Approach to Bleeding Disorders

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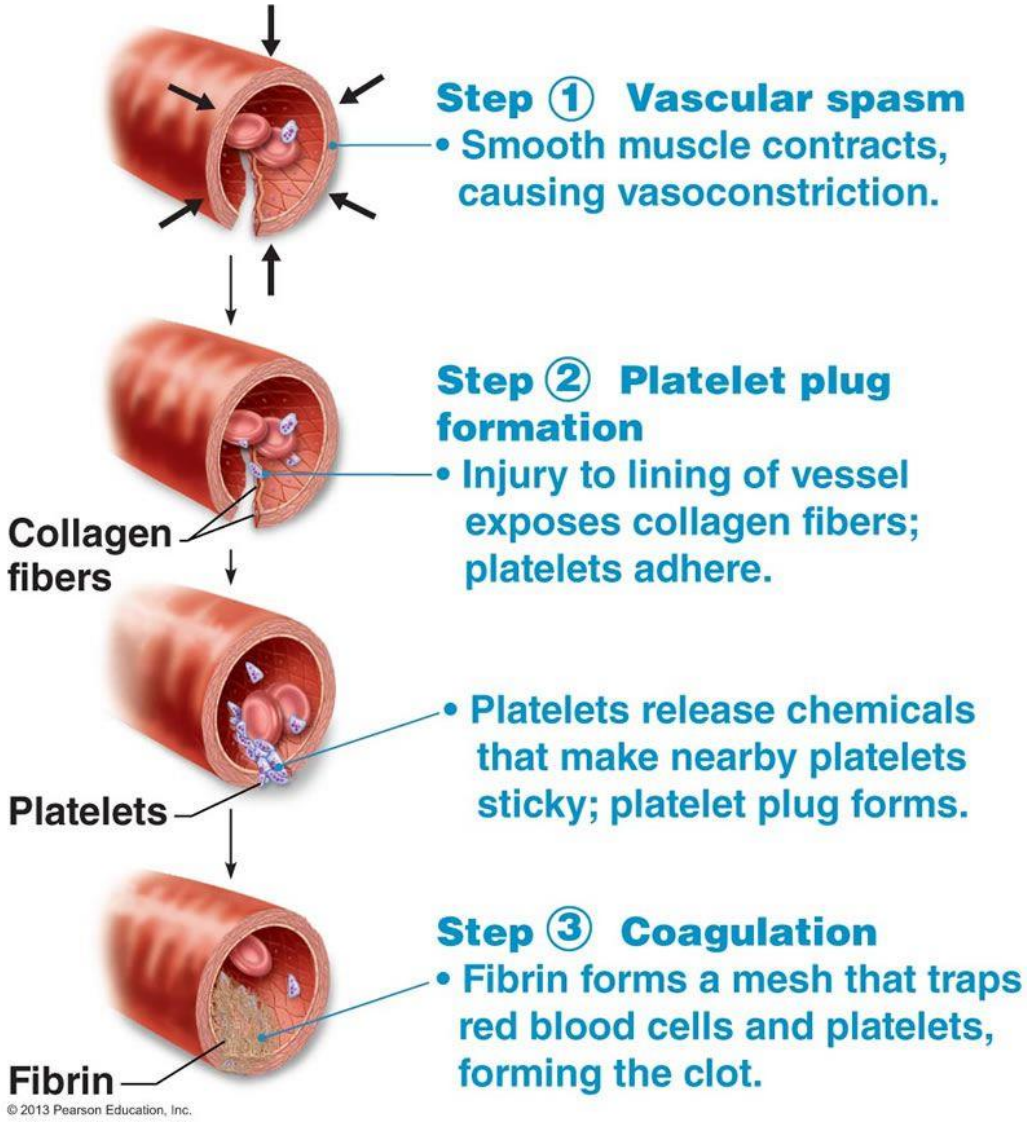
LEARNING OBJECTIVES

- To know the function of platelets
- To learn about different types of inherited and aquired platelet quantitative and qualitative defects.
- To know about the diseases associated with (i) a failure of platelet production and (ii) a shortened platelet lifespan.
- To know the main sequence of events in the coagulation pathways
- To understand normal fibrinolysis and the principles of fibrinolytic therapy
- To know the principles of different coagulation tests.

3 Steps of normal hemostasis



Classification of haemostatic defects

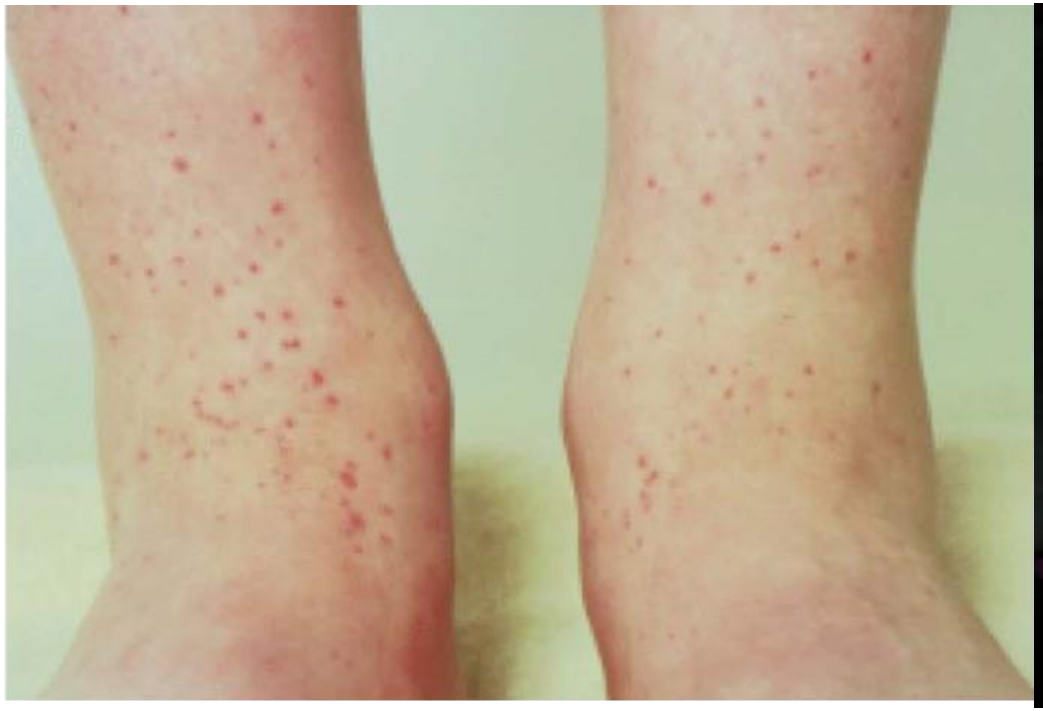
Bleeding arise from defects in one of the three processes:

- Thrombocytopenia (a low platelet count) (the commonest cause)
- Abnormal platelet function.
- A defect in the clotting mechanism (the second commonest cause)

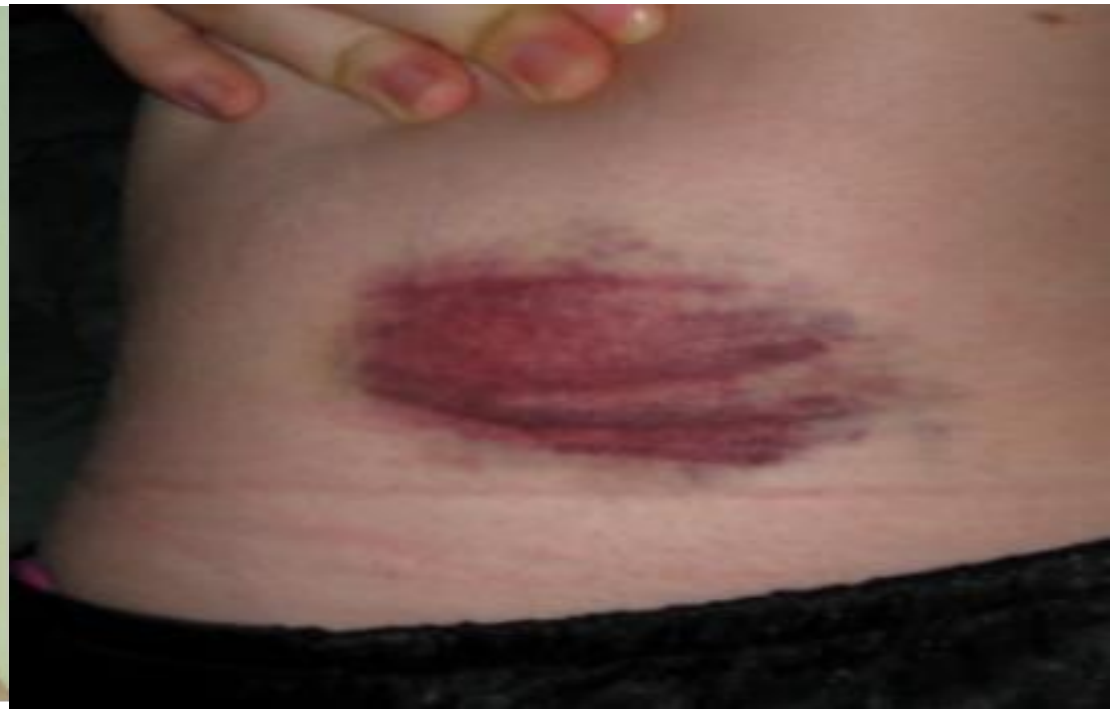
clotting defects usually present with bleeding into deep tissues (muscles or joints).

Platelet defects usually present with mucocutaneous bleeding.

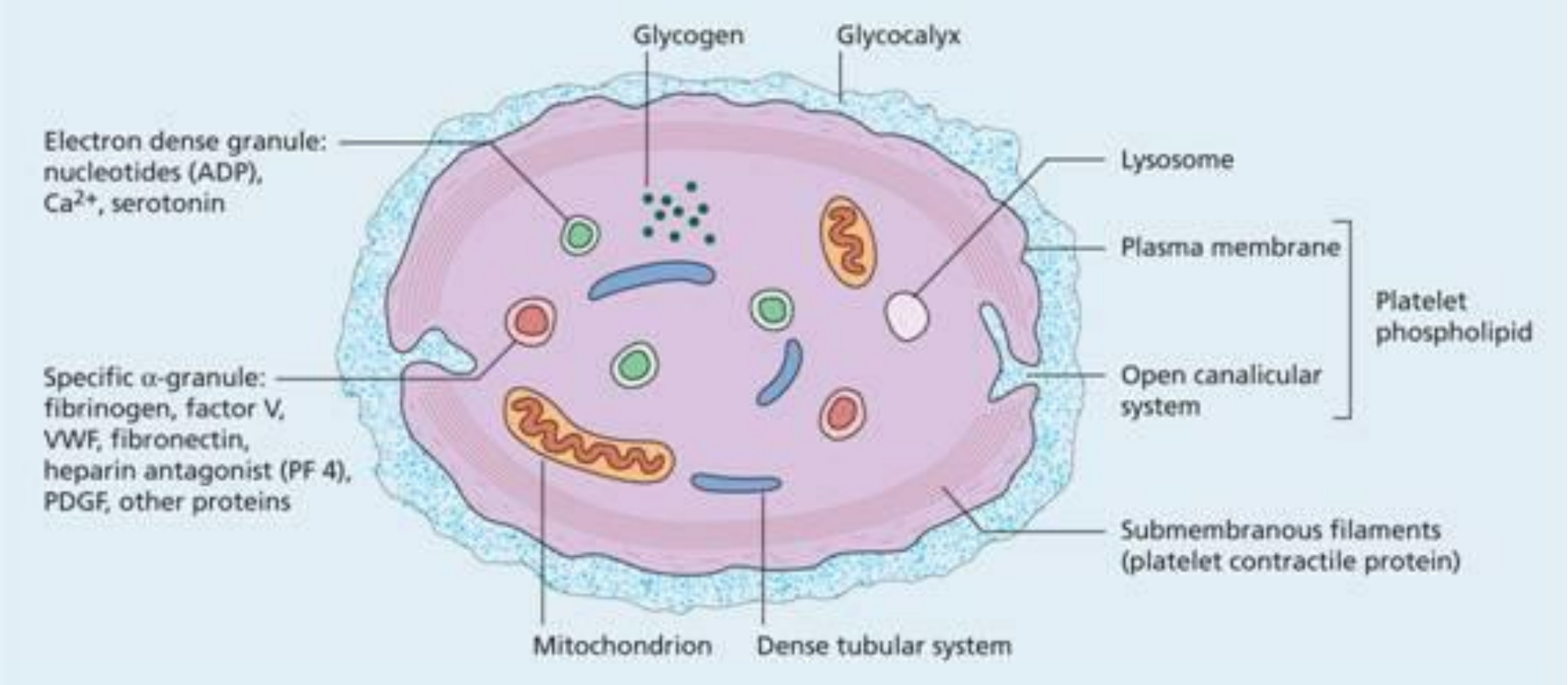
Petechiae



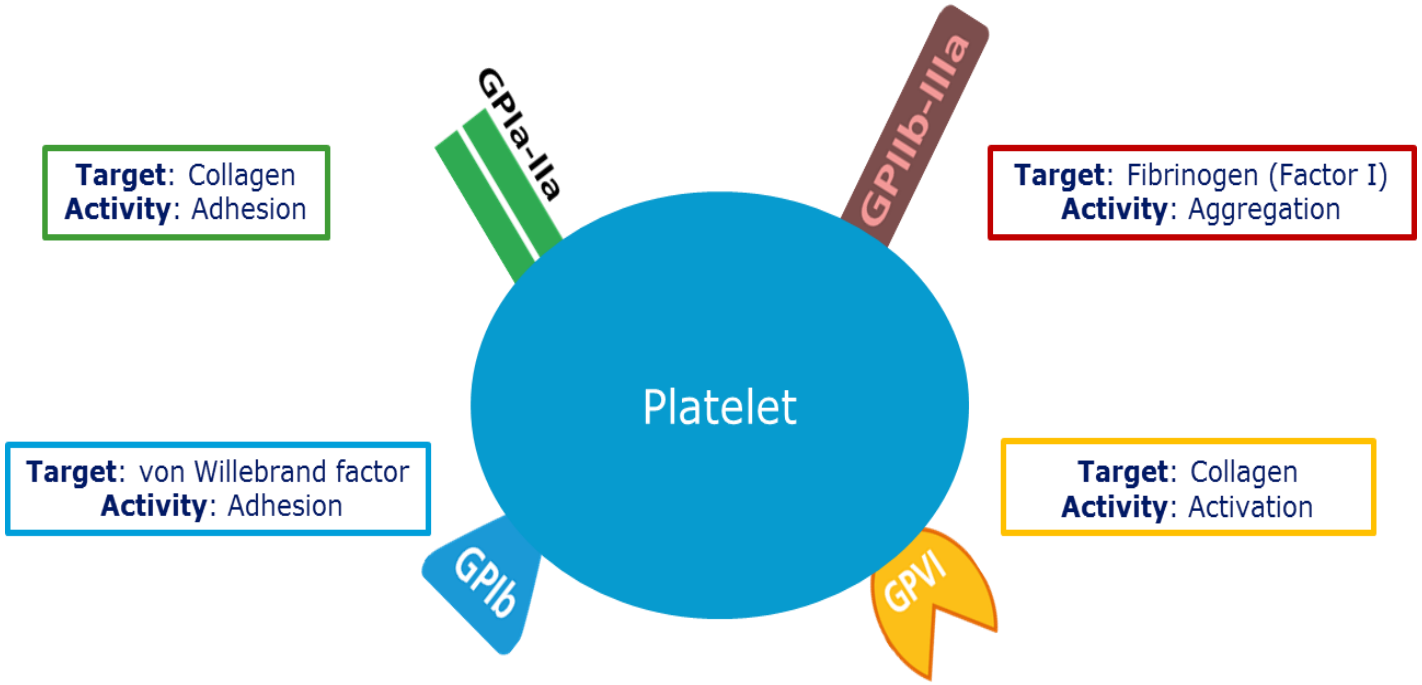
Ecchymoses



Platelet structure



- The plasma membrane of a platelet contains glycoproteins (GPs) that are important in the interaction of platelets with subendothelial connective tissue and other platelets.
- GP Ia and VI, which bind to collagen
- GP Ib, which binds to von Willebrand factor (VWF)
- and GP IIb/IIIa, which binds to fibrinogen.



Platelets

Formed in the bone marrow by the fragmentation of megakaryocyte cytoplasm.

Their concentration in normal blood is 150-450 *X* 10^9/L.

The lifespan of the platelet around 10 days.

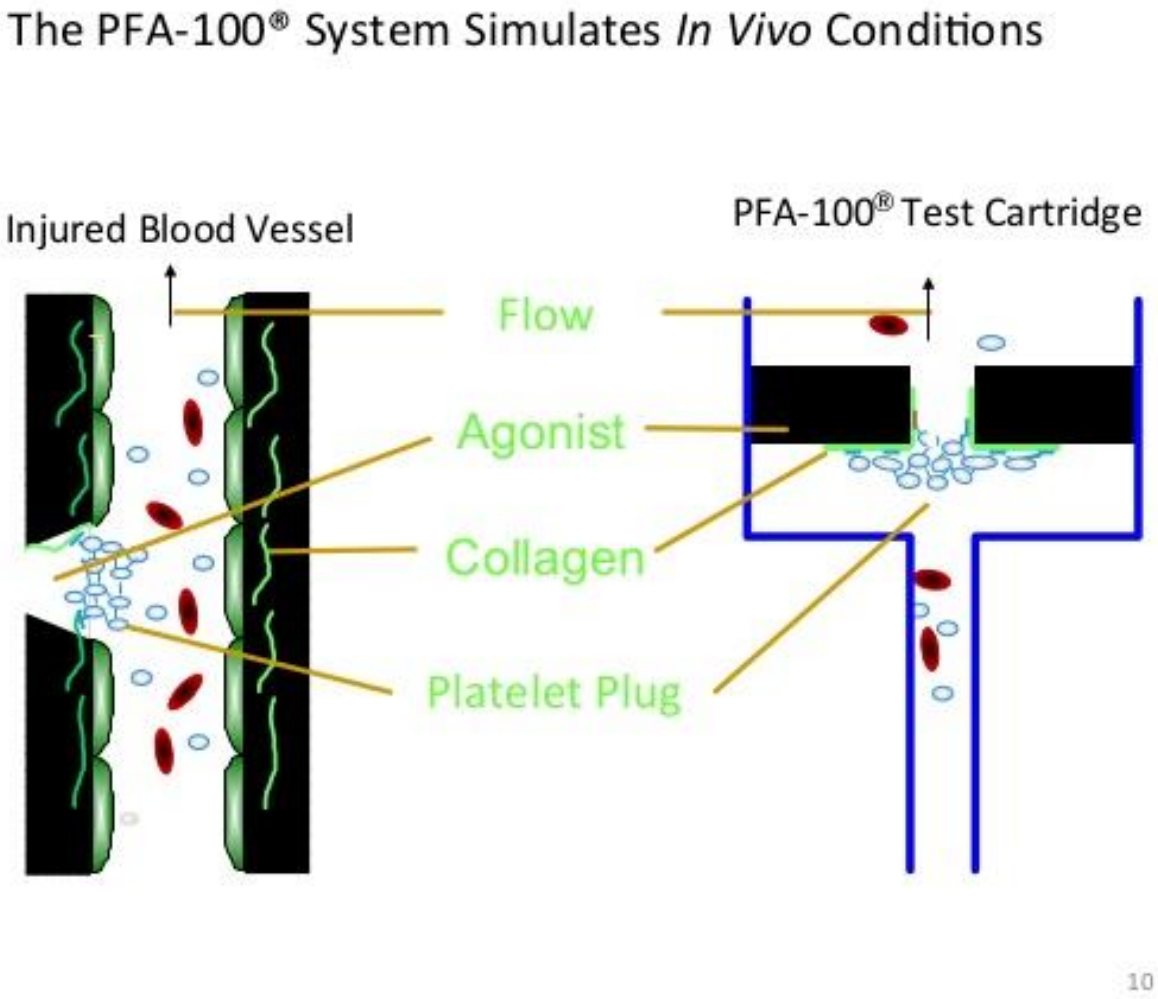
Tests of platelet function

Bleeding time

- Old method not used in routine practice.
- It is estimated by making small wounds in the skin of the forearm after applying a blood pressure cuff to the upper arm and inflating it to 40mmHg; the average time that elapses until bleeding ceases is then measured.

PFA-100

The bleeding time has largely been replaced by an *in vitro* estimation of primary haemostasis using a machine called a PFA-100.

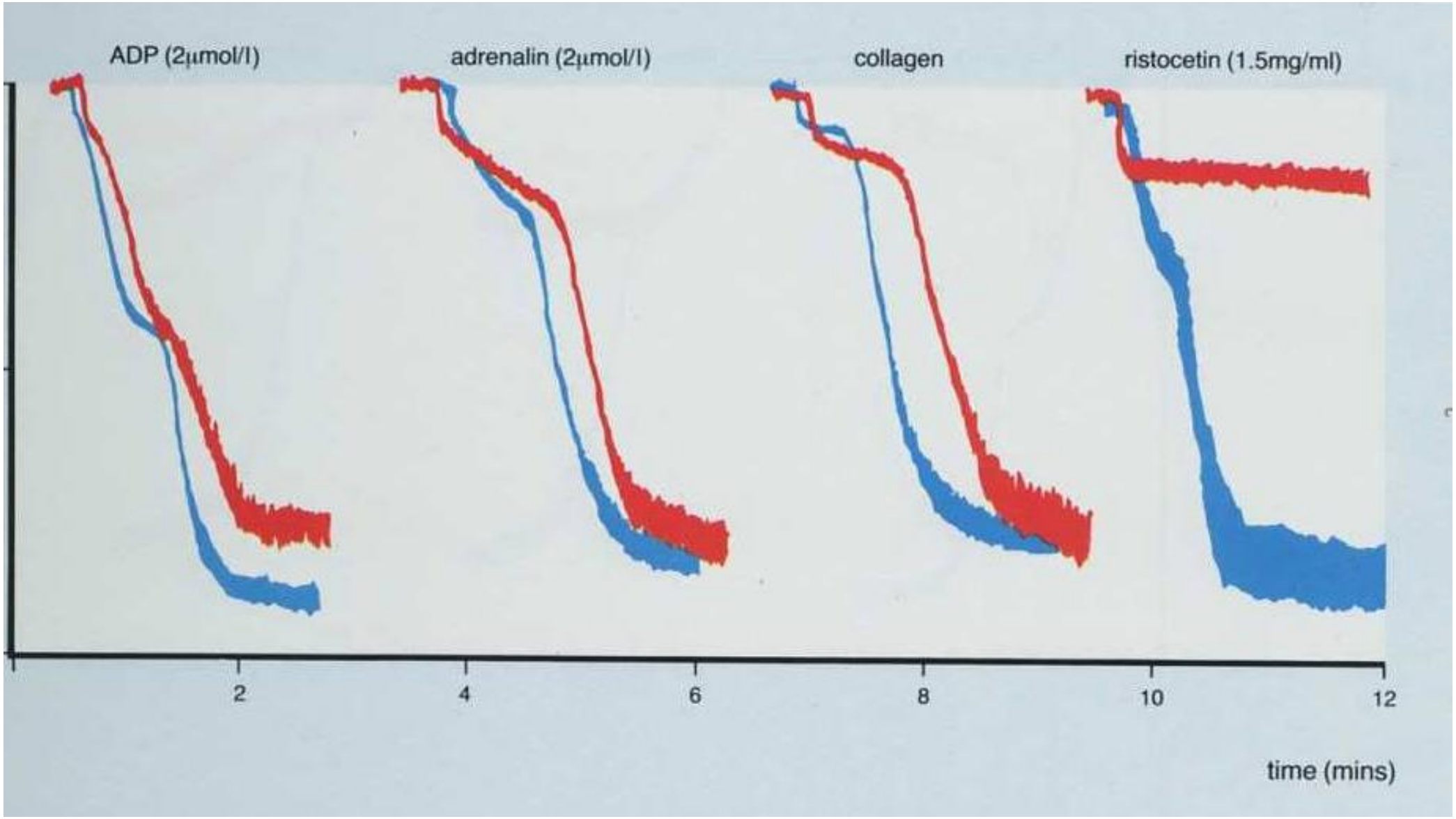


Platelet aggregation studies

The most common is light transmission aggregometry.

The aggregation of platelets is studied following the addition of substances such ADP, epinephrine, arachidonate, collagen and ristocetin to platelet-rich plasma.

Aggregation causes an increase in the light transmitted through the sample and the test is performed using special equipment capable of continuously recording light transmission.


ADP (2μmol/l)
adrenalin (2μmol/l)
collagen
ristocetin (1.5mg/ml)
2
4
6
8
10
12
time (mins)

Thrombocytopenia

- Low platelet count

Table 14.1 Some causes of thrombocytopenia.

Failure of platelet production

- Aplastic anaemia
- Drugs
- Viruses
- Myelodysplasia
- Paroxysmal nocturnal haemoglobinuria
- Bone marrow infiltration (carcinoma, leukaemia, lymphoma, myeloma, myelofibrosis, storage diseases including Gaucher's disease, osteopetrosis)
- Megaloblastic anaemia due to B12 or folate deficiency
- Hereditary thrombocytopenia (e.g. thrombocytopenia with absent radii, grey platelet syndrome, Bernard-Soulier syndrome, Wiskott-Aldrich syndrome)

Shortened platelet survival

Immune

- Autoimmune (idiopathic) thrombocytopenic purpura
- Secondary autoimmune thrombocytopenic purpura (SLE and other collagen diseases, lymphoma, chronic lymphocytic leukaemia, HIV infection)
- Drugs
- Post-transfusion purpura
- Neonatal alloimmune thrombocytopenia
- Thrombotic thrombocytopenic purpura (most cases)

Non-immune

- Disseminated intravascular coagulation (p. 127)

Increased splenic pooling

Immune thrombocytopenic purpura (ITP)

ITP is characterized by thrombocytopenia and mucocutaneous bleeding .

Acute or Chronic form.

Acute ITP

- Most common before the age of 10 years but can affect any age
- Commonly prceeded by viral infection (e.g. upper respiratory tract infection, chicken pox, measles).
- Platelet counts are often less than $20 X 10^9/L$.
- in most pateints has a self-limiting course of 2-4 weeks.
- In approximately 20% it becomes chronic (lasts more than 6 months).
- The mortality is low, the main danger being intracranial bleeding.

ITP

Chronic ITP

- This occurs mainly in the age period 15-50 years

- Higher incidence in women than in men. Platelet counts are usually between 20 and 80 *X* 10^9/L.

- Spontaneous cures are rare and the disease is characterized by relapses and remissions.

Diagnosis

- Children with the appropriate clinical features, acute thrombocytopenia with large platelets (high MPV) and an otherwise normal blood count **(i.e. no evidence of acute leukaemia).**
- In ITP, bone marrow megakaryocytes are normal or increased in number (up to four- or eightfold) and increased in size.
- An absence or reduction of megakaryocytes rules out the disease.

Treatment

Acute ITP

Over 80% of patients recover without any treatment.

- Corticosteroids are widely used
- High dose of intravenous immunoglobulin (Ig) cause a rapid increase in the platelet count

Chronic ITP

Treatment is usually not needed in patients with platelet counts above 30-50 X 10^9/L who have no significant spontaneous bleeding.

- High-dose corticosteroid therapy increases the platelet count to more than 50 X 10^9/L

❖Splenectomy, thrombopoietin receptor agonists, and rituximab are reserved for refractory cases.

Thrombotic thrombocytopenic purpura (TTP)

- In healthy individuals a VWF-cleaving protease (ADAMTS 13) VWF.
- In the absence of the protease (Inherited or acquired), ultra-large VWF multimers are released that lead to platelet aggregation and the disease known as ‘thrombotic thrombocytopenic purpura’ (TTP).
- This is a serious illness characterized by widespread arteriolar platelet thrombi leading to fragmentation of red cells (schistocytes), thrombocytopenia, neurological symptoms and renal impairment.
- Coagulation tests are NORMAL.
- Treatment is by plasma exchange.
- Platelet transfusion is CONTRAINDICATED.

❖ HUS (hemolytic uremic syndrome) is a similar condition affecting children after infection by Escherichia coli or Shigella dysenteriae and treated conservatively.

Increased splenic pooling

- A normal spleen contains within its microcirculation about 30% of all the blood platelets.
- The splenic platelet pool increases with increasing splenic size, so that in patients with moderate to massive splenomegaly it may account for 50-90% of all blood platelets, thus causing thrombocytopenia.

Abnormalities of platelet function (Acquired)

❖Causes:

- ➢Drugs (aspirin and other antiplatelet drugs).
- ➢Chronic myeloproliferative disorders
- ➢Myelodysplastic syndromes
- ➢Paraproteinaemias (e.g. myeloma or Waldenström's macroglobulinaemia)
- ➢Uraemia.

Inherited platelet disorders:

Glanzmann’s disease:

- Rare but severe platelet disorder caused by a lack of glycoprotein IIb/IIIa receptors.
- Autosomal recessive
- Platelets are normal in morphology and number.

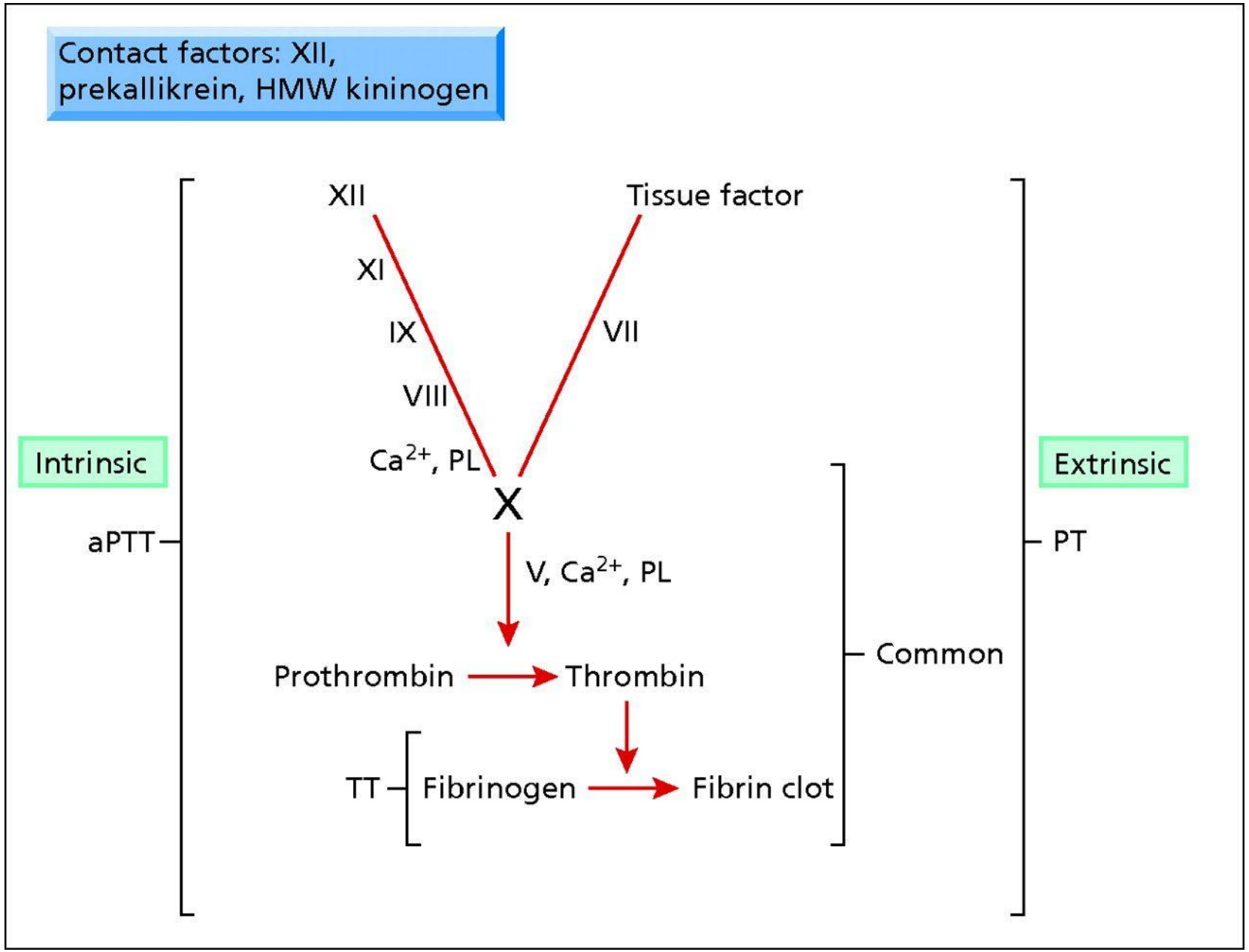
Bernard-Soulier disease:

- Caused by a lack of glycoprotein Ib receptors.
- Autosomal recessive.
- Platelets are larger than normal and usually the platelet count is reduced.

Storage pool diseases:

These are inherited group of diseses resulting in defective platelet granules.

Coagulation cascade



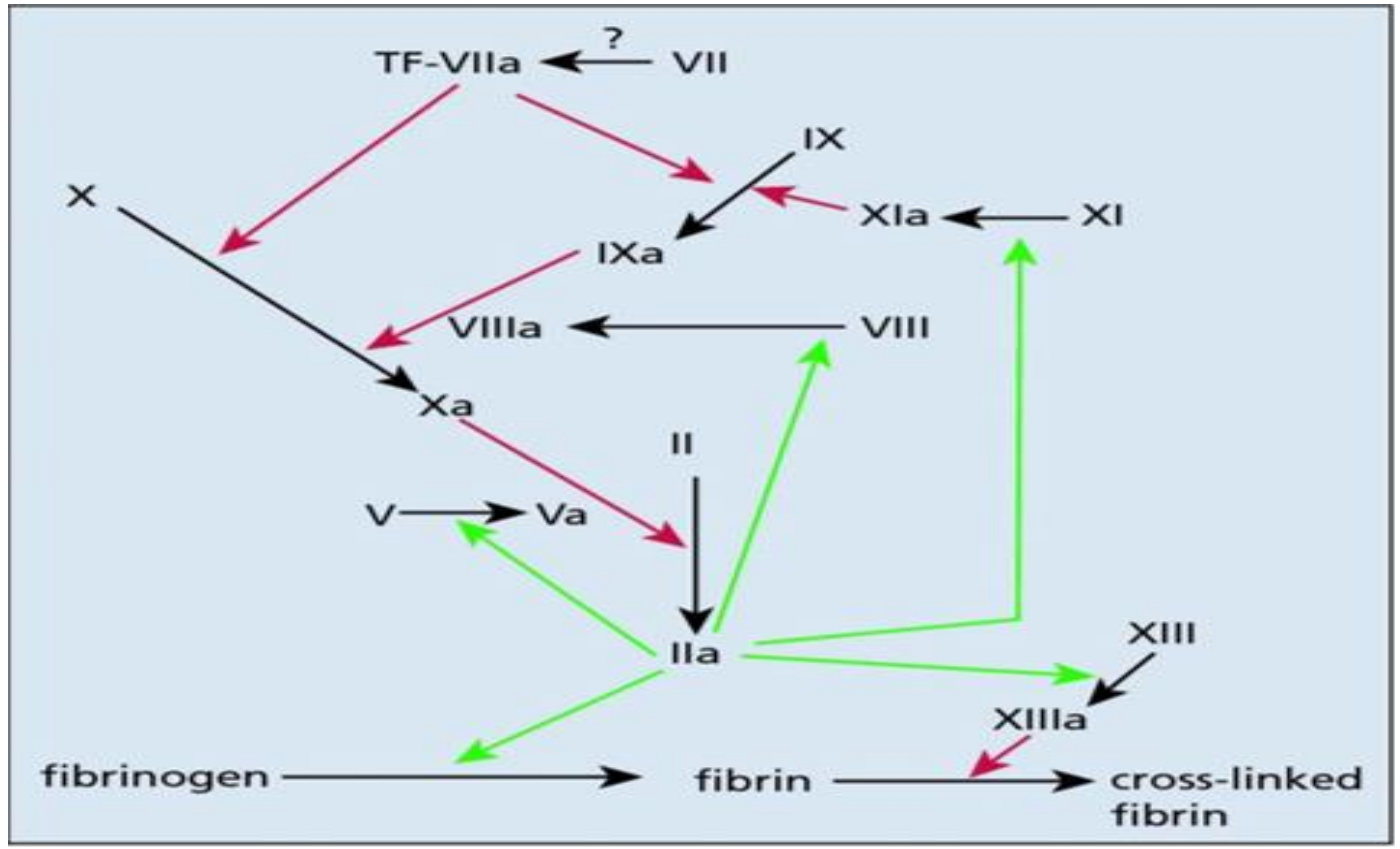


Figure 14.4 Pathways involved in fibrin generation after the activation of coagulation *in vivo* by TF. The suffix 'a' denotes the active form of each coagulation factor. *Notes:* Green arrows – actions of thrombin; red arrows – actions of other active enzymes; dashed blue arrows – inhibition.

The fibrinolytic mechanism

- After haemostasis has been achieved, the body has a mechanism for the enzymatic lysis of clots. The dissolution of the fibrin into fibrin-degradation products (FDPs) is carried out by the proteolytic plasma enzyme plasmin. Plasmin is present in the plasma in an inactive form.
- D-dimer is a measurement of fibrin degradation products

D-dimer

- D-dimers are raised in thrombosis.
  It has a high negative predictive value.
  D-dimers are raised in a variety of clinical situations and so have a low positive predictive value for thrombosis.
- They can be raised in:
  - Pregnancy
  - Malignancy
  - Infection
  - **DIC**
  - Vaso-occlusive sickle cell crisis
  - Surgery
  - Burns
  - Liver disease
  - Snake bites
  - Atrial fibrillation
  - Renal failure
  - Cardiac failure
  - Venous thromboembolic disease [VTED]
  - Aortic dissection

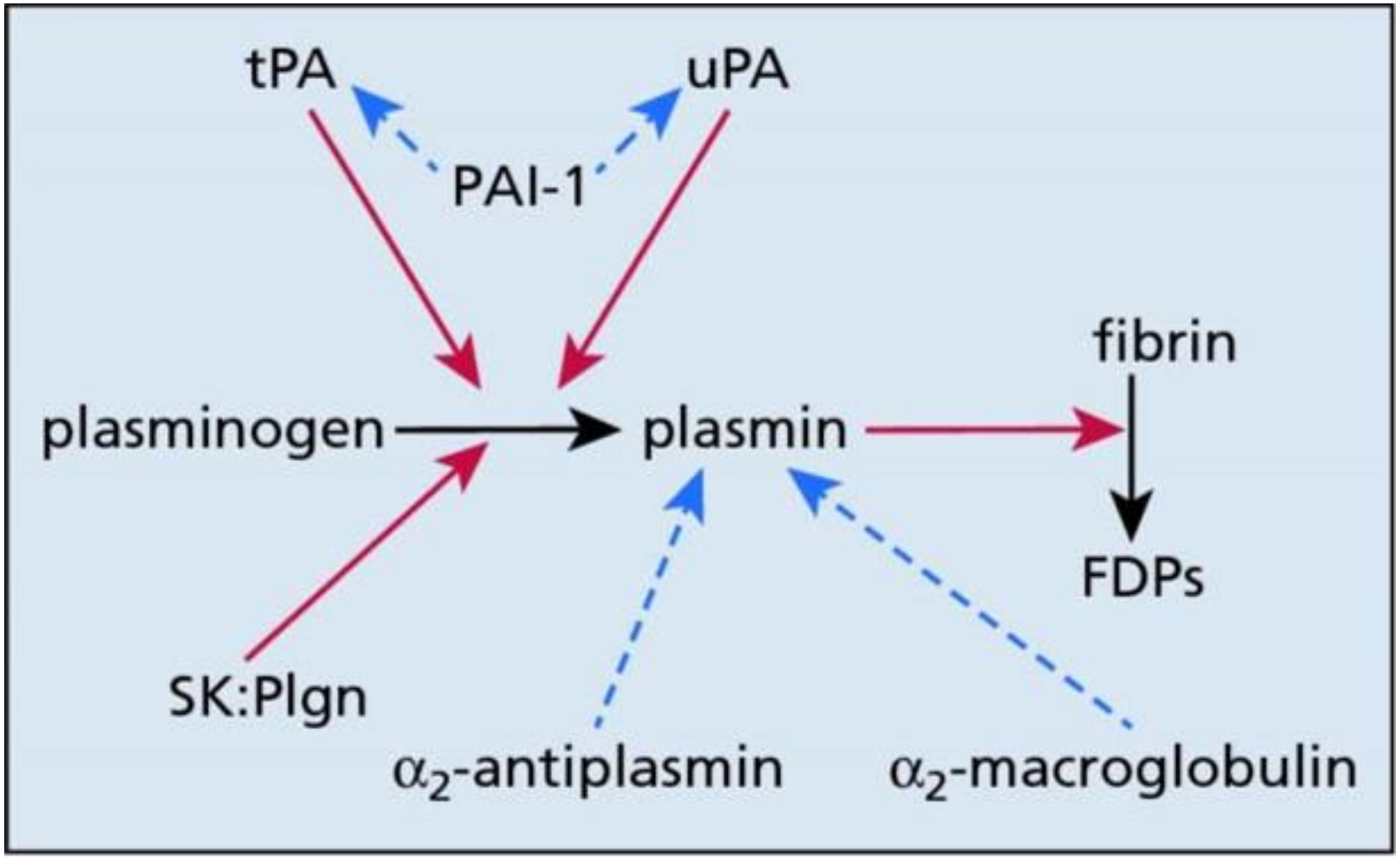
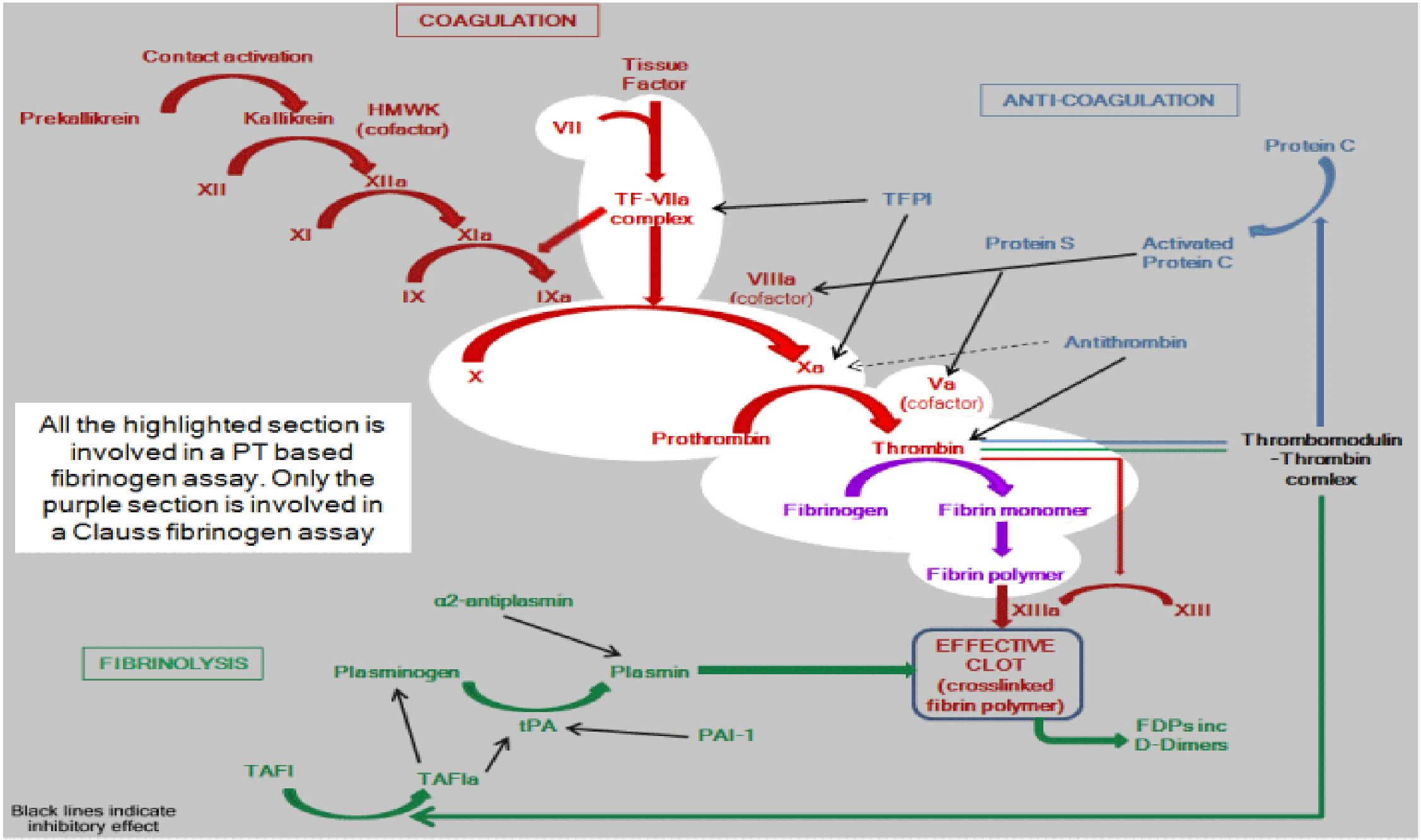
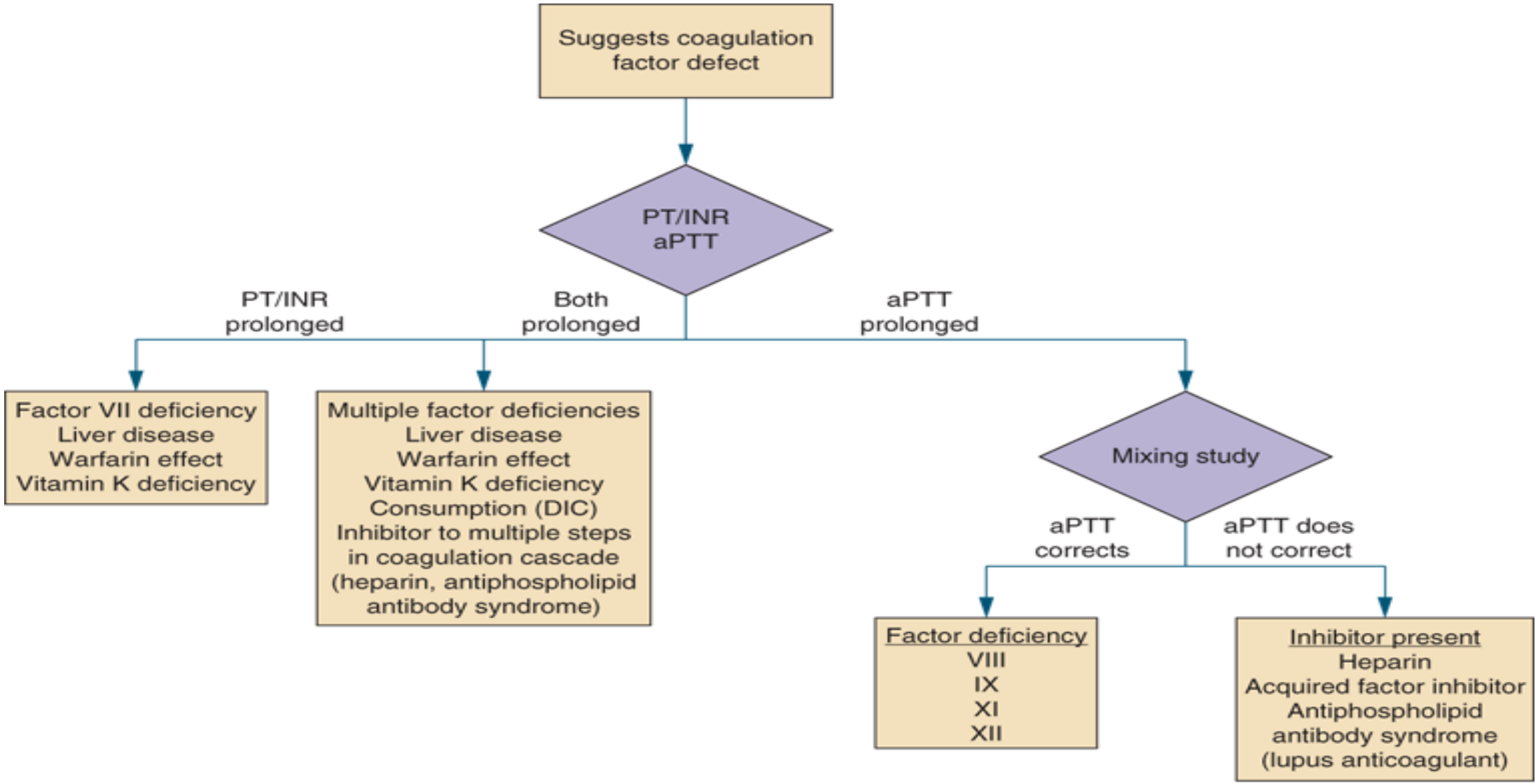


Figure 14.6 The fibrinolytic mechanism.


COAGULATION
Contact activation
Prekallikrein
Kallikrein
HMWK
(cofactor)
XII
XIIa
XI
XIa
IX
IXa
Tissue
Factor
VII
TF-VIIa
complex
X
Xa
Prothrombin
Thrombin
Fibrinogen
Fibrin monomer
Fibrin polymer
XIIIa
XIII
VIIIa
(cofactor)
Va
(cofactor)
ANTI-COAGULATION
TFPI
Protein C
Protein S
Activated
Protein C
Antithrombin
Thrombomodulin
-Thrombin
complex
All the highlighted section is involved in a PT based fibrinogen assay. Only the purple section is involved in a Clauss fibrinogen assay
FIBRINOLYSIS
α2-antiplasmin
Plasminogen
Plasmin
tPA
PAI-1
TAFI
TAFIa
EFFECTIVE
CLOT
(crosslinked
fibrin polymer)
FDPs inc
D-Dimers
Black lines indicate
inhibitory effect

Coagulation tests

- PT(INR),APTT.
- Fibrinogen.
- D-Dimer.
- Factors Assay.
- Mixing study.
- VWF test



aPTT, activated partial thromboplastin time; CAD, coronary artery disease; DIC, disseminated intravascular coagulation; GI, gastrointestinal; INR, international normalized ratio; ITP, idiopathic thrombocytopenia purpura; NSAIDs, nonsteroidal antiinflammatory drugs; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura.

INR	aPTT	TT/Fib	Platelets	Disorders
↑	N	N	N	Liver disease Vit K def Coumadin Factor VII
N	↑	N	N	Heparin Antiphospholipid Ab Factor VIII, IX, XI von Willebrand's (Factor XII)
N	N	↓	N	Hypofibrinogenemia Dysfibrinogenemia Thrombin Inhibitors Heparin
N	N	N	↓	ITP TTP/HUS Drugs Bone Marrow Splenomegaly

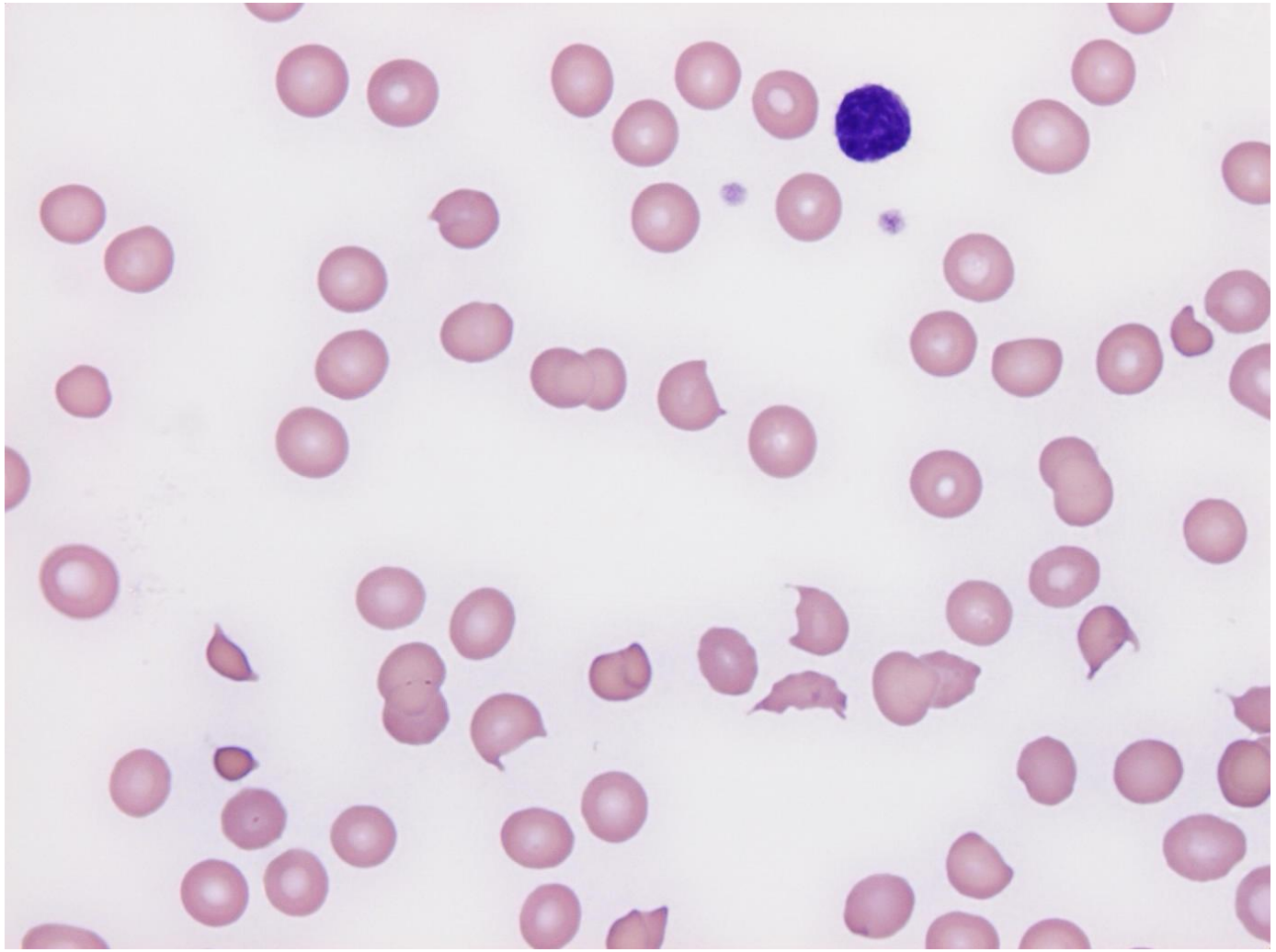
- A 30-year-old woman is admitted through A & E with a 2 days history of easy bruising, upon admission she had convulsion.

Test	Patient	Reference Range
Hb	7.6 g/dL	11.5-13.5g/dL
WCC	11.9 x 10^9/L	4 -11 x 10^9/L
Platelets	10 x 10^9/L	150 - 400 x 10^9/L
PT	13s	11-14s
APTT	35.6s	23-35s
Fibrinogen	2.1g/L	1.5-4.0g/L

. The LDH is elevated at 2389 U/dL

. The creatinine is raised at 389 µmol/mL

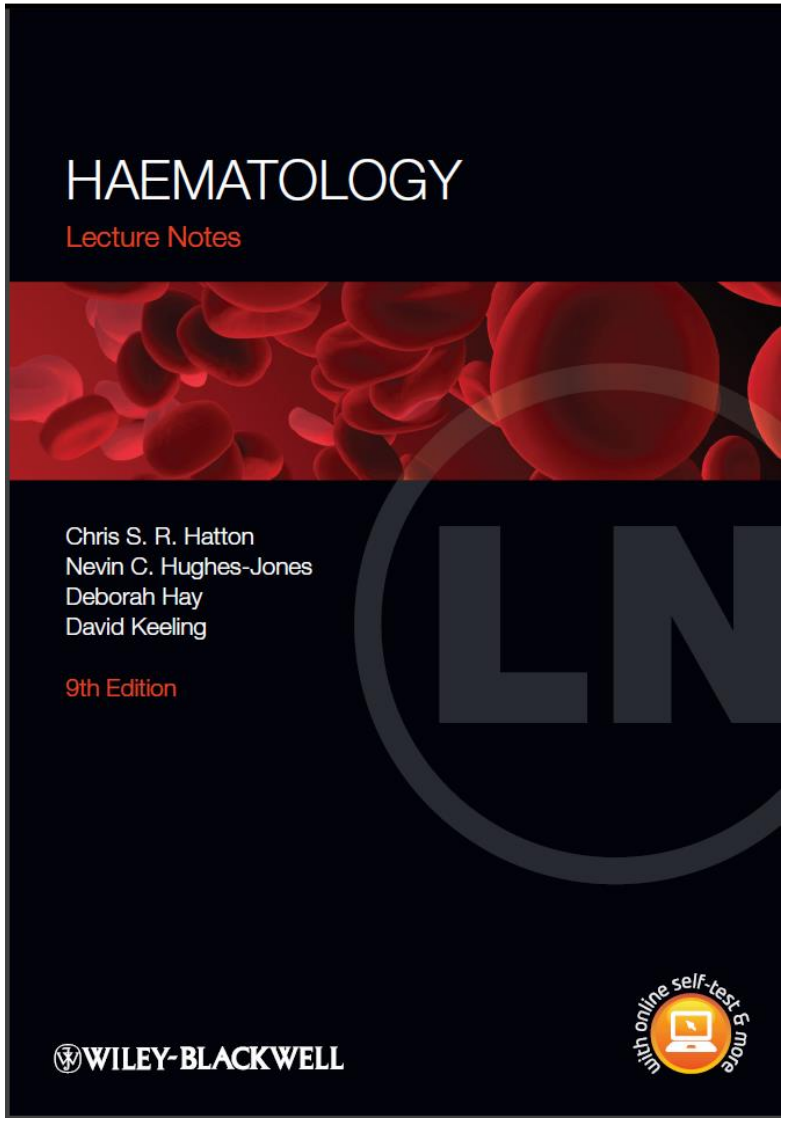
. A blood film is shown



- What is the diagnosis?
  Are there any additional tests you would request?

Test	Patient	Reference Range
ADAMTS13 Activity	<5%	66-126%
ADAMTS13 Inhibitor Assay	28 AU/mL	<11 AU/mL

What is the treatment in this disorder?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