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

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- 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)

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- 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

# Blood drugs



- Platelet aggregation inhibitors
- Anticoagulants
- Thrombolytic agents
- Drugs used for treatment of bleeding

# 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 A<sub>2</sub> 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

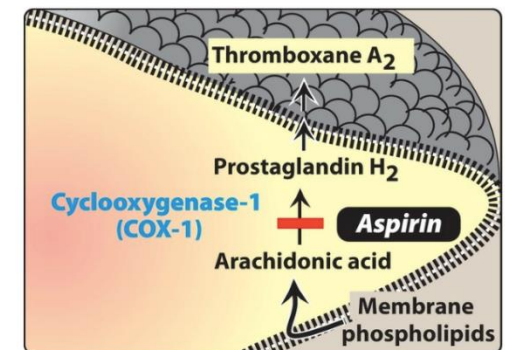


Figure 21.6 Aspirin irreversibly inhibits platelet cyclooxygenase-1.

# 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

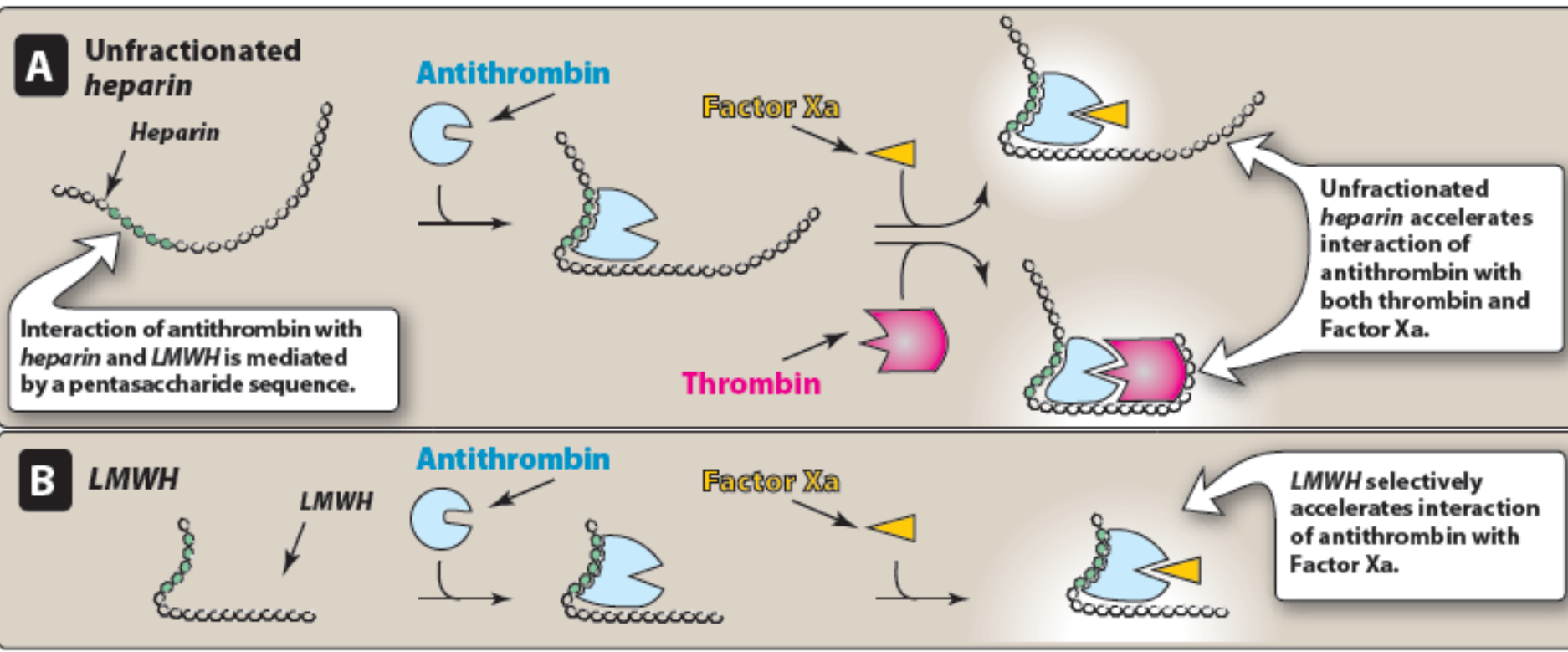
### □ Mechanism of action

- Binds to antithrombin III and inactivates coagulation factors


### □ Heparin is administered IV, LMWHs are administered SC


# Anticoagulants-Heparin

- Adverse effects:
  - Bleeding complications
  - Hypersensitivity 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

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- 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

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

# Anticoagulants

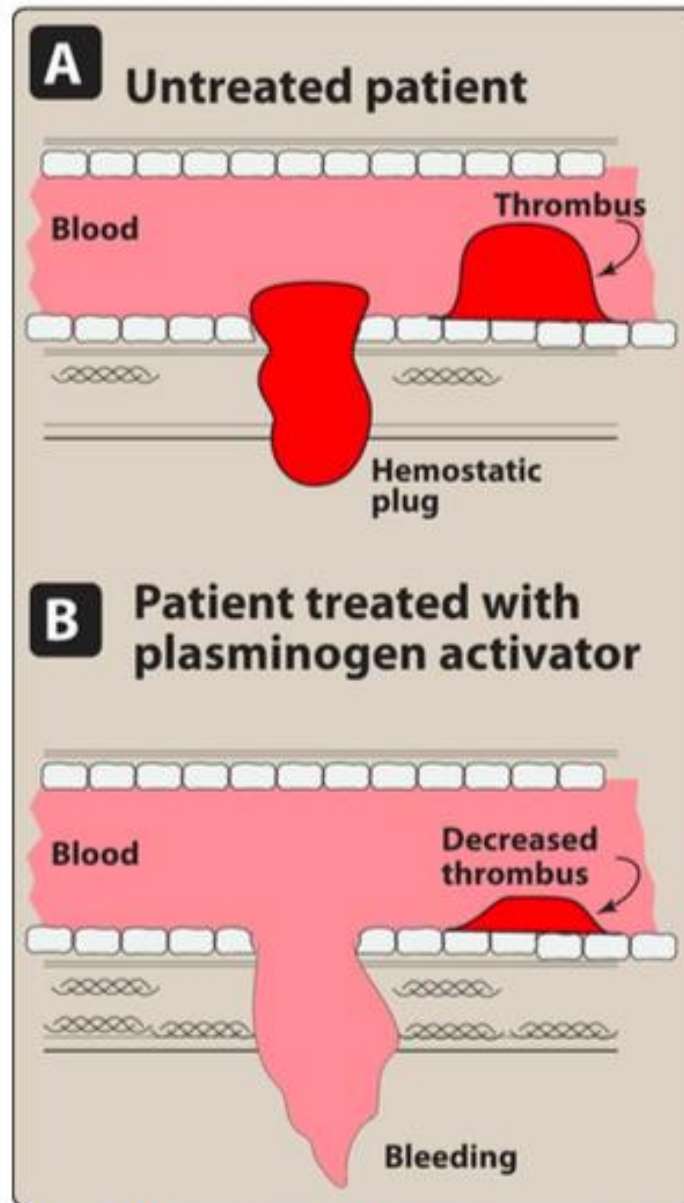
## Warfarin

- 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
- Antidote: vitamin 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.

# 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
<i>Aminocaproic acid</i> <i>Tranexamic acid</i>	Fibrinolytic state	Muscle necrosis Thrombosis CVA Seizure	CBC Muscle enzymes Blood pressure
<i>Idarucizumab</i>	<i>Dabigatran</i>	Hypokalemia Thrombosis	aPTT Clotting time Thrombin time
<i>Protamine sulfate</i>	<i>Heparin</i>	Flushing Nausea/vomiting Dyspnea Bradycardia Hypotension Anaphylaxis	Coagulation monitoring Blood pressure Heart rate
<i>Vitamin K1</i>	<i>Warfarin</i>	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.