Approach to bleeding disorders

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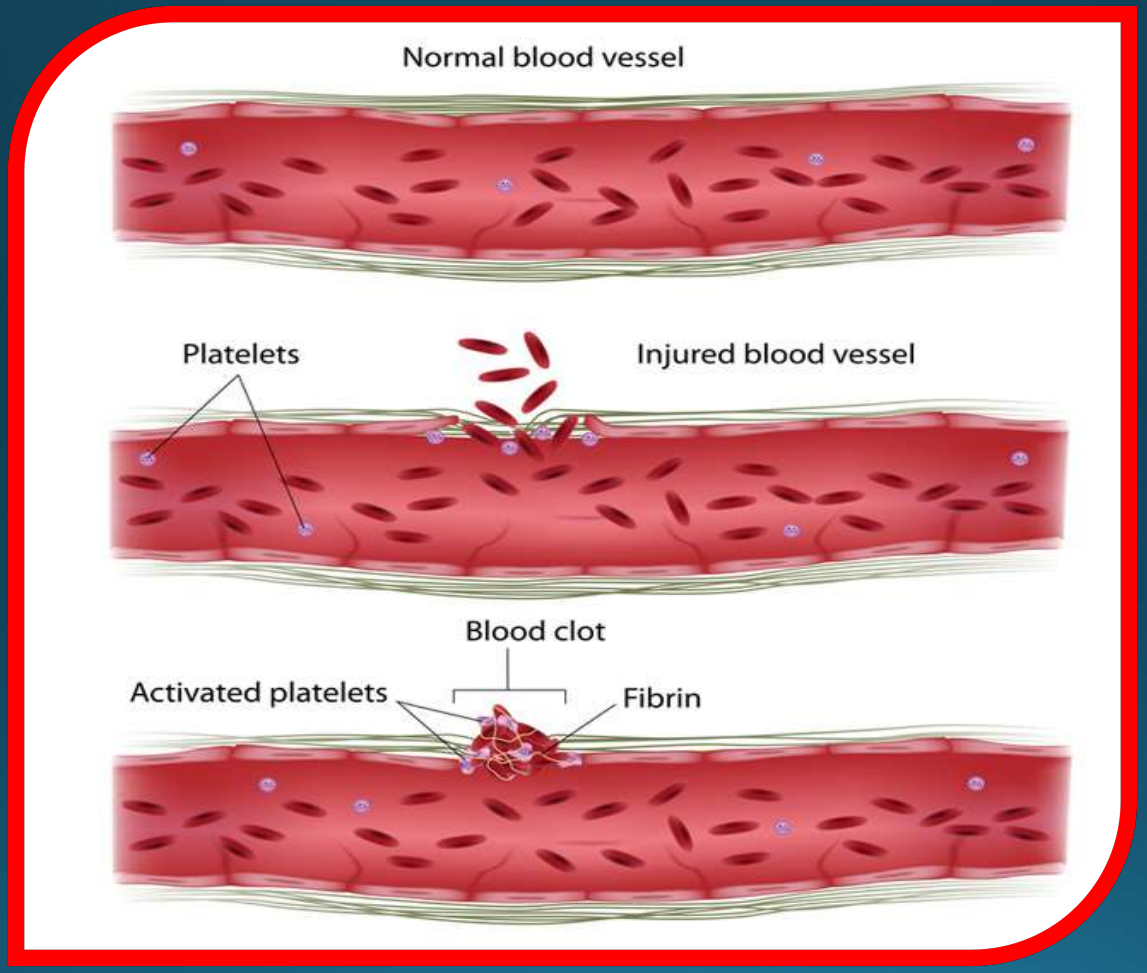
Normal hemostasis

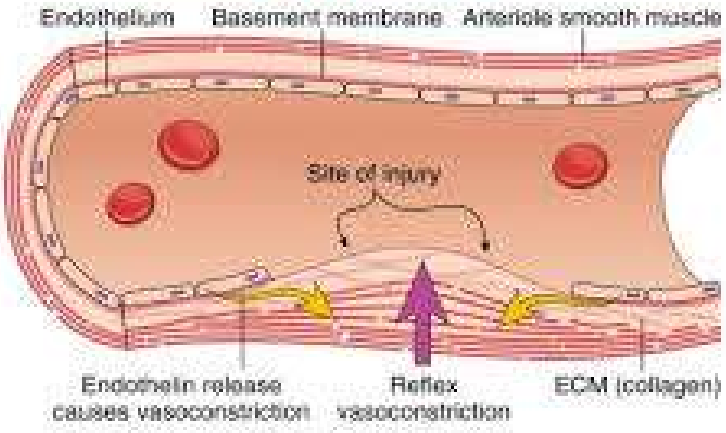
In health, hemostasis is the biologic process that limits hemorrhage after blood vessel injury.
If a vessel wall is damaged, a number of mechanisms are promptly activated to limit bleeding by a complex series of interrelated reactions involving endothelial cells, platelets, plasma coagulation factors, anticoagulant proteins and fibrinolytic proteins.


Normal blood vessel
Platelets
Injured blood vessel
Blood clot
Activated platelets
Fibrin

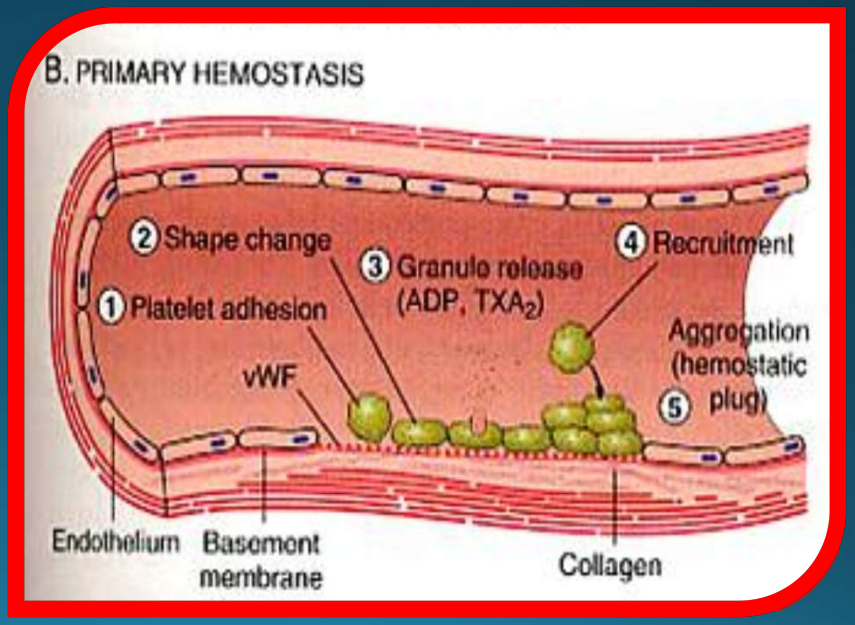
Primary hemostasis

- *Primary hemostasis occurs after damage to the vessel wall, and involves vasoconstriction and adhesion of platelets in a monolayer on exposed subendothelial fibrils. Subsequently, further platelets aggregate to form a platelet plug, which stems the flow of blood.*

Primary Hemostasis



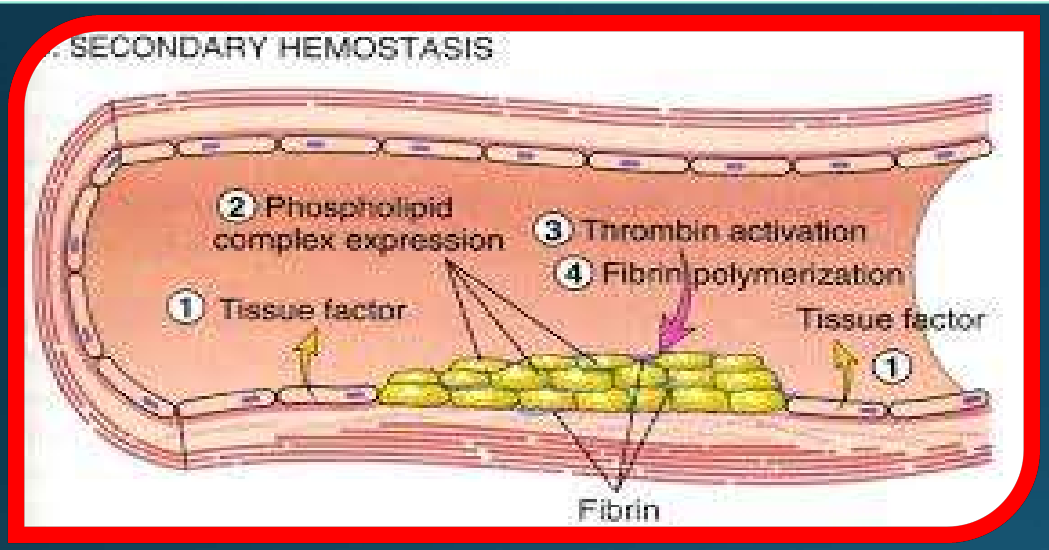
Step 1: Local Vasoconstriction



Secondary hemostasis

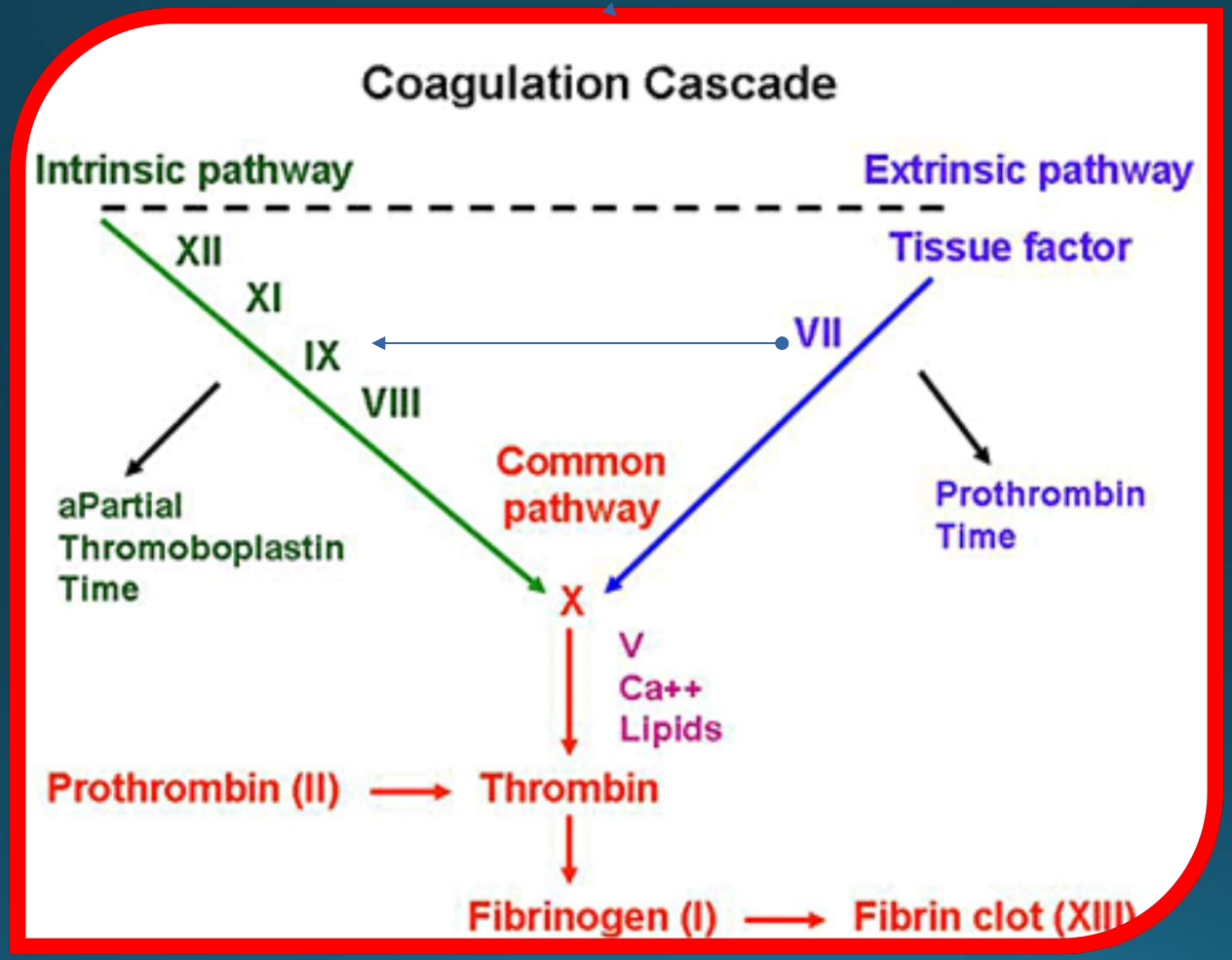
- ***Secondary hemostasis*** ***involves activation of the coagulation system, leading to the generation of fibrin strands, which are laid down between platelets and reinforce the platelet plug.***

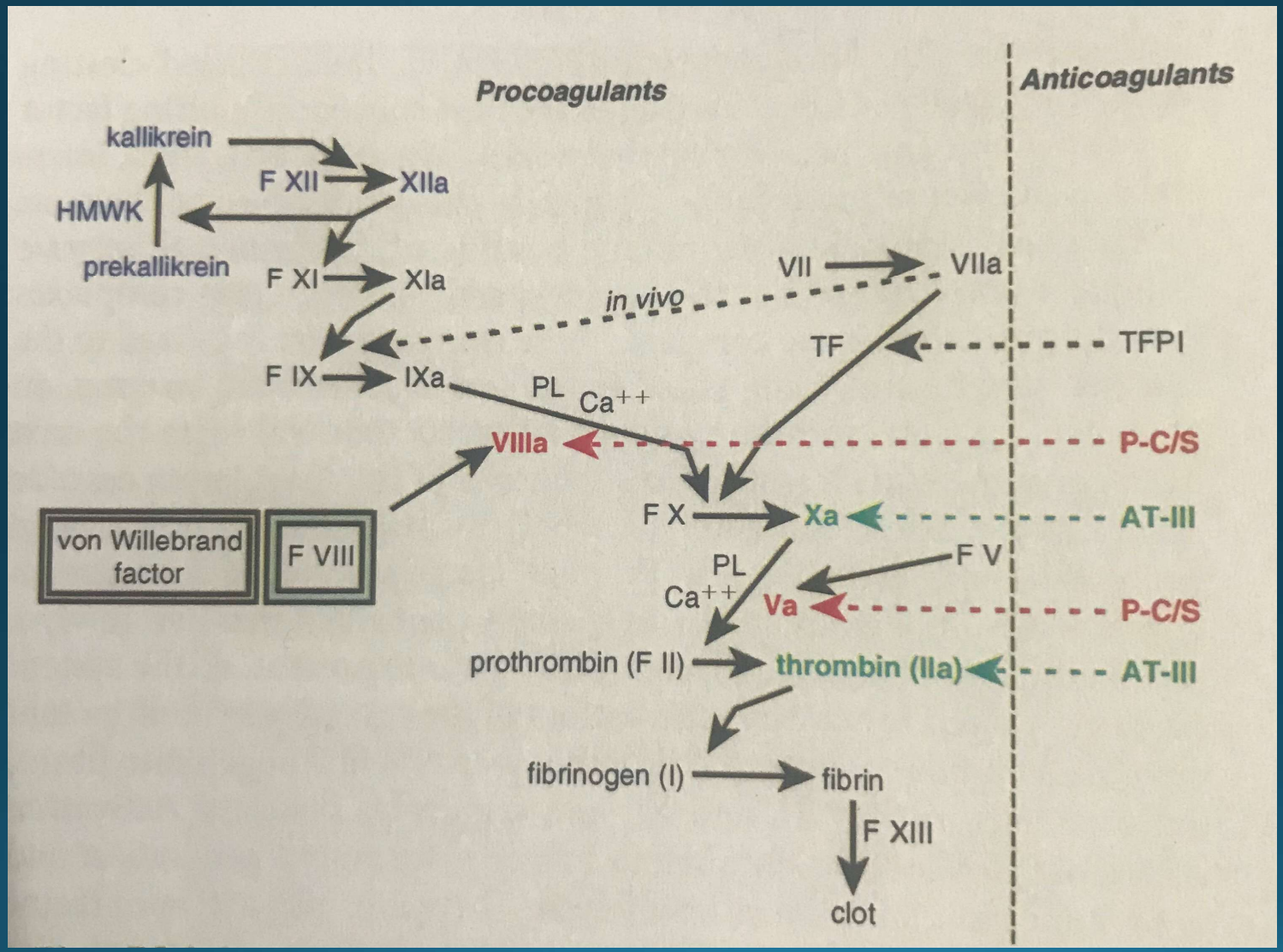
Initiation phase: The TF–FVIIa complex activates. The TF–FVIIa complex activates FIX and FX, and the activated FX cleaves prothrombin to form small amounts of thrombin.

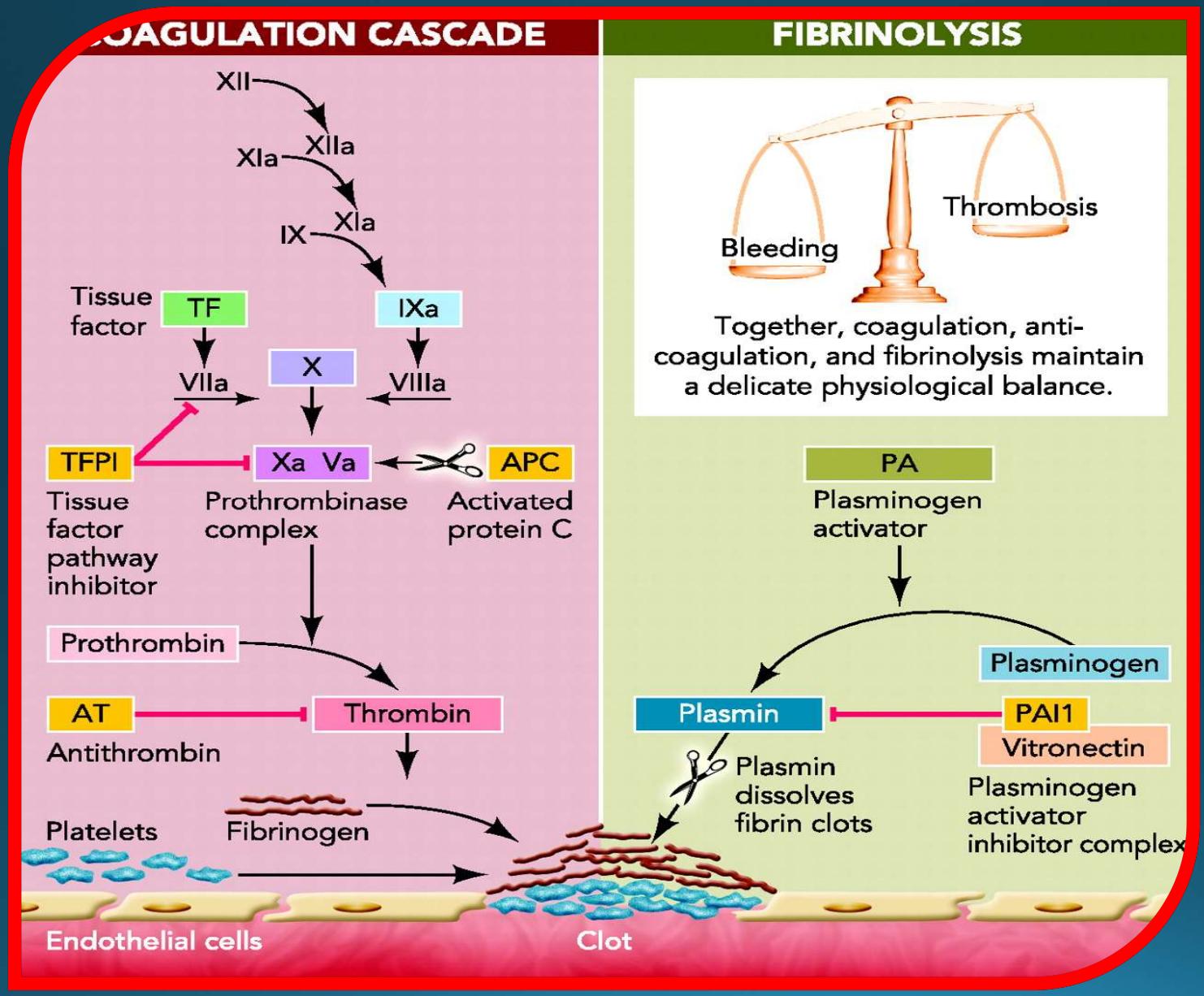


Propagation phase

The small amounts of thrombin that are formed activate FV, FVIII and FXI, leading to the formation of sufficient thrombin to overcome inhibitors and generate fibrin from fibrinogen, as well as activate FXIII to cross-link the fibrin and form a stable clot.


Coagulation Cascade
Intrinsic pathway
Extrinsic pathway
XII
XI
IX
VIII
VII
Tissue factor
aPartial
Thromoboplastin
Time
Common
pathway
Prothrombin
Time
X
V
Ca++
Lipids
Prothrombin (II)
Thrombin
Fibrinogen (I)
Fibrin clot (XIII)


Procoagulants
Anticoagulants
kallikrein
F XII
XIIa
HMWK
prekallikrein
F XI
XIa
VII
VIIa
in vivo
TF
TFPI
F IX
IXa
PL
Ca++
VIIIa
P-C/S
F X
Xa
AT-III
von Willebrand factor
F VIII
PL
Ca++
F V
Va
P-C/S
prothrombin (F II)
thrombin (IIa)
AT-III
fibrinogen (I)
fibrin
F XIII
clot


OAGULATION CASCADE
FIBRINOLYSIS
XII
XIIa
XIa
XIa
IX
Tissue factor
TF
IXa
VIIa
X
VIIIa
TFPI
Xa Va
APC
Tissue factor pathway inhibitor
Prothrombinase complex
Activated protein C
Prothrombin
AT
Thrombin
Antithrombin
Platelets
Fibrinogen
Endothelial cells
Clot
Bleeding
Thrombosis
Together, coagulation, anti-coagulation, and fibrinolysis maintain a delicate physiological balance.
PA
Plasminogen activator
Plasminogen
Plasmin
PAI1
Vitronectin
Plasmin dissolves fibrin clots
Plasminogen activator inhibitor complex

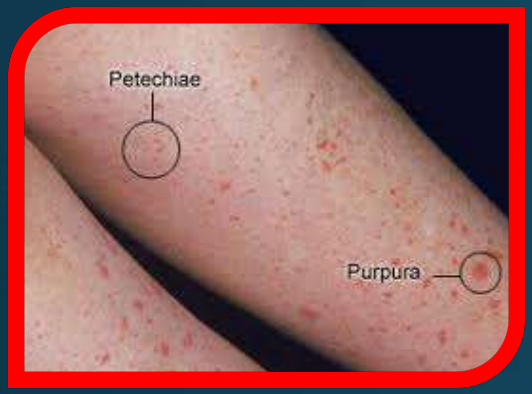
Assessment of bleeding symptoms

The assessment of an individual patient is a two-stage process:

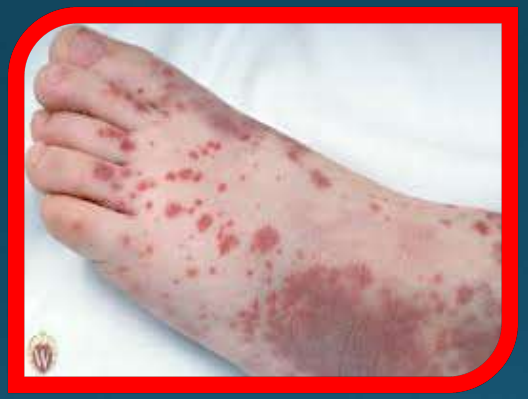
١. *History (Patient & family history, Drugs, Systemic illness) and focused clinical examination; and*

٢. *Laboratory investigation*

Kind of haemorrhage	Primary haemostasis	Secondary haemostasis
Petechiae- Purpura	++	--
Hemarthrosis	--	++
Ecchymosis - Hematoma	+	+
Beginning of haemorrhage after trauma	Immediate	Late
Mucosal bleeding	Spontaneous	With trauma
Local pressure	Effective	Non effective



Petechiae & Purpura



Ecchymosis

Hemarthrosis

Laboratory investigations

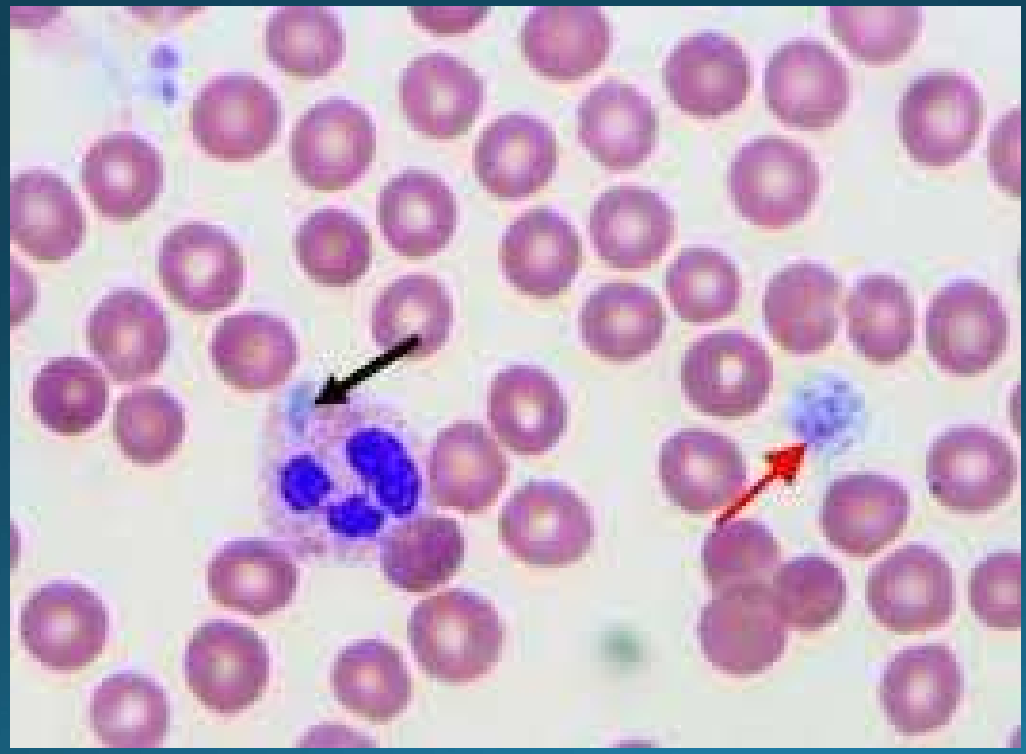
Test for Primary Hemostasis

- **Platelet Count**
- **Bleeding time**
  - **Duke's method**-ear lobule or Ant. Forearm two pricks 4 mm deep with special Lancet.

    Normal=3-5 min
  - **Ivy method--**two 10 mm long and 1mm deep incisions on fore arm with a blade.BP Apparatus cuff pressure 40 mm Hg.

    Normal -3-10min
- **Platelet aggregation tests**

May-Hegglin anomaly *is an autosomal dominant disorder characterized by:*
prominent Dohle bodies in granulocytic cells,
poorly granulated giant platelets,
and variable thombocytopenia that may cause purpura.



Bleeding time (BT)

Duke Bleeding Time

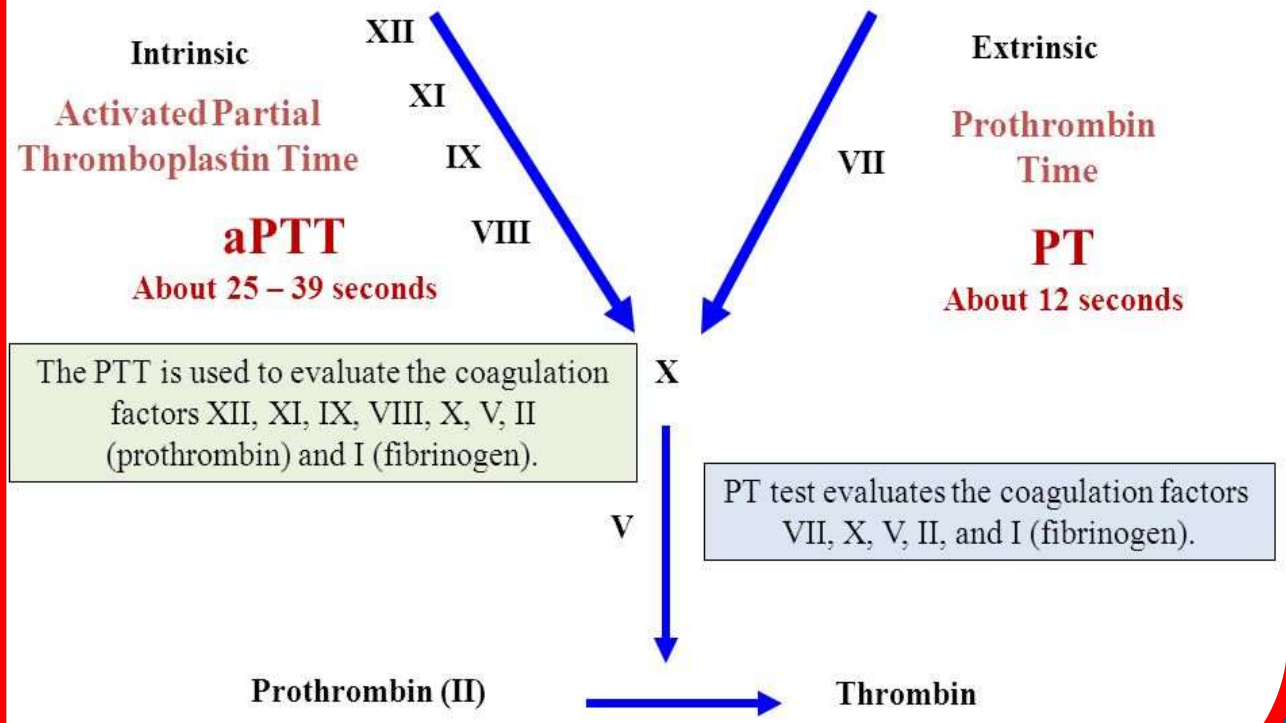
With the Duke method, the patient is pricked with a special needle or lancet, preferably on the earlobe or fingertip, after having been swabbed with alcohol. The prick is about 3-4 mm deep. The patient then wipes the blood every 30 seconds with a filter paper. The test ceases when bleeding ceases. The usual time is about 1-3 minutes.

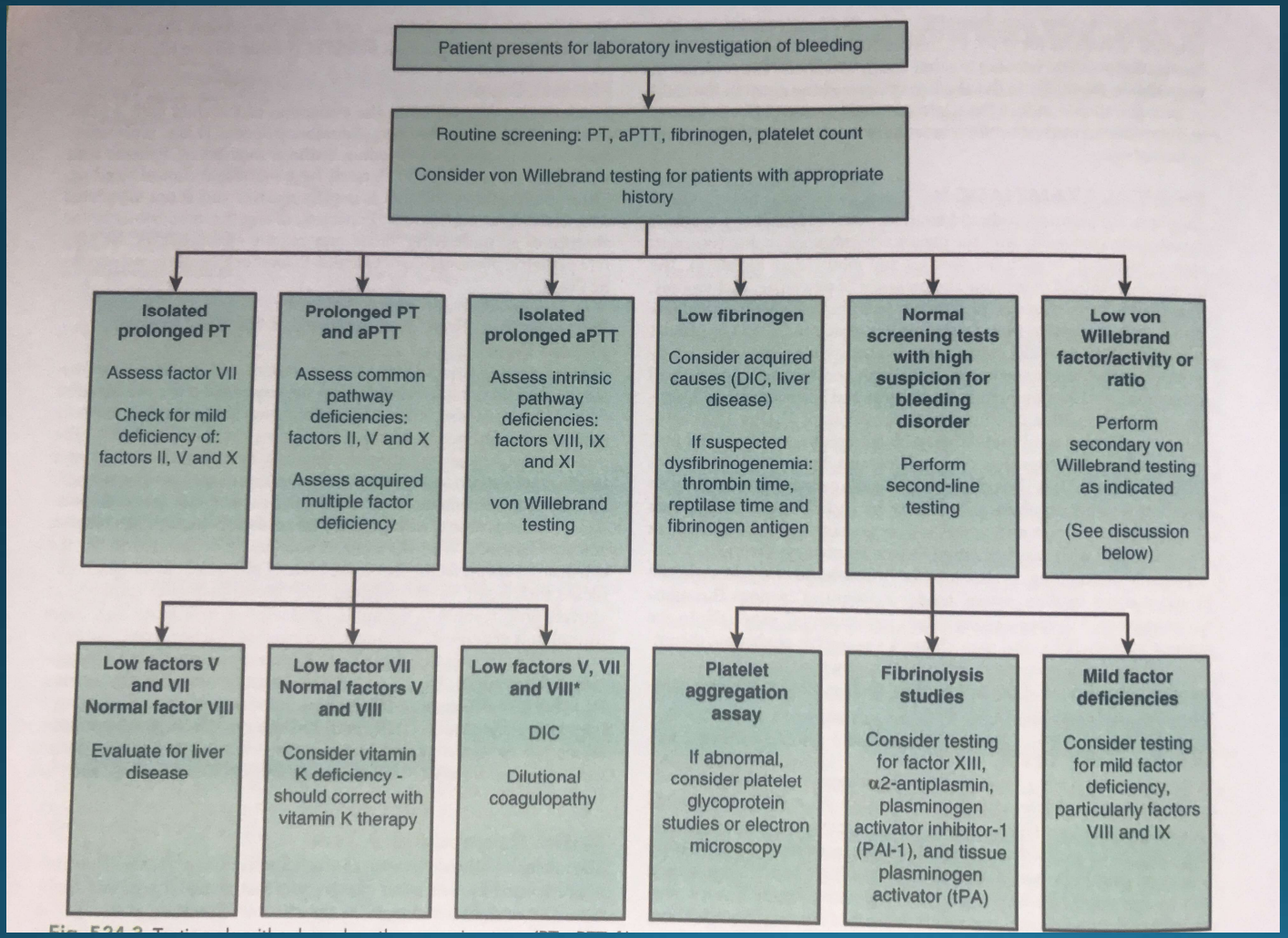
Ivy Method

1. A blood pressure cuff is used to maintain constant pressure within the capillaries to help standardize the procedure. The cuff is inflated to 40 mm Hg on the upper arm to control capillary tone and to improve the sensitivity and reproducibility.
2. The forearm is the bleeding time site used.
3. A sterile, disposable blood lancet is used and the length of time required for bleeding to cease is recorded.
4. The greatest source of variation in this test is largely due to difficulty in performing a standardized puncture. This usually leads to erroneously low results.

Normal Ivy BT = ٣- ١٠ min

Tests of Clotting Pathway




Patient presents for laboratory investigation of bleeding
Routine screening: PT, aPTT, fibrinogen, platelet count
Consider von Willebrand testing for patients with appropriate history
Isolated prolonged PT
Assess factor VII
Check for mild deficiency of: factors II, V and X
Prolonged PT and aPTT
Assess common pathway deficiencies: factors II, V and X
Assess acquired multiple factor deficiency
Isolated prolonged aPTT
Assess intrinsic pathway deficiencies: factors VIII, IX and XI
von Willebrand testing
Low fibrinogen
Consider acquired causes (DIC, liver disease)
If suspected dysfibrinogenemia: thrombin time, reptilase time and fibrinogen antigen
Normal screening tests with high suspicion for bleeding disorder
Perform second-line testing
Low von Willebrand factor/activity or ratio
Perform secondary von Willebrand testing as indicated
(See discussion below)
Low factors V and VII Normal factor VIII
Evaluate for liver disease
Low factor VII Normal factors V and VIII
Consider vitamin K deficiency - should correct with vitamin K therapy
Low factors V, VII and VIII*
DIC
Dilutional coagulopathy
Platelet aggregation assay
If abnormal, consider platelet glycoprotein studies or electron microscopy
Fibrinolysis studies
Consider testing for factor XIII, α2-antiplasmin, plasminogen activator inhibitor-1 (PAI-1), and tissue plasminogen activator (tPA)
Mild factor deficiencies
Consider testing for mild factor deficiency, particularly factors VIII and IX

If the patient has a very convincing history but normal screening tests:

it would be appropriate to consider measuring levels of the individual coagulation factors, usually beginning with FVIII and von Willebrand factor (VWF), as hemophilia A and von Willebrand disease are the most common congenital bleeding disorders

Other causes:

- *Factor XIII deficiency*
- *Platelet dysfunction*
- *Mild deficiency of FVIII, FIX, and FXI*
- *Antiplasmin deficiency and other cause hyperfibrinolysis*
- *Collagen vascular diseases (Ehler-Danlos syndrome)*
- *DOAC (Direct Oral Anticoagulants)*

Thank you for your attention