Anti coagulant toxicity

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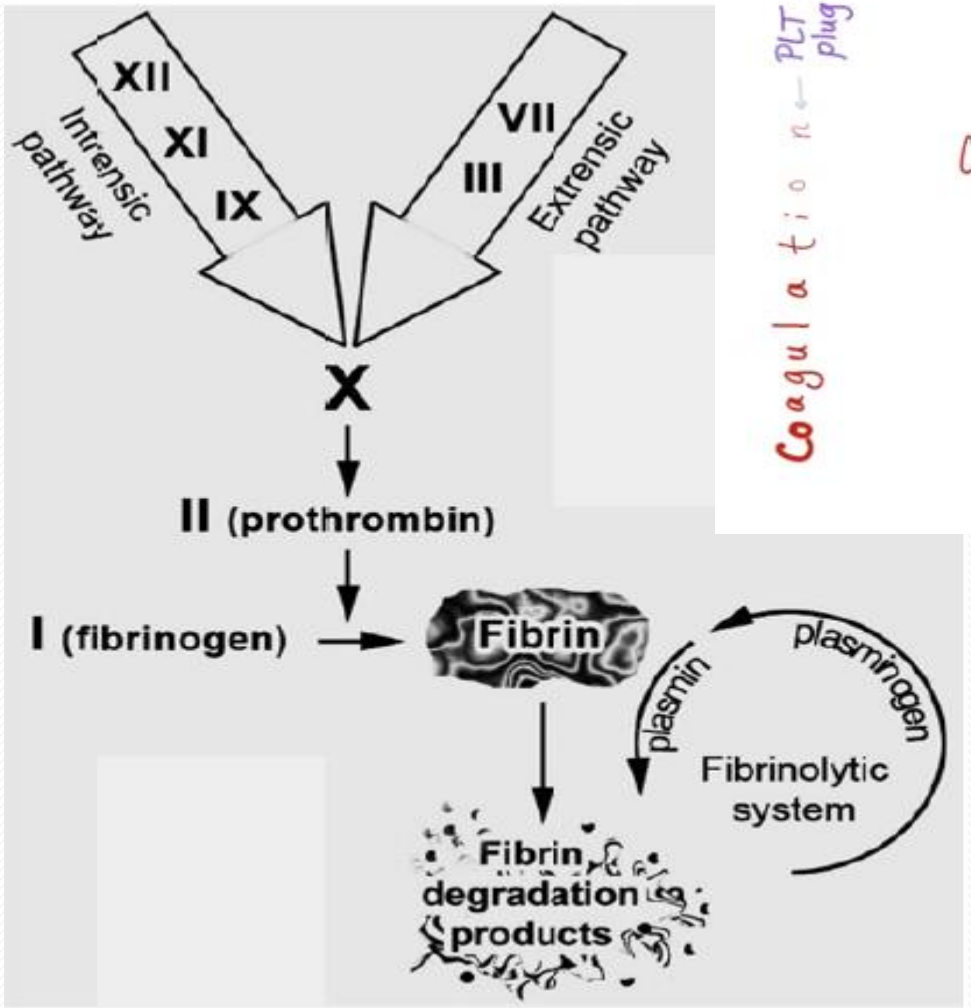
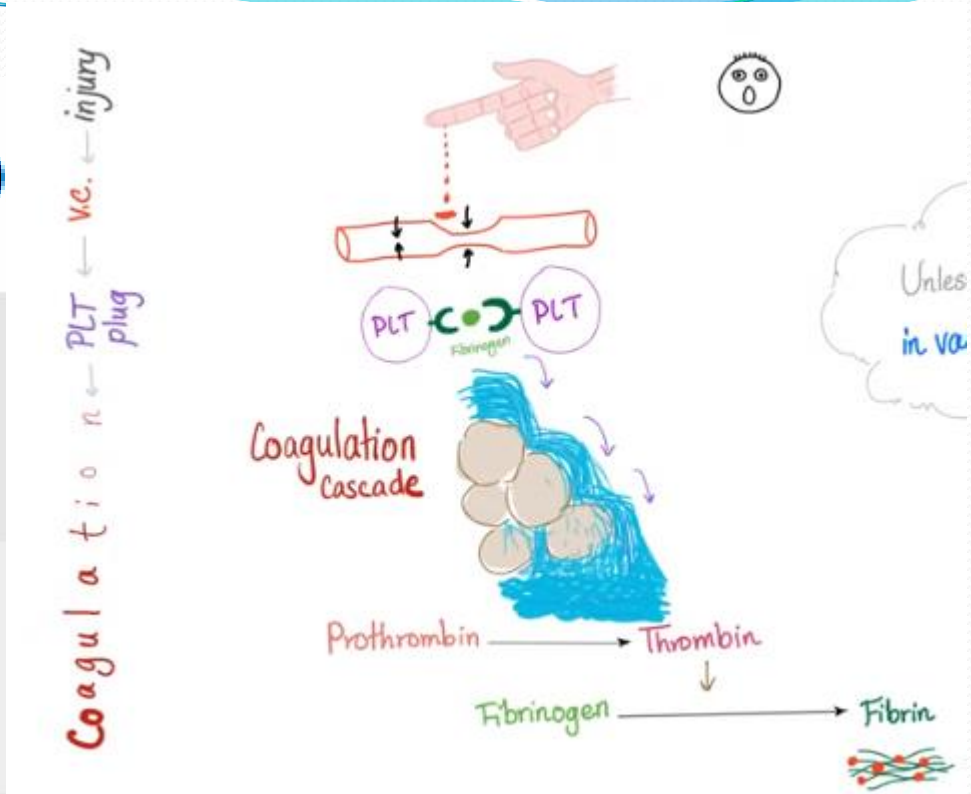
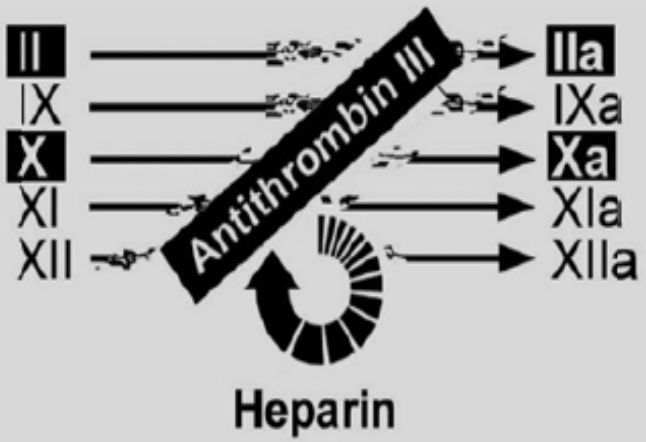


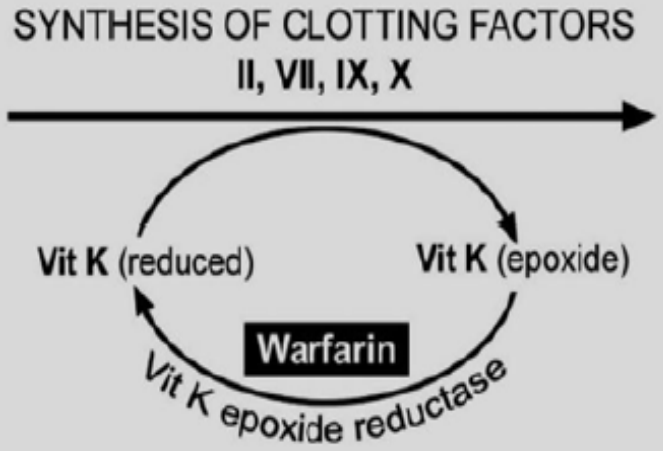


Anticoagulant

	Heparin	Warfarin (Oral anticoagulant)
Source & chemistry	Natural sulfated polysaccharide present in mast cells & carries **–ve** charge Commercial preparations are de-rived from bovine lung or porcine intestinal extracts	Synthetic cuomarin compound
Absorption **Distribtion**	▪ **No** because it precipitates by gastric HCl. ▪ Can**not** cross BBB or placenta.	▪ **Good** (bioavailability is 100%). ▪ Can cross BBB and placenta.

Mechanism of action		
	▪ Its action depends on the presence of a natural clotting inhibitor called heparin cofactor **(antithrombin III)** in plasma. ▪ Small quantities of heparin can activate antithrombin III leading to inhibition of several clotting factors especially factor X & thrombin (factor II).	▪ Warfarin inhibits **vitamin K epoxide reductase enzyme** in the **liver** leading to inhibition of formation of the active form of vitamin K → ↓ synthesis of vitamin K-dependent clotting factors **(II, VII, IX,** and **X)**. ▪ The action of warfarin could be antagonized by vitamin K.





Therapeutic uses	▪ **Treatment of established thrombosis:** heparin is given parenteral 5000-10,000 U **i.v.** then 5000 U **s.c.**/8h to maintain blood coagulation 2-3 times as normal and prevent further extension of the thrombus. ▪ **Prevention of thrombosis:** 5000 U **s.c.**/8-12 hrs.	Warfarin is given oral 2-10 mg/day for **prevention and treatment of:** – Deep vein thrombosis **(DVT)** – Postoperative thrombosis. – Cerebral venous thrombosis. – Coronary thrombosis: treatment continued for several years. – Acute arterial & pulmonary **embolism**: anticoagulation is initiated by heparin and maintained by warfarin. – **AF** and **artificial** heart valves

Monitor-ing of therapy	By **activated partial thrombo-plastin time (APTT).** It must be kept 2-3 times as the normal value.	By **prothrombin time (PT) or International Normalized Ratio (INR).** It is the ratio of the PT in the patient to that of normal person. It must be kept 2-3 times as the normal value.

Adverse effects

- **Bleeding is the most common and dangerous SE** (e.g. hematuria & major organ bleeding). It could be treated by the following:

(a) Immediate stopping of the drug.

(b) Fresh frozen plasma (FFP): to provide fresh clotting factors.

(c) Protamine sulfate (Protam):

- Protamine carries **+ve** charge that combines with heparin (carries **-ve** charge) to form stable complex.
- **1 mg** of protamine can bind to **100 U** of heparin.

(c) Vitamin K_1: 10 mg slowly i.v. or i.m. to enhance synthesis of clotting factors.

	▪ **Hematoma** if given **IM** (so, contraindicated to give it IM). ▪ **Thrombocytopenia:** immune-mediated reaction due to formation of antibodies that can bind to platelets. Platelet count should be performed regularly ▪ **Osteoporosis** and spontaneous fractures on long-term therapy ▪ **Alopecia and dermatitis:** rare and transient.	▪ **Hemorrhagic skin necrosis**: when starting warfarin, biosynthesis of protein C is reduced leading to temporary procoagulant state. This can lead to hemorrhagic infarction of skin, breast, intestine and fatty tissue. normally avoided by concurent heparin administration. ▪ **Teratogenicity:** abnormal bone formation in early pregnancy *(fetal warfarin syndrome).* ▪ **CNS Hemorrhage** in the fetus if given in late pregnancy. ▪ **Sudden withdrawal** may lead to thrombotic catastrophes.

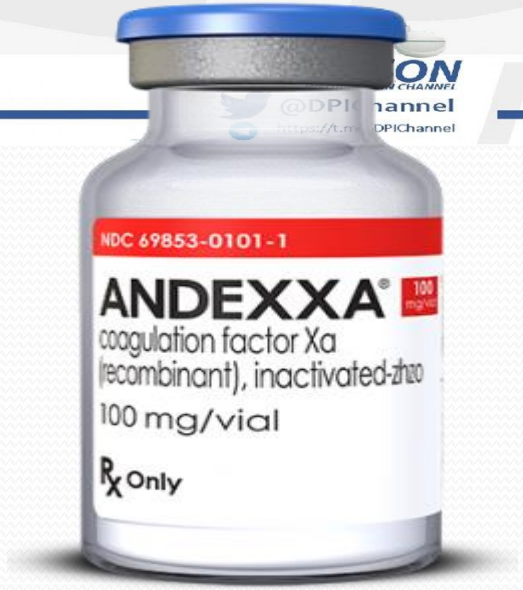
	Unfractionated heparin	LMWH
Molecular weight range	Wide (ranges from 3000 to 30,000 Da)	Less than 8000 Da
Anti-factor Xa activity	Less specific	More specific
Non-specific binding to vascular endothelium and plasma proteins	High	Low
Bioavailability after s.c. injection	Low *(due to binding to s.c. tissue)*	High
Half-life	Short (given 3 times/d)	Long (given once/d)
Thrombocytopenia	Common (10%)	Less common (<2%)
Risk of bleeding	High	Low
Lab monitoring	APTT (Essential)	Anti-factor Xa levels (May be unnecessary)

Novel anticoagulants

- **Factors x inhibitors** :
- **Fondaparinux** :selective inhibitors of factor Xa given by s.c injection once daily.
- **Rivaroxaban (xarelto) , apixaban(Eliquis):** selective inhibitors of factor Xa given by oral route

Andexxa—An Antidote for Apixaban and Rivaroxaban

May 7, 2018 — The U.S. Food and Drug Administration (FDA) has approved Portola Pharmaceuticals' Andexxa, the first factor Xa inhibitor antidote indicated for patients treated with rivaroxaban (Xarelto) and apixaban (Eliquis), when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.



Direct thrombin(factor 2) inhibitors

- **Argatroban** :direct thrombin inhibitors ,it can be used as alternative to heparin to treat patient with HIT. gevin by i.v route

- Dabigatran (pradaxa) given by oral route
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Idarucizumab (Praxbind®)

- Therapeutic Class
  - Monoclonal Antibody; Antidote
- FDA Indications and Uses
  - Reversal of the anticoagulant effects of dabigatran for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding

Praxbind®. [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2015.