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- Blood dysfunctions
 - Thrombosis
 - Bleeding
 - Circulation problems
 - Anemia

- Thrombosis: Formation of unwanted clot in a blood vessel
- Thrombotic disorders
 - Acute myocardial infarction
 - Deep vein thrombosis
 - Pulmonary embolism
 - Acute ischemic stroke
- Treatment of thrombotic disorders
 - Anticoagulants and antiplatelets
 - Fibrinolytics (thrombolytics)

Thrombus: a clot that adheres to a vessel

Embolus: a clot that floats in the blood

Thrombi and emboli are dangerous, they occlude blood vessels and deprive tissues of oxygen and nutrients

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- Platelet aggregation inhibitors
- Anticoagulants
- Thrombolytic agents

Drugs used for treatment of bleeding

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Platelet aggregation inhibitors

- □ Aspirin
- Clopidogrel
- Decrease the formation or the actions of chemical signals that promote platelet aggregation
- They act by different mechanisms of action and can be used in combination for additive effects

Platelet aggregation inhibitors

□ Aspirin

Inhibits formation of thromboxane A2 by inhibiting cyclooxygenase 1 (COX1)

- Used for:
 - Prophylactic treatment of transient cerebral ischemia
 - Reduction of the incidence of recurrent MI
 - Decrease mortality in pre- and post- MI patients
- Adverse effects
 - Bleeding



Platelet aggregation inhibitors

Clopidogrel ,prasugrel

Irreversibly inhibits binding of ADP to its receptors on platelets, thus inhibiting platelet aggregation

Used for

- Prevention of atherosclerotic events following recent MI and stroke
- Decrease of thrombotic cardiovascular events in patients with acute coronary syndrome

Adverse effects:

Bleeding

Anticoagulants

- 🗆 Heparin
- Enoxaparin (low molecular weight form of heparin) (LMWH)
- 🗆 Warfarin
- Mechanism of action of anticoagulant drugs
 - Inhibit the action of coagulation factors (such as the thrombin inhibitor heparin)
 - Interfere with the synthesis of coagulation factors (the vitamin K antagonist warfarin)

Anticoagulants

Heparin, Enoxaparin (Clexane)

Uses:

- Prevention of venous thrombosis
- Treatment of thrombotic disorders like pulmonary embolism, acute MI, and acute deep vein thrombosis
- Can be used in pregnant women with thromboembolism because it does not cross the placenta due to its large size and negative charge
- Mechanism of action
 - Binds to antithrombin III and inactivates coagulation factors
- Heparin is administered IV, LMWHs are administered SC

Anticoagulants-Heparin

- Adverse effects:
 - Bleeding complications
 - Hypersensetivity reactions
 - Thrombocytopenia
 - HIT; Heparin induced thrombocytopenia, Thrombosis: chronic administration of heparin can reduce antithrombin III activity and decrease the inactivation of coagulation factors increasing the risk of thrombosis (Treated with argotroban)
- Antidote: Protamine sulfate



Figure 20.14

Heparin- and low-molecular-weight heparin (LMWH)-mediated inactivation of thrombin or Factor Xa.

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- Heparin is often administered IV in a bolus to achieve immediate anticoagulation
- This is followed by lower doses or continuous infusion of heparin for 7-10 days
- The dose is titrated so that the activated partial thromboplastin time (aPTT) is 1.5-2.5 fold that of the normal control
- LMWH do not require such testing

INR= international normalized ratio, the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system used

Argatroban

- Directly inhibits thrombin
- Used prophylactically for the treatment of thromboembolism in patients with HIT
- Requires monitoring by aPTT
- Adverse effect
 - Bleeding

Anticoagulants

Warfarin

- Mechanism of action: vitamin K antagonist
- Vitamin K is a cofactor for the synthesis of several protein coagulation factors including II, VII, IX, and X
- Warfarin takes a longer time period (~ 5 days) to have an anti-coagulant effect
- Uses of Warfarin
 - Maintenance therapy for prevention of the progression of acute deep vein thrombosis or pulmonary embolism after initial heparin treatment
- Adverse effects
 - Bleeding disorders
- Contraindicated in pregnancy, FDA category X, can cause abortion and birth defects
- ISTADEICIOSTAUDItamin K

Thrombolytic agents

- Alteplase (tPA)
- Tenecteplase
- Activate the conversion of plasminogen to plasmin which hydrolyzes fibrin and thus dissolves clots
- Used IV for certain acute thromboembolic diseases
- Adverse effects
 - Bleeding disorders
- Contraindicated in pregnancy, patients with healing wounds, history of cerebrovascular accidents, intracranial bleeding
- Antidote: Aminocaproic acid



Figure 21.18 Degradation of an unwanted thrombus and a beneficial hemostatic plug by plasminogen activators.

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Bleeding disorders

- Bleeding disorders
 - Hemophilia, treated by transfusion of factor VIII
 - Vitamin K deficiency, treated by Vitamin K supplements
- Concentrated preparations of coagulation factors are available from human donors
- Blood transfusion is also an option for treating severe hemorrhage

Drugs used for treatment of bleeding

Aminocaproic acid inhibits plasminogen activator

 Vitamin K is administered to stop bleeding problems due to oral anticoagulants (warfarin)

Aprotinin: stops bleeding by blocking plasmin

Drugs used for treatment of bleeding

Medication	Antidote for Bleeding Caused by	Adverse Effects	Monitoring Parameters
Aminocaproic acid Tranexamic acid	Fibrinolytic state	Muscle necrosis Thrombosis CVA Seizure	CBC Muscle enzymes Blood pressure
Idarucizumab	Dabigatran	Hypokalemia Thrombosis	aPTT Clotting time Thrombin time
Protamine sulfate	Heparin	Flushing Nausea/vomiting Dyspnea Bradyarrhythmia Hypotension Anaphylaxis	Coagulation monitoring Blood pressure Heart rate
Vitamin K1	Warfarin	Skin reaction Anaphylaxis	PT/INR

Figure 21.19 Summary of drugs used to treat bleeding. aPTT = activated partial thromboplastin time, CBC = complete blood count, CVA = cerebrovascular accident, INR = international normalized ratio, PT = prothrombin time.