of aspirin to the serine residue and, thereby, antagonize platelet inhibition by aspirin.
- Immediate release aspirin should be taken at least 60 minutes before or at least 8 hours after ibuprofen.
- Although celecoxib (a selective COX-2 inhibitor) does not interfere with the antiaggregation activity of aspirin, there is some evidence that it may contribute to cardiovascular events by shifting the balance of chemical mediators in favor of thromboxane A2.
P2Y12 ADP receptor inhibitors: Ticlopidine, Clopidogrel, Prasugrel, Ticagrelor (oral)

- These drugs inhibit the binding of ADP to its receptors on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other.

- **Clopidogrel** is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and in those with established peripheral arterial disease.
- It is also approved for prophylaxis of thrombotic events in acute coronary syndromes.
- Additionally, clopidogrel is used to prevent thrombotic events associated with percutaneous coronary intervention (PCI) with or without coronary stenting.
- These agents can cause prolonged bleeding for which there is no antidote.
- agranulocytosis, thrombotic thrombocytopenic purpura (TTP)
• **GP IIb/IIIa receptor inhibitors: Abciximab, Eptifibatide, and Tirofiban (parenteral)**

• The GP IIb/IIIa receptor plays a key role in stimulating platelet aggregation.

• monoclonal antibody, abciximab inhibits the GP IIb/IIIa receptor complex. By binding to GP IIb/IIIa, abciximab blocks the binding of fibrinogen and von Willebrand factor consequently, aggregation does not occur.

• Eptifibatide and tirofiban act similarly to abciximab, by blocking the GP IIb/IIIa receptor.
GP IIb/IIIa Receptor Blockers

**Death or Nonfatal Myocardial Infarction**

- **Abciximab**
  - Standard therapy: 5.5%
  - Plus GP IIb/IIIa antagonists: 9.6%

- **Eptifibatide**
  - Standard therapy: 7.1%
  - Plus GP IIb/IIIa antagonists: 8.4%

- **Tirofiban**
  - Standard therapy: 5.1%
  - Plus GP IIb/IIIa antagonists: 6.3%

**Key:**
- Red: Standard therapy plus GP IIb/IIIa antagonists
- Blue: Standard therapy

*Abciximab, eptifibatide and tirofiban block the GP IIb/IIIa receptor of platelets.*
• **Dipyridamole**
• a coronary vasodilator, increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, thereby resulting in decreased thromboxane A2 synthesis.
• The drug may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces
• Dipyridamole is used for stroke prevention and is usually given in combination with aspirin
• Dipyridamole has variable bioavailability following oral administration. It is highly protein bound.
• Patients with unstable angina should not use dipyridamole because of its vasodilating properties, which may worsen ischemia.
• Dipyridamole commonly causes headache and can lead to orthostatic hypotension (especially if administered IV).
Cilostazol

Cilostazol and its active metabolites inhibit phosphodiesterase type III, which prevents the degradation of cAMP, thereby increasing levels of cAMP in platelets and vascular tissues.

The increase in cAMP levels in platelets and the vasculature prevents platelet aggregation and promotes vasodilation of blood vessels, respectively.

favorably alters the lipid profile, causing a decrease in plasma triglycerides and an increase in high-density lipoprotein cholesterol.

Cilostazol is an oral antiplatelet agent that also has vasodilating activity.
Anticoagulants

These factors are inactivated by heparin–antithrombin complex.

Intrinsic pathway

XII → XIIa
XI → Xla
IX → IXa
X → Xa

Extrinsic pathway

VIIa → VII

Prothrombin (II) → Thrombin (IIa)

Fibrinogen → Fibrin

Synthesis of these factors is inhibited by coumarins
**Parenteral Anticoagulants**

A. **Heparin and low molecular weight heparins:**

- Injectable, rapidly acting anticoagulant.
- Heparin occurs naturally as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown.
- It is extracted for commercial use from porcine intestinal mucosa.
- Inhibits the action of the coagulation factors.
- In the absence of heparin, antithrombin III interacts very slowly with thrombin and factor Xa.
- When heparin molecules bind to antithrombin III, a conformational change occurs that catalyzes the inhibition of thrombin about 1000-fold.
- LMWHs complex with antithrombin III and inactivate factor Xa (including that located on platelet surfaces) but do not bind as avidly to thrombin.
• A unique pentasaccharide sequence contained in heparin and LMWHs permits their binding to antithrombin III.

• Heparin and the LMWHs limit the expansion of thrombi by preventing fibrin formation.

• These agents are used for the treatment of acute venous thromboembolism (DVT or PE).

• Prophylaxis of postoperative venous thrombosis in patients undergoing surgery (for example, hip replacement).

• Acute MI.

• These drugs are the anticoagulants of choice for treating pregnant women, because they do not cross the placenta, due to their large size and negative charge.
• Activated partial thromboplastin time (a ptt) is 1.5- to 2.5-fold that of the normal control.
• The a ptt is the standard test used to monitor the extent of anticoagulation with heparin.
• The anticoagulant effect with heparin occurs within minutes of IV administration. 1 to 2 hours after subcutaneous injection.
• The maximum anti–factor Xa activity of the LMWHS occurs about 4 hours after subcutaneous injection.
• It is usually not necessary to monitor coagulation values with LMWHS because the plasma levels and pharmacokinetics of these drugs are more predictable.
• However, in renally impaired, pregnant, and obese patients, monitoring of factor Xa levels is recommended with LMWHs.
Adverse Effects

- Heparin-induced thrombocytopenia (HIT) is a serious condition, in which circulating blood contains an abnormally low number of platelets.
- This reaction is immune-mediated and carries a risk of venous and arterial embolism.
- Heparin therapy should be discontinued when patients develop HIT or show severe thrombocytopenia.
- In cases of HIT, heparin can be replaced by another anticoagulant, such as argatroban.
- LMWHs can have cross-sensitivity and are not recommended in HIT.
- Osteoporosis has been observed in patients on long-term heparin therapy.
- Heparin and LMWHs are contraindicated in patients who have hypersensitivity to heparin, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.
Side effects
Pharmacokinetics

Heparin and LMWH are mostly confined to the vascular system.

- Bleeding
- Hypersensitivity
- Thrombocytopenia

Partially degraded heparin and LMWHs appear in the urine.

Heparin: IV, deep SC
LMWHs: SC

Heparin and LMWHs
Unfractionated heparin binds to plasma proteins, endothelium, and macrophages, activating factor Xa. Antithrombin inactivates activated factor Xa and factor IIa (thrombin). Inactivated factors are indicated. aPTT measures anti-factor IIa activity.
Heparin accelerates inactivation of coagulation factors by antithrombin III
Heparin- and low molecular weight heparin (LMWH)-mediated inactivation of thrombin or factor Xa
B. Argatroban:

- synthetic parenteral anticoagulant
- It is a direct thrombin inhibitor.
- Argatroban is used for the prophylaxis or treatment of venous thromboembolism in patients with HIT.

C. Bivalirudin and desirudin:

- Parenteral anticoagulants that are analogs of hirudin, a thrombin inhibitor derived from medicinal leech saliva.
- These drugs are selective direct thrombin inhibitors that reversibly inhibit the catalytic site of both free and clot-bound thrombin.
- **Fondaparinux** is a pentasaccharide anticoagulant that is synthetically derived.
  - This agent selectively **inhibits only factor Xa**.
  - By selectively binding to antithrombin III, *fondaparinux* potentiates (300- to 1000-fold) the innate neutralization of factor Xa by antithrombin III.
- SC.
- **Dabigatran etexilate**
  - Prodrug of the active moiety dabigatran, which is an **oral direct thrombin inhibitor**.
  - Due to the **breakdown of the product and reduction of potency** when exposed to **moisture**, capsules should be stored in the original container and swallowed whole.
  - **Abrupt discontinuation should be avoided**, as patients may be at increased risk for thrombotic events.
• **Rivaroxaban and Apixaban**
  • Oral inhibitors of factor Xa.
  • Abrupt discontinuation of these agents should be avoided.
Warfarin

- Interfere with the synthesis of the coagulation factors by inhibiting (vitamin K epoxide reductase) Vitamin K antagonists.
- Oral anticoagulant Coumarins.
- Warfarin is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation).
- 72-96 hrs to start its action.
- Narrow therapeutic agents

**Adverse effect:**
- Hemorrhage.
- Teratogenic.
- Skin lesions and necrosis are rare complications of warfarin therapy.
- Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with warfarin therapy.
Oral Anticoagulant (Warfarin)

- Inhibition of platelet aggregation
- Potentiation of anticoagulation
- Inhibition of metabolism of warfarin
- Acute alcohol intoxication
- Amiodarone
- Fluconazole
- Metronidazole
- Sulfamethoxazole/trimethoprim

Warfarin

- Chronic alcohol ingestion
- Barbiturates
- Dicloxacillin
- Rifampin

Stimulation of metabolism of warfarin

Attenuation of anticoagulation

- Polypeptide precursors of clotting factors II, VII, IX, and X
- Vitamin K reduced
- Vitamin K epoxide (oxidized)
- Active clotting factors II, VII, IX, and X
- γ-Carboxyglutamyl (Gla) residue
Thrombolytic agents

• Acute thromboembolic disease.
• Agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and dissolves clots.
  • Streptokinase, one of the first such agents can lead to bleeding problems.
  • Alteplase acts more locally on the thrombotic fibrin to produce fibrinolysis.
  • Urokinase is produced naturally in human kidneys and directly converts plasminogen into active plasmin.
• Fibrinolytic drugs may lyse both normal and pathologic thrombi.
Mechanism of Action

• All act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi. Clot dissolution and reperfusion occur.

• When therapy is initiated early after clot formation because clots become more resistant to lysis as they age.

• Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis.

• Strategies to prevent this include administration of antiplatelet drugs, such as aspirin, or antithrombotics such as heparin.
Adverse Effects

- **Hemorrhage** is a major side effect
- These drugs are contraindicated in:
  - Pregnancy
  - In patients with healing wounds or history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.
A. Alteplase, reteplase, and tenecteplase

- Alteplase: tissue plasminogen activator or tPA is a serine protease originally derived from cultured human melanoma cells.

- Now obtained as a product of recombinant DNA technology.

- Low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug.

- Short half-life (5 to 30 minutes), 10% of the total dose is injected intravenously as a bolus and the remaining drug is administered over 60 minutes.

- Cause orolingual angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.
• **Streptokinase:**
  • Extracellular protein purified from culture broths of group C β-hemolytic streptococci.
  • It forms an active one-to-one complex with plasminogen.
  • This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin.
  • Rarely used and is no longer available in many markets.
  • In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen, as well as clotting factors V and VII.
Streptokinase
Urokinase

• Urokinase is produced naturally in the body by the kidneys.
• Therapeutic urokinase is isolated from cultures of human kidney cells and has low antigenicity.
• Urokinase directly cleaves the arginine–valine bond of plasminogen to yield active plasmin.
• It is only approved for lysis of pulmonary emboli.
Drugs Used to Treat Bleeding

A. Aminocaproic acid and tranexamic acid

- Control fibrinolytic states that may arise after GI surgery or prostatectomy.

Both agents are:

- Synthetic
- Orally active
- Excreted in the urine
- Inhibit plasminogen activation.

- Tranexamic acid is 10 times more potent than Aminocaproic acid
- A potential side effect is intravascular thrombosis.
B. Protamine sulfate

- Antagonizes the anticoagulant effects of heparin.
- This protein is derived from fish sperm or testes.
- High in arginine content, which explains its basicity.
- The positively charged protamine interacts with the negatively charged heparin, forming a stable complex without anticoagulant activity.

Adverse effects:
- Hypersensitivity
- Dyspnea,
- Flushing,
- Bradycardia and hypotension when rapidly injected.
C. Vitamin K

- Vitamin K1 (phytonadione) administration can stop bleeding problems due to warfarin by increasing the supply of active vitamin K1, thereby inhibiting the effect of warfarin.
- Vitamin K1 may be administered via the oral, subcutaneous, or intravenous route.
- Intravenous vitamin K should be administered by slow IV infusion to minimize the risk of hypersensitivity or anaphylactoid reactions.
- For the treatment of bleeding, the subcutaneous route of vitamin K1 is not preferred, as it is not as effective as oral or IV administration.
- The response to vitamin K1 is slow, requiring about 24 hours to reduce INR (time to synthesize new coagulation factors).
- If immediate hemostasis is required, fresh frozen plasma should be infused.