Coagulation Disorder

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Coagulation disorders

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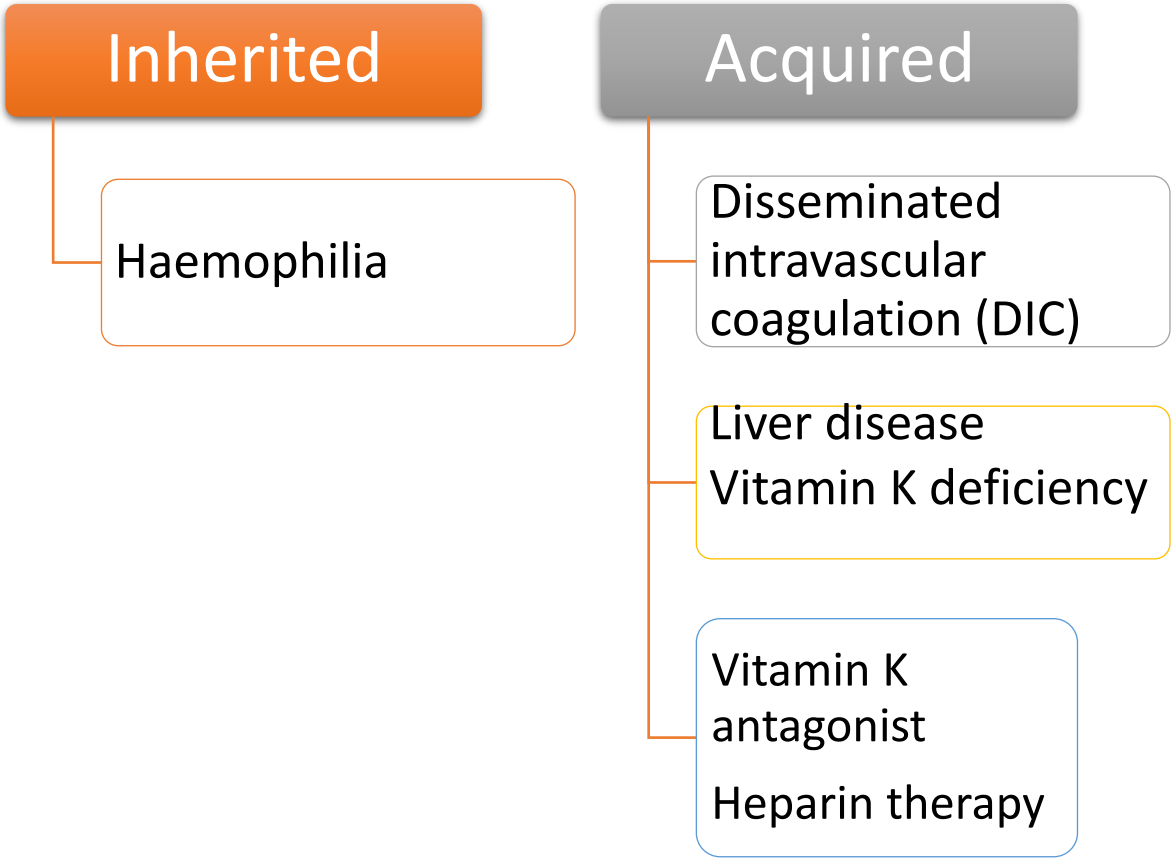


Inherited coagulation disorders

Hemophillia

Hemophilia is an inherited bleeding disorder in which there is a deficiency or lack of factor VIII (hemophilia A) or factor IX (hemophilia B)

Haemophilia

Hemophilia A is an X-linked, recessive disorder caused by deficiency of functional plasma clotting factor VIII (FVIII), which may be inherited or arise from spontaneous mutation

Type	Inheritance	Cause	Frequency
Hemophilia A	X linked recessive	Factor VIII	80%
Hemophilia B	X linked recessive	Factor IX	15%

Diagnosis of Haemophilia

- Normal factor VIII or IX level = 50-150%
- Family history
- Symptoms (bruising, bleeding with circumcision, muscle, joint, or soft tissue bleeding)
- Hemostatic challenges (surgery, dental work, trauma, accidents,)
- Laboratory testing

Grading	Clotting factor level	Clinical features
Severe(60% of hemophilia)	< 1 IU/dL or <1% of normal	Spontaneous bleeding
Moderate (15%)	1-5 IU/dL or 1-5% of normal	Occasional spontaneous bleeding and prolonged bleeding after trauma or surgery
Mild (25%)	5-40 IU/dL or 5-40% of normal	Bleeding after major trauma or surgery

Laboratory findings in hemophilia

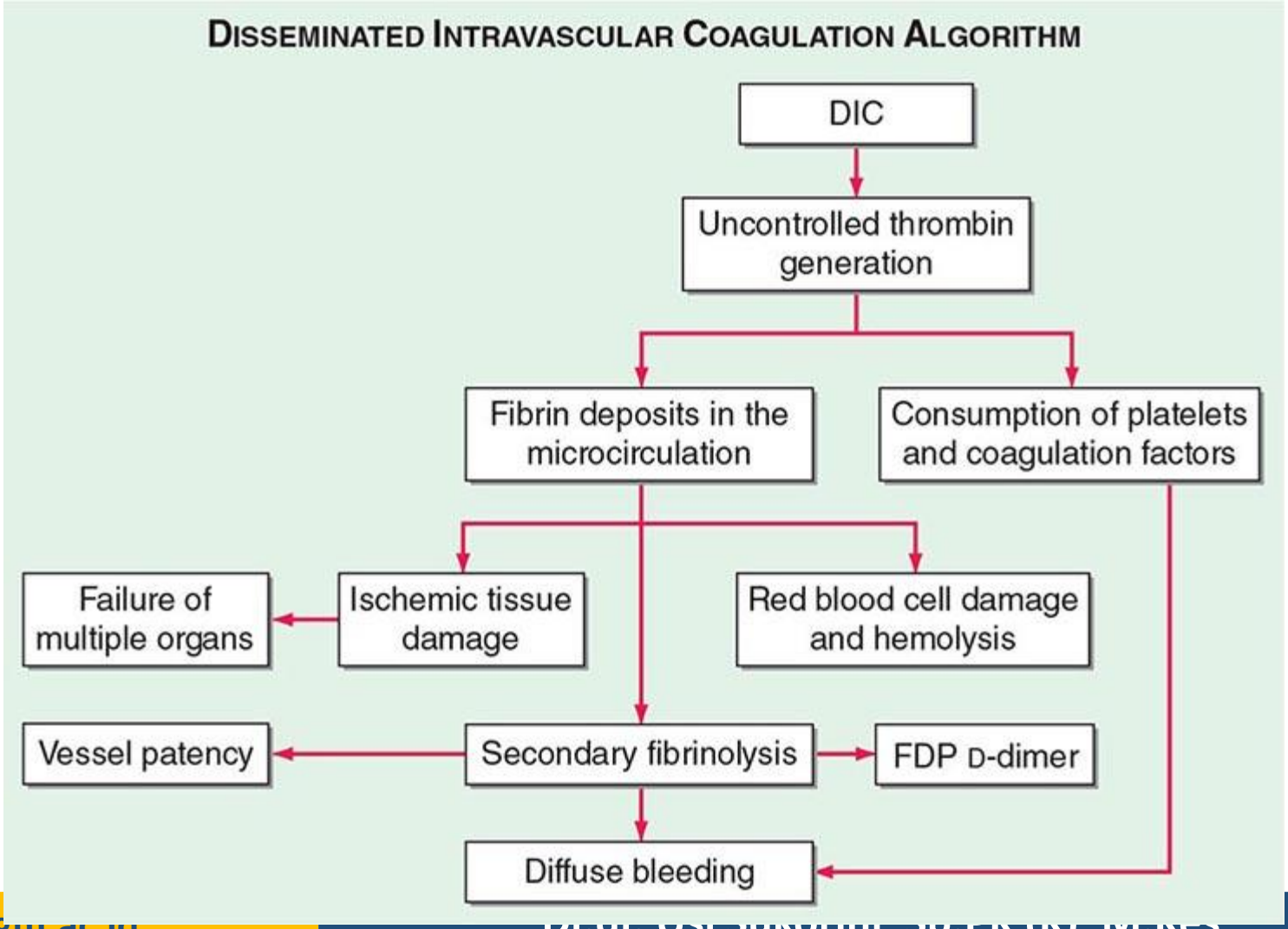
- Platelet count: normal
- Bleeding time: normal
- **Prolongation APTT**
- Normal PT

INHIBITOR to factor VIII ? → Inhibitor screening test

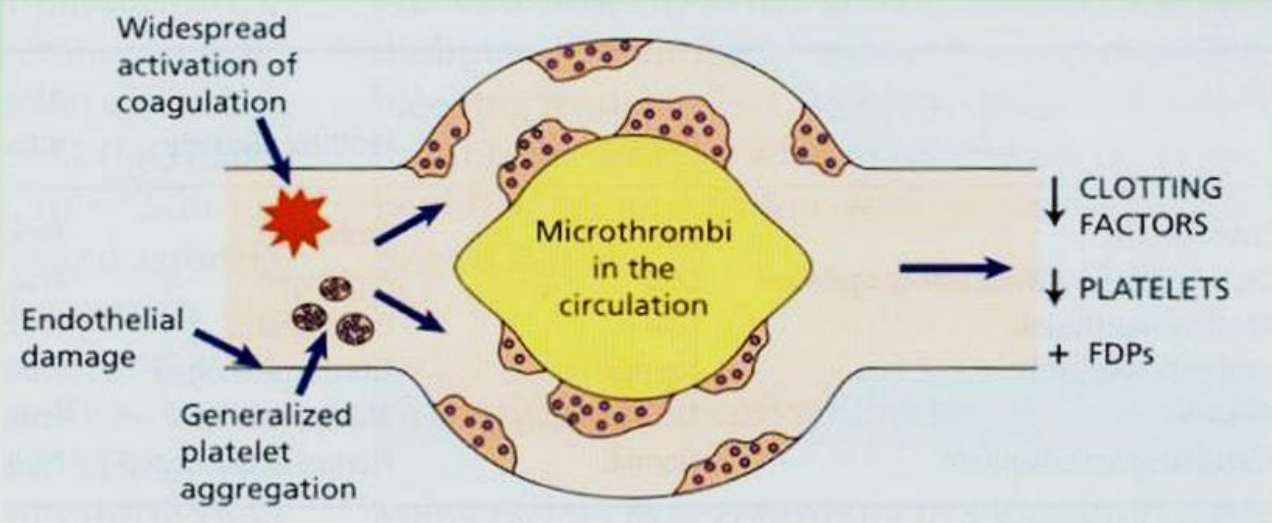
DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- DIC triggered by the entry of **procoagulant** material into circulation
- Initiated by **widespread endothelial damaged** and collagen exposure
- Widespresd intravascular **platelet aggregation**
- **Increased thrombin generation**
- **Depression** of physiologic **anticoagulation** mechanism
- Delayed removal of fibrin due to **impaired fibrinolysis**

Pathophysiology of DIC



Pathogenesis of DIC



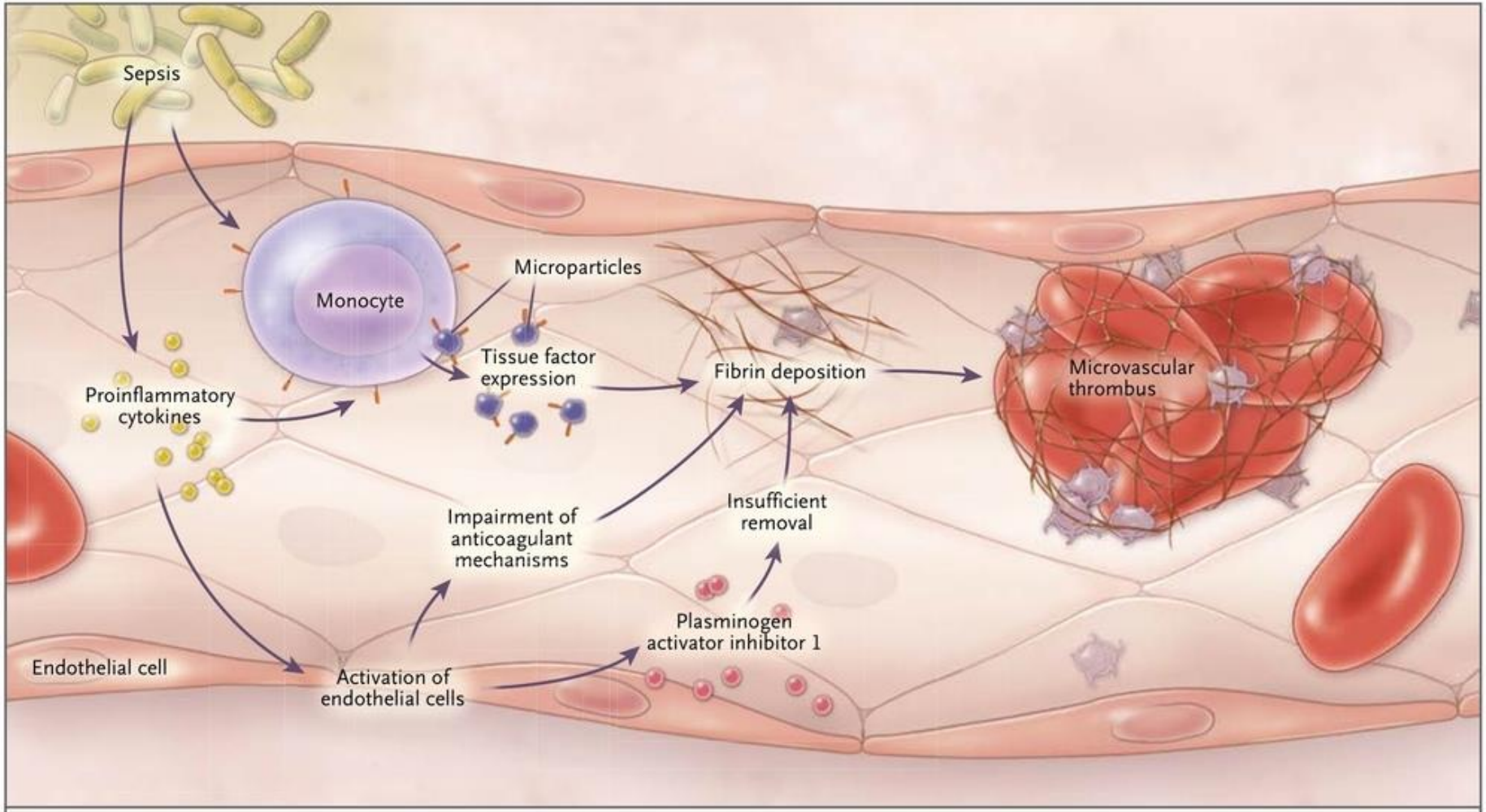
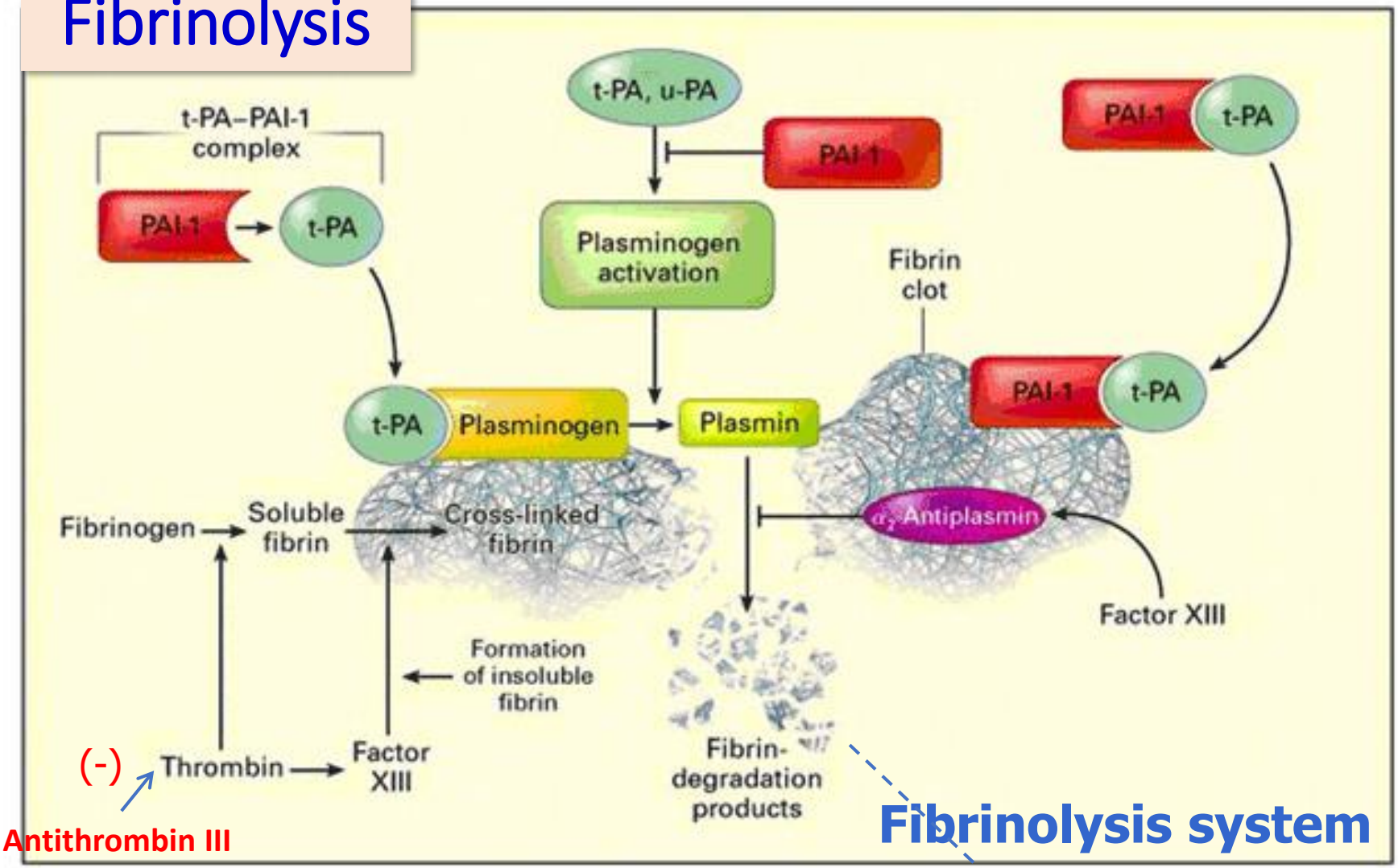


Figure 2. Pathogenesis of Disseminated Intravascular Coagulation in Sepsis.

Through the generation of proinflammatory cytokines and the activation of monocytes, bacteria cause the up-regulation of tissue factor as well as the release of microparticles expressing tissue factor, thus leading to the activation of coagulation. Proinflammatory cytokines also cause the activation of endothelial cells, a process that impairs anticoagulant mechanisms and down-regulates fibrinolysis by generating increased amounts of plasminogen activator inhibitor.

Fibrinolysis

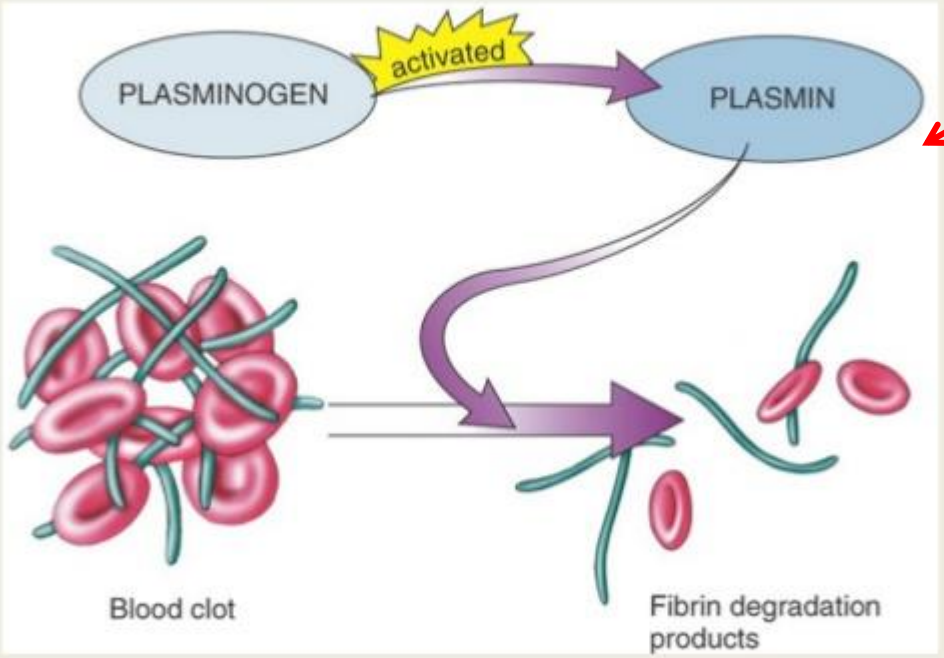


- t-PA = tissue plasminogen activator
- PAI-1 = plasminogen activator inhibitor tipe 1

D-dimer
(fibrin cross-linked degradation product)

Fibrinolysis: Clot Breakdown

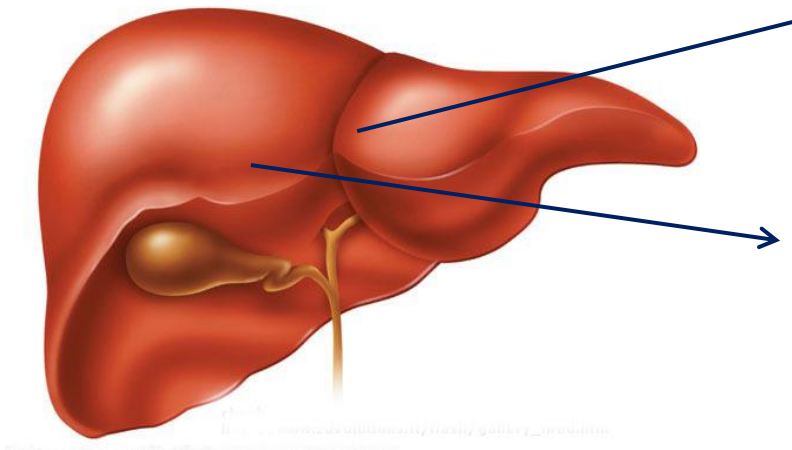
antiplasmin



Laboratory findings in DIC

- Low level of platelet count
- Prolongation of bleeding time
- Prolongation of PT and APTT
- Decreased of fibrinogen
- High level of D-dimer

Liver disease



- The liver is the principal site of synthesis of pro-coagulant, fibrinolytic, and coagulation inhibitory proteins

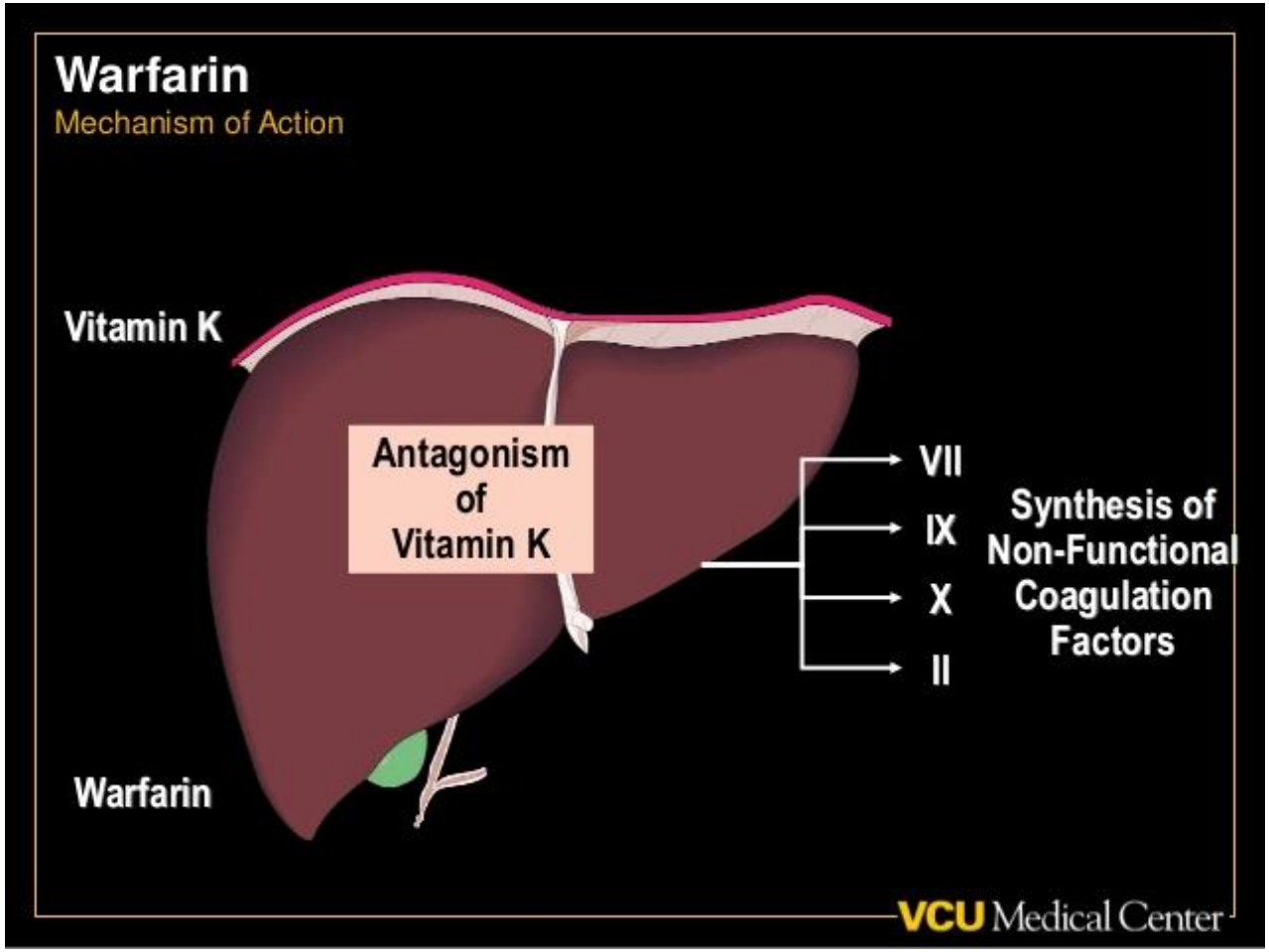
- **Liver disease** →

  1. Decreased synthesis of coagulation, fibrinolysis and inhibitory proteins
  2. Impaired clearance of activated haemostatic components

Lab. findings in liver disease

- Early prolongation of PT
- Decreased synthesis of vitamin K dependent proteins → decrease of F. II, VII, IX, X → PT and APTT >>
- Decrease synthesis almost all coagulation factor
- Decreased clearance of activated clotting factors
- Increased fibrinolysis due to decreased antiplasmin
- Dysfibrinogenemia due to synthesis of abnormal fibrinogen
- Increased fibrin split products
- Decreased platelets (hypersplenism)

VITAMIN K DEFICIENCY



VITAMIN K DEFICIENCY

Synthesis of protein vitamin K dependent:

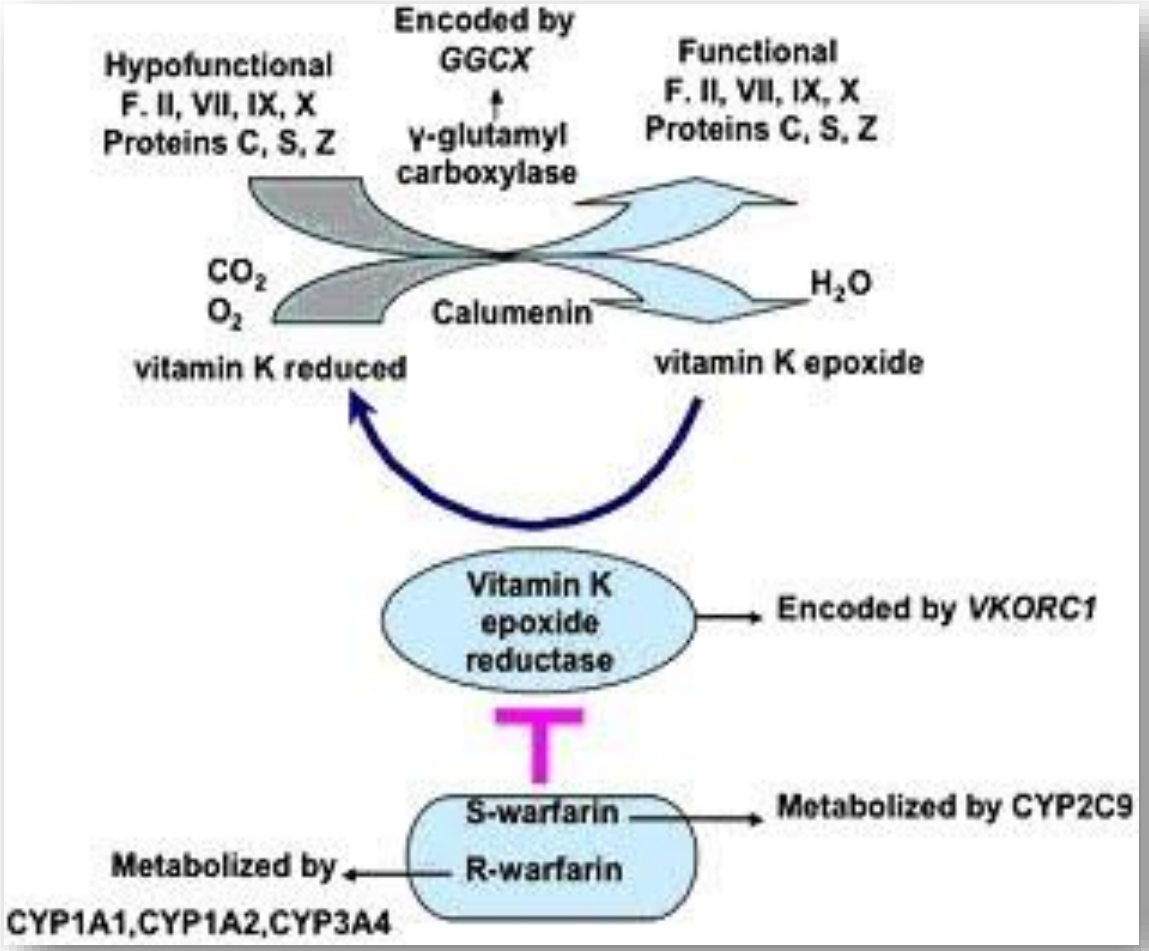
For coagulation factors (II, VII, IX, and X) to become active they have to bind Calcium. This is preceded by carboxylation which is mediated by Vitamin K

- Calcium can only bind after gamma carboxylation of specific glutamic acid residu in proteins

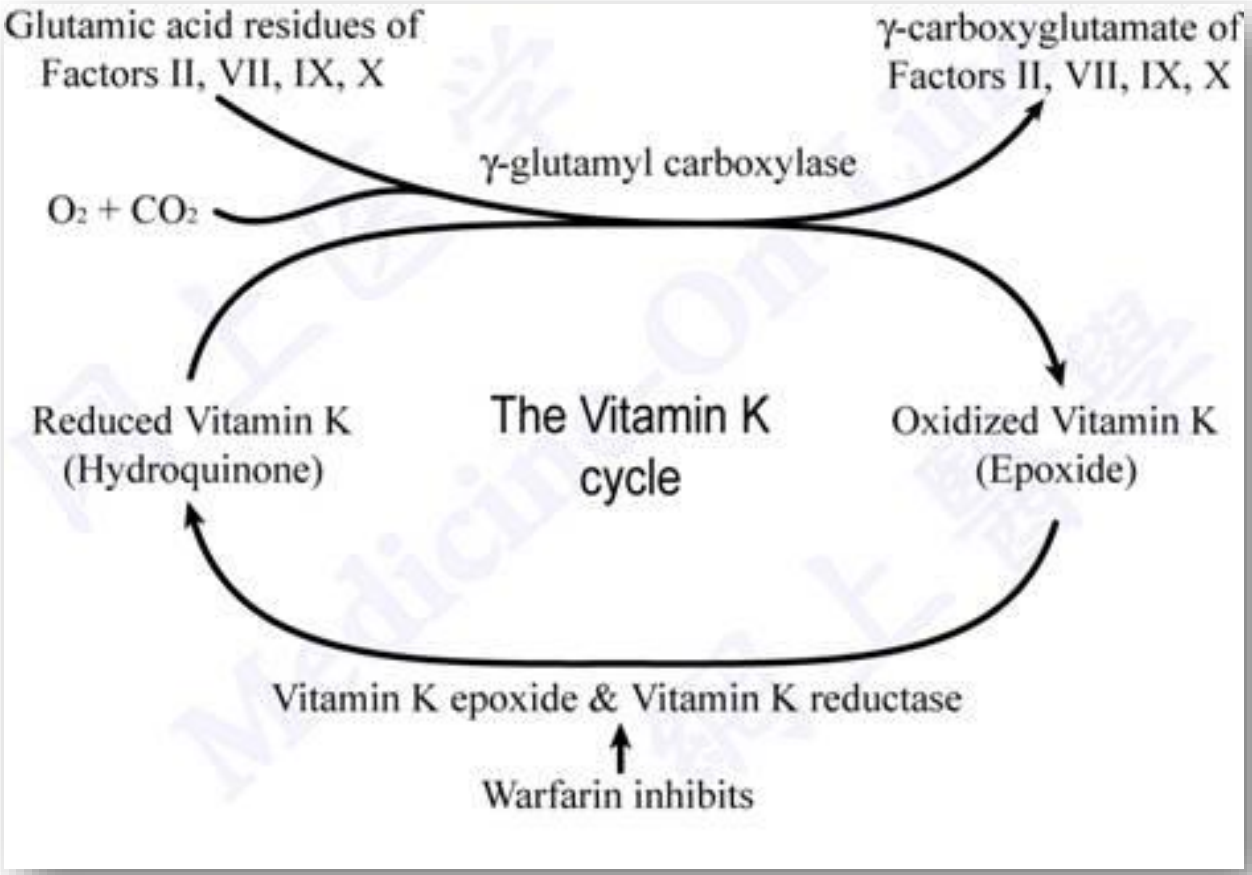
Vitamin K:

- Is fat soluble vitamin, stored in the liver in small amounts so can be depleted in 2-3 days
- Patients with **depleted vitamin K** or on **K antagonists** **cannot carboxylate** these coagulation factors.

Gamma carboxylation of protein plasma by vitamin K



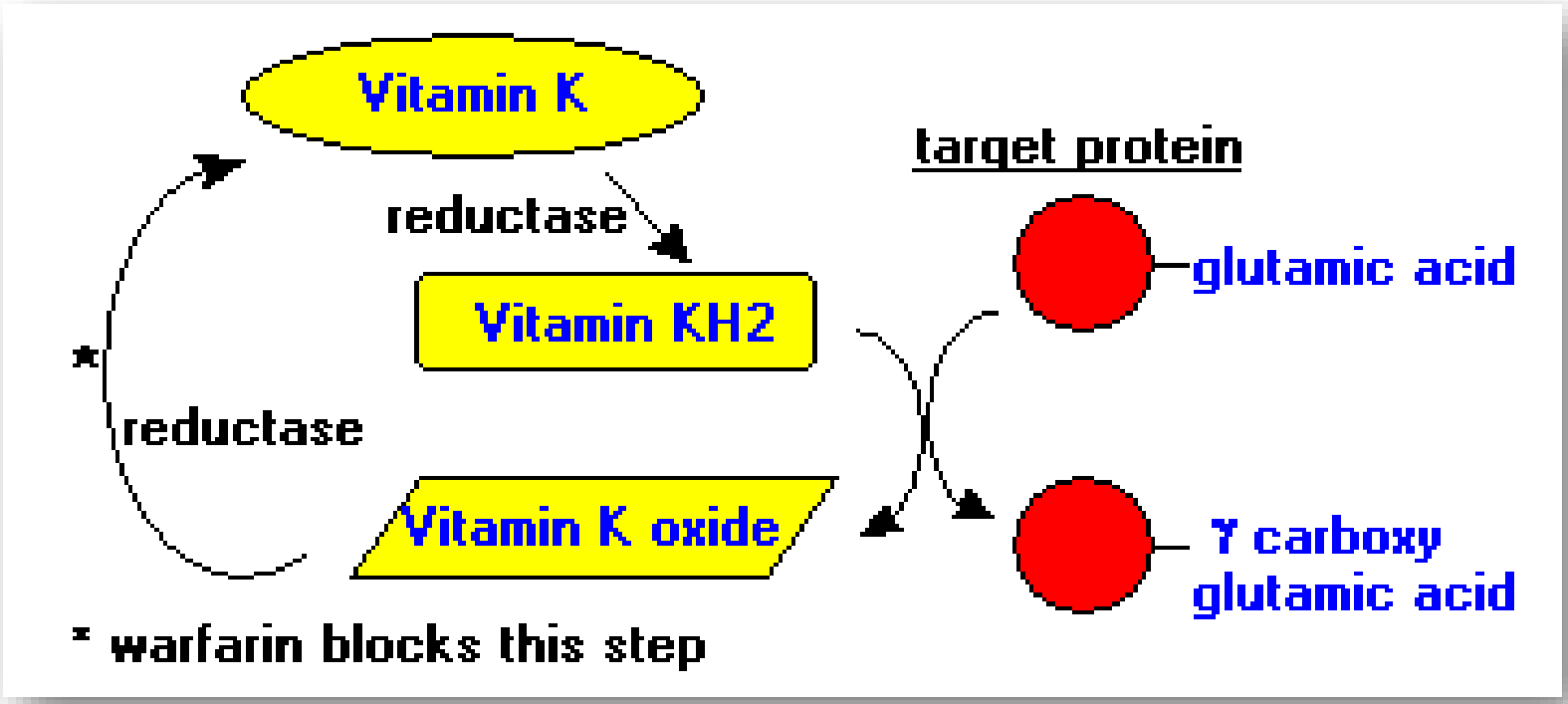
Gamma carboxylation of protein plasma by vitamin K



Vitamin K deficiency → haemorrhagic disease of the Newborn (HDN)

- Early-onset vitamin K deficiency bleeding usually occurs during first 24 hours after birth
- Late-onset vitamin K deficiency bleeding in the newborn
- PT and APTT → >>
- Platelet count: N
- Levels of protein induced by vitamin K antagonism (PIVKA II) are increased

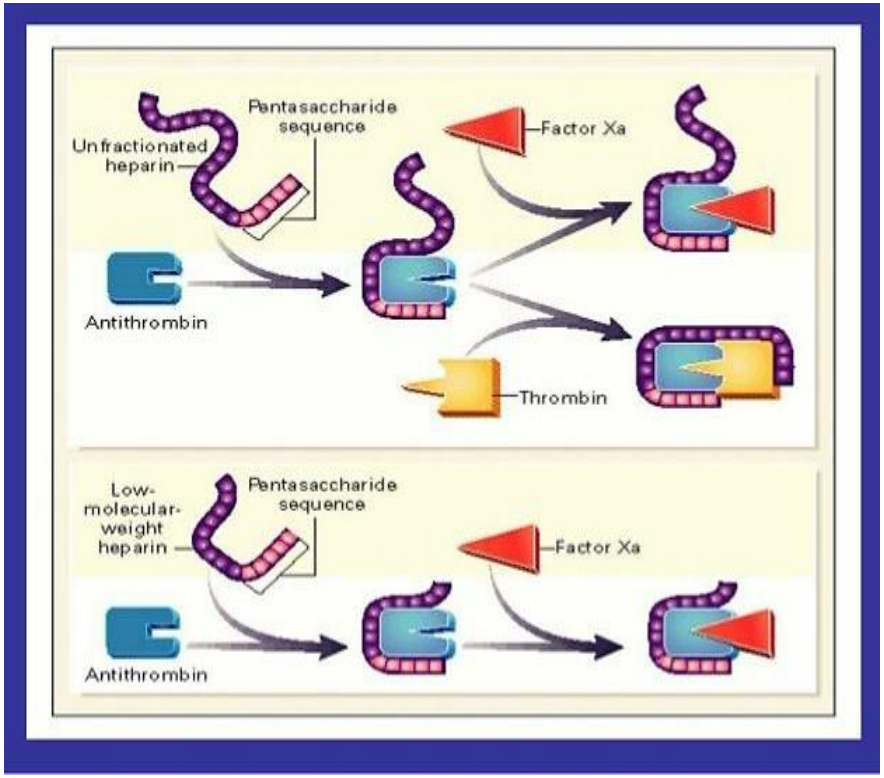
Vitamin K antagonist

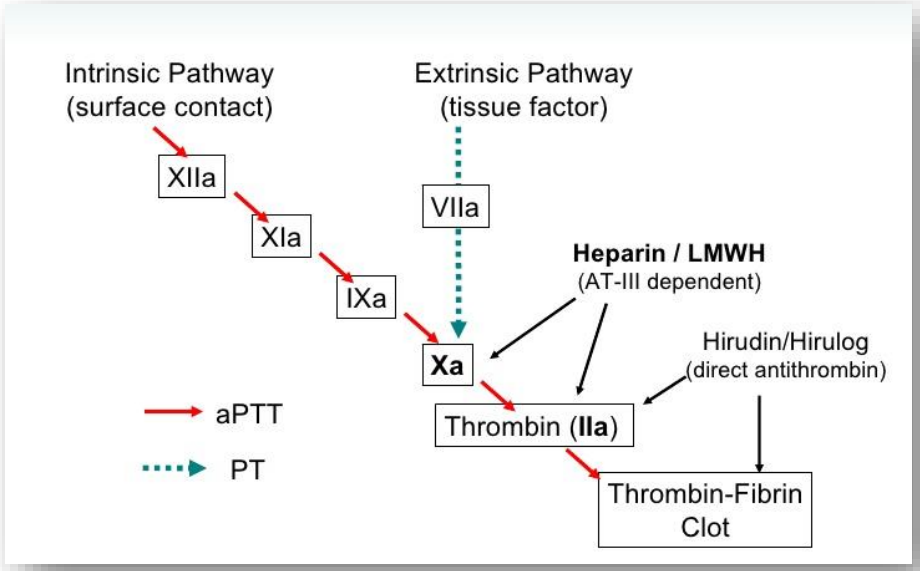


Vitamin K antagonist

- Anamnesis
- History
- Bleeding
- Laboratory findings:
  - Prolongation of **PT** and APTT
  - Therapy monitoring: **INR**

Heparin therapy





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Disadvantages of Using aPTT to Monitor Heparin

- aPTT has variable a response to heparin determined by the different coagulometers and the reagents
  - There is no aPTT "standard"
  - When the tissue thromboplastin lot changes, a new therapeutic range needs to be established for the new lot of reagent
- Test may be affected by numerous factors other than heparin concentration
  - Baseline elevated aPTT makes titration difficult and inaccurate

Eikelboom JW. Thromb Haemost 2006;96:547-52.
Francis JL. Pharmacotherapy 2004;24:108S-19S.

Proposed → Antifactor Xa assay → ?

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THANK YOU

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