Drugs Used in Disorders of Coagulation

Dr Laith M Abbas Al-Huseini
M.B.Ch.B, M.Sc., M.Res., Ph.D.
Hemostasis refers to the finely regulated dynamic process of maintaining fluidity of the blood, repairing vascular injury, and limiting blood loss while avoiding vessel occlusion (thrombosis) and inadequate perfusion of vital organs.

**Diagram:** Thrombus formation at the site of the damaged vascular wall (EC, endothelial cell) and the role of platelets and clotting factors.
Thrombosis vs. bleeding

- Thrombosis is the most common abnormality of hemostasis. Thrombotic disorders include acute myocardial infarction, deep vein thrombosis, pulmonary embolism, and acute ischemic stroke.
- These are treated with drugs such as anticoagulants and fibrinolytics.

- Bleeding disorders involving the failure of hemostasis are less common than thromboembolic diseases.
- These disorders include
  - hemophilia, which is treated with transfusion of Factor VIII prepared by recombinant DNA techniques
  - vitamin K deficiency, which is treated with dietary supplements of the vitamin.
1. Resting platelets

2. Healthy, intact endothelial cells release 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<sup>2+</sup>.

3. Platelet adhesion

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

4. Platelet activation

   - Thromboxane A<sub>2</sub>, ADP, serotonin, PAF
   - Chemical mediators released by platelets
   - Platelets are recruited into the platelet plug.

5. Platelet aggregation

   - Activated platelets release chemical mediators.
ANTIPLATELET DRUGS

- Platelet function is regulated by three categories of substances.
  - 1-Agents generated outside the platelet interact with platelet membrane receptors, eg, catecholamines, collagen, thrombin, and prostacyclin.
  - 2-Agents generated within the platelet interact with membrane receptors, eg, ADP, prostaglandin D2, prostaglandin E2, and serotonin.
  - 3-Agents generated within the platelet that act within the platelet, eg, prostaglandin endoperoxides and thromboxane A2, the cyclic nucleotides cAMP and cGMP, and calcium ion.

- From this list of agents, several targets for platelet inhibitory drugs have been identified:
  - Inhibition of prostaglandin synthesis (aspirin), inhibition of ADP-induced platelet aggregation (clopidogrel, ticlopidine), and blockade of glycoprotein IIb/IIIa receptor on platelets (abciximab, tirofiban, and eptifibatide).

- Dipyridamole and cilostazol are additional antiplatelet drugs.
ASPIRIN

- Aspirin inhibits the synthesis of thromboxane A2 by irreversible acetylation of the enzyme cyclooxygenase and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days.
- Repeated administration of aspirin has a cumulative effect on the function of platelets.
- The recommended dose of aspirin ranges from 50 to 325 mg.
- Formerly known as “baby aspirin,” 81-mg aspirin is most commonly used in the United States.
Ticlopidine, clopidogrel, and prasugrel

- These drugs irreversibly 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.
- The duration of the antiplatelet effect is 7–10 days.
- These drugs have no effect on prostaglandin metabolism.
- Commonly used in patients undergoing placement of a coronary stent for prevention of atherosclerotic events following recent myocardial infarction.
- Adverse effects of ticlopidine include nausea, dyspepsia, and diarrhea in up to 20% of patients, hemorrhage in 5%, and, most seriously, leukopenia in 1%.
- Clopidogrel has fewer adverse effects than ticlopidine and is rarely associated with neutropenia.
**Abciximab**

- Platelet GP IIb/IIIa receptor monoclonal antibody.
- By binding to GP IIb/IIIa, the antibody blocks the binding of fibrinogen and von Willebrand factor, and, consequently, aggregation does not occur.
- Abciximab is given iv in percutaneous coronary intervention for the prevention of cardiac ischemic complications.
- Used for unresponsive unstable angina and for prophylactic use in myocardial infarction.
- After cessation of infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours.
- Major adverse effect is the potential for bleeding.
- Abciximab is expensive, limiting its use in some settings.
Eptifibatide and tirofiban

- These two antiplatelet drugs act similarly to *abciximab*, namely, by blocking the GP IIb/IIIa receptor.
- When intravenous (IV) infusion is stopped, these agents are rapidly cleared from the plasma, but their effect can persist for as long as 4 hours.
- The major adverse effect of both drugs is bleeding.
Dipyridamole

- A coronary vasodilator, is used prophylactically to treat angina pectoris. It is usually given in combination with aspirin or warfarin.

- It increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, resulting in decreased thromboxane A2 synthesis.

- It may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces.

- In combination with warfarin, however, dipyridamole is effective for inhibiting embolization from prosthetic heart valves.
Cilostazol

➢ A newer phosphodiesterase inhibitor that promotes vasodilation and inhibition of platelet aggregation.

➢ Used to treat intermittent claudication, vascular sclerosis complicating diabetes mellitus, and the improvement of symptoms in patients with chronic cerebral ischemia.

➢ Causing a decrease in plasma triglycerides and an increase in HDL.

➢ Headache and GI side effects are the most common adverse effects.
Pentoxifyllines

- Xanthine analogue,
- Increases deformability of RBCs thus increases microcirculation, reduce fibrinogen levels and inhibits platelets aggregation.

Uses - CVAs esp. TIA (transient ischemic attacks), Ischemic ulcers of legs
BLOOD COAGULATION

- Two major pathways
  - Intrinsic pathway
  - Extrinsic pathway

- 13 soluble factors are involved in clotting
- Biosynthesis of these factors are dependent on Vitamin K1 and K2
- Most of these factors are proteases
- Normally inactive and sequentially activated
- Hereditary lack of clotting factors lead to hemophilia – A
FACTORS WHICH PROMOTE BLOOD FLUIDITY

Normal Hemostasis

- Natural Anticoagulants
  - Protein C
  - Protein S
  - Antithrombin III
- Endothelial-Derived Anti-Platelet Substances
  - Nitric Oxide
  - Prostacyclin (PGI₂)
- Fibrinolytic System "clot busters"
  - Plasmin
  - Plasminogen
  - Tissue Plasminogen Activator (tPA)
ANTICOAGULANTS

• These are the drugs used to reduce coagulability of blood.

• Classification

A) Heparin (the thrombin inhibitor)
   - Low molecular weight Heparin
   - Danaparoid
   - Lepirudin
   - Heparan sulfate

B) Oral anticoagulants
   - Warfarin (vitamin K antagonist)
   - Bishydroxycoumarin (dicumarol)
   - Acenocoumarol
   - Phenindione
Heparin

- Straight chain mucopolysaccharide extracted for commercial use from porcine intestinal mucosa, very strong acid with MW 20000.

- LMWH isolated from standard heparin by gel filtration chromatography or partial depolymerization (1000-10000 daltons).

- MOA: Heparin binds to antithrombin III complex
  Increases thrombin – AT reaction 1000folds
  ATIII inhibits activated clotting factors of intrinsic and common pathway including thrombin, Xa, IXa and thus acts as Suicide substrate
Anticoagulant Properties of Heparin

1. Inhibits the thrombin-mediated conversion of fibrinogen to fibrin
2. Inhibits the aggregation of platelets by thrombin
3. Inhibits activation of fibrin stabilizing enzyme
4. Inhibits activated factors XII, XI, IX, X and II

Pharmacokinetics

• Not effective orally
• Sc/ iv administration
• Onset immediate, peak in 5-10mins
• Metabolized in liver
• Excretion through kidney.
Therapeutic uses

- acute deep vein thrombosis
- pulmonary embolism
- Prophylactically to prevent postoperative venous thrombosis in patients undergoing elective surgery
- acute phase of myocardial infarction
- Anticoagulant of choice for treating pregnant women with prosthetic heart valves or venous thromboembolism, because these agents do not cross the placenta
Adverse effects

- Bleeding complications: Careful monitoring of the bleeding time, prothrombin time (PT) and its international normalized ratio (INR) is required to minimize this problem. Excessive bleeding may be managed by ceasing administration of the drug or by treating with antidote (protamine sulfate).
- Hypersensitivity reactions:
- Thrombocytopenia:
- Thrombosis: reduction in AT III activity, thus decreasing the inactivation of coagulation factors and, thereby, increasing the risk of thrombosis.
- Osteoporosis
- Alopecia
- Hyperkalemia
**LMWH**

- Enoxaparin
- Dalteparin
- Ardeparin
- Nadroparin
- Tinzaprin
- Reviparin

No monitoring is required in most patients.
Warfarin

- Coumarin derivative, is the most commonly used oral anticoagulant.
- Is a vitamin K antagonist - Impairs the generation of active vitamin K, decreasing the amounts of vitamin K dependent coagulation factors.
- Absorption rapid – high plasma protein binding binds to albumin.
- Delayed onset 8 - 12 hrs.
- Clearance is slow - 36 hrs.
- Overdose - reversed by vitamin K infusion.
- Can cross placenta - do not use during late pregnancies.
**Therapeutic uses:**

- Used to prevent the progression or recurrence of acute deep vein thrombosis or pulmonary embolism after initial heparin treatment.
- Prevention of venous thromboembolism during orthopedic or gynecologic surgery.
- Prophylactically, it is used in patients with acute myocardial infarction, prosthetic heart valves, and chronic atrial fibrillation.

**Adverse effects:**

- Bleeding disorders:
- Drug and other interactions:
- Disease states:
New Anticoagulants

Parenteral FXa Inhibitors

- *Fondaparinux*: selectively inhibits only Factor Xa by binding to ATIII
- *Danaparoid*: Fast acting, generally predictable dose response

Direct thrombin inhibitors (DTIs)

- *Hirudin*: bind at both the catalytic or active site of thrombin as well as at a substrate recognition site
- *Lepirudin*: derived from medicinal leech saliva and produced in yeast cells by recombinant DNA technology
- *Bivalirudin*: Synthetic polypeptide, used parenterally, Short half life
- *Argatroban*: small synthetic molecule parenteral anticoagulant directly inhibits thrombin
- *Ximelagatran*: similar efficacy and bleeding risk to warfarin and does not need monitoring
Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissipates clots.
Fibrinolytics

Conventional Nonselective Agents
- Streptokinase
- Urokinase

Fibrin Selective Agents
- Recombinant Tissue plasminogen activator (tPA)
  - Alteplase
  - Reteplase
  - Tenectaplastase
Streptokinase

- is a protein (but not an enzyme in itself) synthesized by streptococci that combines with the pro-activator plasminogen.
- This enzymatic complex catalyzes the conversion of inactive plasminogen to active plasmin.

Urokinase

- is a human enzyme synthesized by the kidney that directly converts plasminogen to active plasmin.
- Plasmin formed inside a thrombus by these activators is protected from plasma antiplasmins, which allows it to lyse the thrombus from within.
- Plasminogen can also be activated endogenously by tissue plasminogen activators (t-PAs).
- Human t-PA is manufactured as ALTEPLASE by means of recombinant DNA technology.
Adverse effects:

- The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major side effect.
- Hypersensitivity

- Contraindicated in patients with healing wounds, pregnancy, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.
Contraindications to Antithrombotic Therapy

- Pre-existing coagulation or platelet defect, thrombocytopenia, or other bleeding abnormality
- Inaccessible ulcerative lesion (e.g., gastrointestinal tract lesion)
- Central nervous system lesion (e.g., caused by stroke, surgery, trauma)
- Malignant hypertension
- Advanced retinopathy
- Old age (relative)
- Aspirin or other antiplatelet drugs
- Neoplastic disease
Fibrinolytic Inhibitors: Aminocaproic Acid

- Similar to the amino acid lysine, is a synthetic inhibitor of fibrinolysis
- Competitively inhibits plasminogen activation
- Oral dosage of EACA is 6 g four times a day
- **Tranexamic acid** is an analog of aminocaproic acid and has the same properties.
- It is administered orally with a 15 mg/kg loading dose followed by 30 mg/kg every 6 hours
USES

- Adjunctive therapy in hemophilia
- Bleeding from fibrinolytic therapy
- Prophylaxis for re-bleeding from intracranial aneurysms.
- Postsurgical gastrointestinal bleeding, post prostatectomy bleeding, bladder hemorrhage secondary to radiation and drug-induced cystitis.

Adverse effects

- Intravascular thrombosis from inhibition of plasminogen activator
- Hypotension, myopathy, abdominal discomfort, diarrhea, and nasal stuffiness