Coagulation, bleeding and thrombosis part I

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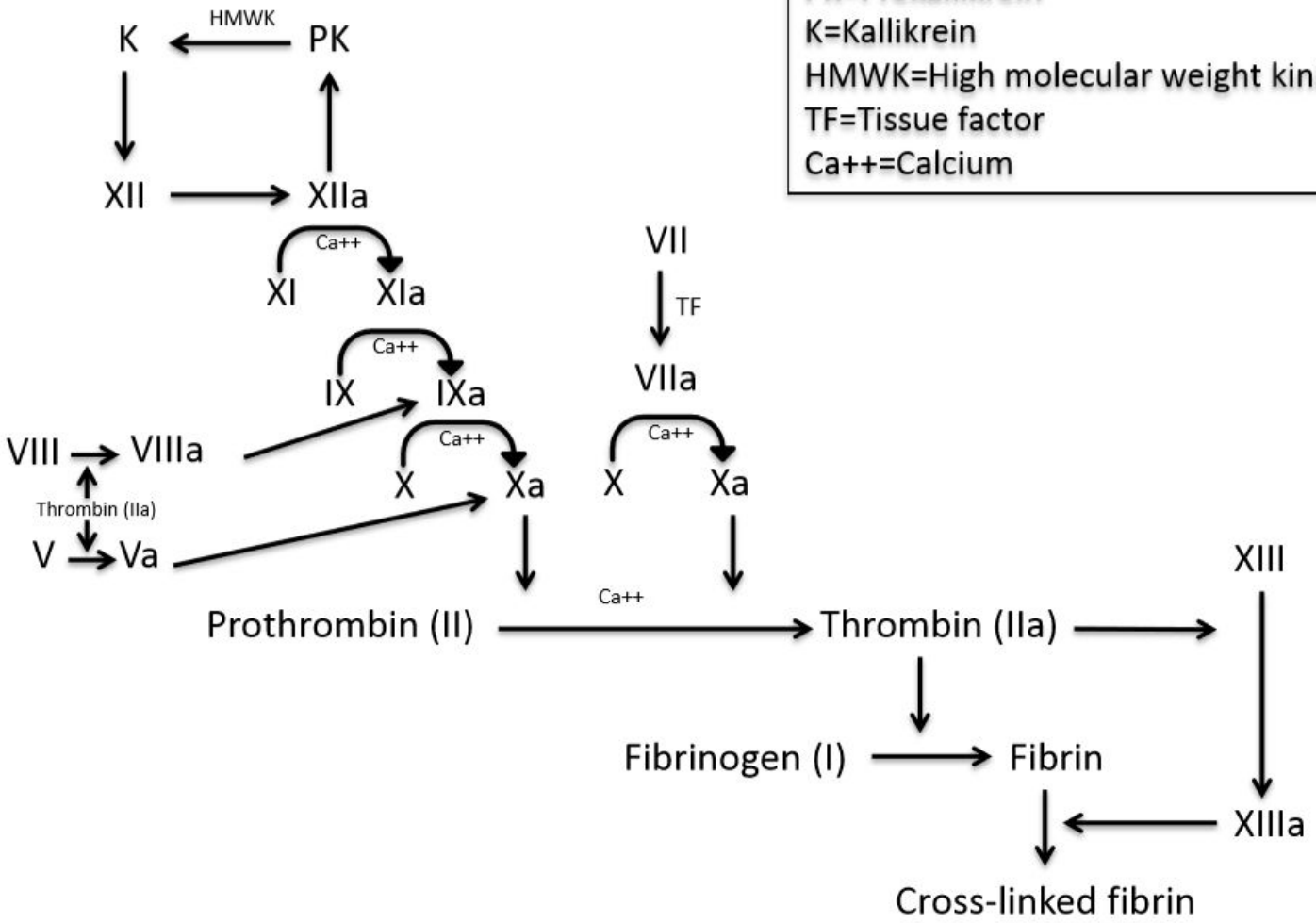
Primary Hemostasis

- Subendothelium
- Platelets
- Platelets

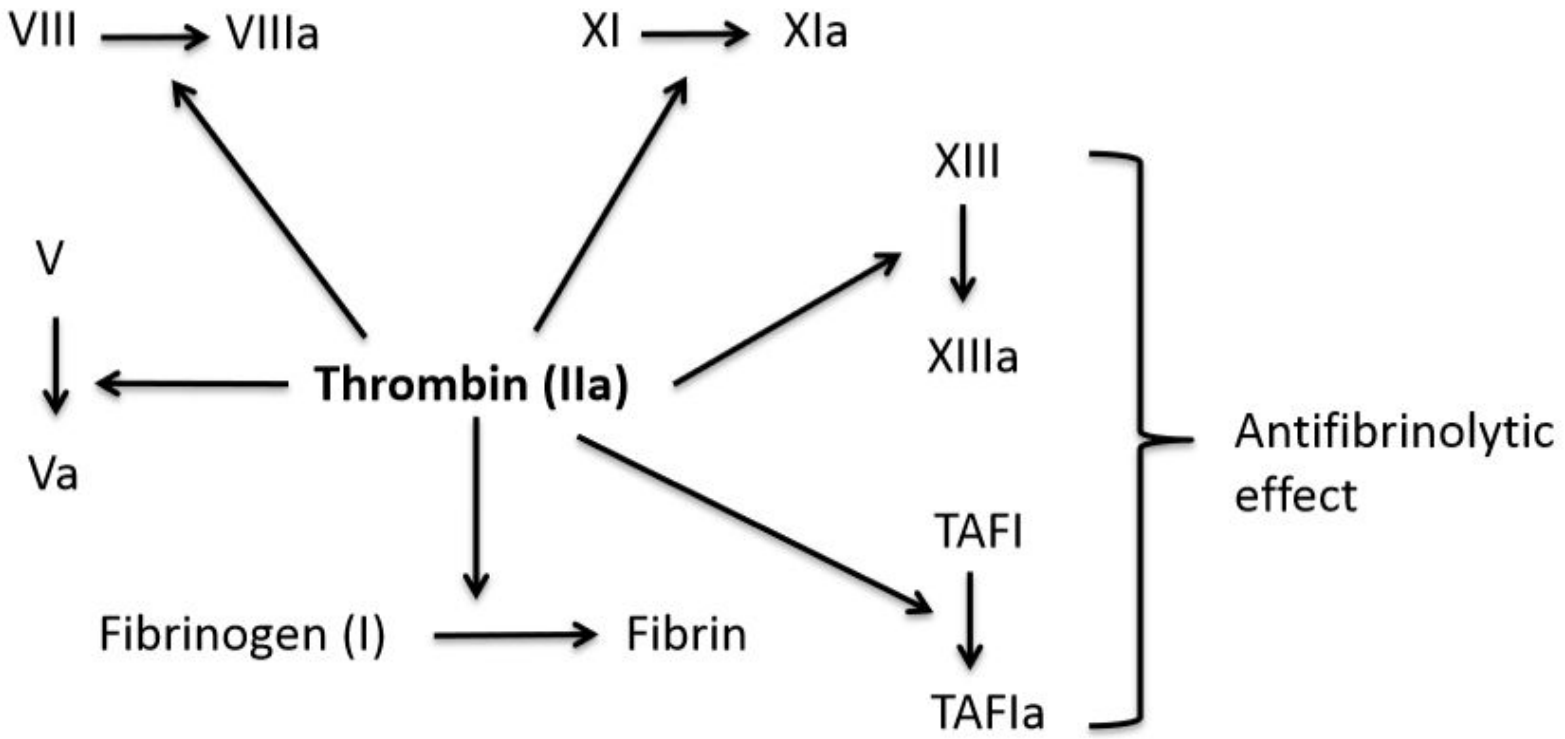
Factor	Site of synthesis	Levels in infancy	Half-life	Vitamin K-dependent	Other
Fibrinogen (I)	Liver	Normal	2-4 d	No	High fibrinogen increases ESR
Prothrombin (II)	Liver	Low	3 d	Yes	
Factor V	Liver Megakaryocytes	Low	36 hr	No	
Factor VII	Liver	Low	3-6 hr	Yes	
Factor VIII	Liver Endothelial Cells	Normal/ High	8-12 hr	No	Circulates with VWF Increased by DDAVP
Factor IX	Liver	Low	22 hr	Yes	
Factor X	Liver	Low	40 hr	Yes	
Factor XI	Liver	Low	80 hr	No	
Factor XIII	Liver/Macrophage	Low	10 d	No	Important in wound healing
VWF	Endothelial cells Megakaryocytes	Normal/ High	12 hr	No	Stored in Weibel-Palade bodies in endothelial cells

Classical Coagulation Cascade

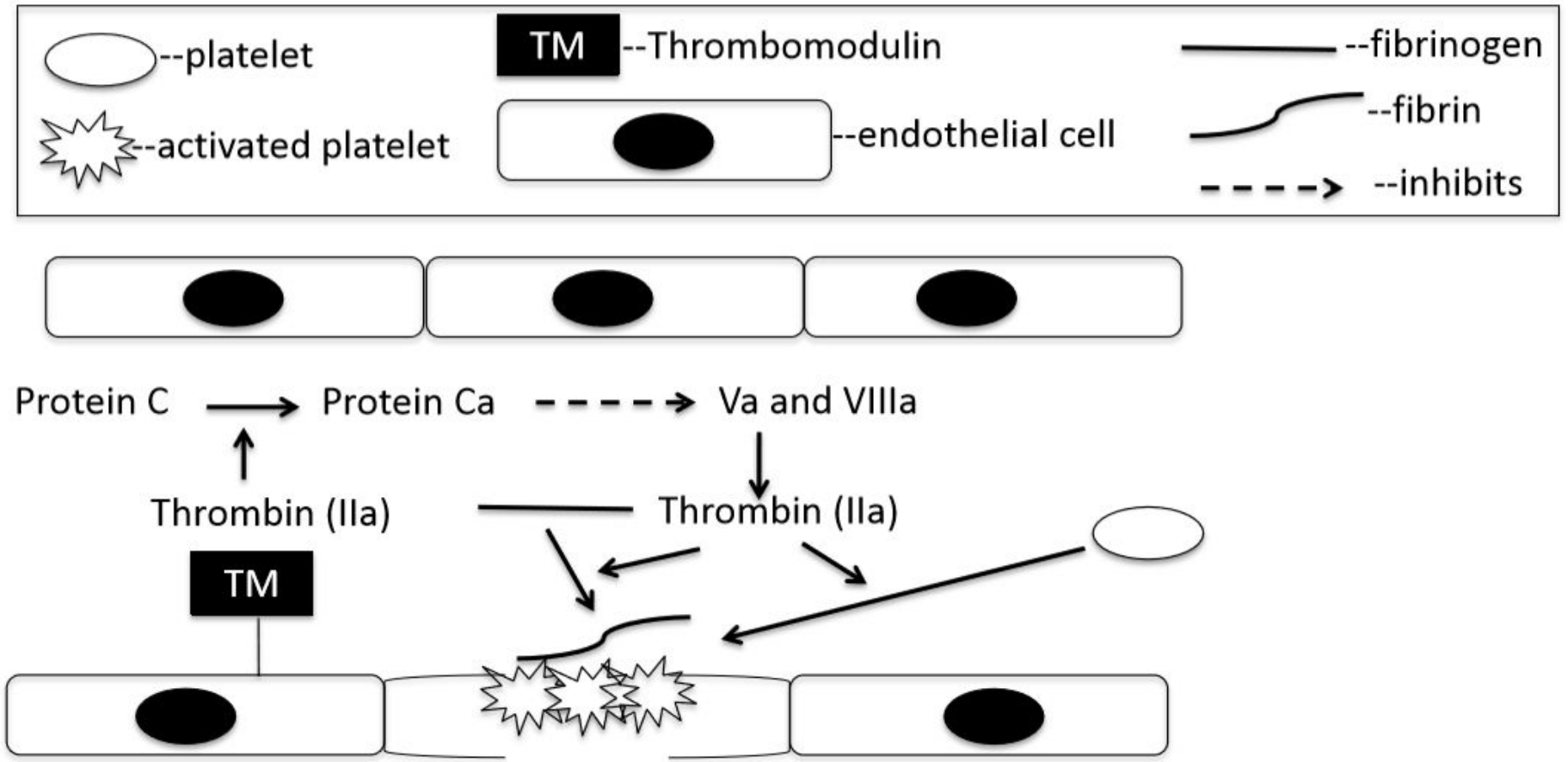
PK=Prekallikrein
K=Kallikrein
HMWK=High molecular weight kininogen
TF=Tissue factor
Ca++=Calcium



Thrombin's procoagulant/antifibrinolytic effects on coagulation factors



Thrombin's interaction with platelets and endothelial cells



Fibrinogen

Is an acute phase reactant

An elevated fibrinogen causes an elevated ESR

Tests for deficiency of fibrinogen – PT, PTT and TT are prolonged when fibrinogen is <1 g/L (100 mg/dL).

Tests for fibrinogen and dysfibrinogens in presence of heparin Reptilase time (insensitive to presence of heparin)

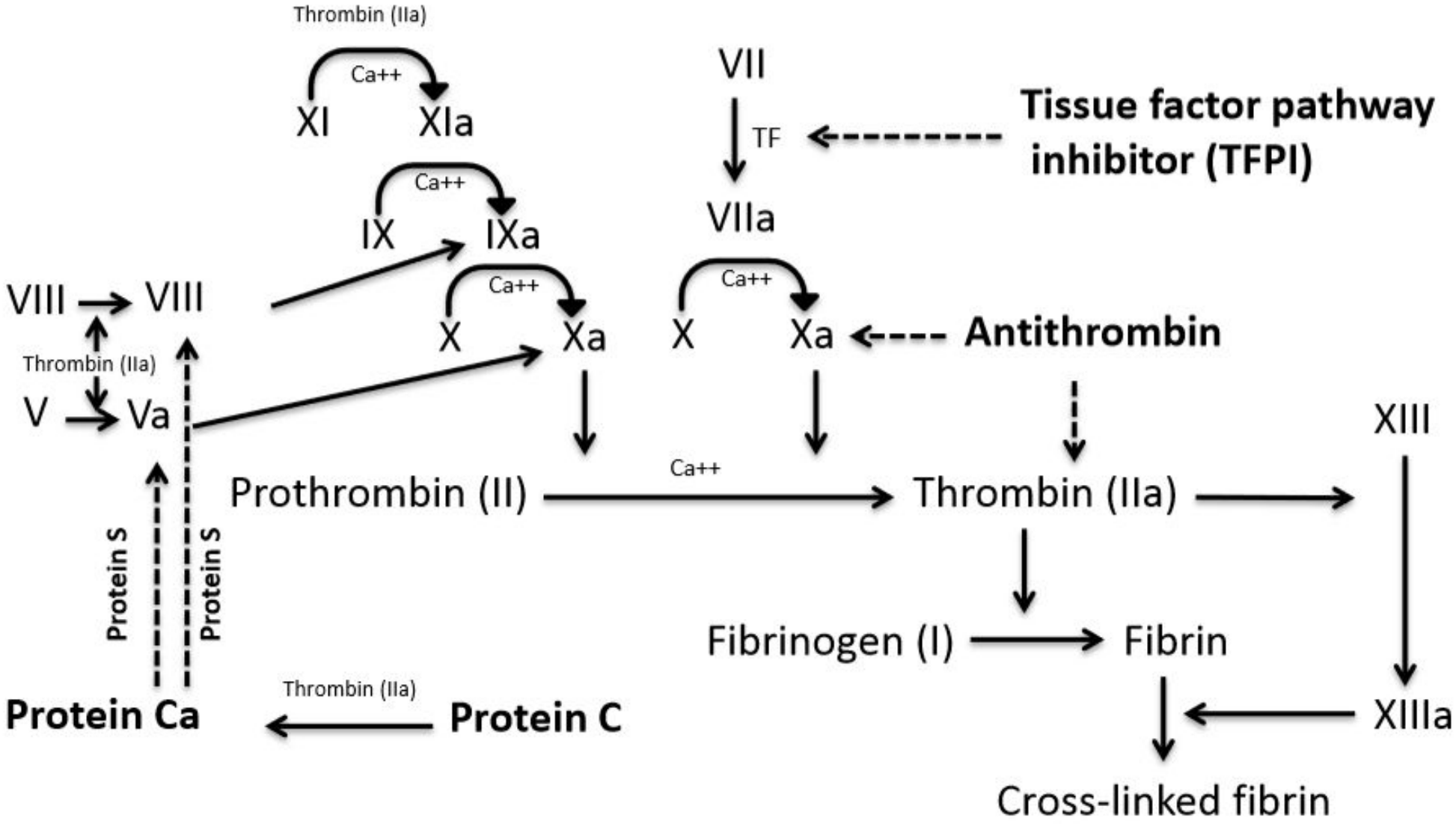
Factor XIII

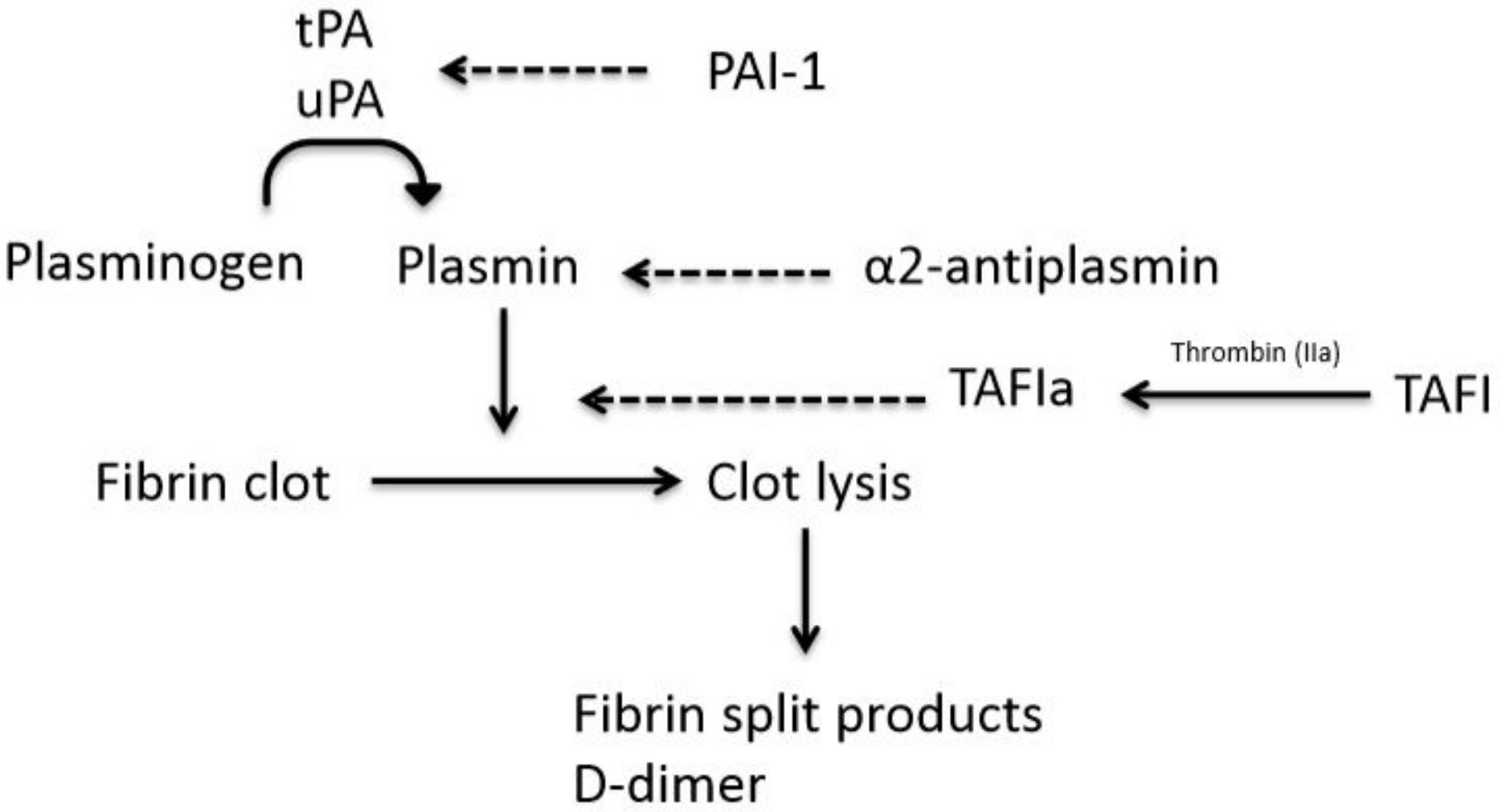
The longest half-life of all the clotting factors (10 days)

Screening coagulation tests (PT and PTT) are normal

Factor XIII deficiency is associated with poor wound healing

Delayed separation of umbilical stump (can also occur with leukocyte adhesion deficiency) and intracranial hemorrhage

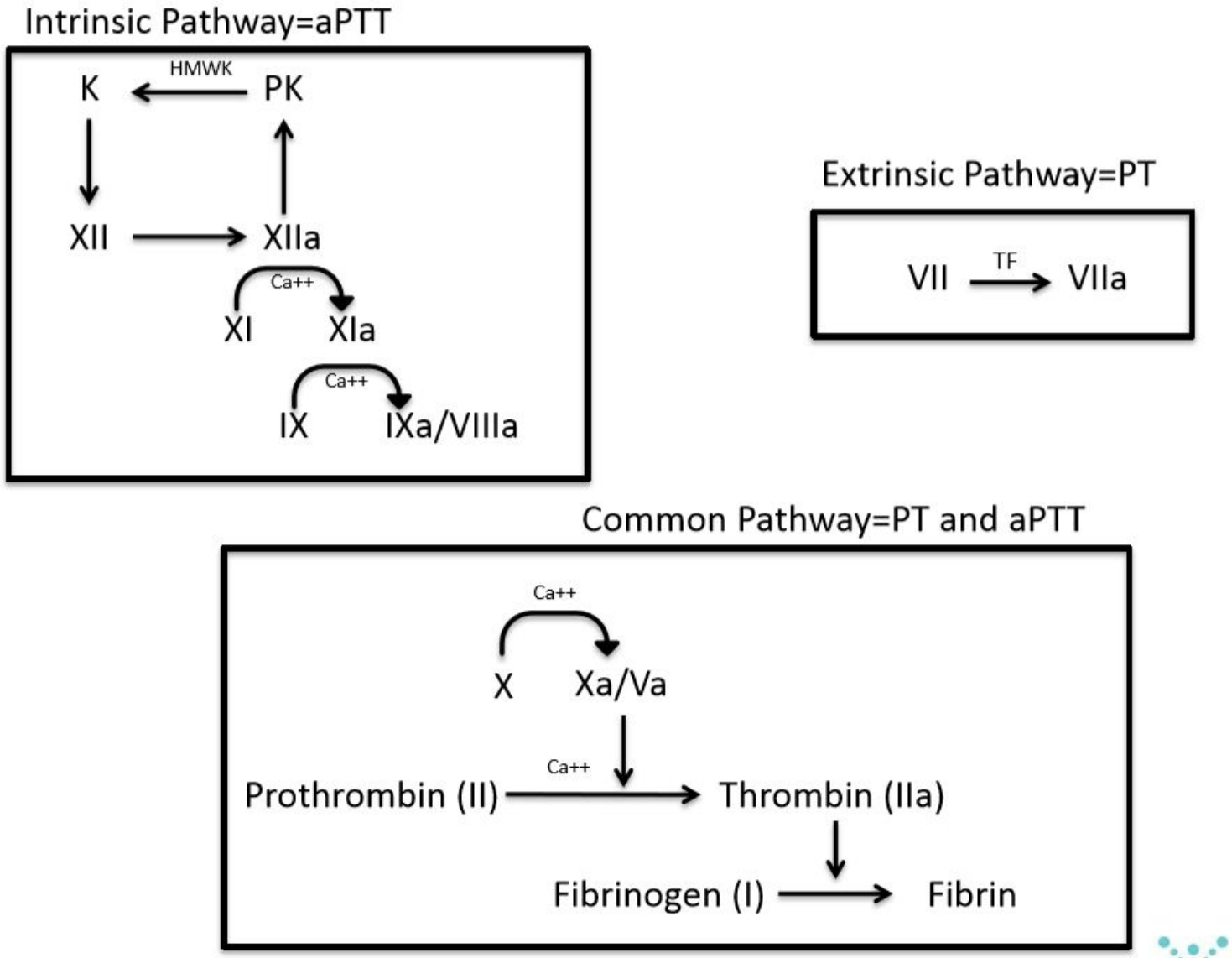

Thrombin (IIa)
Ca++
XI
XIa
VII
TF
Tissue factor pathway inhibitor (TFPI)
Ca++
IX
IXa
VIIa
Ca++
Ca++
VIII
VIII
X
Xa
X
Xa
Antithrombin
Thrombin (IIa)
V
Va
XIII
Ca++
Prothrombin (II)
Thrombin (IIa)
Protein S
Protein S
Fibrinogen (I)
Fibrin
Thrombin (IIa)
Protein Ca
Protein C
XIIIa
Cross-linked fibrin


tPA
uPA
PAI-1
Plasminogen
Plasmin
α2-antiplasmin
Thrombin (IIa)
TAFIa
TAFI
Fibrin clot
Clot lysis
Fibrin split products
D-dimer

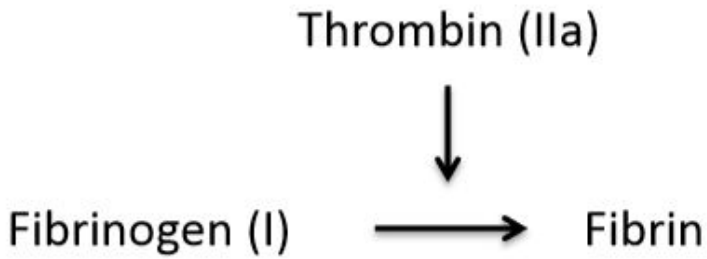
Fibrinolytic and anti-fibrinolytic drugs

Fibrinolytic – tPA , uPA

Antifibrinolytic ε-aminocaproic acid / tranexamic acid: inhibit fibrinolysis by blocking plasmin's binding site for fibrin


Intrinsic Pathway=aPTT
HMWK
K
PK
XII
XIIa
Ca++
XI
XIa
Ca++
IX
IXa/VIIIa
Extrinsic Pathway=PT
VII
TF
VIIa
Common Pathway=PT and aPTT
Ca++
X
Xa/Va
Ca++
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin

Thrombin Time



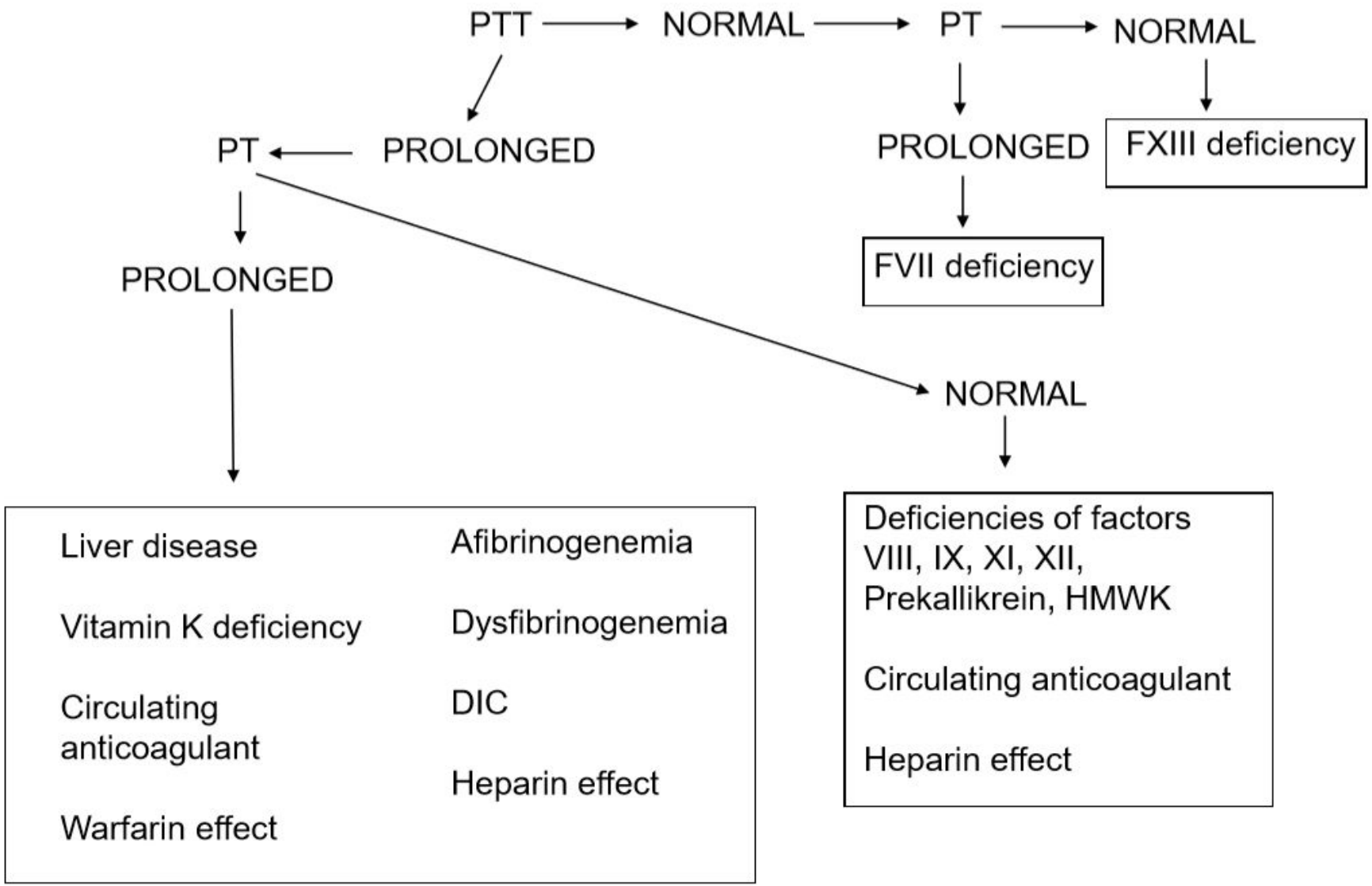
Assesses presence and function of fibrinogen

Abnormal in hypo- and afibrinogenemia
Abnormal in dysfibrinogenemia

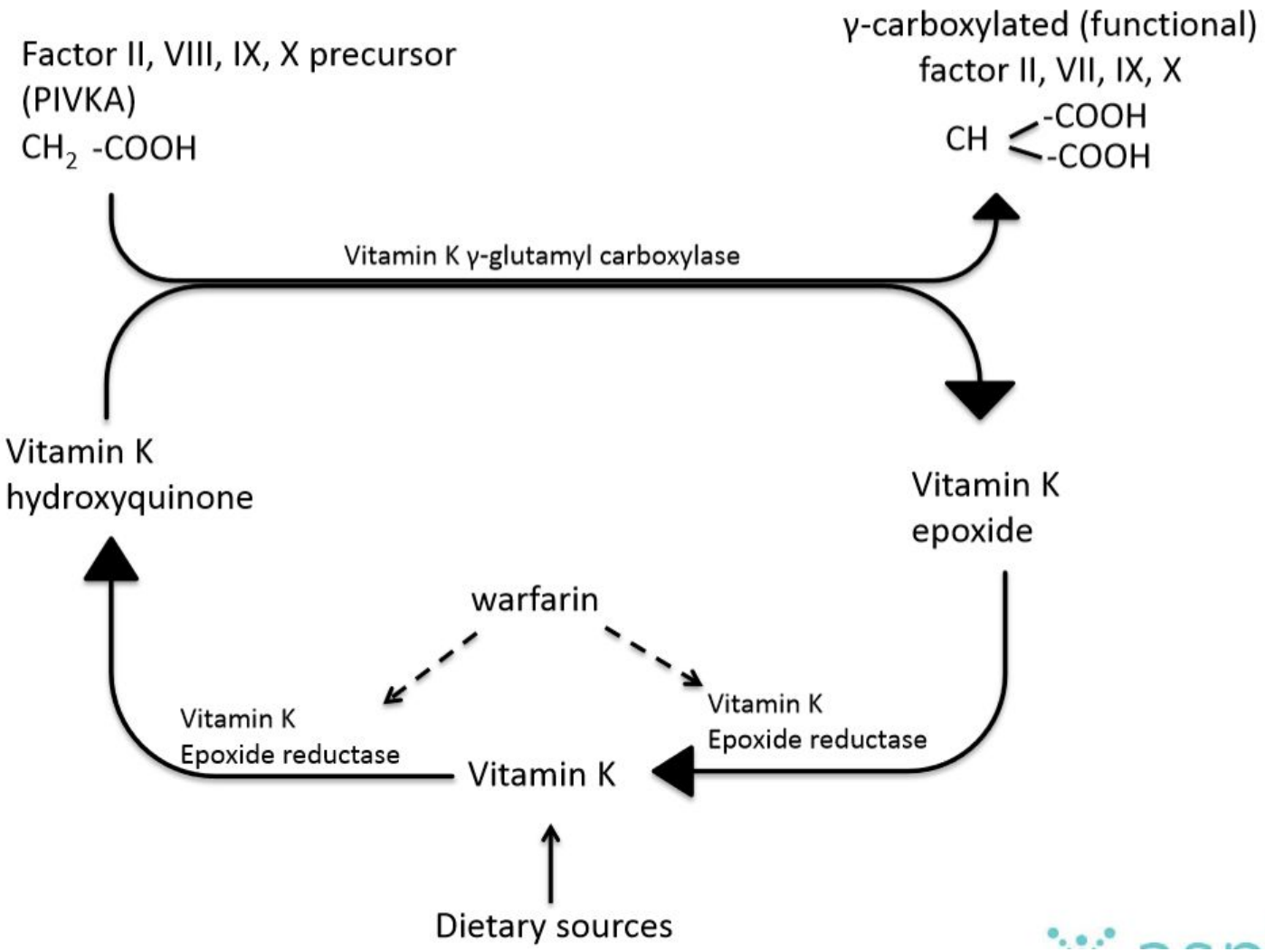
Factor Deficiencies and Coagulation Assays

- aPTT
  - Contact factors
    - PK, HWMK, FXI, FXII
  - Factor IX
  - Factor VIII
  - Common Pathway
    - Factor X
    - Factor V
    - Factor II (Prothrombin)
    - Fibrinogen

- PT
  - Factor VII
  - Common Pathway
    - Factor X
    - Factor V
    - Factor II (Prothrombin)
    - Fibrinogen


PTT
NORMAL
PT
NORMAL
PROLONGED
FXIII deficiency
PT
PROLONGED
PROLONGED
FVII deficiency
NORMAL
Liver disease
Vitamin K deficiency
Circulating anticoagulant
Warfarin effect
Afibrinogenemia
Dysfibrinogenemia
DIC
Heparin effect
Deficiencies of factors VIII, IX, XI, XII, Prekallikrein, HMWK
Circulating anticoagulant
Heparin effect

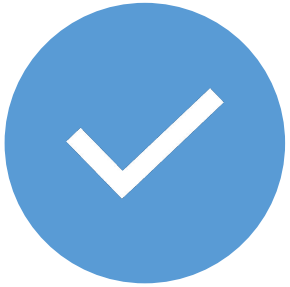
Vitamin K metabolism and warfarin



Warfarin is monitored with the INR

The half-life of FVII (3-6 hours) and factor's X is long (40 hours)

Early rise in INR due to the drop in factor VII.



It's not a sign of therapeutic warfarin as that effects takes 5-7 days when the factor X level falls

Always overlap warfarin with heparin or LMWH, etc. for 2 days after INR therapeutic.

Proteins C and S are vitamin K dependent too (skin necrosis).

False low and high PT,PTT

Ratio of plasma to citrate (9:1)

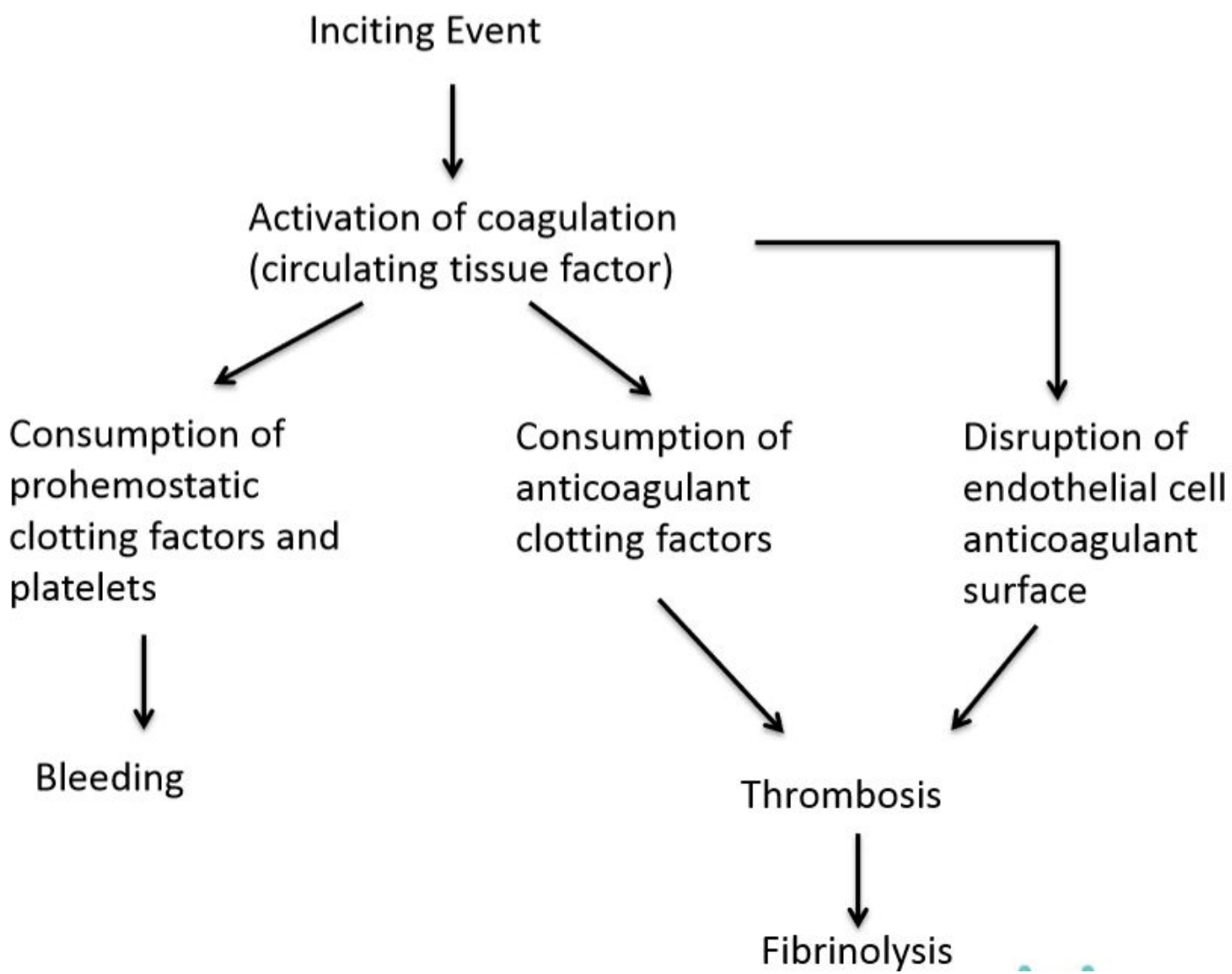
- Too little plasma leads to elevated levels (tube not properly filled, patient with polycythemia)
- Too much plasma (severe anemia) falsely normal results)
- Sample not processed quickly
- Difficult lab draw (sample begins to clot consuming the factors)
- Heparin in sample

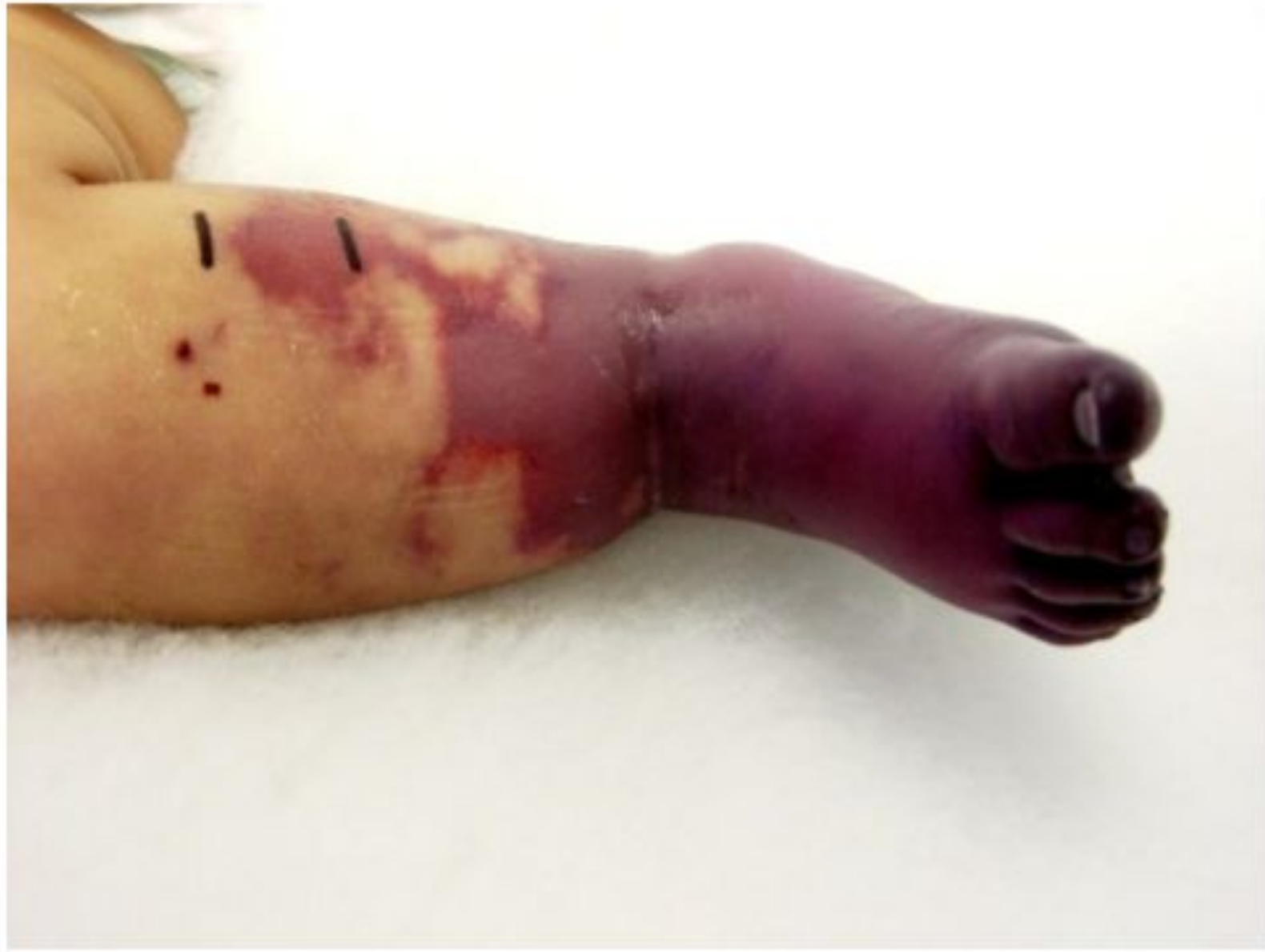
Factors that are acute phase reactants

Factor VIII

vWF

Fibrinogen


Inciting Event
Activation of coagulation (circulating tissue factor)
Consumption of prohemostatic clotting factors and platelets
Consumption of anticoagulant clotting factors
Disruption of endothelial cell anticoagulant surface
Bleeding
Thrombosis
Fibrinolysis



Be aware!

Patient may have no bleeding or thrombosis but still have DIC

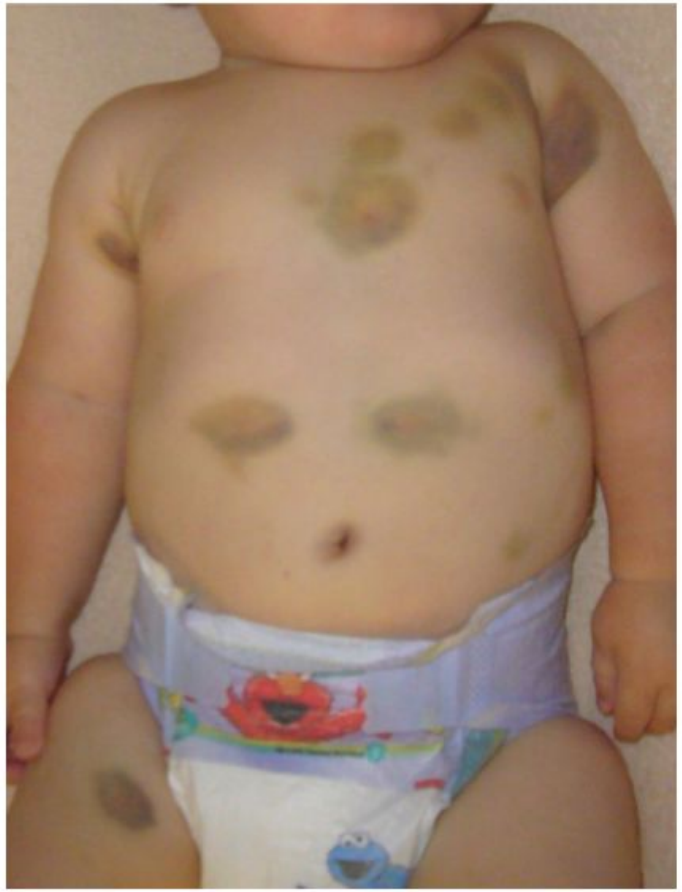
Don’t transfuse with platelets!

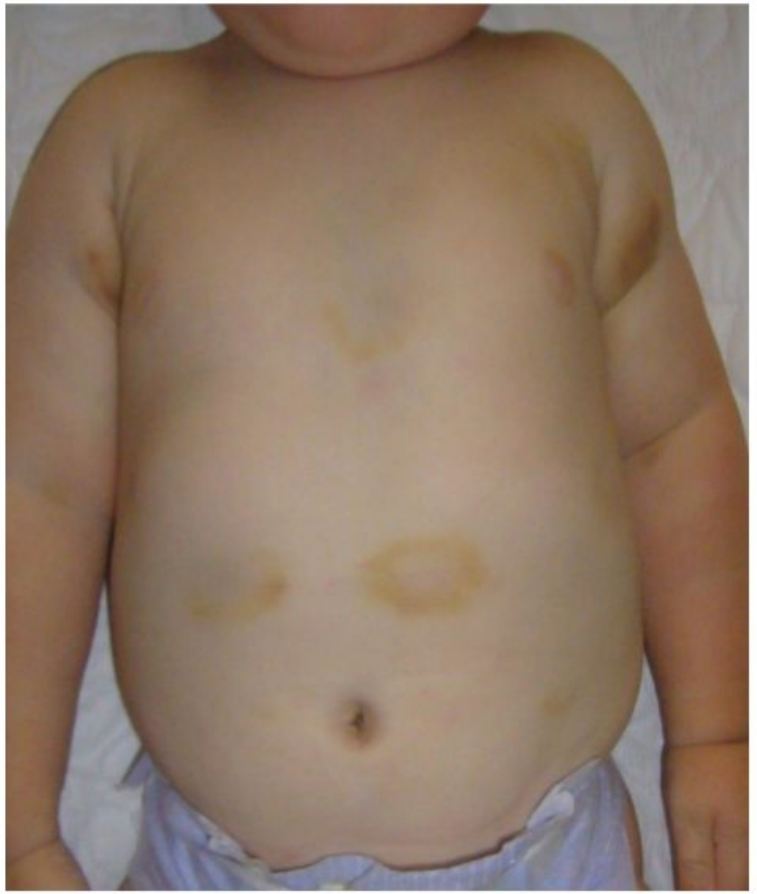
Don’t anticoagulated!

Vitamin K deficiency in neonates/ infants

	Early	Classical	Late
Age	First 24 hours	2-7 days	1-6 months (even later)
Risk factors	Maternal use of drugs that interfere with vitamin K metabolism (warfarin, anticonvulsants)	None (all newborns are prone)	Disorders that interfere with vitamin K intake (cystic fibrosis, other GI fat malabosrption disorders, chronic antibiotic use, liver disease)
Bleeding sites	ICH, GI, umbilical stump, bruising	ICH, GI, umbilical stump, bruising	ICH, GI, mucocutaneous
Treatment	Recognition of drugs that can cause this and eliminating them from maternal use	Prevention with neonatal vitamin K administration	Parenteral vitamin K

Response to treatment happens typically in less than 24 hours.



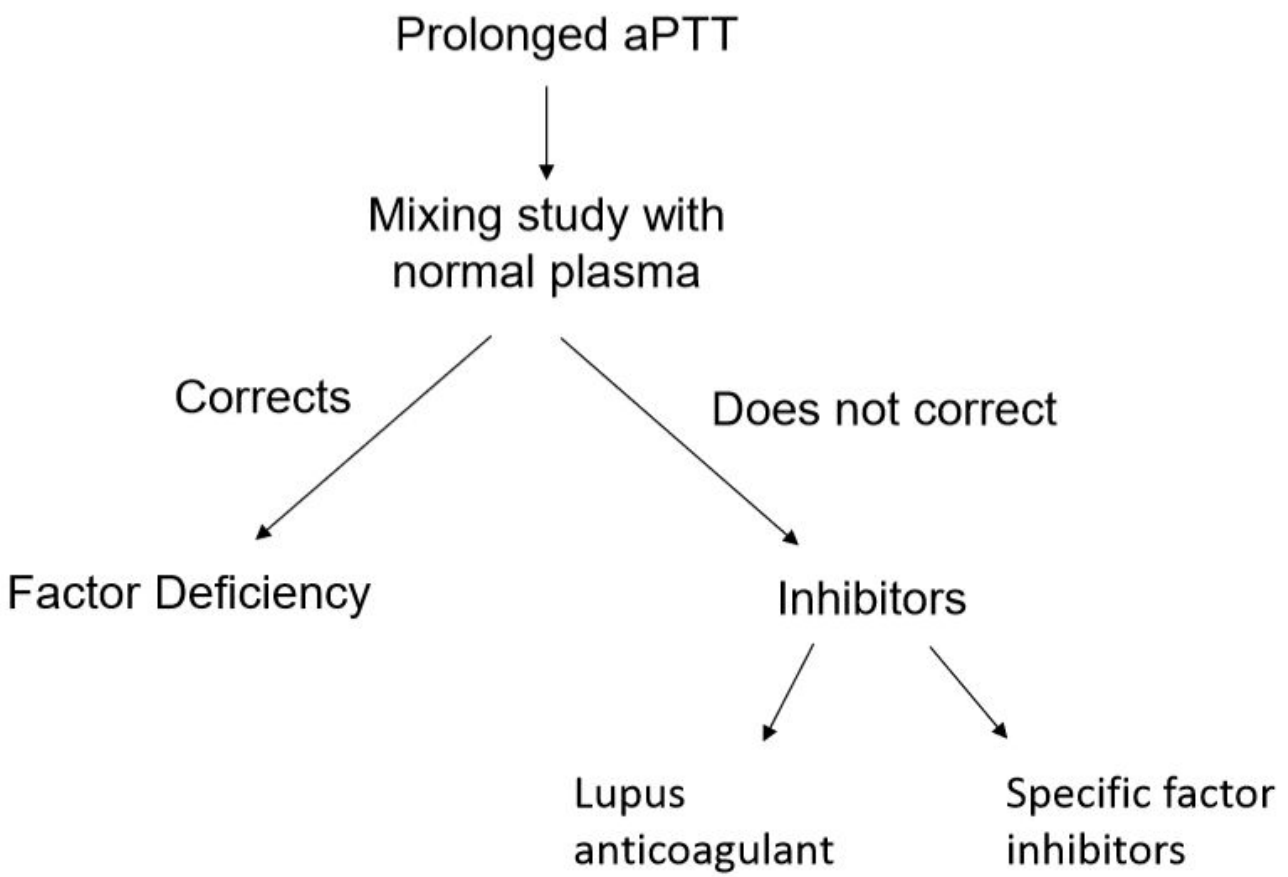


coagulation inhibitors

Inhibitors against specific factors

Lupus-type anticoagulants

Mixing Studies



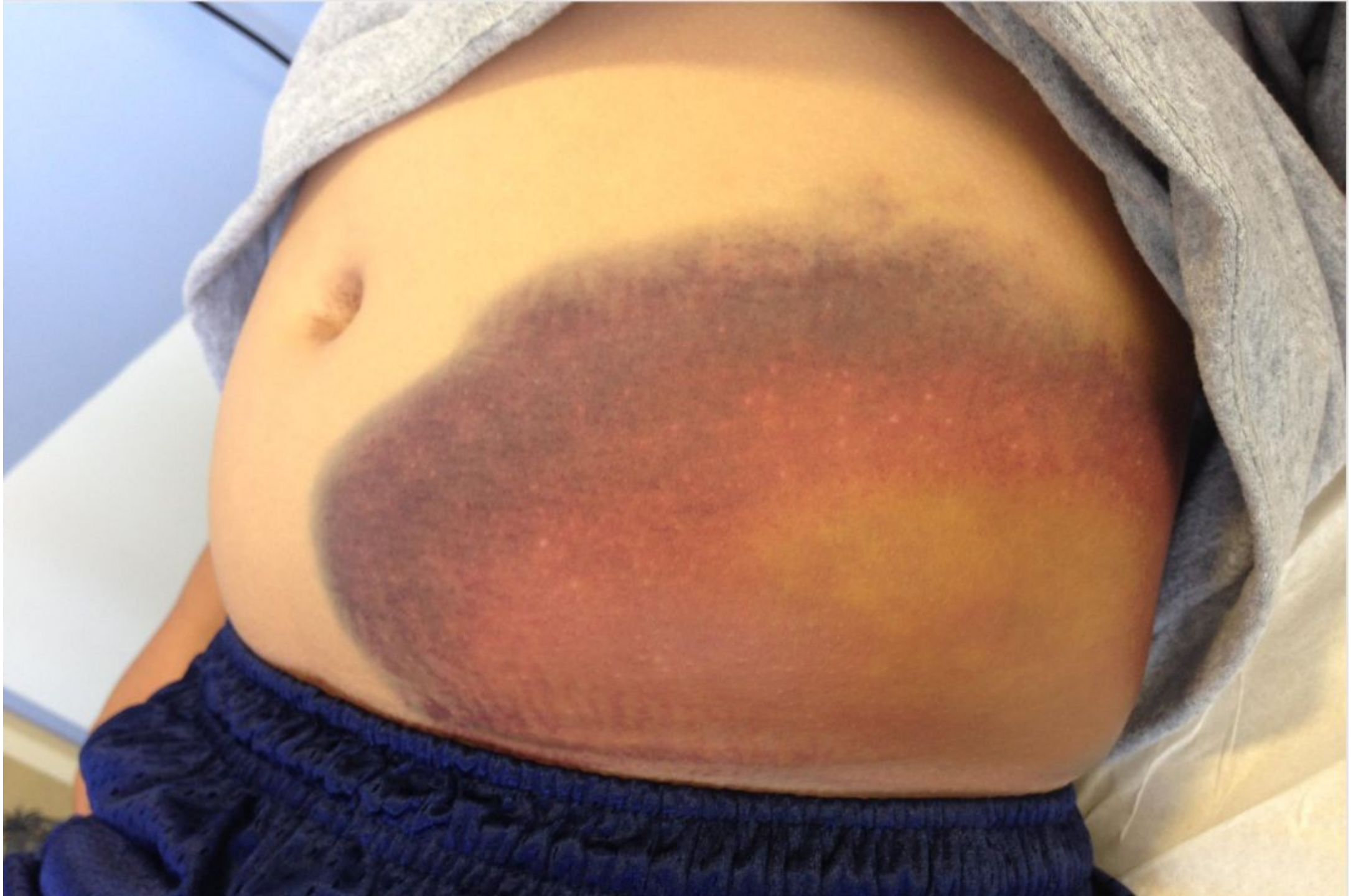
Lupus anticoagulant

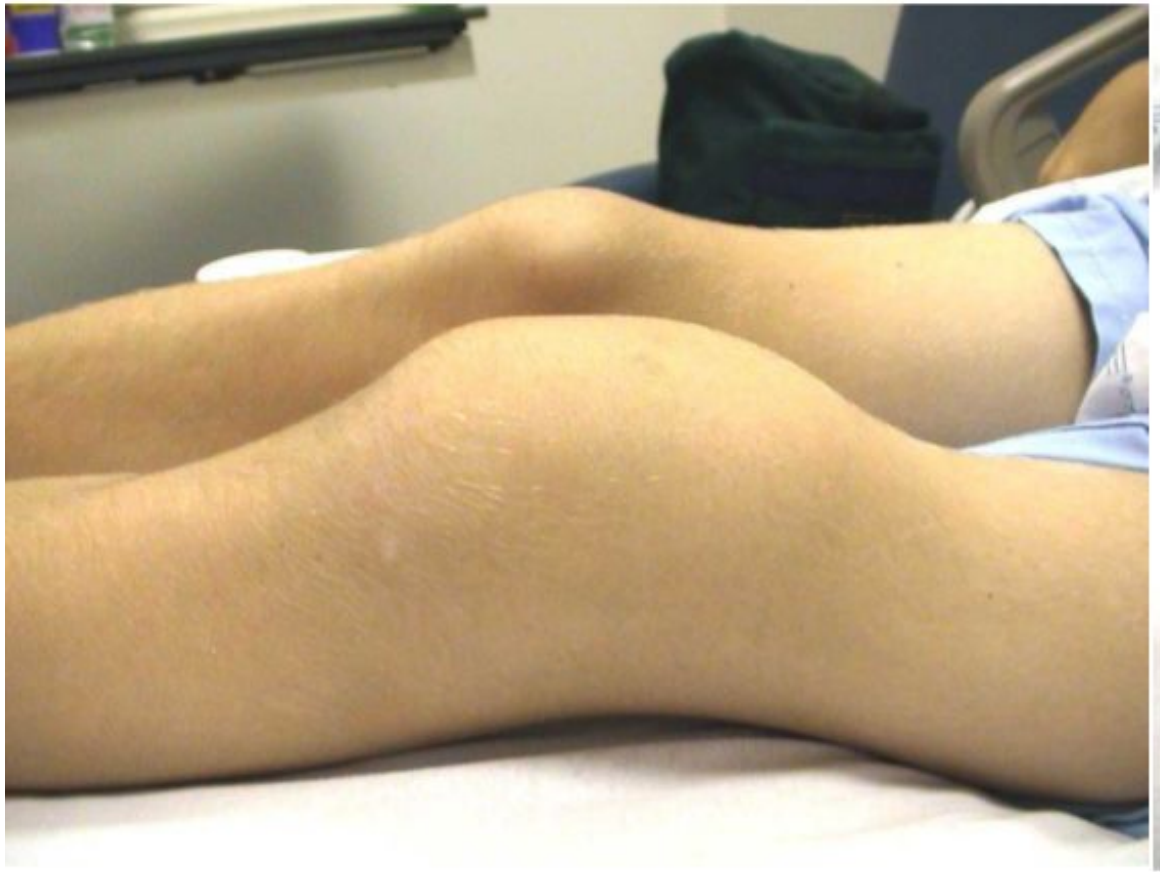
- Most are transient, asymptomatic and result from an acute viral infection (one of the most common causes of a prolonged PTT).
- Can be part of the antiphospholipid syndrome and cause thrombosis.
- Rarely, associated with acquired hypoprothrombinemia which can result in bleeding “Lupus anticoagulant hypoprothrombinemia syndrome”
- Detected by dilute Russell’s viper venom time (dRVVT)

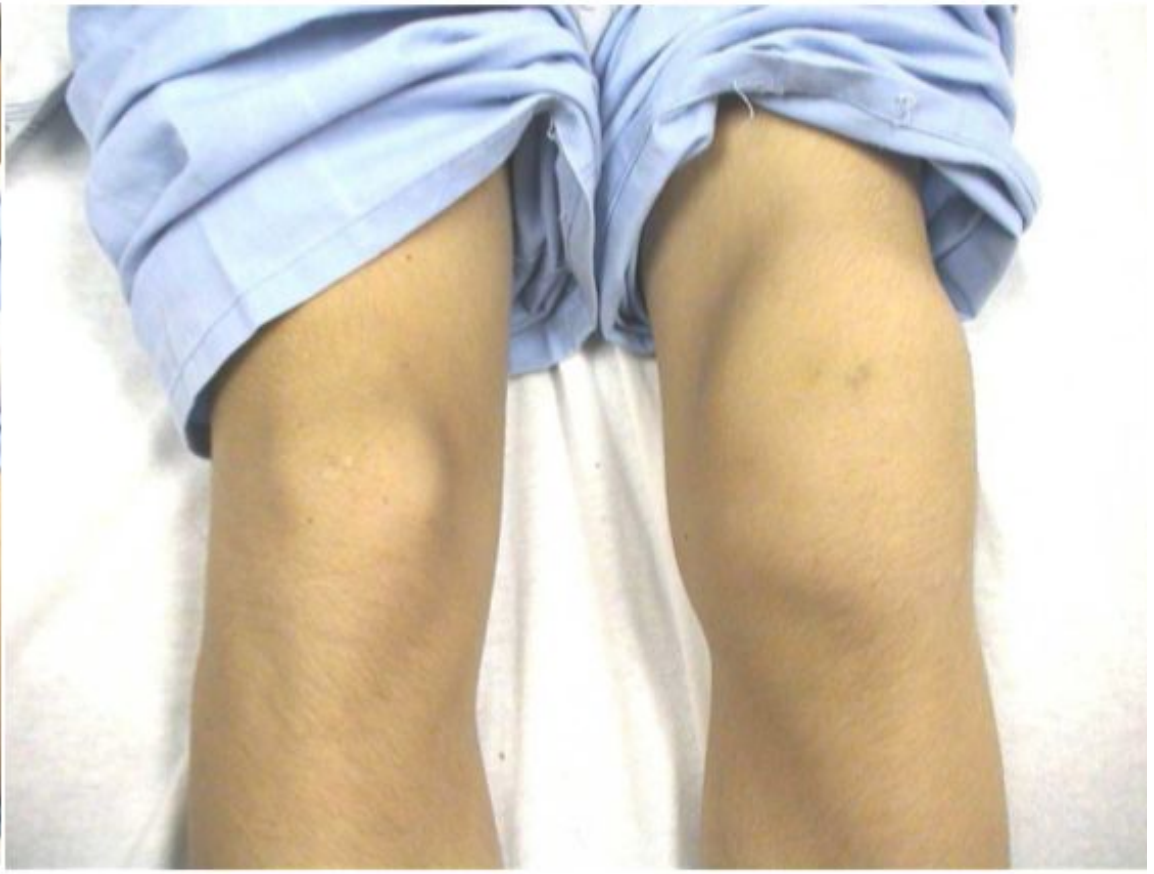
Hemophilia

- Low factor VIII (A) or factor IX (B, charismas disease) levels.
- Inheritance is X linked recessive.
- Carrier or heterozygote females can still have mild disease.
- Many mutations. Type of mutation dictates severity.

	Severe	Moderate	Mild
Factor level	<1%	1-5%	5-40%
Age at presentation	Birth-3 years*	2-10 years*	5->21 years*
Presentation	• Family history (pre- or postnatal screening) • Neonatal bleeding (circumcision, heel sticks) • Bruising (<1 year) • Vaccine-related bleed • Mucosal bleed • Joint bleed	• Family history (pre- or post natal screening) • Neonatal bleeding (less likely than severe) • Vaccine-related bleed • Mucosal bleed • Joint bleed	• Post-traumatic bleed • Post-surgical bleed
Risk for inhibitor development	~25% in FVIII ~5% in FIX	~1-2%	Very rare
Risk for hemophilic arthropathy	Universal without prophylaxis	Very common without prophylaxis	Rare







Diagnosis

- Family history
- Bleeding pattern
- Elevated PTT
- Factor assay
- Mutation analysis.

Treatment modalities

1

Supportive.

2

Factor replacement

3

Desmopressin (DDAVP)

4

Antifibrionlytic therapy