Chapter 34

Drugs Used in Disorders of Coagulation
Objectives

- understand classification of drugs
- understand mechanism of drug action
- master major pharmacological effects, clinical applications and adverse reactions
1. Blood coagulation is a normal body defense mechanism to prevent blood loss. Thrombogenesis may be *life saving* if it occurs as a response to hemorrhage.

2. However, it may also be *life threatening* when it occurs other times, because the thrombus can obstruct a blood vessel and reduce the blood supply of tissues.
The drugs used to *limit abnormal bleeding* and *to inhibit thrombosis* are the subjects of this chapter.
I. Mechanism of blood coagulation and fibrinolysis

If the balance between thrombogenesis and thrombolysis is destroyed, thrombotic or bleeding disorders result.
Blood coagulation can be divided into three phases:

(a) **the intrinsic system** in which factor XII is activated to XII\(_a\), resulting in activation of factor X to X\(_a\). 

(b) **the extrinsic factor**, leading to activation of factor VII to VII\(_a\) and then factor X to X\(_a\). 

(c) the subsequent common pathway in which factor II is activated to II\(_a\) followed by the formation of fibrin from fibrinogen.
B. Thrombogenesis
- **Vasospasm** is the immediate hemostatic response of injured blood vessels.

- **Platelets adhere** to the exposed collagen of damaged vessel wall and aggregate to each other within seconds.

- Then platelets lose their individual membranes and **form a plug** which quickly arrests bleeding from a damaged vessel.
This *platelet plug* must be reinforced by *fibrin* resulting from local activation of blood coagulation.
Platelet ADP, a powerful inducer of platelet aggregation, is released from the local production of thrombin, and thromboxane A$_2$ (TXA$_2$), an inducer of thrombogenesis and vasoconstriction is synthesized within platelets.
Role of platelet

The platelet is central to hemostasis and thrombogenesis.
RBC(hanging on fibrin) (left×2000, right×5200)
C. Regulation of coagulation and fibrinolysis

- Two major systems regulate these processes: fibrin inhibition and fibrinolysis.
- Plasma contains protease inhibitors, e.g. $\alpha_1$-antiprotease, $\alpha_2$-antiplasmin and antithrombin III, which inactivate the coagulation proteins as soon as they escape from the site of vessel injury.

- The process of fibrinolysis is conversion of plasminogen to plasmin. Plasmin remodels the thrombus and limits the extension of thrombosis by digestion of fibrin.
Classification of drugs

I. Anticoagulants
   (a) indirect thrombin inhibitors: heparin;
   (b) direct thrombin inhibitors: argatroban
   (c) coumarin derivatives: (e.g., warfarin, dicoumarol)

II. Fibrinolytic drugs
    (a) streptokinase; (b) urokinase; (c) anistreplase and (d) tissue plasminogen activator (t-PA)
III. Antiplatelet drugs:

(a) aspirin; (b) clopidogrel and ticlopidine; and (c) glycoprotein II$_b$/III$_a$ inhibitors (d) dipyridamole

IV. Drugs used in bleeding disorder

(a) vitamin K
(b) plasma fractions
(c) fibrinolytic inhibitors: aminocaproic acid
(d) serine protease inhibitors: aprotinin
Anticoagulants

I . indirect thrombin inhibitors: Heparin

A. The discovery of heparin

Heparin is an anticoagulant and commonly used in the treatment of bleeding disorders.
It was originally isolated from canine liver cells, hence its name (hepar is Greek for "liver").

Heparin's discovery can be attributed to the research activities of two men: Jay McLean and William Henry Howell.
In 1916, McLean, a second-year medical student at Johns Hopkins University, was working under the guidance of Howell investigating pro-coagulant preparations, when he isolated a fat-soluble phosphatide anti-coagulant in canine liver tissue.
- It was Howell in 1918 who coined the term *heparin*.
- He pioneered the use of heparin as a blood anti-coagulant.
B. Pharmacokinetics

(a) strong electronegative charge and size

(b) not absorbed orally and must be administered **parenterally**, e.g., by continuous drop or by intermittent intravenous injections or given subcutaneously.

Because of the danger of hematoma formation at the injection site, heparin must **never** be administered **intramuscularly**.

(a) acts immediately after intravenous administration
C. Mechanism of action

- The indirect thrombin inhibitors are so-named because their antithrombotic effect is exerted by their interaction with a separate protein, *antithrombin*. 
C. Mechanism of action

inhibits blood coagulation both *in vivo* and *in vitro*

increase anticoagulant activity of *antithrombin*

inhibits *clotting factors IX, X, and thrombin(IIa)* by forming equimolar complexes with them
Activated antithrombin III (AT III) degrades thrombin, factor X, and several other factors. Binding of these drugs to AT III can increase the catalytic action of AT III 1000-fold. The combination of AT III with unfractionated heparin increases degradation of both factor Xa and thrombin. Combination with fondaparinux or LMWH more selectively increases degradation of Xa.
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D. Therapeutic applications

1. Treatment of acute thromboembolic disorders

prevent further thrombus formation and embolization

Prevent pulmonary emboli in patients with established venous thrombosis.

2. Treatment of disseminated intravascular coagulation (DIC)

The goal of therapy in DIC is to prevent blood coagulation long enough for the replenishment of clotting factors and thus hemorrhage is controlled.
3. Prevention and treatment of arterial occlusive diseases, acute coronary syndrome, myocardial infarction and stroke

4. Maintaining extracorporeal circulation during cardiac and vascular surgery, hemodialysis and blood transfusion
Toxicity (p547)

- **Bleeding** (major adverse effect)

Elderly women and patients with renal failure are more prone to hemorrhage.

Close monitoring of the *activated partial thromboplastin time* (aPTT) is necessary.
Toxicity (p547)

- allergy, osteoporosis and spontaneous fractures, mineralocorticoid deficiency
- Heparin-Induced Thrombocytopenia (HIT)
Contraindications

- HIT, hypersensitivity to the drug, active bleeding, hemophilia, significant thrombocytopenia, purpura, severe hypertension, intracranial hemorrhage, infective endocarditis, active tuberculosis, ulcerative lesions of the gastrointestinal tract, threatened abortion, visceral carcinoma, or advanced hepatic or renal disease.
Heparin should be avoided in patients who have recently had surgery of the brain, spinal cord, or eye, and in patients who are undergoing lumbar puncture or regional anesthetic block.
Reversal of Heparin Action **

The chief complication is hemorrhage. If bleeding occurs, the anticoagulant effect of heparin can be neutralized by administration of protamine sulfate. (p548)

Protamine is a highly basic peptide that combines with heparin as an ion pair to form a stable complex devoid of anticoagulant activity.
II. direct thrombin inhibitors (p548)

- The direct thrombin inhibitors (DTIs) exert their anti-coagulant effect by directly \textit{binding to the active site of thrombin}, thereby inhibiting thrombin's downstream effects.

- This is in contrast to indirect thrombin inhibitors such as heparin, which act through \textit{antithrombin}. 
Hirudin, bivalirudin, argatroban and melagatran
III. Coumarin Derivatives (p549)

A. Warfarin
A. Warfarin

1. Mechanism of action

- antagonist of vitamin K
- orally effective and long acting properties
- Coumarin derivatives block the synthesis of vitamin K-dependent clotting factors $II$ (prothrombin), $VII$, $IX$, $X$ as well as the endogenous anticoagulant proteins $C$ and $S$, resulting in inhibition of blood coagulation. (p549 bottom line)
2. Therapeutic applications

- most useful in long-term prevention and treatment of venous thromboembolic diseases
- prevent embolization from prosthetic heart valves
- prevent reinfarction after myocardial infarction
Toxicity

- Warfarin crosses the placenta readily and can cause a *hemorrhagic disorder* in the fetus. Furthermore, can cause a serious birth defect characterized by *abnormal bone formation*. Thus, warfarin should never be administered during *pregnancy*. 
Drug Interactions

- The most serious interactions with warfarin are those that increase the anticoagulant effect and the risk of bleeding.
- The most dangerous of these interactions are the pharmacokinetic interactions with the pyrazolones phenylbutazone and sulfinpyrazone. (p552)
3. **Adverse reactions (p552)** Reversal of Warfarin Action

Excessive doses → **hemorrhagic disorder**
3. **Adverse reactions (p552) Reversal of Warfarin Action**

Excessive doses → **hemorrhagic disorder**

*What can we do?*

A. stop the drug

B. administer large amounts of vitamin K, fresh-frozen plasma, prothrombin complex concentrates, and recombinant factor VIIa (rFVIIa).
Classification of drugs

I. Anticoagulants

II. Fibrinolytic drugs (p552)

III. Antiplatelet drugs

IV. Drugs used in bleeding disorder
II. Fibrinolytic drugs

Fibrinolytic drugs rapidly dissolve intravascular clots by *catalyzing the formation of plasmin*, an enzyme that digests fibrin, from its precursor, plasminogen.
A. **Streptokinase**

dissolves acute embolus

used in multiple pulmonary emboli, deep venous thrombosis, and acute myocardial infarction.

B. **Urokinase**

used when streptokinase resistance is high

or patients need a second course of treatment
C. Anistreplase

used in acute myocardial infarction to lyse coronary artery clots

D. Tissue-type plasminogen activator (t-PA)

effective in lysing thrombi for treatment of acute myocardial infarction
Classification of drugs**

I. Anticoagulants

II. Fibrinolytic drugs

III. Antiplatelet drugs

IV. Drugs used in bleeding disorder
III. Antiplatelet drugs

A. Aspirin

✓ analgesic
✓ antipyretic
✓ anti-inflammatory
✓ potent antiplatelet effects (treat heart attacks and strokes)

widely used
Aspirin works to help prevent blood clots

Aspirin helps prevent the aggregation of platelets or blood clotting. Platelets release a prostaglandin called thromboxane. Aspirin's irreversible prostaglandin blocking ability inhibits the biosynthesis of thromboxane and, consequently, reduces the tendency for blood to clot.
2. Therapeutic applications

prevent myocardial infarction and ischemic brain disorder

- The maximum antithrombotic effect: at the dose of 160 to 320 mg per day
- Higher doses do not improve efficacy but reduce it because of the inhibition of prostacyclin.
- Higher doses increase toxicity especially bleeding.
B. Clopidogrel and Ticlopidine (p554)

inhibit ADP-induced platelet aggregation

prevent vascular events among patients with

*completed strokes,*

*transient ischemic attacks,*

*and unstable angina pectoris.*
C. Glycoprotein llb/IIIa inhibitors

IIb/IIIa complex is a receptor for fibrinogen and von Willebrand factor, which anchor platelets to foreign surfaces and to each other, thereby mediating aggregation. Activation of this receptor is the final common pathway for platelet aggregation. Thus, inhibitors of this receptor are potent antiplatelet agents.
1. Abciximab

Abciximab, a monoclonal antibody directed against the $\alpha_{\text{IIb}} \beta_3$ receptor, is the first used agent for percutaneous coronary intervention (PTCA) and in acute coronary syndromes.

2. Eptifibatide

unstable angina and angioplasty coronary interventions
3. Tirofiban

non-Q-wave myocardial infarction and unstable angina
ADDITIONAL ANTIPLATELET-DIRECTED DRUGS

- **Dipyridamole** is a vasodilator that inhibits platelet function by inhibiting adenosine uptake and cyclic GMP phosphodiesterase activity.
Classification of drugs**

I. Anticoagulants

II. Fibrinolytic drugs

III. Antiplatelet drugs

IV. Drugs used in bleeding disorder(p555)
IV. Drugs used in bleeding disorder

I. Vitamin K

*vitamin K$_1$ and K2*: fat-soluble, require bile salts for absorption from the intestinal tract

*vitamin K$_3$ and K$_4$*: water-soluble
A. Pharmacologic properties

Vitamin K is required for the liver synthesis of clotting factors *II, VII, IX and X*

B. Therapeutic applications

1. Hypoprothrombinemia *due to obstructive jaundice*

2. Hemorrhagic disease of newborn

3. *Anticoagulant* toxicity
Severe hepatic failure results in diminished protein synthesis and a hemorrhagic diathesis that is unresponsive to vitamin K.
II. fibrinolytic inhibitors: aminocaproic acid

competitively inhibit plasminogen activation

III. serine protease inhibitors: aprotinin

1. inhibits fibrinolysis by free plasmin

2. inhibits the plasmin-streptokinase complex in patients who have received that thrombolytic agent
Aprotinin was shown to reduce bleeding—by as much as 50%—from many types of surgery, especially that involving extracorporeal circulation for open heart procedures and liver transplantation.
- However, clinical trials and internal data from the manufacturer suggested that use of the drug was associated with an increased risk of renal failure, heart attack, and stroke.

- A prospective trial was initiated in Canada but halted early because of concerns that use of the drug was associated with increased mortality.

- The drug was removed from the market in 2007.
Summary

A. The primarily used anticoagulants are *heparin*, *coumarin derivatives*.

The anticoagulative activity of *heparin* depends upon *antithrombin III*.

*Coumarin derivatives* are antagonists of *vitamin K*.

They are all used in prevention and treatment of *thromboembolic diseases*. 
B. **Aspirin** is a widely used antiplatelet agent. It inhibits *thromboxane A₂*, thereby interferes with platelet aggregation and may be used to prevent myocardial infarction and ischemic brain disorder.

**Streptokinase** catalyze the conversion of inactive plasminogen to active *plasmin*, therefore are effective in lysing thrombi for treatment of multiple thrombosis and acute myocardial infarction.
C. *Vitamin K* promotes the liver synthesis of *clotting factors II, VII, IX and X*, and can be used for treatment of hypoprothrombinemia due to obstructive jaundice, hemorrhagic disease of newborn and anticoagulant toxicity.