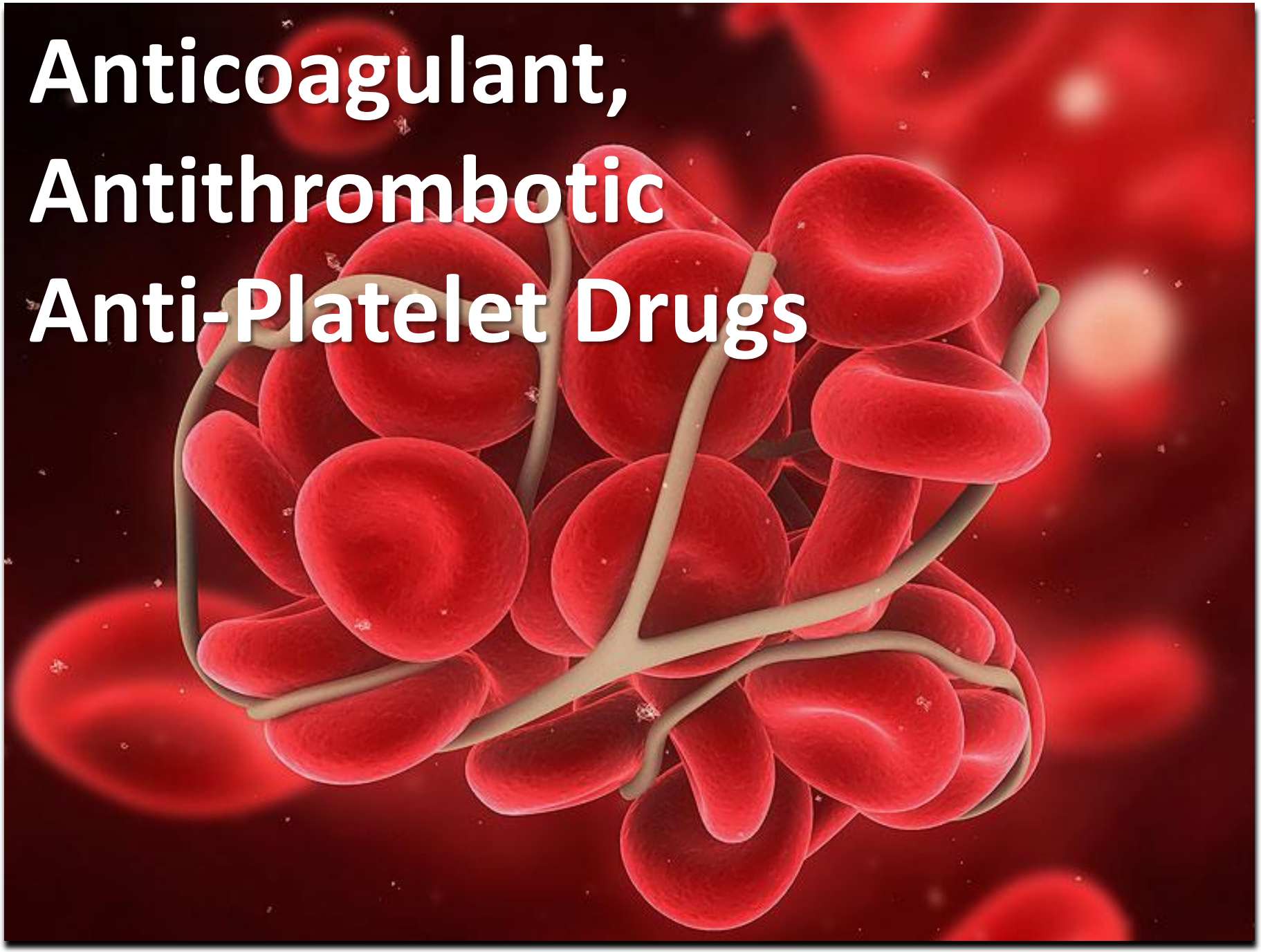
بسم الله الرحمن الرحیم

دارودرمانی اختلالات انعقاد خون

دکتر آزاده خلیلی
دکترای فارماکولوژی
دانشگاه علوم پزشکی البرز

Anticoagulant, Antithrombotic Anti-Platelet Drugs



HAEMOSTASIS

- **Haemostasis** refers to the finely regulated dynamic process of :
  - **Maintaining fluidity of the blood**
  - **Repairing vascular injury**
  - **Limiting blood loss while avoiding vessel occlusion (thrombosis) and inadequate perfusion of vital organs**

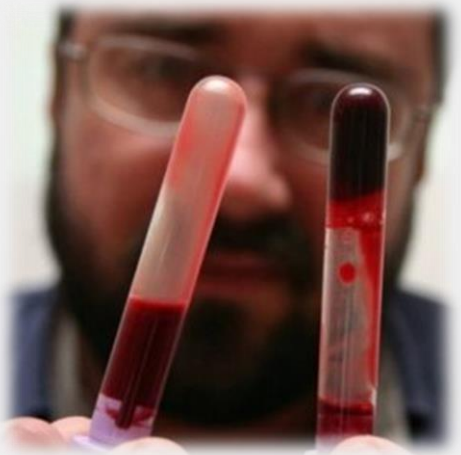
- **Imbalance between pro-coagulant and anti-coagulant factors leads to abnormal haemostasis**

Thrombosis

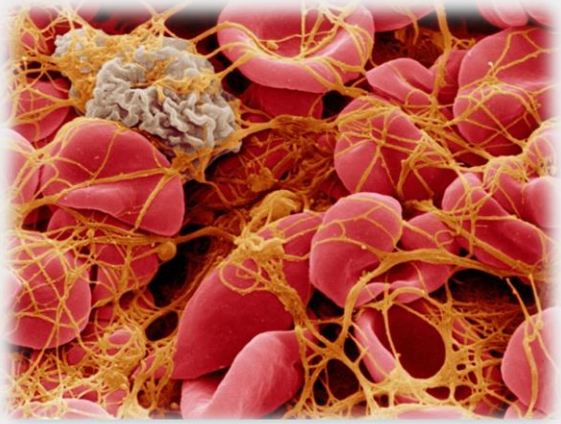
- The formation of an unwanted clot within a blood vessel is the most common **abnormality of hemostasis.**
- Thrombotic disorders include acute myocardial infarction, deep-vein thrombosis, pulmonary embolism, and acute ischemic stroke. These are treated with drugs such as anticoagulants and fibrinolytics.

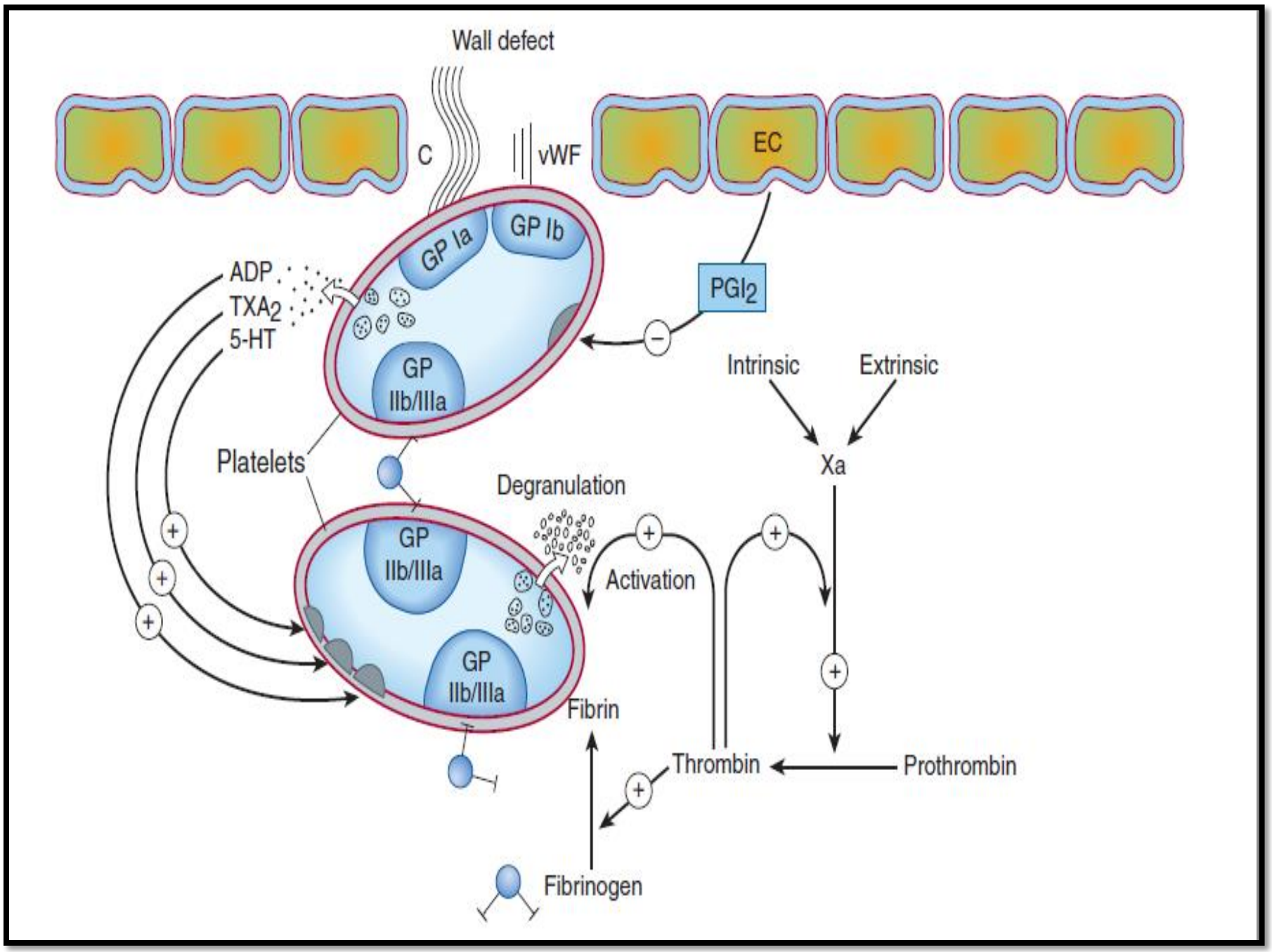
- A clot that adheres to a vessel wall is called a **thrombus**, whereas an intravascular clot that floats in the blood is termed an **embolus**

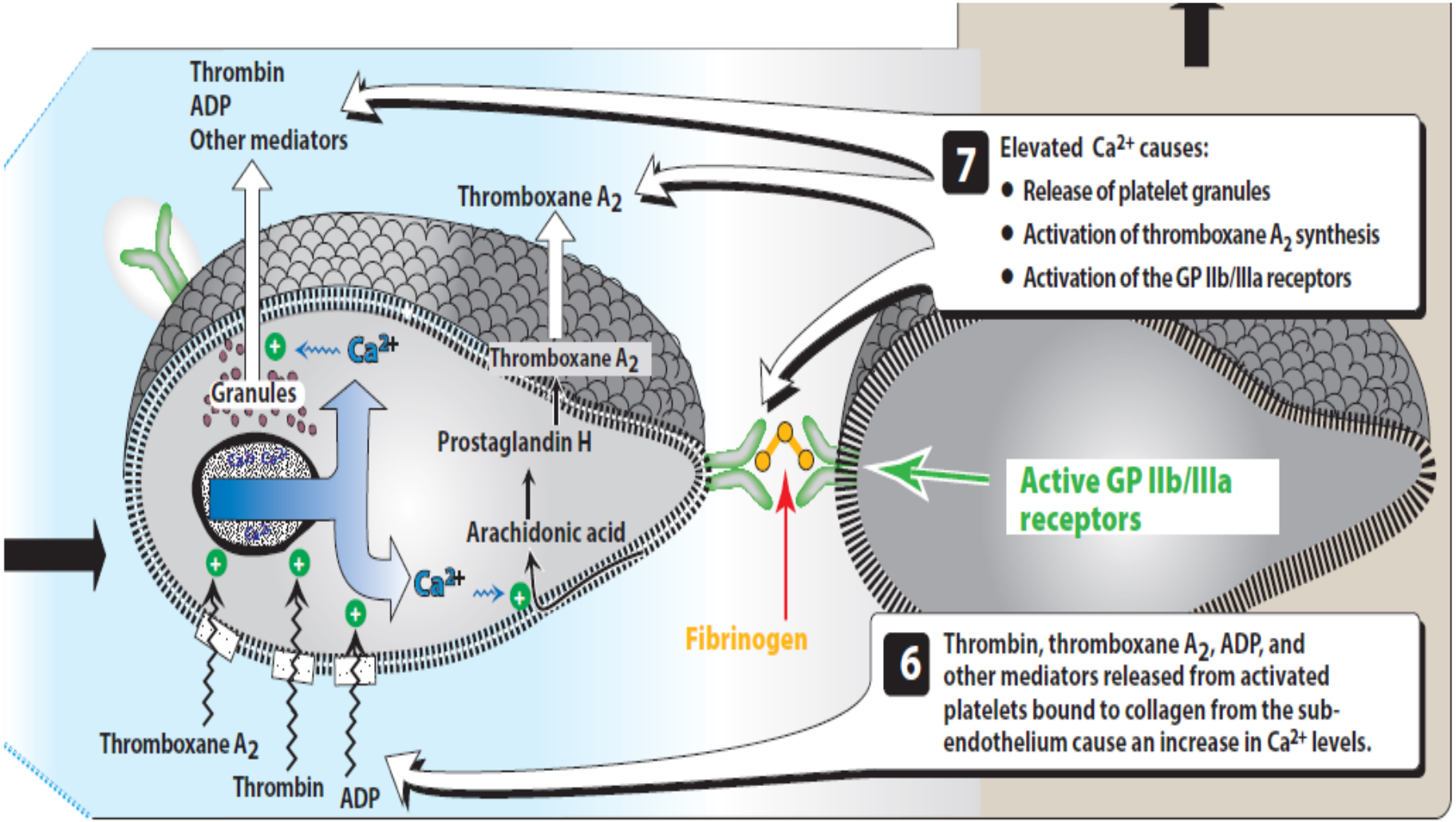
Mechanism



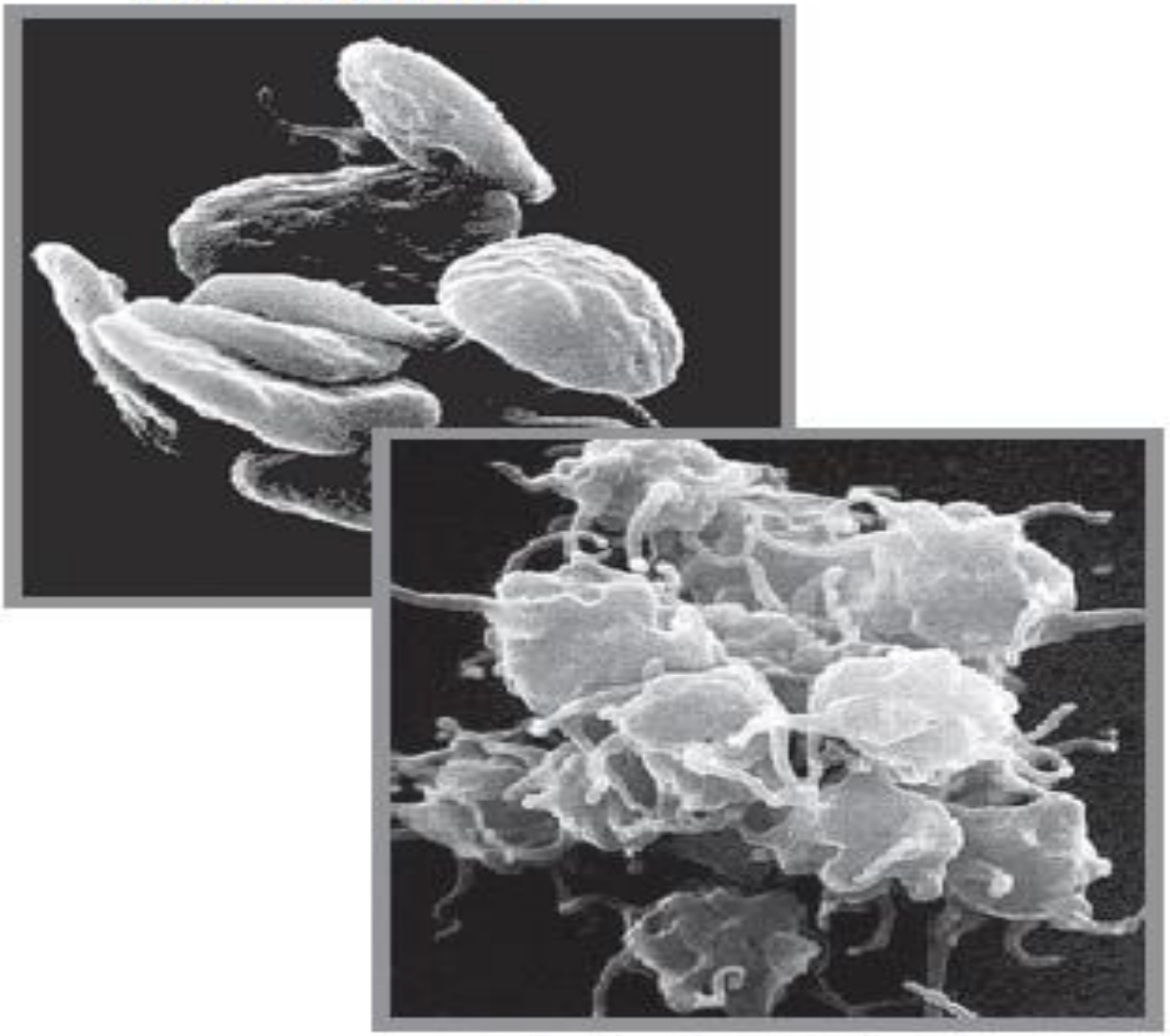
1. Vascular spasm
2. Platelets reaction
3. Formation of platelet plug
3. Blood coagulation




Wall defect
C
vWF
EC
GP Ia
GP Ib
ADP
TXA2
5-HT
PGI2
GP
IIb/IIIa
Intrinsic
Extrinsic
Platelets
Xa
Degranulation
GP
IIb/IIIa
Activation
GP
IIb/IIIa
Fibrin
Thrombin
Prothrombin
Fibrinogen

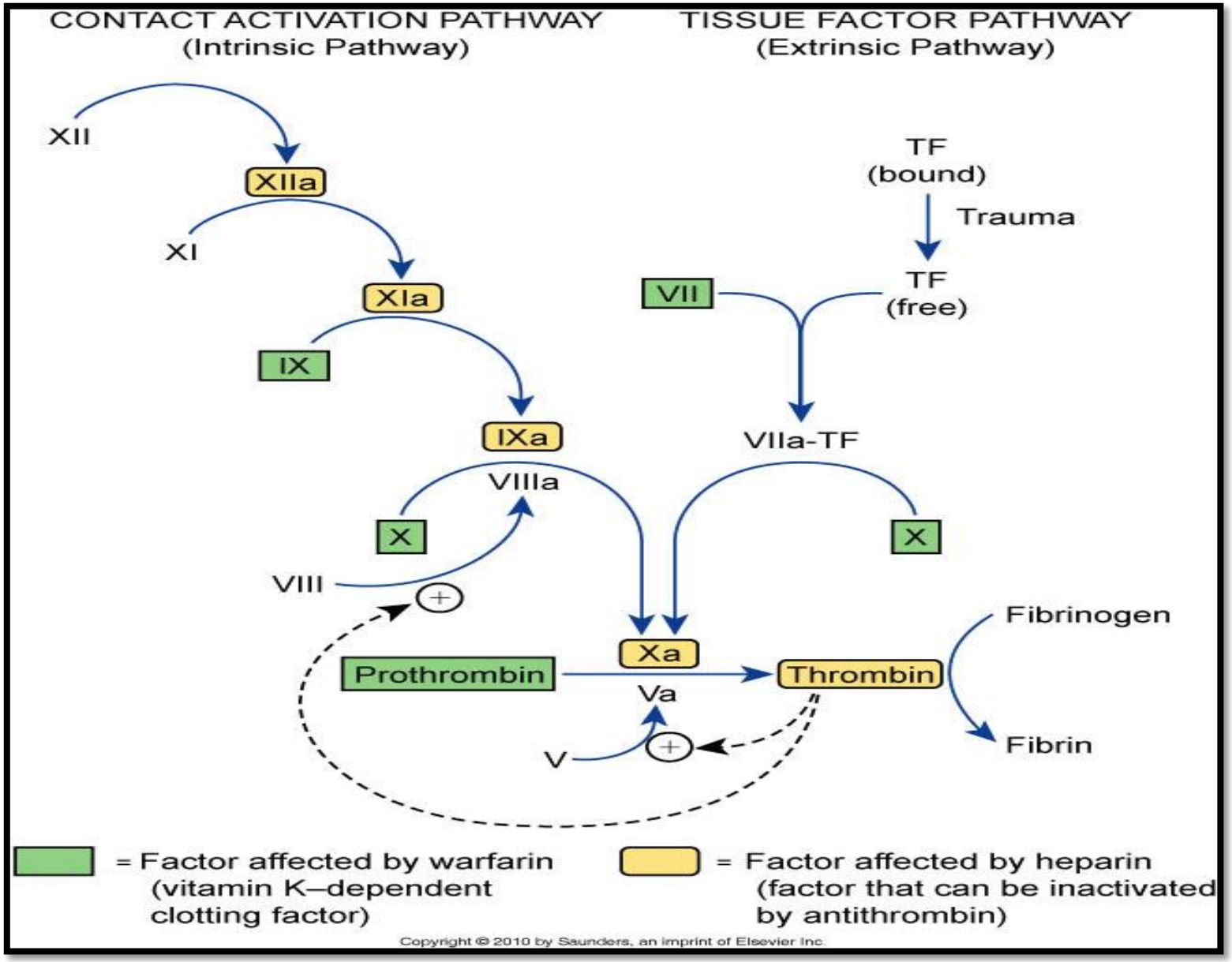

Thrombin
ADP
Other mediators
Thromboxane A2
7
Elevated Ca2+ causes:
• Release of platelet granules
• Activation of thromboxane A2 synthesis
• Activation of the GP IIb/IIIa receptors
Ca2+
Granules
Thromboxane A2
Prostaglandin H
Arachidonic acid
Ca2+
Active GP IIb/IIIa receptors
Fibrinogen
6
Thrombin, thromboxane A2, ADP, and other mediators released from activated platelets bound to collagen from the sub-endothelium cause an increase in Ca2+ levels.
Thromboxane A2
Thrombin
ADP

Resting platelet



Activated platelet

Clotting pathway

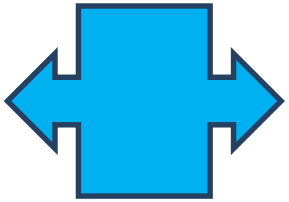


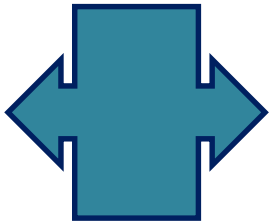
FACTORS WHICH PROMOTE BLOOD FLUIDITY

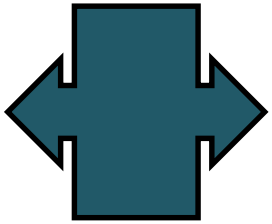
Normal Hemostasis

- **Natural Anticoagulants**
  - Protein C
  - Protein S
  - Antithrombin III
- **Endothelial-Derived Anti-Platelet Substances**
  - Nitric Oxide
  - Prostacyclin (PGI_2)
- **Fibrinolytic System "clot busters"**
  - Plasmin
  - Plasminogen
  - Tissue Plasminogen Activator (tPA)

FORMATION OF “BLOOD CLOT”

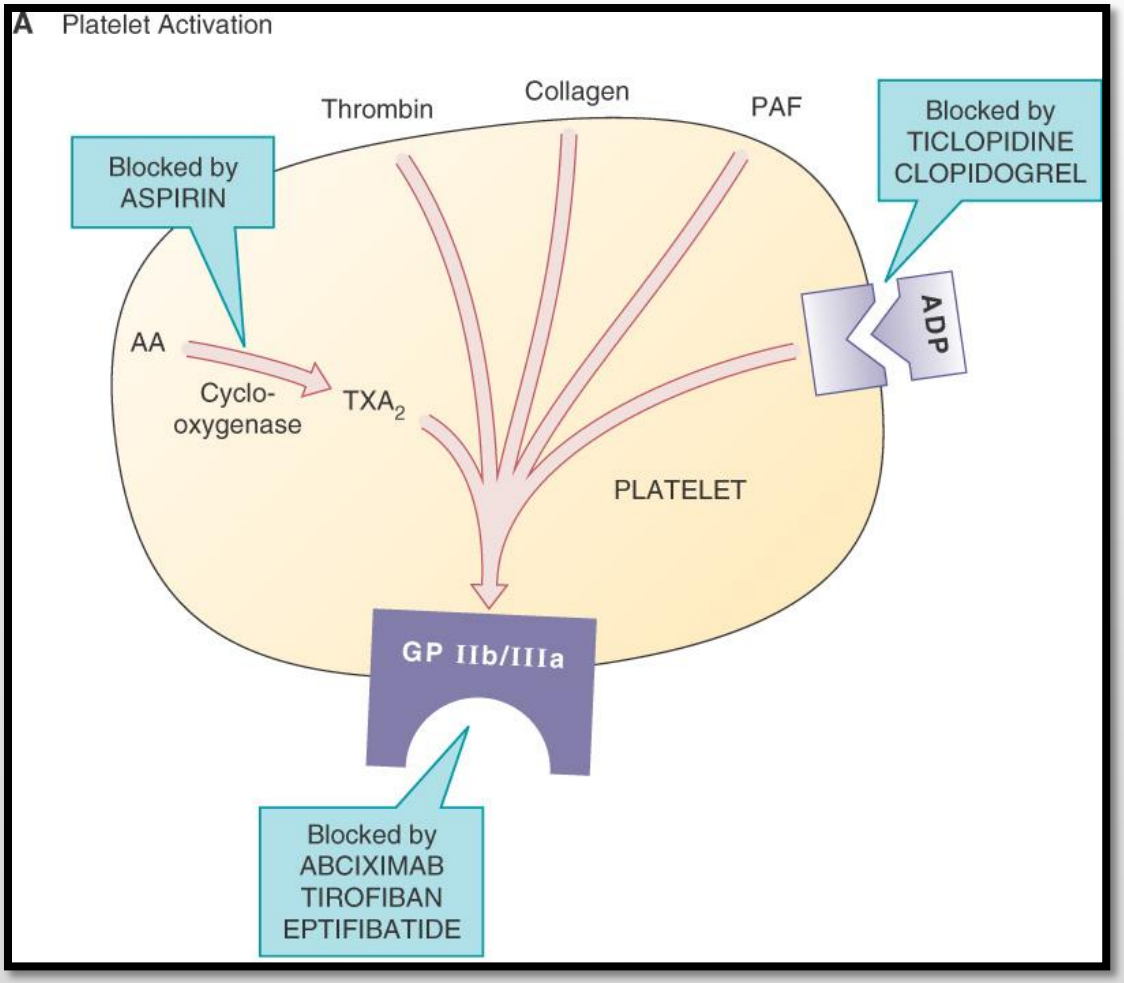
Platelet aggregation  ANTIPLATELETS

Clot formation  ANTICOAGULANTS

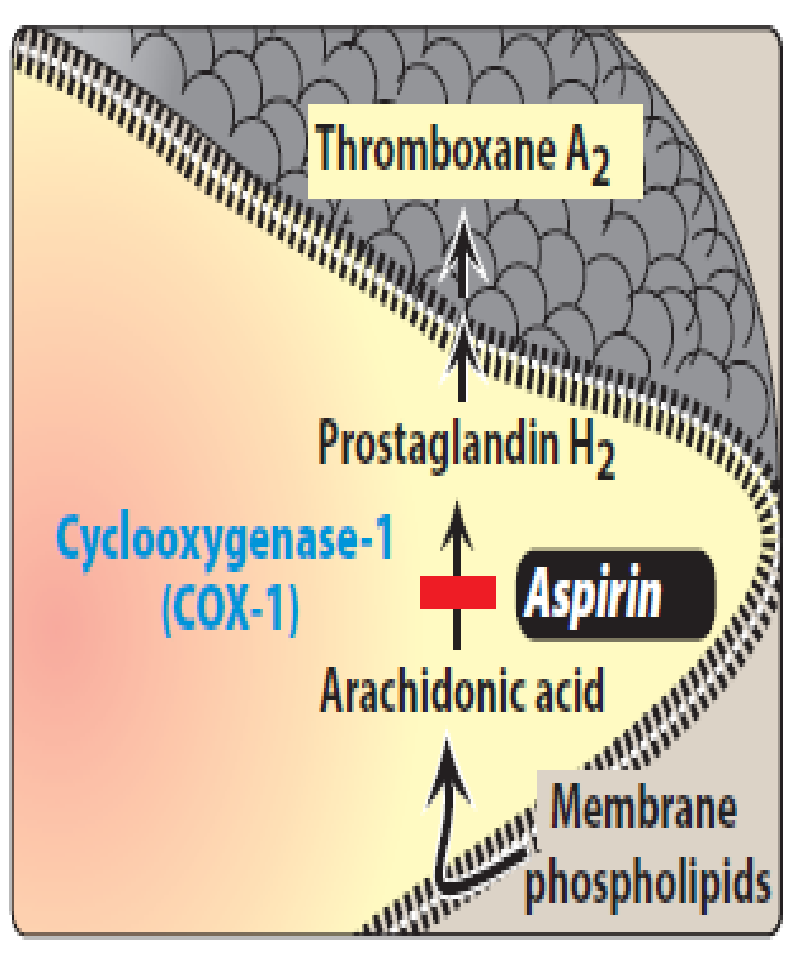
Clot resolution  THROMBOLYTICS

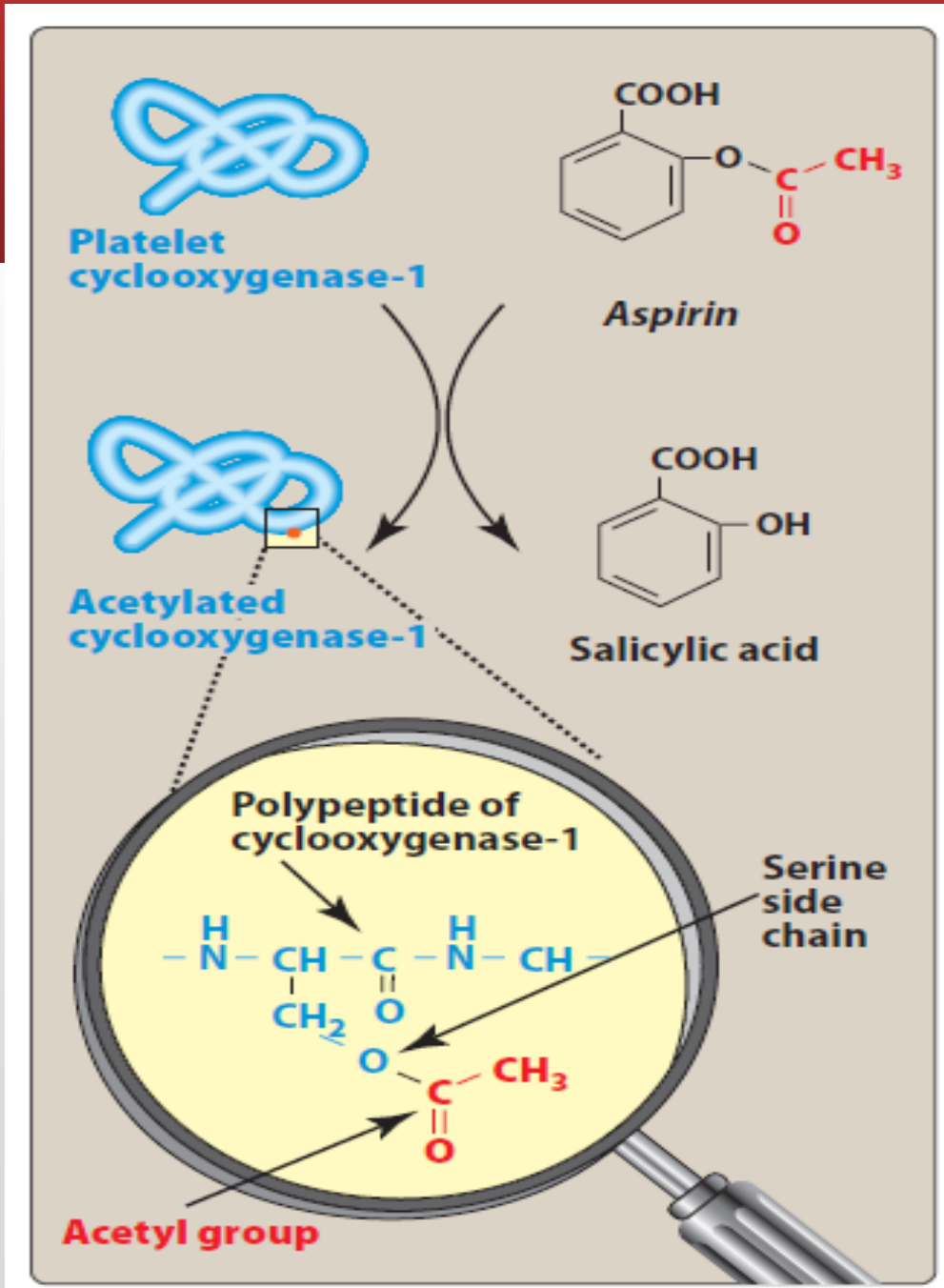

Antiplatelet Drugs

Antiplatelet Drugs



Antiplatelet Drugs: Aspirin





Antiplatelet Drugs

- **Aspirin (ASA)**
  - **Irreversible** Inhibition of cyclooxygenase

    Reducing Txa2

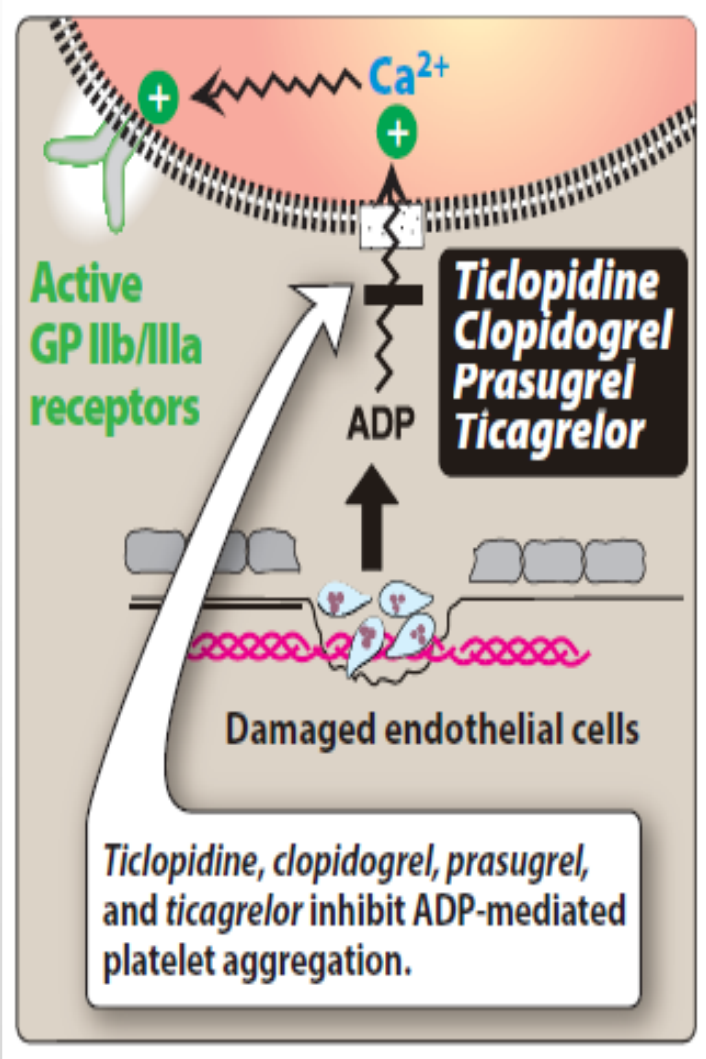
    Effect lasts for 7 days.
  - Adverse effects
    - Increase risk of GI bleeding
    - Hypersensitivity
    - Bronchospasms
    - Interstitial nephritis and proteinuria
- ASA-irreversible. Reduces risk of MI and death by 15-25% in patients with CVS diseases

P2Y12 ADP receptor antagonists

- **Ticlopidine, Clopidogrel, Prasugrel, Ticagrelor**

Reduce platelet aggregation by:

- Inhibition of ADP receptor on platelet
- Clopidogrel [*Plavix*]
  - Orally active
  - ADP receptor antagonist
    - ❑ Prevents/reduces thrombotic events (MI, ischemic stroke, vascular death)
    - ❑ Before and after Coronary intervention
    - ❑ Prevention of MI and stroke



P2Y12 ADP receptor antagonists

Important points to know:

- Clopidogrel is a Prodrug
- It is metabolized with CYP450 2C19
- CYP450 2C19 has genetic polymorphism
- Genetic polymorphism of CYP 2C19 leads to a Reduced clinical response in patients who are "Poor metabolizers" of clopidogrel
- Inhibitors of CYP 2C19:
  - Omeprazole
  - Esomeprazole

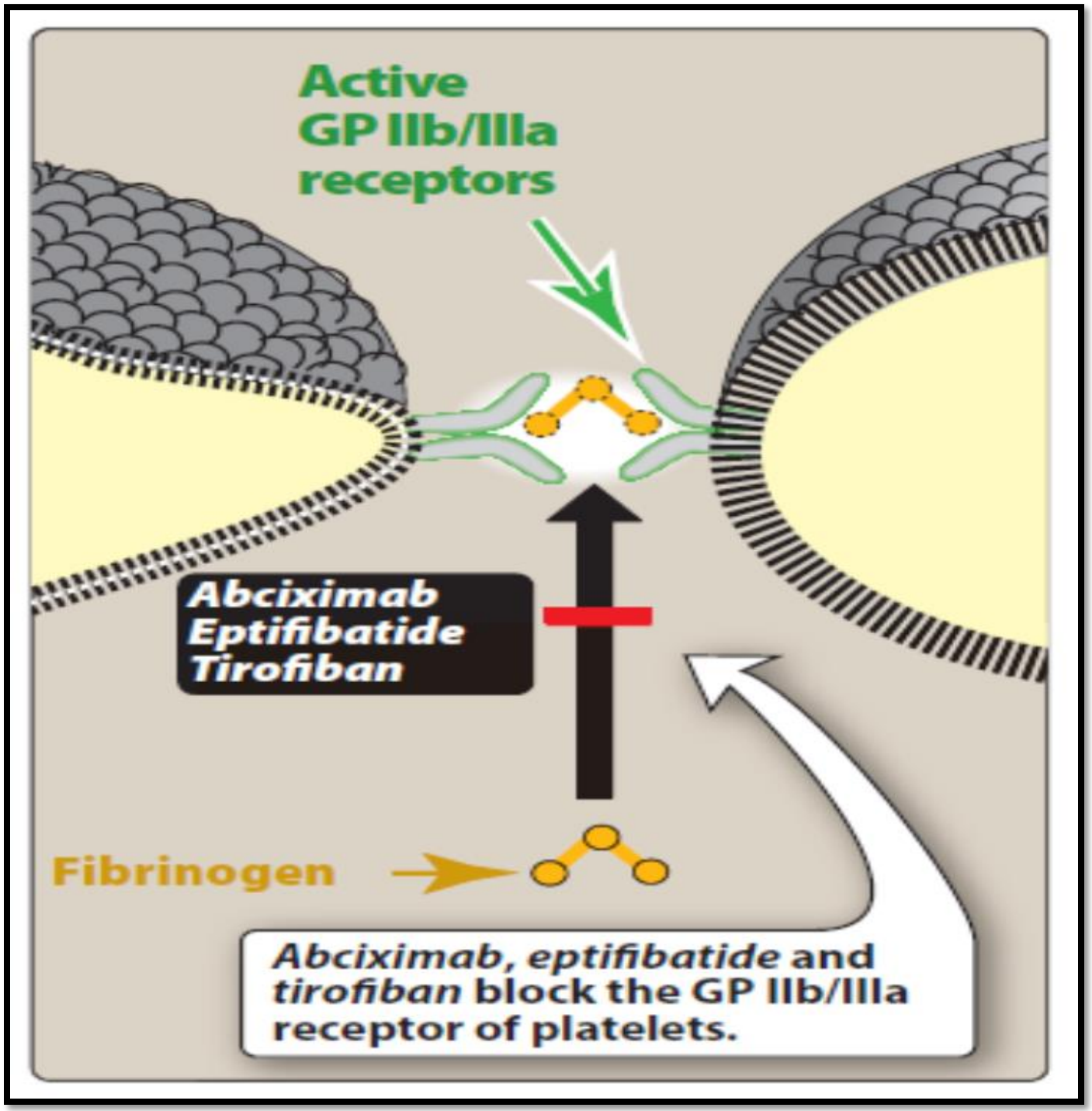
P2Y12 ADP receptor antagonists

Important points to know:

- Prasugrel is contraindicated in patients with history of TIA or stroke
- Prasugrel and Ticagrelor carry black box warnings for bleeding
- Clopidogrel has fewer adverse effects than ticlopidine and is rarely associated with neutropenia

P2Y12 ADP receptor antagonists

- Adverse effects of **Ticlopidine** :
- Nausea, dyspepsia, and diarrhea in up to 20
- Hemorrhage In 5%
- Severe hematologic reactions:
  - Agranulocytosis
  - Thrombotic thrombocytopenic purpura (TTP)
  - Most seriously leukopenia in 1%.
- **Monitoring of the WBC count** during the first 3 months of treatment.
- Higher risk of bleeding with **Prasugrel and Ticagrelor**


Active
GP IIb/IIIa
receptors
Abciximab
Eptifibatide
Tirofiban
Fibrinogen
Abciximab, eptifibatide and tirofiban block the GP IIb/IIIa receptor of platelets.

Glycoprotein 2b/3a Receptor Antagonists

- **Abciximab, Eptifibatide, Tirofiban**
- All given IV infusion
- Short half life, **rapid clearance after stop infusion**
- Acute coronary syndrome
- Abciximab is also approved for patients with unstable angina
- Acute need for coronary intervention (with ASA or Heparin)
- Excessive bleeding
- Serious Thrombocytopenia

Dipyridamole and Cilostazol

- Dipyridamole is a vasodilator and also antiplatelet
- It is an PDE inhibitor with increase cAMP, cGMP level in the platelets and vasculature
- It has low effectiveness in single therapy
- Usually combined with ASA/Warfarin for stroke prevention
- If given as IV: Orthostatic hypertension; headache
- Newer agent in this group: Cilostazol
  - FDA approved for intermittent claudication
  - PDE III inhibitor then act as antiplatelet agent
  - Could not be used in CHF patients

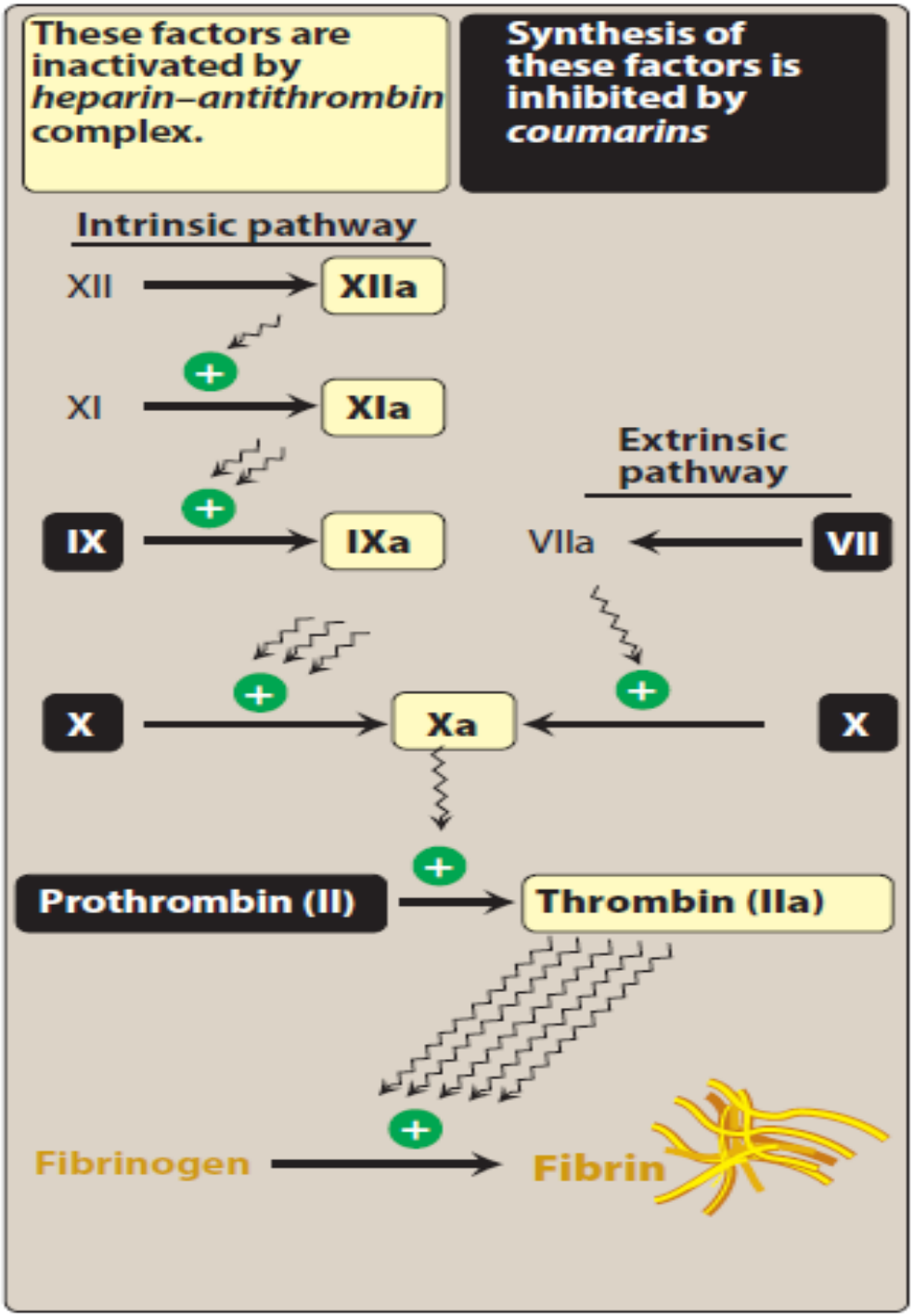
ANTI-COAGULANTS

- PARENTERAL
- ORAL

Anticoagulant drugs

The anticoagulant drugs inhibit:

- Function of coagulation factors (*heparin family*)
- Interfere with the synthesis of the coagulation factors (*warfarin*)



INDIRECT THROMBIN INHIBITORS

Parenteral Anticoagulants: Heparin and Related Drugs

- **Their antithrombotic effect is exerted by their interaction with a separate protein, antithrombin III**

- **Unfractionated heparin (UFH)**
- **Low molecular-weight heparin (LMWH)**
- **The synthetic pentasaccharide Fondaparinux**

INDIRECT THROMBIN INHIBITORS

Heparin (Unfractionated Heparin)

- ❑ In combination with histamine in mast cell
- ❑ Lungs of cattle
- ❑ Intestines of pigs
- ❑ Anionic with strong acidic activity
- ❑ UFH is a mixture with a wide range of molecular weights
- ❑ No GI absorption
- ❑ Only IV or SC
- ❑ Dose-dependent action?
- ❑ Short half life then multiple use/day
- ❑ No across from placenta

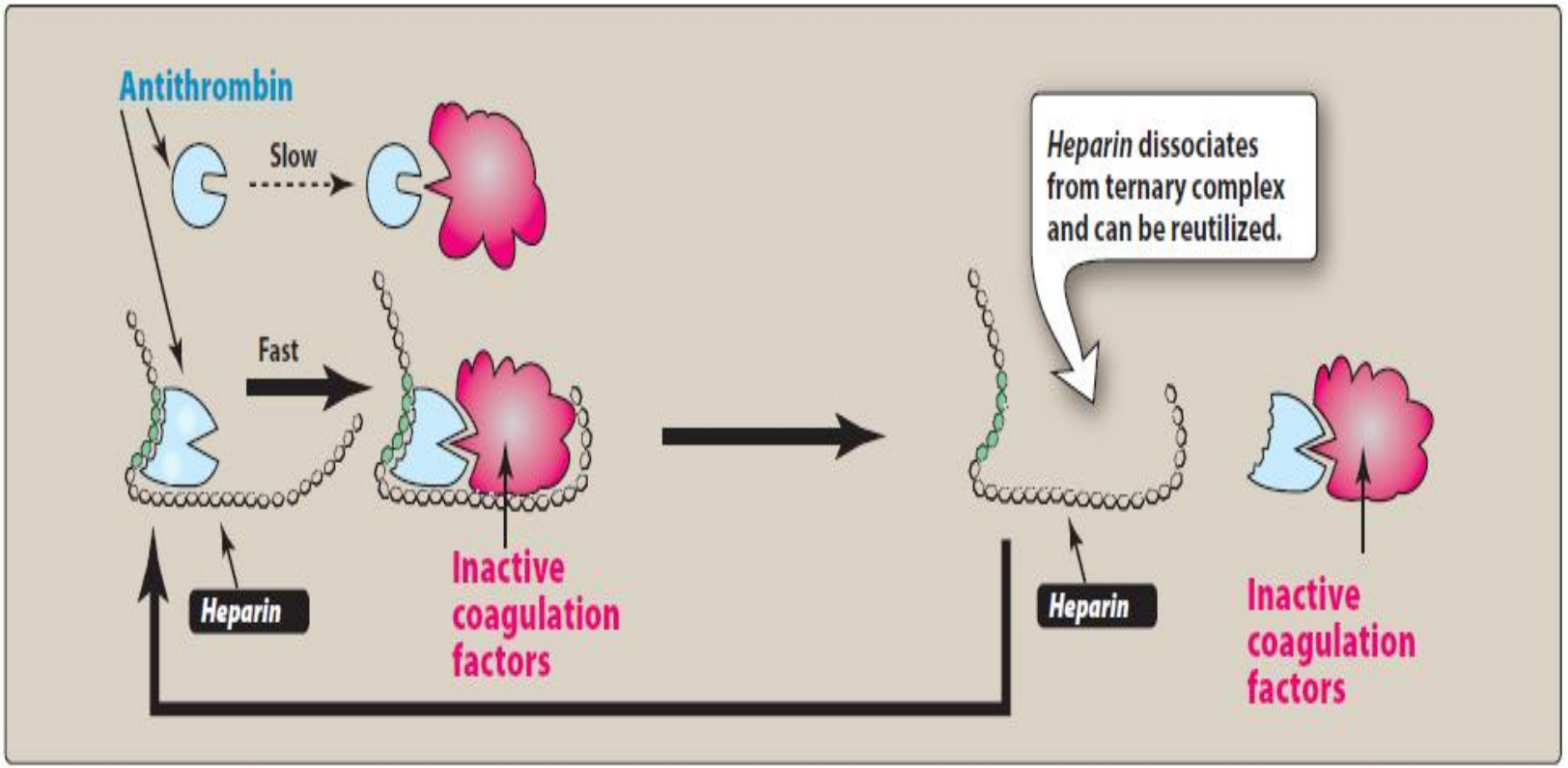
Rapid-acting anticoagulant

Mechanism of action

- Heparin **increases the rate of the thrombin-antithrombin reaction at least 1000-fold**

- Antithrombin inhibits clotting factor proteases, especially thrombin (**IIa**), IXa, and **Xa**, by forming stable complexes with them.
- In the absence of heparin, the reactions are slow
- In the presence of heparin, accelerated **1000-fold**

Heparin mechanism of action



CLINICAL USE

Therapeutic uses:

- **Prevents pulmonary emboli in patients with established venous thrombosis**
- **Venous thrombosis (DVT)**
- **Unstable angina and acute MI**
- **Thrombolytic events during the pregnancy**
- **In combination with warfarin**
  - An oral anticoagulant usually is started concurrently, and heparin is continued for at least 4–5 days to allow the oral anticoagulant to achieve its full therapeutic effect.

Parenteral Anticoagulants : Heparin

- **Adverse effects**

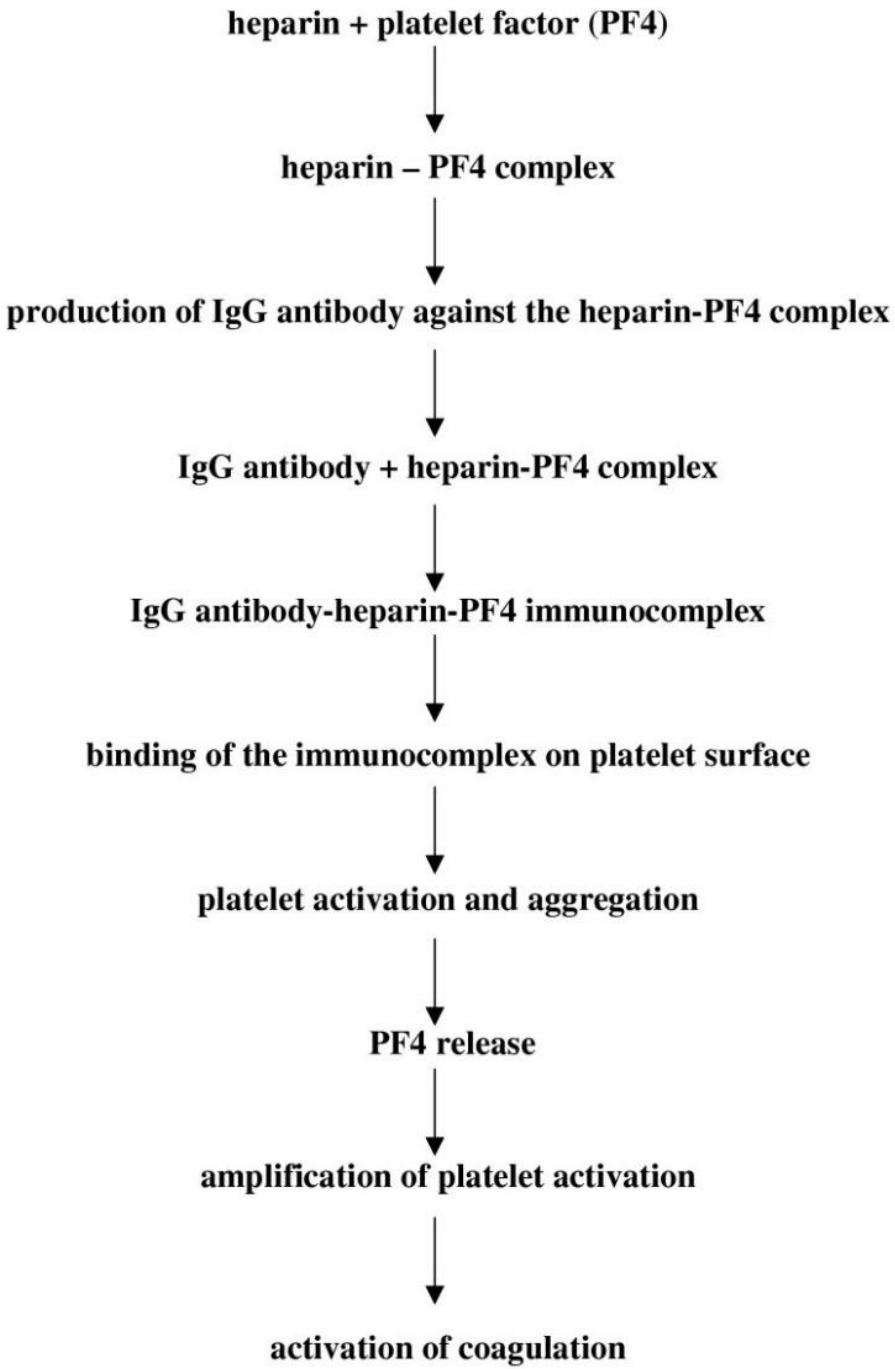
- ❑ **Hemorrhage**
- ❑ **Heparin-induced thrombocytopenia (HIT)** ➡ **treatment?**
- ❑ **Direct thrombocytopenia**
- ❑ **Hypersensitivity reactions**
- ❑ **Anaphylactic reactions**
- ❑ **Osteoporosis (if >20,000 units/d) for extended periods (3-6 months)**
- ❑ **Alopecia**
- ❑ **Hyperkalemia (can inhibit the synthesis of aldosterone by the adrenal glands)**
- ❑ **Good effect on TG!**

Parenteral Anticoagulants : Heparin

Heparin-induced thrombocytopenia (HIT)

- **HIT type I**
  - Usually occurs within the first 48–72 h after initiation of heparin
  - A non-immunologic response to heparin treatment
- **HIT type II**
  - Immune-mediated and associated with a risk of thrombosis
  - Platelet count < 150,000/ml or a 50% decrease from the pretreatment value
  - Occurs in about 0.5% of medical patients 5–10 days after initiation of therapy with heparin
  - Life-threatening thrombotic complications that can lead to limb amputation, which occurs in up to 50% of the HIP cases
  - Thrombocytopenia is more common in surgical patients than medical patients
  - Venous thromboembolism occurs most commonly, but arterial thrombosis causing limb ischemia, MI, or stroke also occurs
  - The development of IgG antibodies against complexes of heparin with platelet factor 4

Mechanism of HIT induced thrombosis



HIT Management

- Management involves:
  - Immediate discontinuation of heparin
  - Initiation of an alternate parenteral anticoagulant to prevent or treat thrombosis.
    - Bivalirudin
    - Argatroban
    - Fondaparinux
- LMWH should be avoided, because it cross-reacts with heparin antibodies.
- Warfarin may precipitate venous limb gangrene or skin necrosis in patients with heparin-induced thrombocytopenia and should not be used until the platelet count returnsto normal.

Something to remember:

Monitoring of Heparin Effect

- Close monitoring of PTT
- Anti Xa activity (after 6 hr)
- PTT ~ 1.5-2.5 fold than normal
- Platelet count
- Close monitoring for new thrombotic events (HIT)
- Risk of IM injection of heparin

Contraindications

- Hypersensitivity to the drug
- Active bleeding
- Alcoholic pts
- hemophilia
- Thrombocytopenia
- Severe hypertension
- Intracranial hemorrhage
- Recent ocular, brain or spinal cord surgery
- Threatened abortion
- Advanced hepatic or renal disease

TOXICITIES

- Excessive anticoagulant action of heparin is treated by **discontinuance of the drug**

If bleeding occurs:

- The effect of heparin can be reversed quickly by the **slow intravenous infusion** of **protamine sulfate**, *a chemical antagonist (slow infusion)*
- **Protamine is a highly basic, positively charged peptide that combines with negatively charged heparin *Bind tightly to* heparin and thereby neutralize its anticoagulant effect.**
- **For every 100 units of heparin ~ 1 mg of protamine sulfate is given intravenously**
- **Excess protamine must be avoided; it also has an anticoagulant effect**

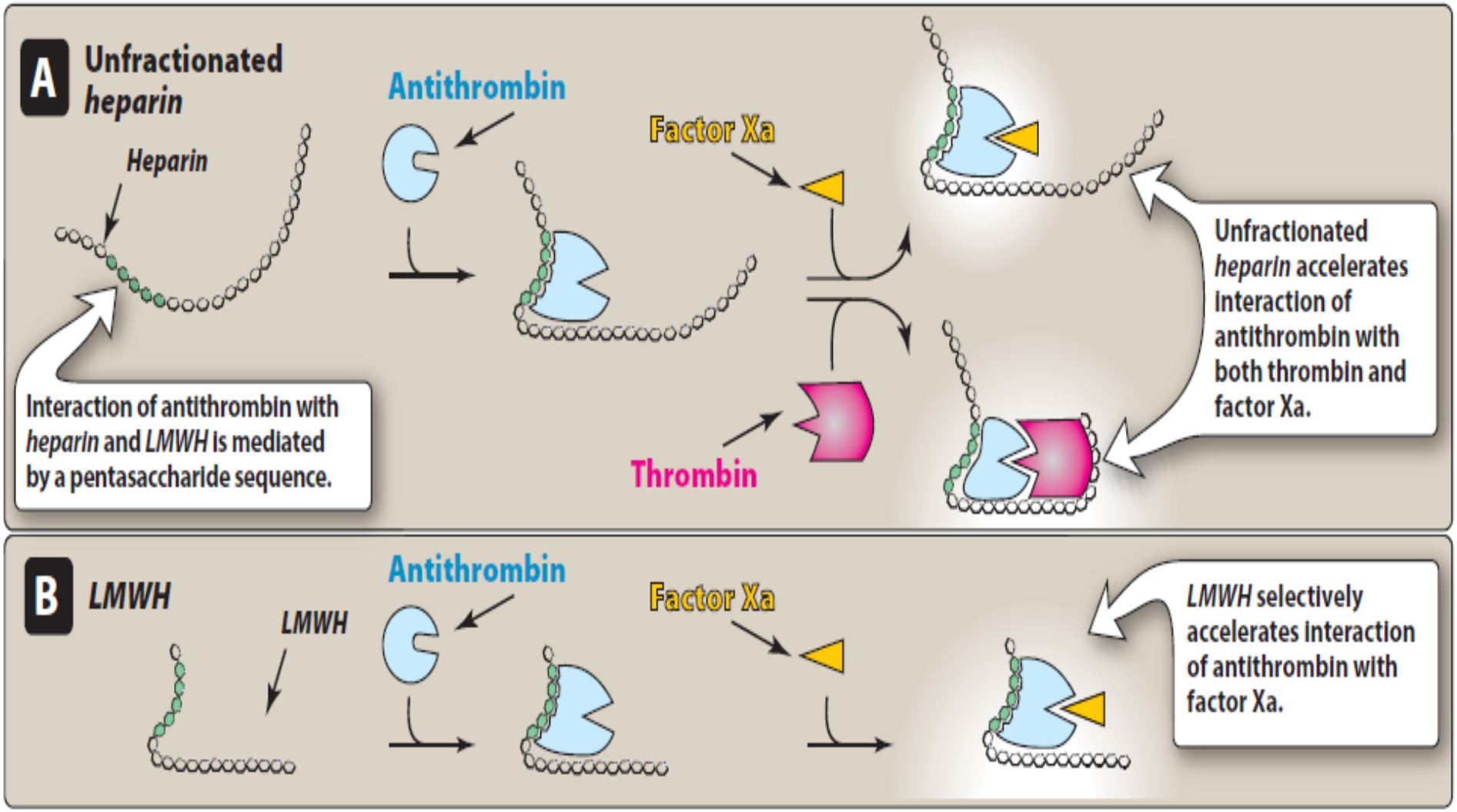
LMW Heparins

- The LMW fractions of heparin inhibit activated factor X but have less effect on thrombin than the HMW species
- Increased bioavailability from the subcutaneous site of injection, and
- Protamine sulfate Partial effect on LMW and no effect on fondaparinux
- Predictable pharmacological effect related to drug concentration, no need to control PTT except in:
- Obese pts.
- Renal failure
- Pregnancy

LMW Heparins

- **Enoxaparin; Dalteparin; Tinzaparin, Danaparoid**
- In comparison with UFH, LMW heparins—have **equal efficacy**
- Improved PK properties
- **Adverse effects and interactions**
  - **Bleeding**
  - **immune-mediated thrombocytopenia**
    - **Cross-sensitivity with heparin and are not recommended in HIT**
    - **Cost**

LMW Heparins



Fondaparinux

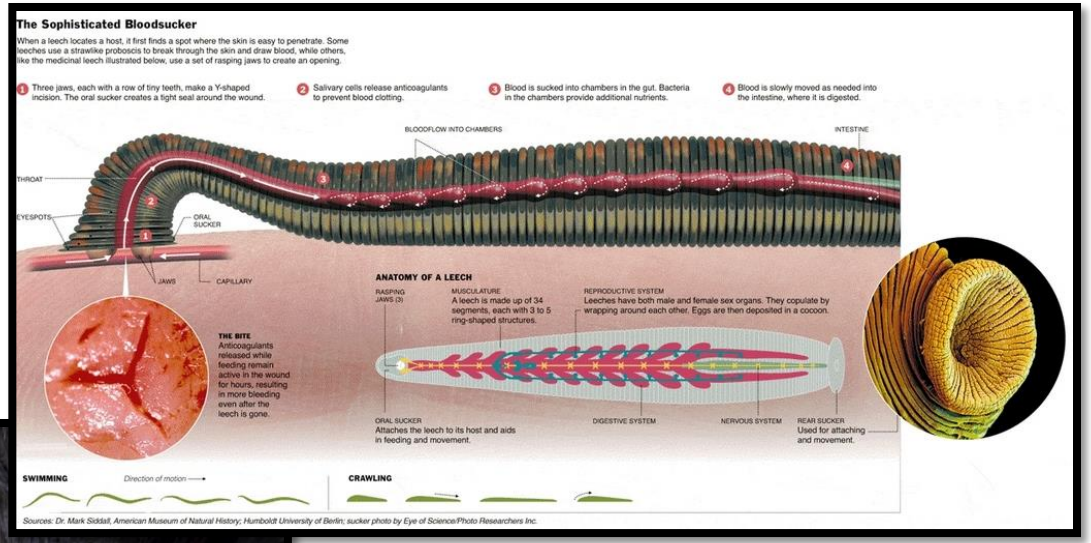
- Synthetic S.C anticoagulant – like LMW heparin
- **Selective inhibition of Factor Xa**
- Once a day
- Limited in renal insufficiency
- **Adverse effects**
  - Bleeding, risk is increased with advancing **age and renal impairment**
- **Protamine will not reverse the activity of fondaparinux.**
- **Fondaparinux as an alternative anticoagulant in HIT**

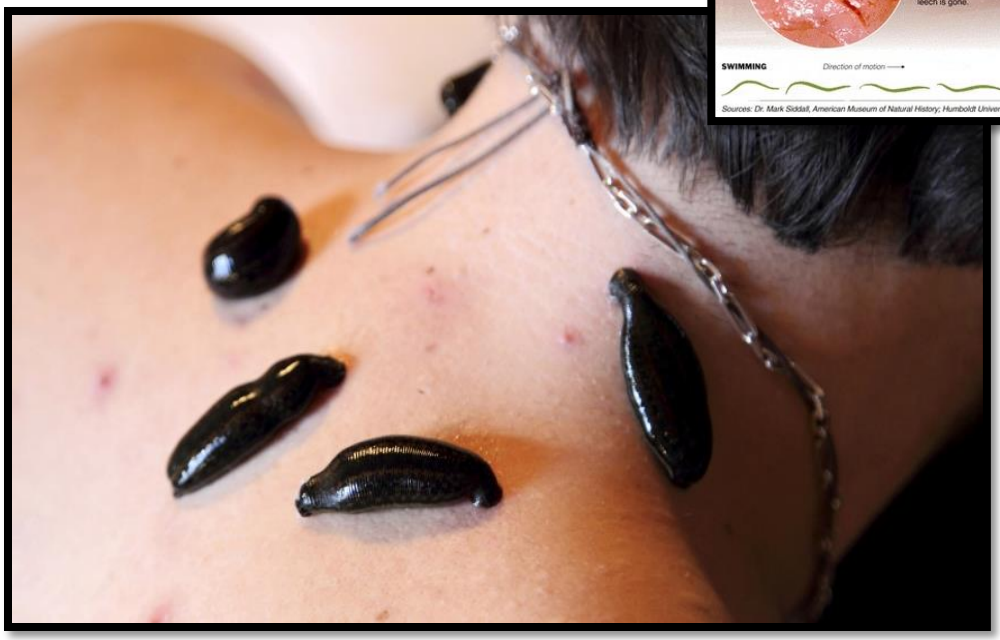
Parenteral Anticoagulants:
Direct Thrombin Inhibitors

LEPIRUDIN:

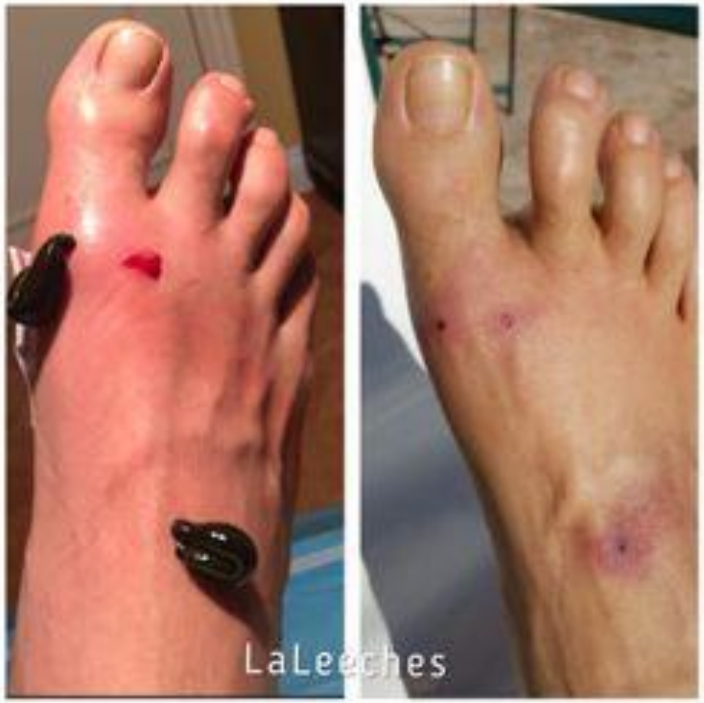
Lepirudin is a recombinant derivative of Hirudin

- A ***Direct thrombin inhibitor*** present in the salivary glands of the medicinal leech.
- It is a 65-amino-acid protein that **binds tightly to both the catalytic site** and the extended substrate recognition site of thrombin.





Medical leech



Parenteral Anticoagulants: Direct Thrombin Inhibitors

BIVALIRUDIN

Bivalirudin *is a synthetic, 20-amino-acid polypeptide that* ***directly inhibits thrombin****.*

- short half-life (25 min)
- Also has Antiplatelet effect
- in combination with ASA during coronary angioplasty

Parenteral Anticoagulants: Direct Thrombin Inhibitors

ARGATROBAN

- **Binds reversibly to the catalytic site of thrombin**
- Administered intravenously
- Has an **immediate onset of action**
- **Argatroban** can be used as an **alternative to** for **prophylaxis** of patients with or **at risk of developing HIT**

- **aPTT test can also be used for these drugs**

Oral dosage form:
Direct Thrombin Inhibitors

Dabigatran:

Oral direct thrombin inhibitor. Both clot-bound and free thrombin are inhibited by Dabigatran

- Prevention of stroke
- Systemic embolism in patients with **non-valvular atrial fibrillation**

Alternative to **enoxaparin** for thromboprophylaxis in orthopedic surgery

Dabigatran etexilate

PKs:

- Prodrug
- Sensitive to moisture
- Capsules should be stored in the original container and swallowed whole
- Hydrolyzed to the active drug by plasma esterases

Dabigatran etexilate

- Dabigatran does not require routine monitoring of the international normalized ratio (INR)
- has fewer drug interactions as compared to warfarin

- There is no approved antidote for reversing bleeding associated with dabigatran
- *Dabigatran* should be used with caution in:

  - Renal impairment or in patients
  - over the age of 75

Rivaroxaban and Apixaban

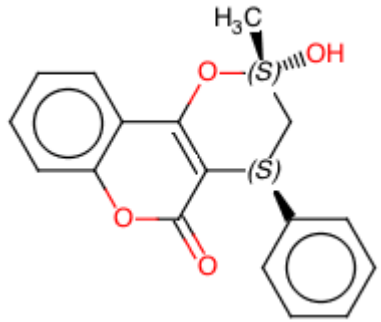
- Oral inhibitors of factor xa
- **Rivaroxaban:**
  - **Prevention of DVT and PE**
  - **Prevention of stroke in non-valvular atrial fibrillation**
- **Apixaban**
  - **Prevention of stroke in non-valvular atrial fibrillation**

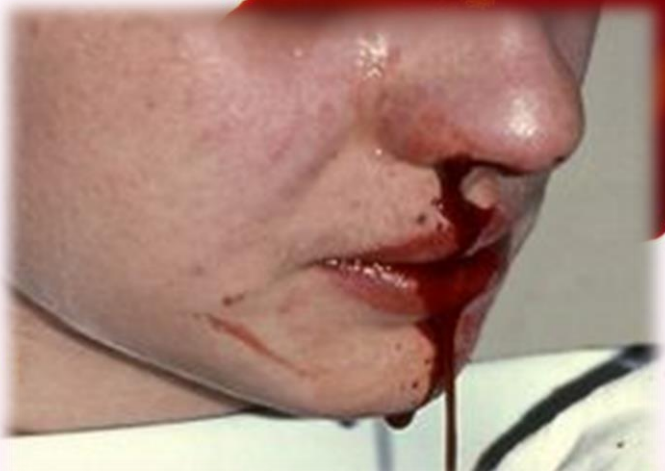
- **No laboratory monitoring requirements**
- **No Antidote**
- **Fewer drug interaction vs. Warfarin**

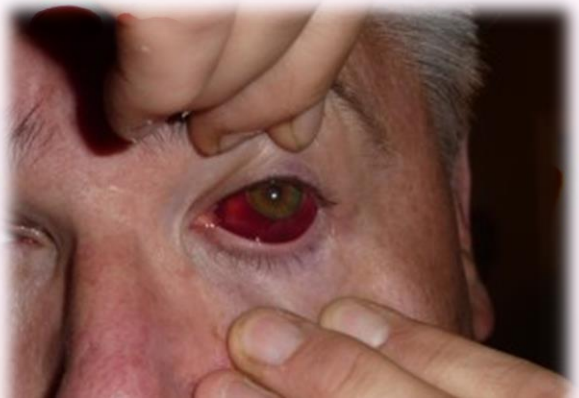
Abrupt discontinuation of these agents should be avoided

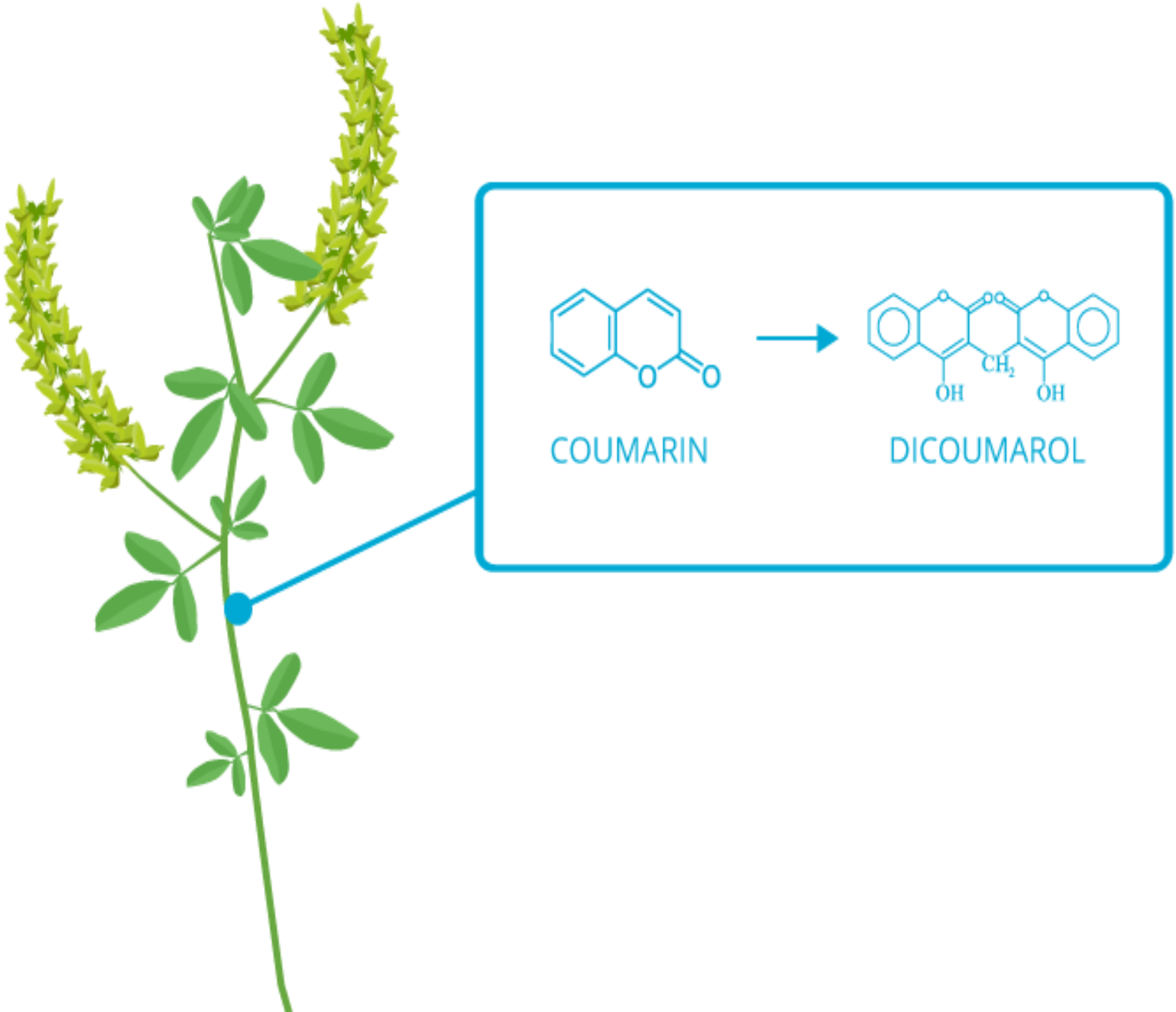
ORAL ANTICOAGULANTS

Warfarin





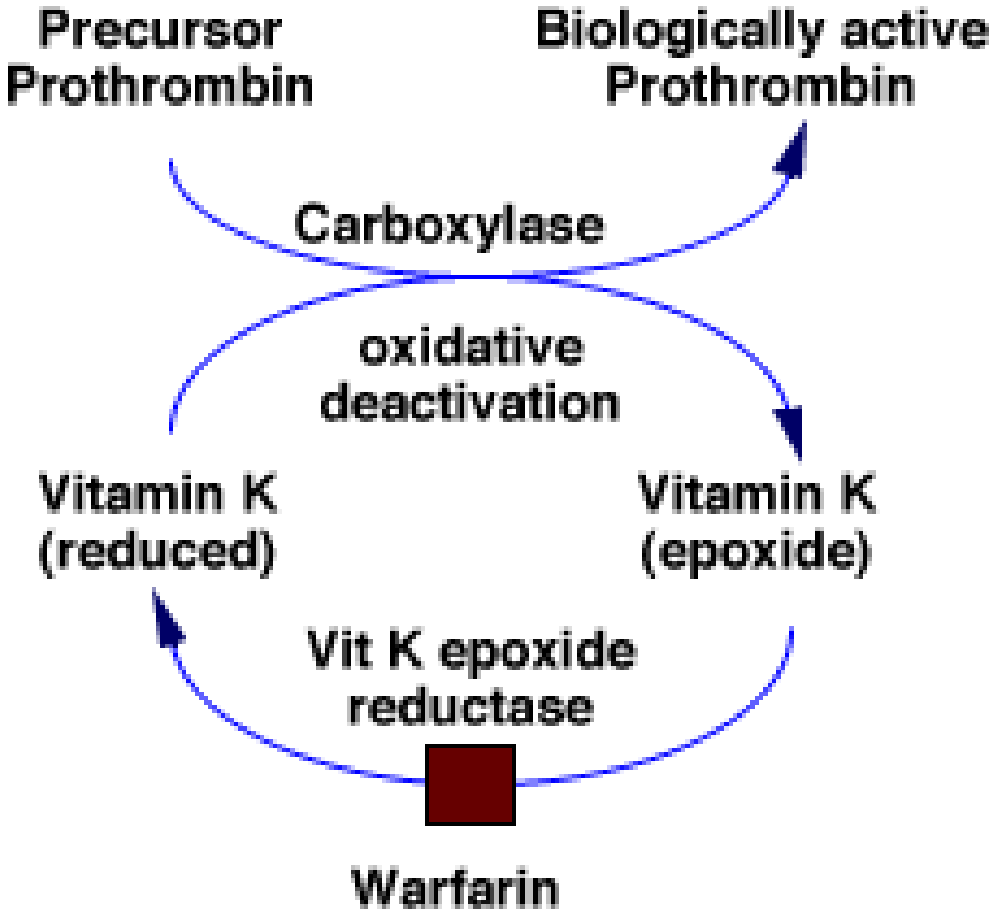



O
O
COUMARIN
CH2
OH
OH
DICOUMAROL

Warfarin

- **Oral** anticoagulant
- **Warfarin is generally administered as the sodium salt and has 100% bioavailability (racemic form)**
- Over 99% of warfarin is bound to plasma albumin
- **long half-life in plasma (36 hours)**
- The oral anticoagulants are **Antagonists of vitamin K**
- Blocks the of four clotting factors: **Factors VII, IX, X, and prothrombin, Pro C, Pro S**
- Reduces production of clotting factors by 30-50%
- Therapeutic uses

Long-term prophylaxis of thrombosis

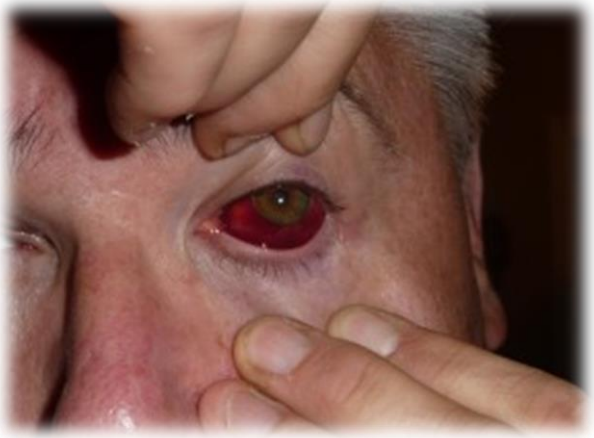


The vitamin must then be reduced to reactivate it
Warfarin prevents reductive metabolism of the inactive vitamin K epoxide back to its active hydroquinone form

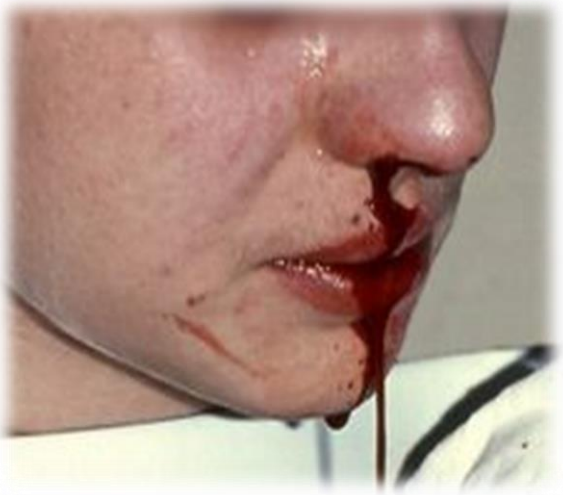
Clinical Use...

- To prevent the progression or recurrence of acute DVT
- Pulmonary embolism following an initial course of heparin.
- In preventing systemic embolization in patients with acute myocardial infarction
- preventing systemic embolization in prosthetic heart valves, or chronic AF.

Warfarin



- **Adverse effects**
  - **Hemorrhage**
  - Crosses the placenta readily and can cause **Fetal hemorrhage**
  - **Teratogenic** from use during pregnancy (abnormal bone formation)
  - During lactation – warfarin enters breast milk



TOXICITIES

- **Bleeding is the chief complain**
- **The risk of bleeding** increases with the intensity and duration of anticoagulant therapy, the use of **other medications** that interfere with hemostasis, and the presence of a potential source of bleeding.
- **Oral vitamin K**
- **Parenteral vitamin k**
- **Prothrombin+ VIIa factor-vitamin K complex: IV**

Warfarin; some points

- **Monitoring of Warfarin Effect**
  - The **prothrombin time (PT)**
  - **International normalized ratio (INR)**
  - The prothrombin time (PT) should be increased to a reduction of prothrombin activity to 25% of normal
  - the activity is **less than 20%,** the warfarin dosage should be reduced or omitted
- **The recommended INR for prophylaxis and treatment of thrombotic disease is 2–3**
- **For high risk pts: 2.5-3.5**

TABLE 34–2 Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	*Pharmacodynamic*	*Pharmacokinetic*	*Pharmacodynamic*
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K
Metronidazole[1]	Heparin		**Body factors**
Fluconazole[1]	**Body factors**		Hereditary resistance
Phenylbutazone[1]	Hepatic disease		Hypothyroidism
Sulfinpyrazone[1]	Hyperthyroidism		
Trimethoprim-sulfamethoxazole			

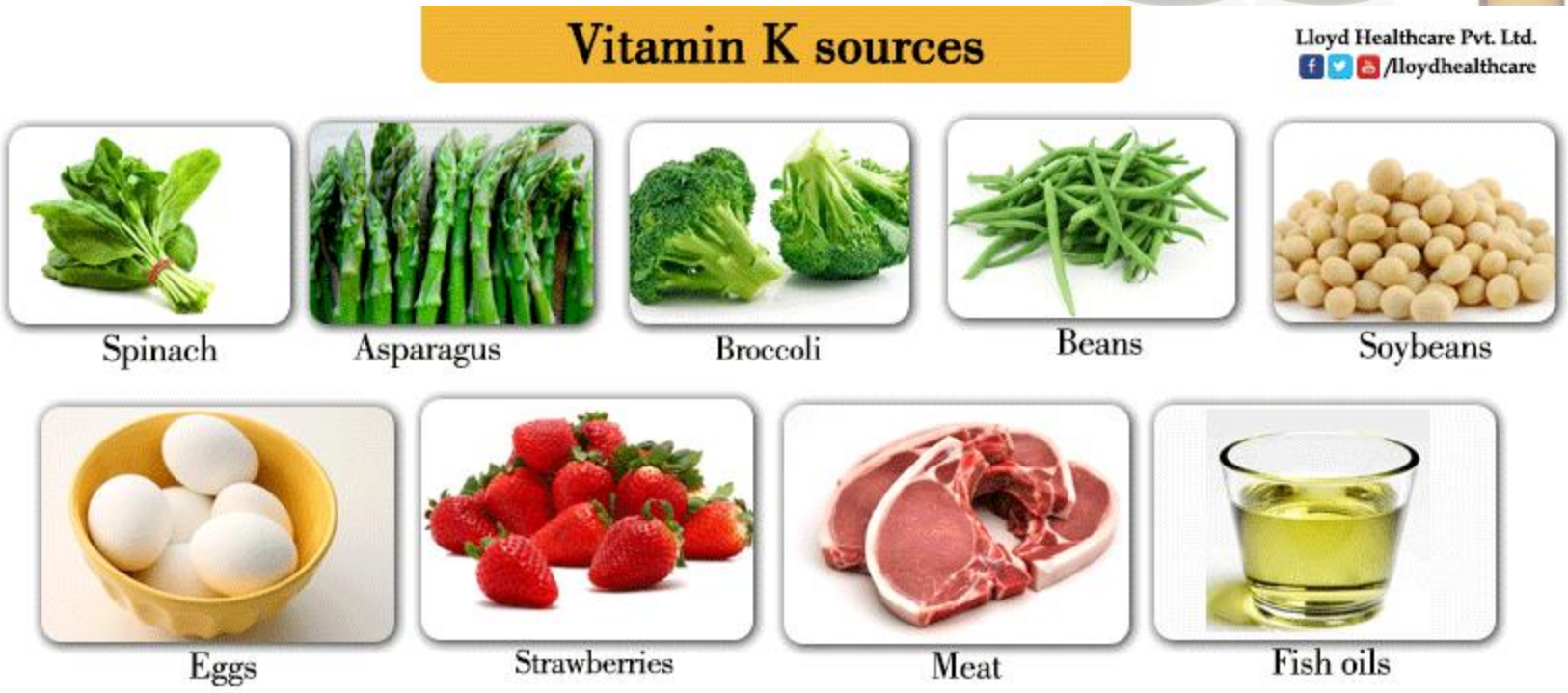
Warfarin: important keys to know

- Advise patients to use drug at **constant time /day**
- Patients should be aware about **risk of bleedings** during treatment
- **Restriction of vitamin K intake** via diet to maintain INR at near fixed range (up to 200µg/day)
- Patients should be aware about the potential peril **drug-drug, drug-food, drug-herb** or even **supplement interaction** (fish oil, ginkgo biloba, ginseng, st. joint wort, grapefruit juice, …)

Reversal of Warfarin Action

Excessive anticoagulant effect and bleeding from warfarin can be reversed by stopping the drug and administering:

oral or parenteral vitamin K_1 (phytonadione), Fresh/frozen plasma

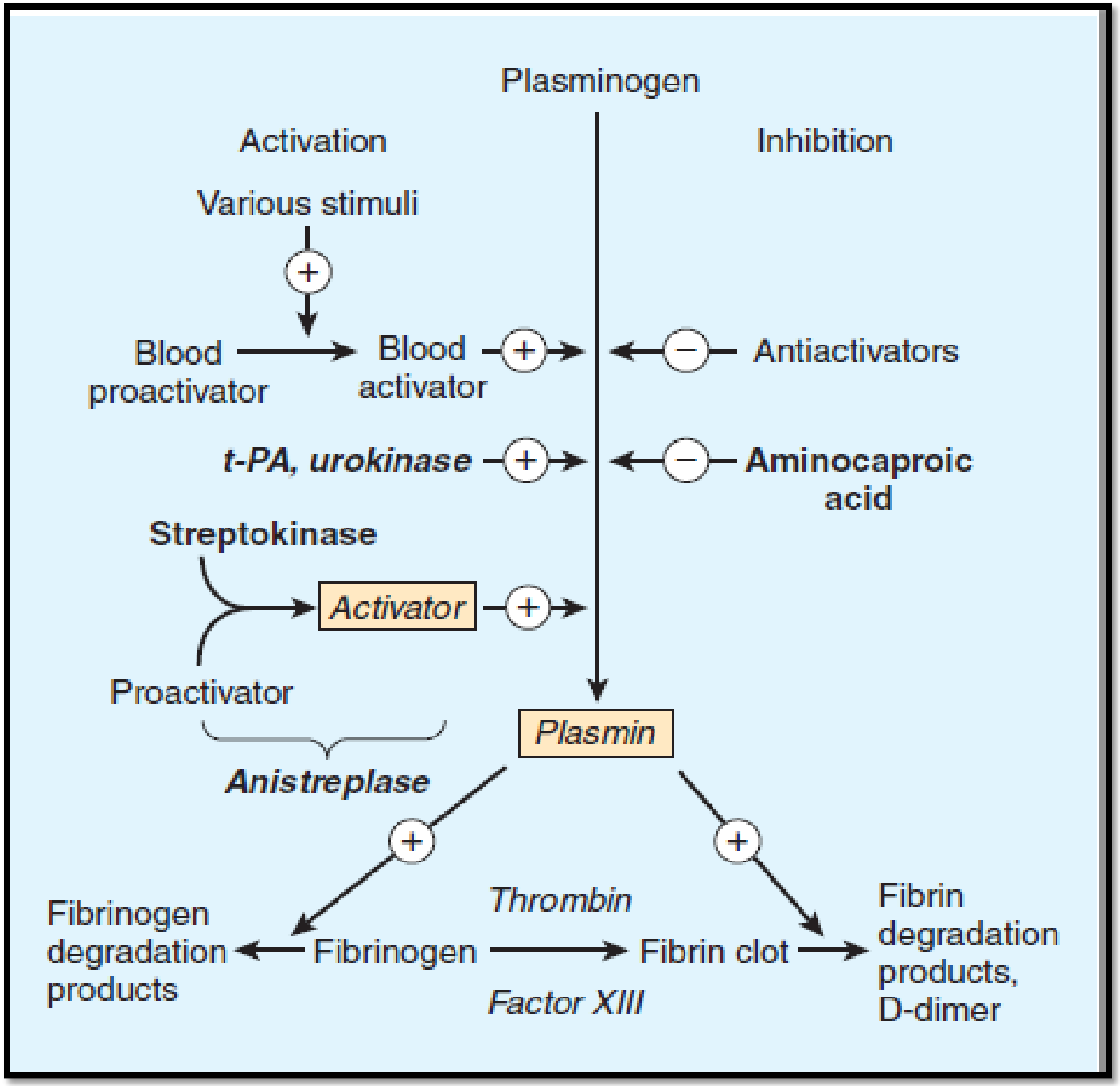



Thrombolytic Drugs

Fibrinolysis (Thrombolysis)

- Physiologic Fibrinolytic system is so selective
- Physiologic Fibrinolytic is limited to fibrin location
- Negative regulators of fibrinolysis:
  - Endothelial cells release plasminogen activator inhibitor (PAI)
    - PAI is an inhibitor of t-PA
    - Presence of high concentration of anti-plasmin in plasma

- Clot specificity is only observed at physiologic levels
- At the pharmacologic levels of t-PA used in thrombolytic therapy, clot specificity is lost and a systemic lytic state is created


Plasminogen
Activation
Inhibition
Various stimuli
Blood proactivator
Blood activator
Antiactivators
t-PA, urokinase
Aminocaproic acid
Streptokinase
Activator
Proactivator
Anistreplase
Plasmin
Fibrinogen degradation products
Fibrinogen
Thrombin
Factor XIII
Fibrin clot
Fibrin degradation products, D-dimer

Thrombolytic Drugs

- **Streptokinase [Streptase]**
  - **Binds plasminogen and facilitates plasmin formation – plasmin digests fibrin of clots**
  - ***Most effective when therapy is begun within 3 hours of symptom onset***
  - Intended for **IV** or **intracoronary** administration
  - Is not clot specific then causes a systemic fibrinolytic state

- **Uses**
  - **Acute coronary thrombosis (acute MI)**
  - **Deep venous thrombosis (DVT)**
  - **Massive pulmonary emboli**
- **Adverse effects**
  - **Bleeding, hypotension**

– **Urokinase** is a human enzyme synthesized by the kidney that directly converts plasminogen to active plasmin.

Uses: Lysis of pulmonary emboli

Tissue plasminogen activator (tPA)

- ❑ Alteplase
- ❑ Reteplase
- ❑ Tenecteplase
  - More clot-specific
  - Fewer bleeding episodes

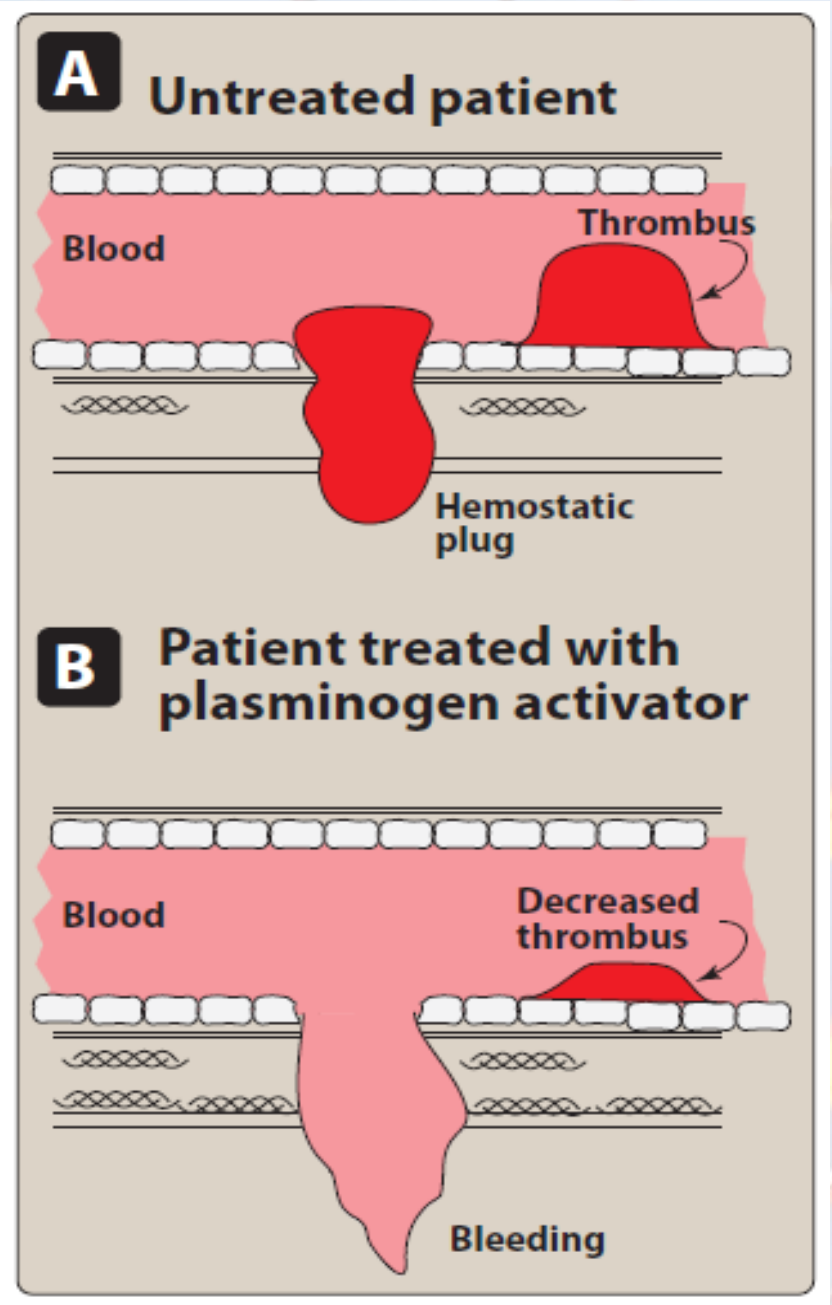
  Uses:
  - Acute stroke
  - Acute MI
  - Lysis of pulmonary emboli

Thrombolytic I

Therapeutic indications:

These drugs are contraindicated in pregnancy, and in patients with:

- ❑ **Healing wounds**
- ❑ **A history of CV-accident**
- ❑ **Brain tumor**
- ❑ **Head trauma**
- ❑ **Intracranial bleeding**
- ❑ **Metastatic cancer**



Good luck