



Table 1. BLOOD CLOTTING FACTORS	
FACTOR	COMMON SYNONYMS
I	Fibrinogen
I'	Fibrin monomer
I''	Fibrin polymer
II	Prothrombin
III	Tissue thromboplastin
IV	Calcium, Ca <sup>2+</sup>
V	Labile factor
VII	Proconvertin
VIII	Antihemophilic globulin, AHG
IX	Christmas factor, PTC
X	Stuart factor
XI	Plasma thromboplastin antecedent, PTA
XII	Hageman factor
XIII	Fibrin-stabilizing factor
HMW-K	High-molecular-weight kininogen, Fitzgerald factor
Pre-K	Prekallikrein, Fletcher factor
Ka	Kallikrein
PL	Platelet phospholipid

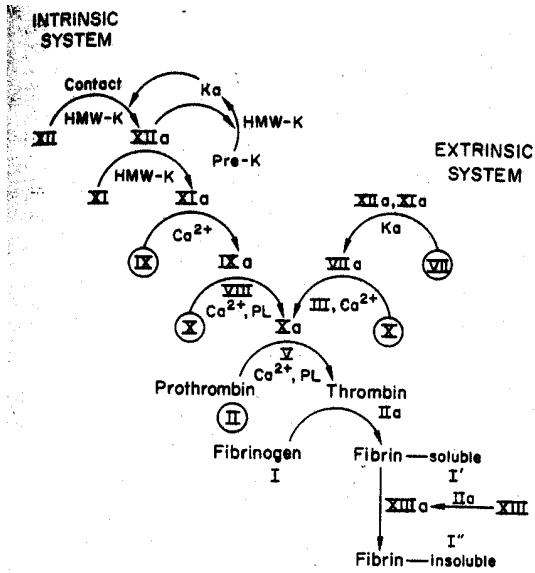


Figure 1. Intrinsic and extrinsic systems of blood coagulation.

## Thrombosis

- The formation of occluding blood clots in blood vessels.
- The leading cause of death in developed countries (e.g., myocardial infarction, stroke, pulmonary embolism).
- High incidence in patients over 40 especially after hip, knee and prostate surgery.
- In veins, red thrombi due to trapped red cells.
- In arteries, white thrombi with no trapped red cells.

Therapeutic aims of thrombosis:

- 1). prevent propagation if already present
- 2). prevent thrombus formation in high risk group
- 3). Lyse existing thrombi

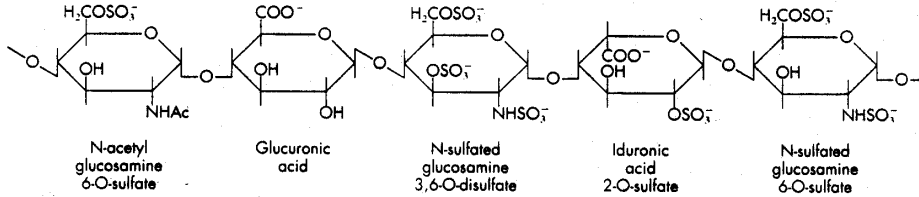
Anti-coagulation and anti-platelet therapy are directed towards aims 1 and 2.  
Thrombolytic therapy with plasminogen activators is directed towards aim 3.

Anticoagulants: 1). Heparin

2). Coumarins (oral anticoagulants)

**Heparin**

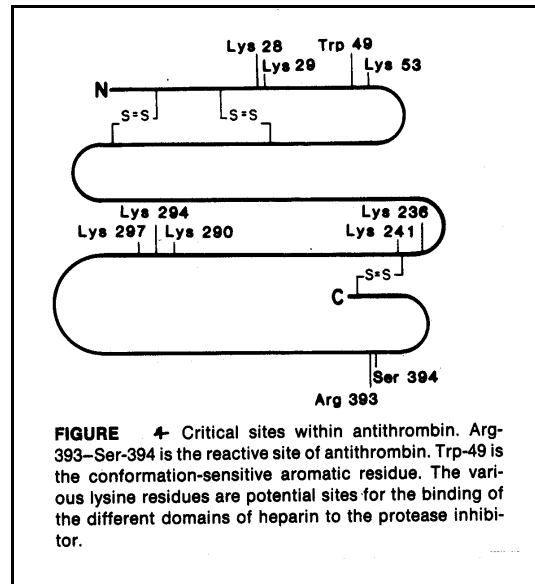
Heparin is a heterogeneous group of anionic mucopolysaccharide called glycosaminoglycans with molecular weight ranging from 3-100 kDa (average 15 kDa).



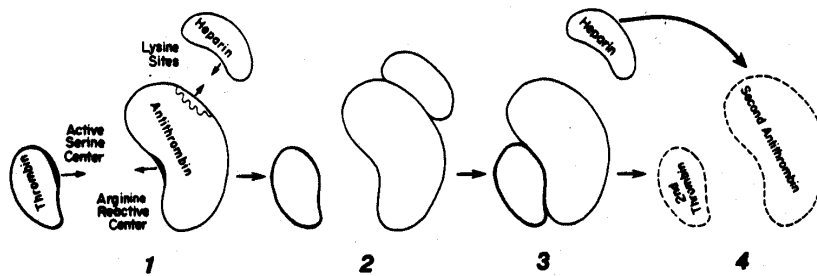
The antithrombin-binding structure of heparin.

Mode of action:

Once the coagulation pathways are activated, Factor IXa, Xa, XIa, XIIa, and thrombin need to be neutralized by anti-thrombin III (AT III). Heparin accelerates the interaction of the active clotting factors with AT III. The negatively charged heparin molecule binds to the positively charged lysine sites on AT III, causing a conformational change of AT III and exposing its reactive arginine site. The serine active sites of the active clotting factors bind to the reactive arginine site of AT III, and the complex is removed by the reticuloendothelial system.



**FIGURE 4** Critical sites within antithrombin. Arg-393-Ser-394 is the reactive site of antithrombin. Trp-49 is the conformation-sensitive aromatic residue. The various lysine residues are potential sites for the binding of the different domains of heparin to the protease inhibitor.



**FIGURE 3** The overall mechanism of action of heparin and antithrombin.

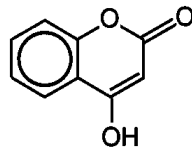
Absorption and clearance:

- Heparin is highly charged, crosses membranes poorly, given parenterally.
- low dose: subcutaneous or intrafat injection
- high dose: intravenous or subcutaneous injection, monitored by aPTT (2x increase)
- Heparin does not cross placenta, given during pregnancy.:
  
- taken up by the reticuloendothelial system, metabolized by the liver.
- Half-life (0.5 - 2.5 h) depends on dosage.
- Patients with high titre of active clotting factor require high dose given by continuous or intermittent injection.

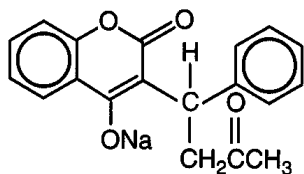
Side effect:

- Non toxic, mild allergic reaction may be encountered.
- Alopecia
- Osteoporosis upon prolonged use.
- Hemorrhage. Use protamine sulfate (a highly basic peptide) as antidote.
- Do not use with anti-platelet drugs.
- Heparin-induced thrombocytopenia. Monitored platelet counts and discontinue use if encountered. Incidence is lower with LMW heparin.
- Thrombotic complications - venous thromboembolism and arterial thrombosis. Heparin binds to platelet factor 4 released by platelets. IgG antibodies against the heparin-platelet factor 4 complex activates platelets to aggregate through Fc receptors.

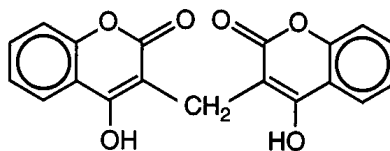
### Oral Anticoagulants (coumarins)



4-Hydroxycoumarin



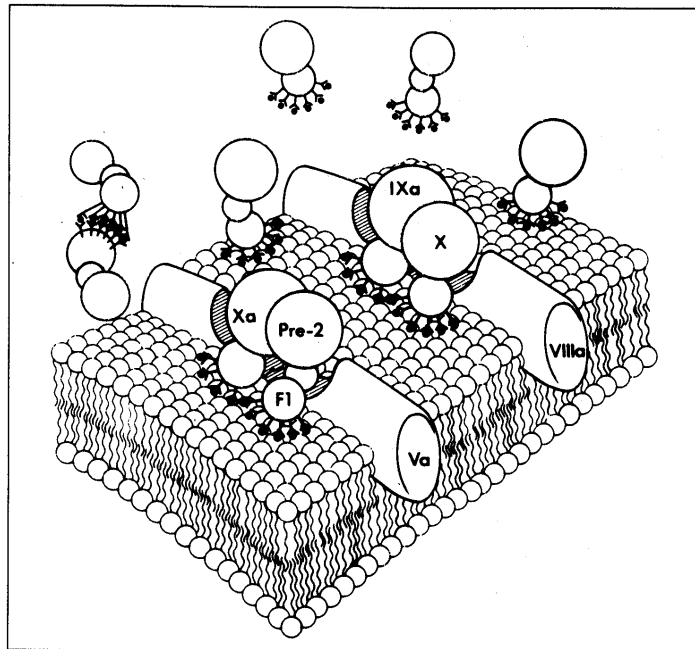
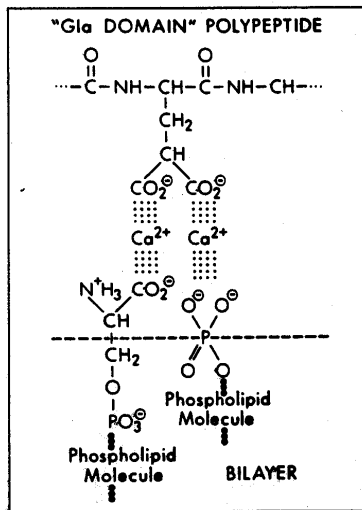
Warfarin Sodium



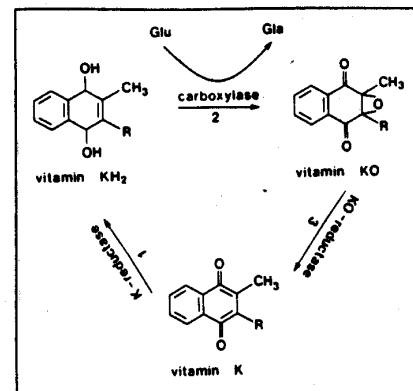
Dicumarol

Mode of action:

Several coagulation factors (Factor II, VII, IX and X) and two anti-clotting proteins in blood (protein C and S) contain  $\gamma$ -carboxylglutamic acid (Gla) which is formed by post-translational modification of glutamic acid (Glu) involving a vitamin K-dependent reaction. The Gla residues on these clotting factors interact with  $\text{Ca}^{2+}$  to promote the formation of coagulation complexes on phospholipid (PL) surfaces. Activated platelets provide the PL surfaces in the form of microparticles (see handout on platelet lecture). As a result, the activation of Factor X by Factor IXa in the presence of  $\text{Ca}^{2+}$ , PL and Factor VIII, and the activation of prothrombin to thrombin by Factor X in the presence of  $\text{Ca}^{2+}$ , PL and Factor V are greatly accelerated.



Vitamin K exists in two forms, the reduced  $\text{KH}_2$  and the oxidized  $\text{KO}$  forms.  $\text{KH}_2$  is the active coenzyme for modification of Glu to Gla in the clotting factors, and  $\text{KH}_2$  is converted to  $\text{KO}$  in this reaction. The reductases responsible for the reduction of  $\text{KO}$  back to  $\text{KH}_2$  are inhibited by coumarins, thus trapping the vitamin K in the inactive  $\text{KO}$  form. Newly synthesized clotting factors will be undercarboxylated.



Absorption and clearance:

- Given orally.
- Warfarin sodium is rapidly and completely absorbed. Peak concentration in plasma is reached within 1 h of ingestion. Food decreases the rate but not extent of adsorption.
- After drug ingestion, there is a lag phase depending on the turnover of existing clotting factors in blood.
- In plasma, 99% is bound to albumin. Only the free form is active. Drugs (e.g., phenylbutazone) that compete with warfarin binding to proteins are dangerous because a transient increase of free warfarin may occur.
- Warfarin is metabolized by the liver with an average half life of 36 h, but there are large variations among individuals.

#### Side effects

- Uricosuria
- Increased SGOT and LDH enzymes in blood
- Anorexia
- Nausea
- Decrease in osteocalcin (also a vitamin K-dependent protein)
- Most serious side effect is hemorrhage - treated with vitamin K and plasma infusion.
- Usually not given with anti-platelet drugs, except with dipyridamole to prevent thromboembolism in patients with prosthetic heart valves.