AL MUSTAQBAL UNIVERSITY COLLEGE
DEPARTMENT OF PHARMACY
4TH STAGE
TOXICOLOGY

LAB. 7

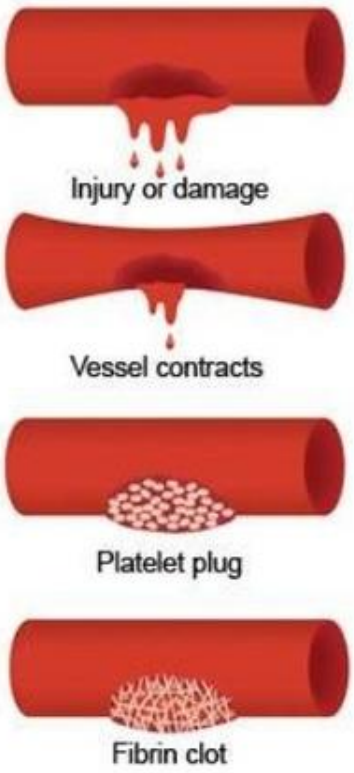
# BLOOD TOXICITY

QASSIM A ZIGAM

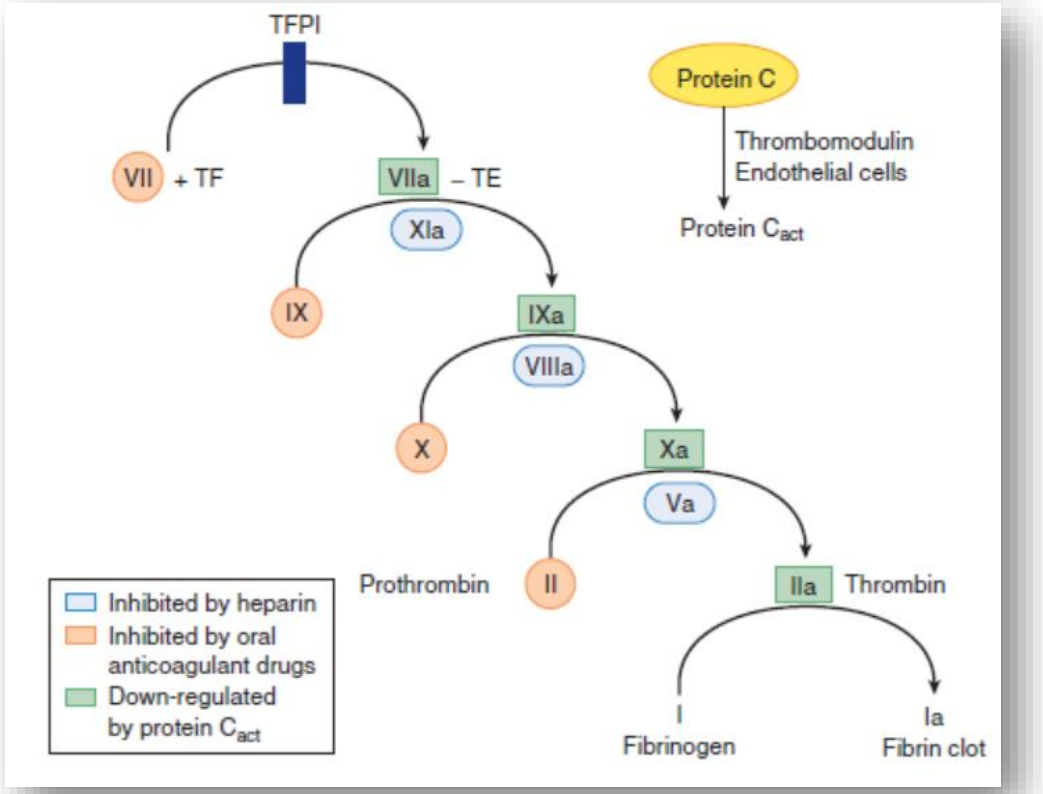
# Agents Used to Modulate Hemostasis

Patients with bleeding or thrombotic problems are commonly encountered in clinical practice.

A variety of agents are available to treat such patients, ranging from recombinant hemostatic proteins to chemical entities that modulate the activity of the coagulation system.



# Agents Used to Modulate Hemostasis




A model of the coagulation cascade

# Agents Used to Modulate Hemostasis

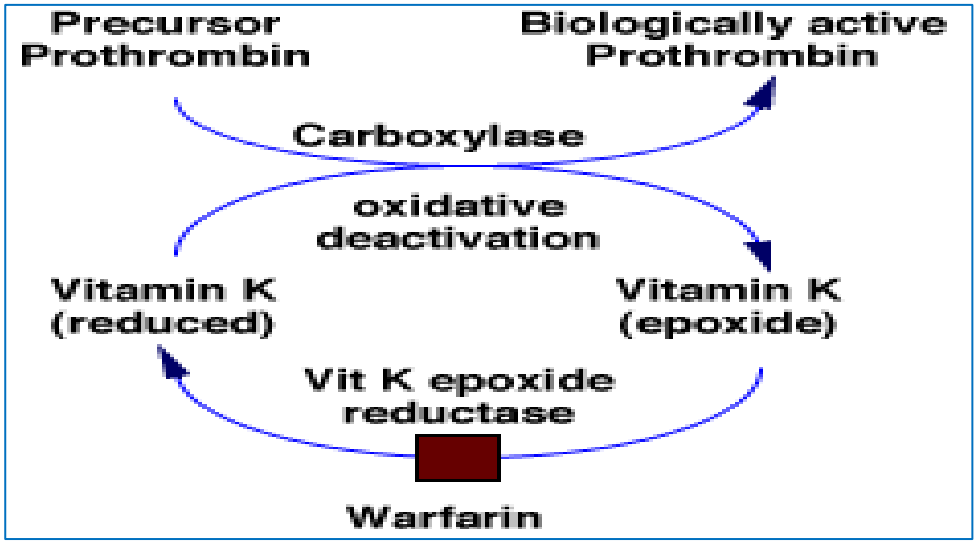
The use of some products has been associated with the development of disseminated intravascular coagulation and/or thrombosis in some patients.

These agents may include:

1. Oral Anticoagulants
2. Heparin
3. Fibrinolytic Drugs
4. Inhibitors of Fibrinolysis

# Oral Anticoagulants

Oral anticoagulants (warfarin) interfere with vitamin K metabolism by preventing the reduction of vitamin K epoxide, resulting in a functional deficiency of reduced vitamin K.



# Oral Anticoagulants

Oral Anticoagulants are widely used for prophylaxis and therapy of venous and arterial thrombosis.

The therapeutic window for oral anticoagulants is relatively narrow, and there is considerable interindividual variation in the response to a given dose.

Therefore these drugs must be routinely monitored to maximize both safety and efficacy.

# Oral Anticoagulants

The routine monitoring of oral anticoagulants performed with the PT, with results expressed in terms of the international normalized ratio (INR).

$$INR = \left\{ \frac{PT\ (pat)}{Pt\ (n)} \right\}^{ISI}$$

PT (pat)= Patient's prothrombin time
PT (n) = Normal reference range
ISI = International sensitivity index
(the optimal ISI is 1.3 to 1.5)

The patients with anticoagulant therapy the INR is maintained between 2 to 3.

# Oral Anticoagulants

A number of xenobiotics, including foods, have been found to affect the response to oral anticoagulants, perhaps the most common mechanism for interference with oral anticoagulants is mediated by:

1. Inhibition of CYP2C9.
2. Induction of CYP2C9, which tends to diminish the effect of warfarin by shortening its half-life.
3. Interference with absorption of warfarin from the gastrointestinal tract.

# Oral Anticoagulants

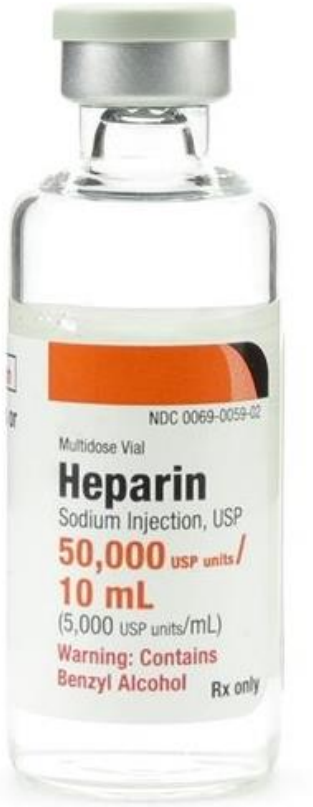
A number of xenobiotics, including foods, have been found to affect the response to oral anticoagulants, perhaps the most common mechanism for interference with oral anticoagulants is mediated by:

4. Displacement of warfarin from albumin in plasma, which temporarily increases the bioavailability of warfarin until equilibrium is reestablished.
1. Diminished vitamin K availability, due to either dietary deficiency or interference with the absorption of this lipid-soluble vitamin.
2. Inhibition of the reduction of vitamin K epoxide, which potentiates the effect of oral anticoagulants.

# Heparin

Heparin is a widely used anticoagulant for both prophylaxis and therapy of acute venous thromboembolism.

In many hospitals, the majority of patients are exposed to this potent anticoagulant at some point during their hospitalization.



# Heparin

Heparin may indicate in:

1. Treatment of DVT
2. Pulmonary embolism
3. Acute myocardial infarction
4. Heparin is used in combination with glycoprotein IIb/IIIa inhibitors during angioplasty and placement of coronary stents.

# Heparin

At low dose heparin inactivates factor Xa and inhibits prothrombin to thrombin conversion.

At high dose heparin inactivates factor IX, X, XI, and XII and inhibits fibrinogen to fibrin conversion.

# Heparin

The major complication associated with heparin therapy are:

1. Bleeding, a direct manifestation of its anticoagulant activity.
2. Heparin-induced thrombocytopenia (HIT).
3. Long-term administration of heparin is associated with an increased risk of clinically significant osteoporosis.

# Heparin

4. Transient rise in serum transaminases, suggesting significant liver dysfunction.
5. Severe allergic reactions, gastrointestinal disturbances, and hypotension.

The presence of over sulfated chondroitin Sulfate (OSCS), as heparin product contaminant, is believed to be responsible for the observed severe allergic reactions, gastrointestinal disturbances, and hypotension

# Fibrinolytic Drugs

Commonly used fibrinolytic agents include tenecteplase, reteplase, alteplase, streptokinase and urokinase.

Fibrinolytic drugs are used in the treatment of acute thromboembolic disease with the goal of dissolving the pathogenic thrombus.

Also used as an alternative to percutaneous coronary angioplasty in the emergency treatment of coronary artery thrombosis.

Each of these drugs works by converting plasminogen, an inactive zymogen, to plasmin, an active proteolytic enzyme.

# Fibrinolytic Drugs

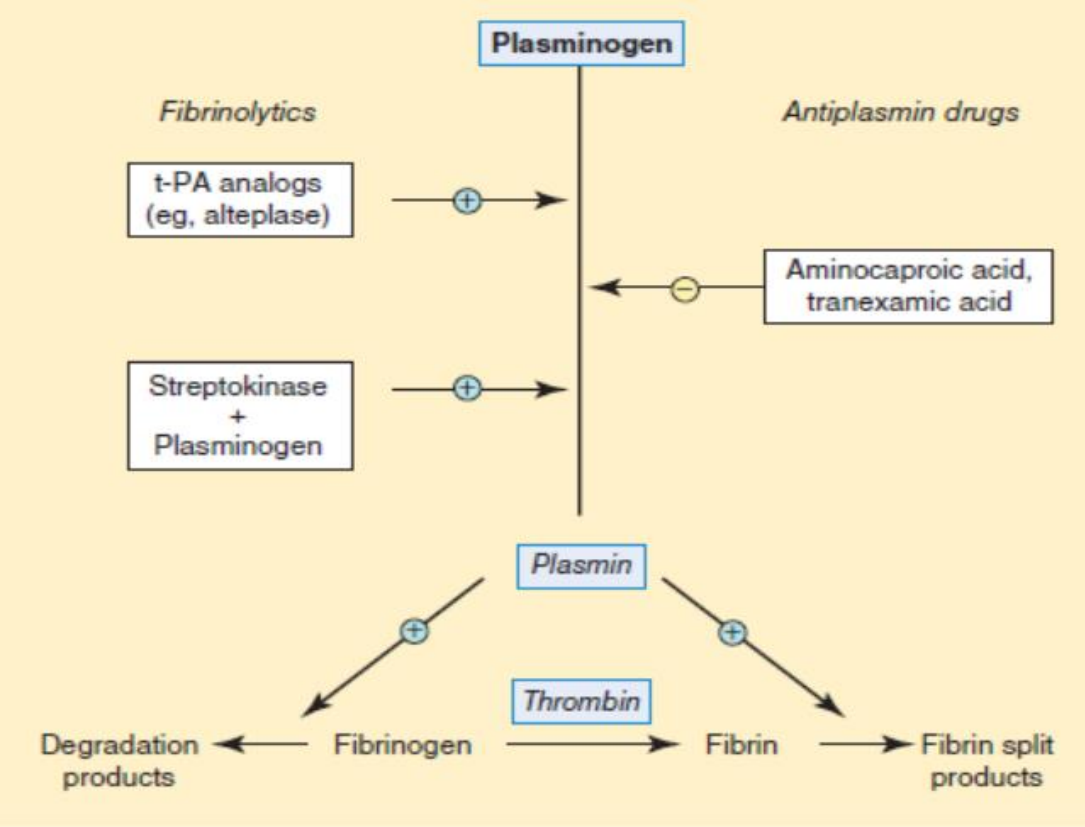
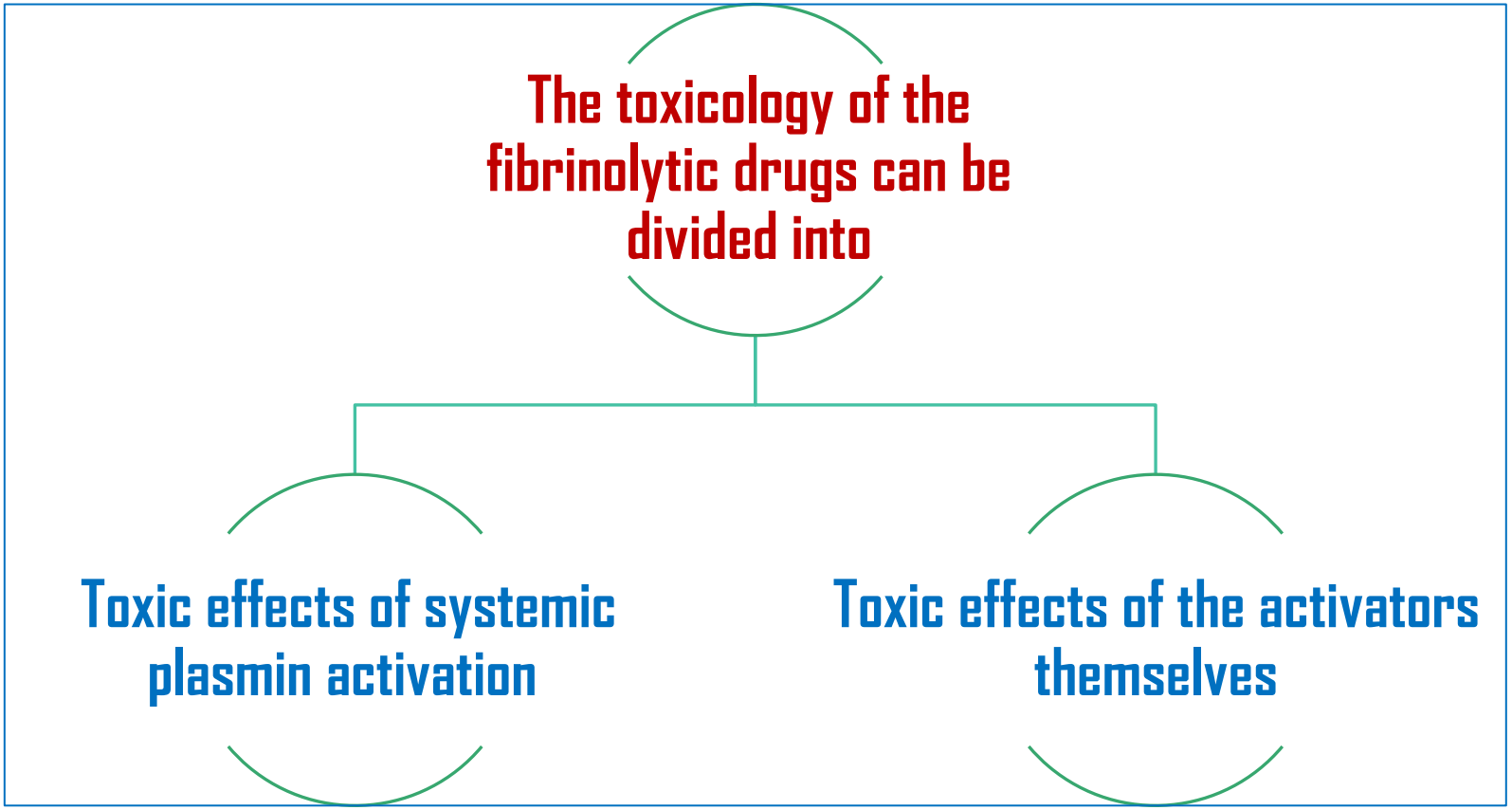



Diagram of the fibrinolytic system

# Fibrinolytic Drugs



# Fibrinolytic Drugs

Systemic fibrinolysis is associated with the development of a complex coagulopathy, leading to potentiate the risk of bleeding, recurrent thrombosis

Anatomic locations that are frequently involved in bleeding complications include the cerebral circulation and sites of recent vascular access.

As systemic plasmin can lyse physiologic as well as pathologic thrombi, reactivation of bleeding from sites of vascular access is not uncommon.

# Fibrinolytic Drugs

Streptokinase is a protein derived from group C β-hemolytic streptococci and is antigenic in humans.

Acute allergic reactions may occur in 1% to 5%, with minor symptoms such as hives and fever as well as major, life-threatening anaphylactic reactions.

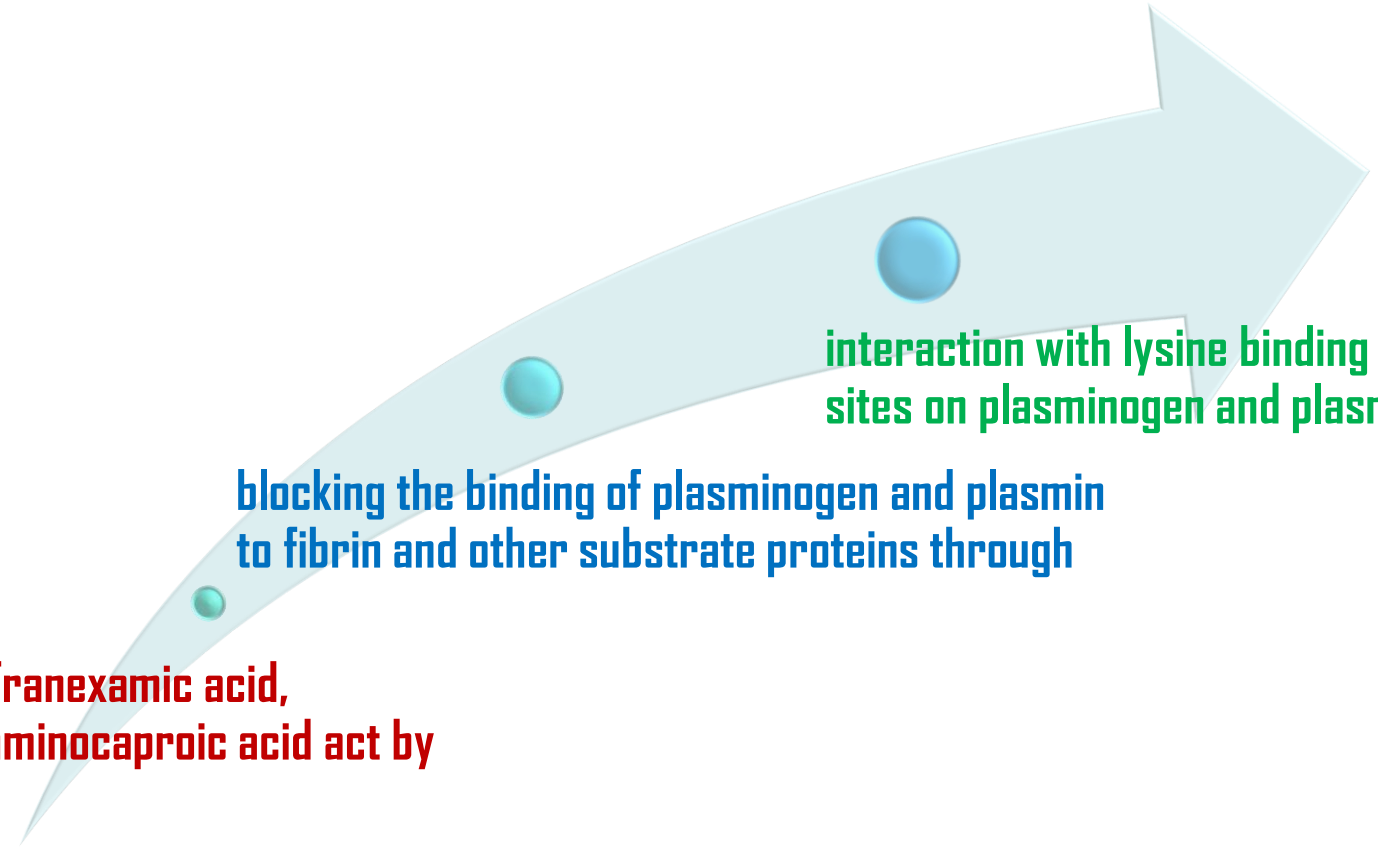
In addition, delayed hypersensitivity reactions associated with severe morbidity may occur

# Anti-fibrinolytics

Inhibitors of fibrinolysis are commonly used to control bleeding in patients with congenital abnormalities of hemostasis, such as von Willebrand disease.

Tranexamic acid, aminocaproic acid, and aprotinin are the main anti-fibrinolytics.

# Anti-fibrinolytics



# Anti-fibrinolytics

Aprotinin is a naturally occurring polypeptide inhibitor of serine proteases.

It is usually derived from bovine material and consequently is immunogenic when administered to humans.

Aprotinin is given by intravenous infusion, as it is inactive when given orally.

Allergic reactions in response to aprotinin have been reported, ranging from minor cutaneous manifestations to anaphylactic reactions

# Thank You
# For Your Attention