بسم الله الرحمن الرحيم

HEMOSTATIC DISORDERS

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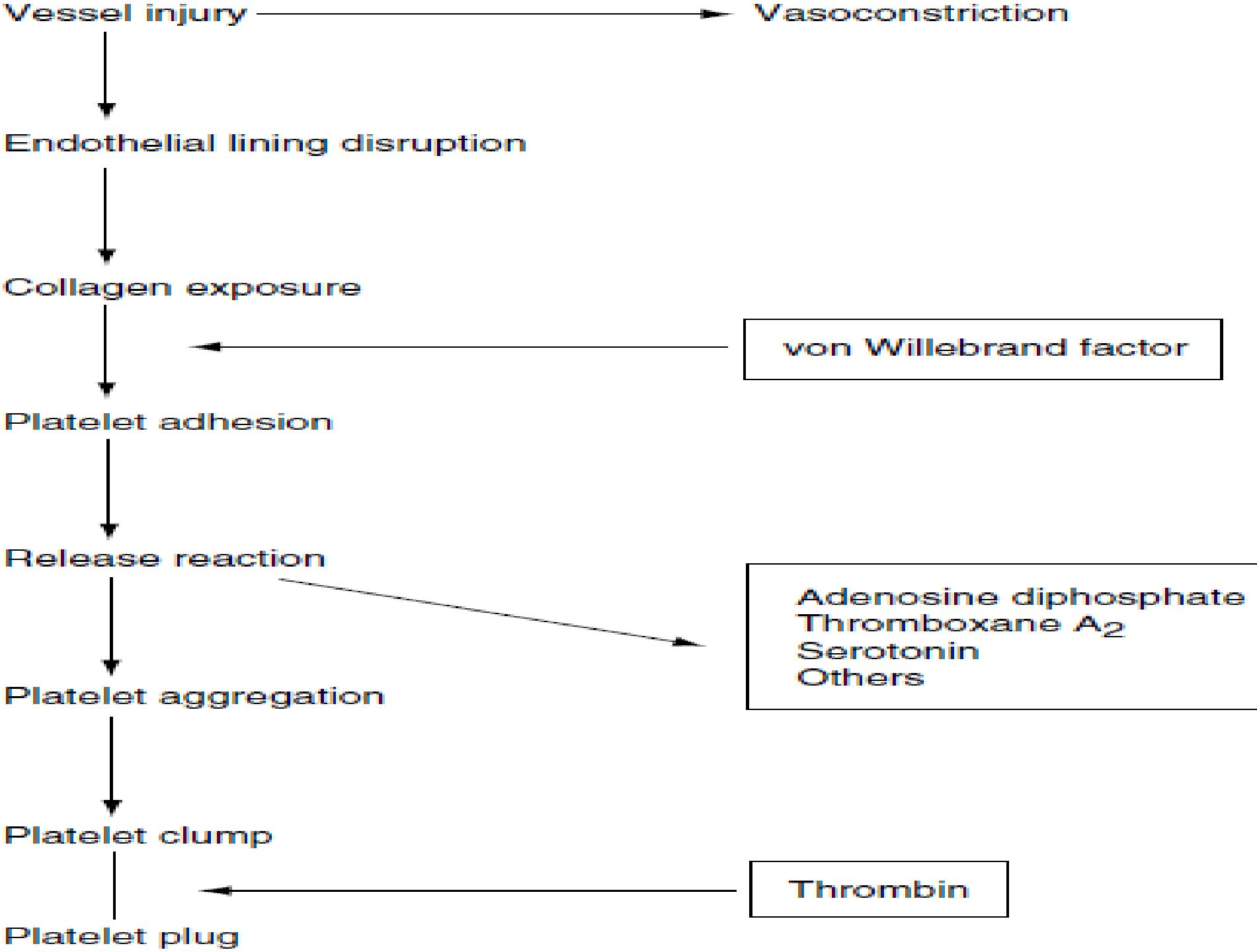
Physiology of Hemostasis

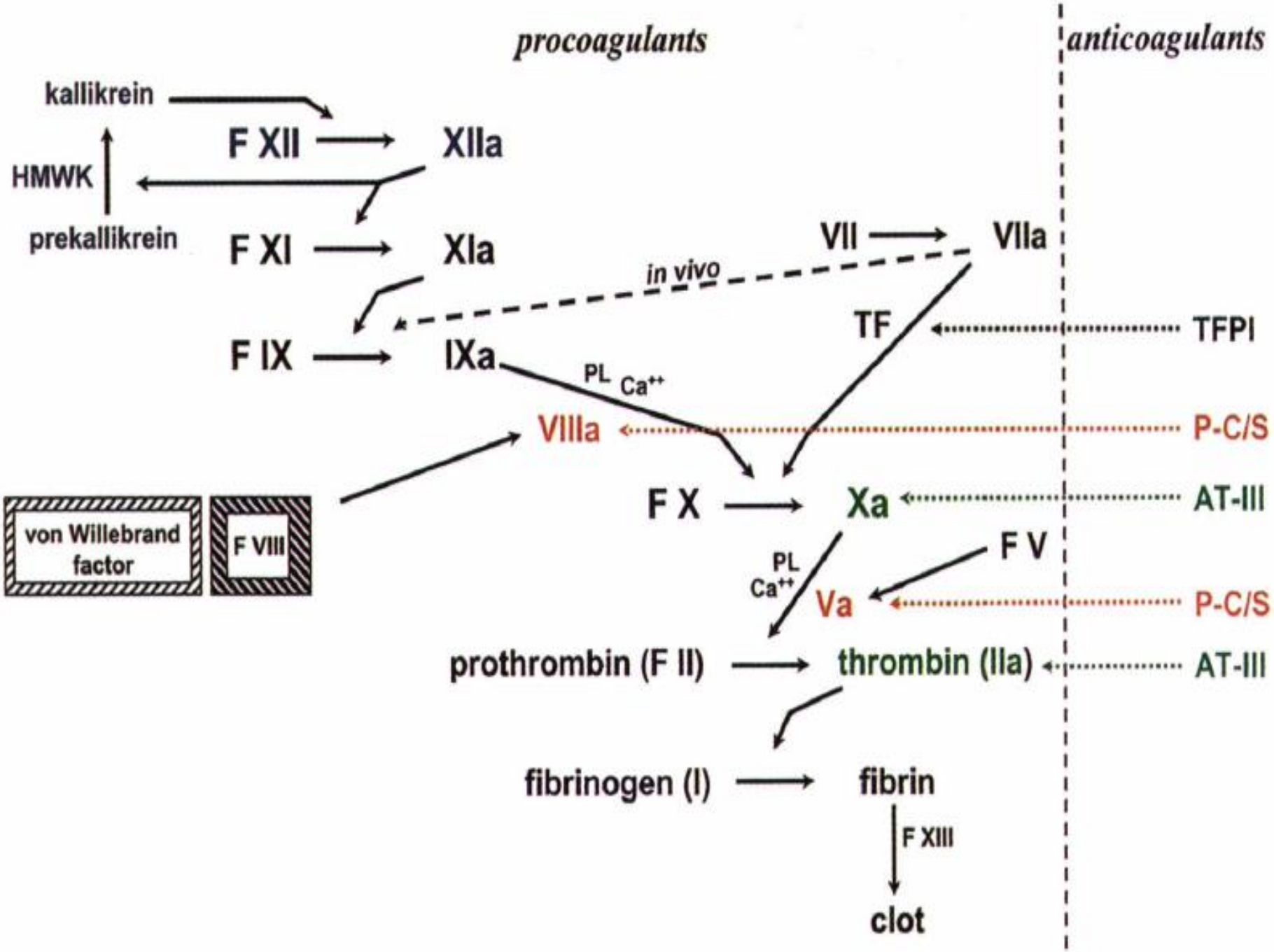
- 1. Vasoconstriction (vascular phase)
- 2. Platelet plug formation (primary hemostatic mechanism—platelet phase)
- 3. Fibrin thrombus formation (initiation, amplification, and propagation phases).

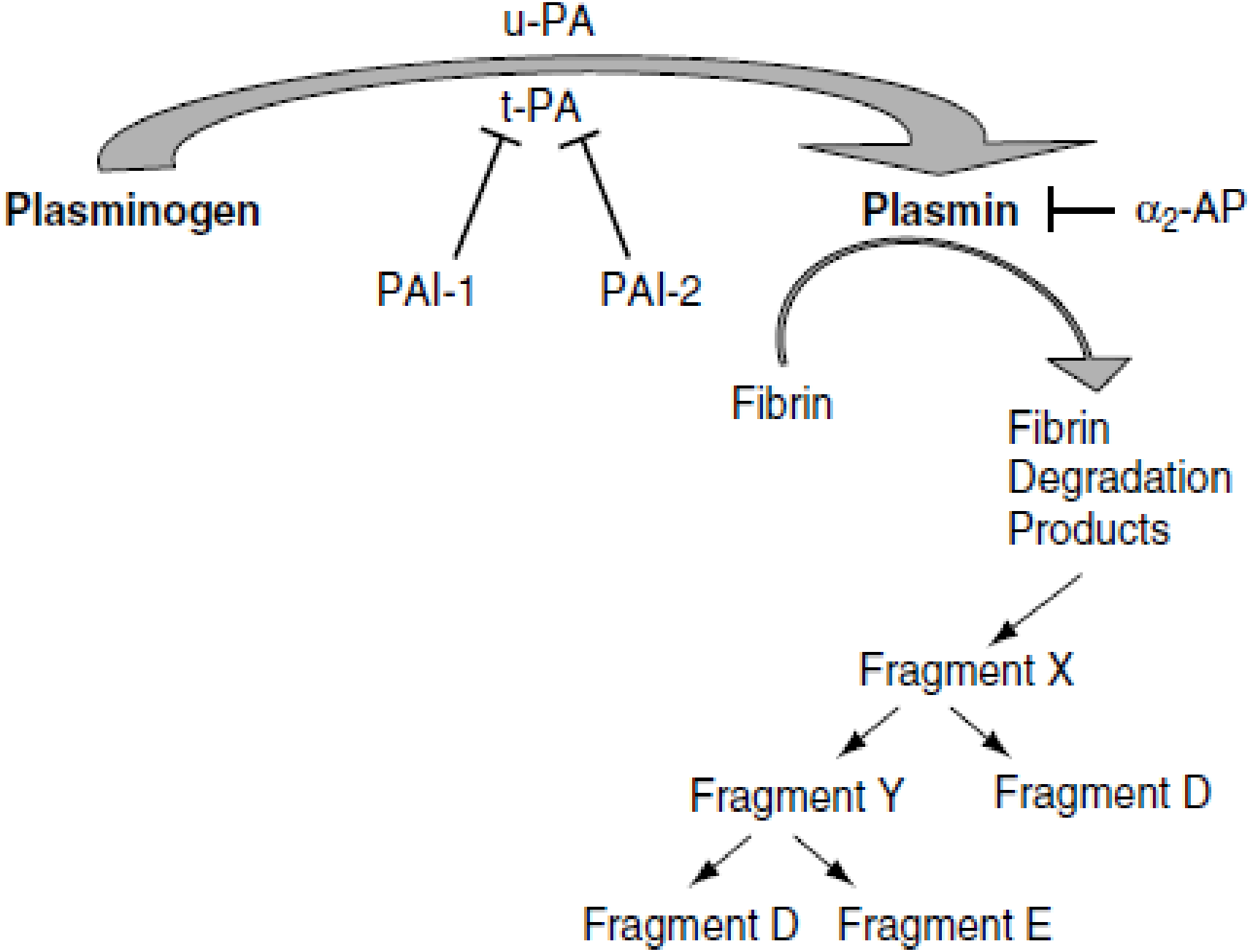

Vessel injury
Vasoconstriction
Endothelial lining disruption
Collagen exposure
von Willebrand factor
Platelet adhesion
Release reaction
Adenosine diphosphate
Thromboxane A_2
Serotonin
Others
Platelet aggregation
Platelet clump
Thrombin
Platelet plug

Primary Hemostatic Mechanism (Platelet Phase)

- Endothelial injury exposes von Willebrand factor and collagen from the subendothelial matrix to flowing blood and shear forces. Plasma vWF binds to the exposed collagen. Initially the vWF interacts with the GPIb platelet receptor, tethering the platelets. Because the platelet collagen receptors GPVI and α2β1 bind to collagen, the platelets adhere and become activated with a resulting release of platelet alpha and dense granule contents. Platelet activation results in a conformational change in the α11bβ3 receptor, activating it and enhancing its avidity for von Willebrand factor, for vessel wall ligands, and for fibrinogen. The enhanced avidity for von Willebrand factor and fibrinogen mediates platelet-to-platelet interactions, which eventually lead to platelet plug

  formation.


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
von Willebrand factor
F VIII
F X
Xa
AT-III
F V
PL
Ca++
Va
P-C/S
prothrombin (F II)
thrombin (IIa)
AT-III
fibrinogen (I)
fibrin
F XIII
clot


u-PA
t-PA
Plasminogen
Plasmin
α_2-AP
PAI-1
PAI-2
Fibrin
Fibrin Degradation Products
Fragment X
Fragment Y
Fragment D
Fragment D
Fragment E

DETECTION OF HEMOSTATIC DEFECTS

1. Detailed history

- Symptoms: epistaxis, gingival bleeding, easy bruising, menorrhagia, hematuria, neonatal bleeding, gastrointestinal bleeding, hemarthrosis, prolongedbleeding after lacerations.
- circumcision, surgery, phlebotomy, immunization/intramuscular injection
- Underlying medical conditions: known associations with hemostatic defects (liver disease, renal failure, vitamin K deficiency).
- Medications: antiplatelet drugs (nonsteroidal anti-inflammatory drugs), anticoagulants(warfarin, heparin, low-molecular-weight heparin), antimetabolite(L-asparaginase).
- Family history(siblings, parents,aunts, uncles, grandparents).

2. Complete physical examination:

- petechiae, ecchymoses, hematomas, synovitis/joint effusion, arthropathy, muscle atrophy

LABORATORY TEST

- PT
- PTT
- Platlet count
- BT
- TT
- Vwf testing

3. Laboratory evaluation

- Complete blood count (CBC): quantitative assessment of platelets.

  Assessments of platelet function:

- Bleeding time: prolonged with impaired platelet function, platelet counts reduced below 80,000–100,000/mm3 or impaired vascular integrity.
- Platelet function analyzer (PFA 100)

  Coagulation factor screening tests

- Prothrombin time (PT) assay (assesses the extrinsic system): utilizes tissue thromboplastin and calcium chloride to initiate the formation of thrombin via the extrinsic pathway.

3. Laboratory evaluation

- Partial thromboplastin time (PTT) assay (assesses the intrinsic system): utilizes a phospholipid reagent, a particulate activator (e.g., ellagic acid, kaolin,silica, soy extract), and calcium chloride to start the enzyme reaction that leads to the formation of thrombin via the intrinsic pathway.
- Thrombin time: prolonged when fibrinogen is reduced or abnormal, in the presence of inhibitors (fibrin degradation products, D dimers), and in the presence of thrombin-inhibiting drugs. Useful when both the PT and PTT are prolonged

3. Laboratory evaluation

- von Willebrand antigen: quantitative assay for von Willebrand factor, useful when bleeding time or PFA-100 closure time is prolonged or when von Willebrand disease is suspected.
- Urea clot lysis assay: useful screen for FXIII deficiency. In the absence of fibrin cross linkage by FXIII, a clot will degrade with incubation in 5 M urea.

Preoperative Evaluation of Hemostasis

- 1. History (the most important element of the evaluation)

a. If negative: no coagulation tests are indicated; only a CBC.

b. If positive or unreliable, the following tests should be performed: CBC,bleeding time, PT, PTT, and fibrinogen.

- 2. Abnormal tests require further investigation

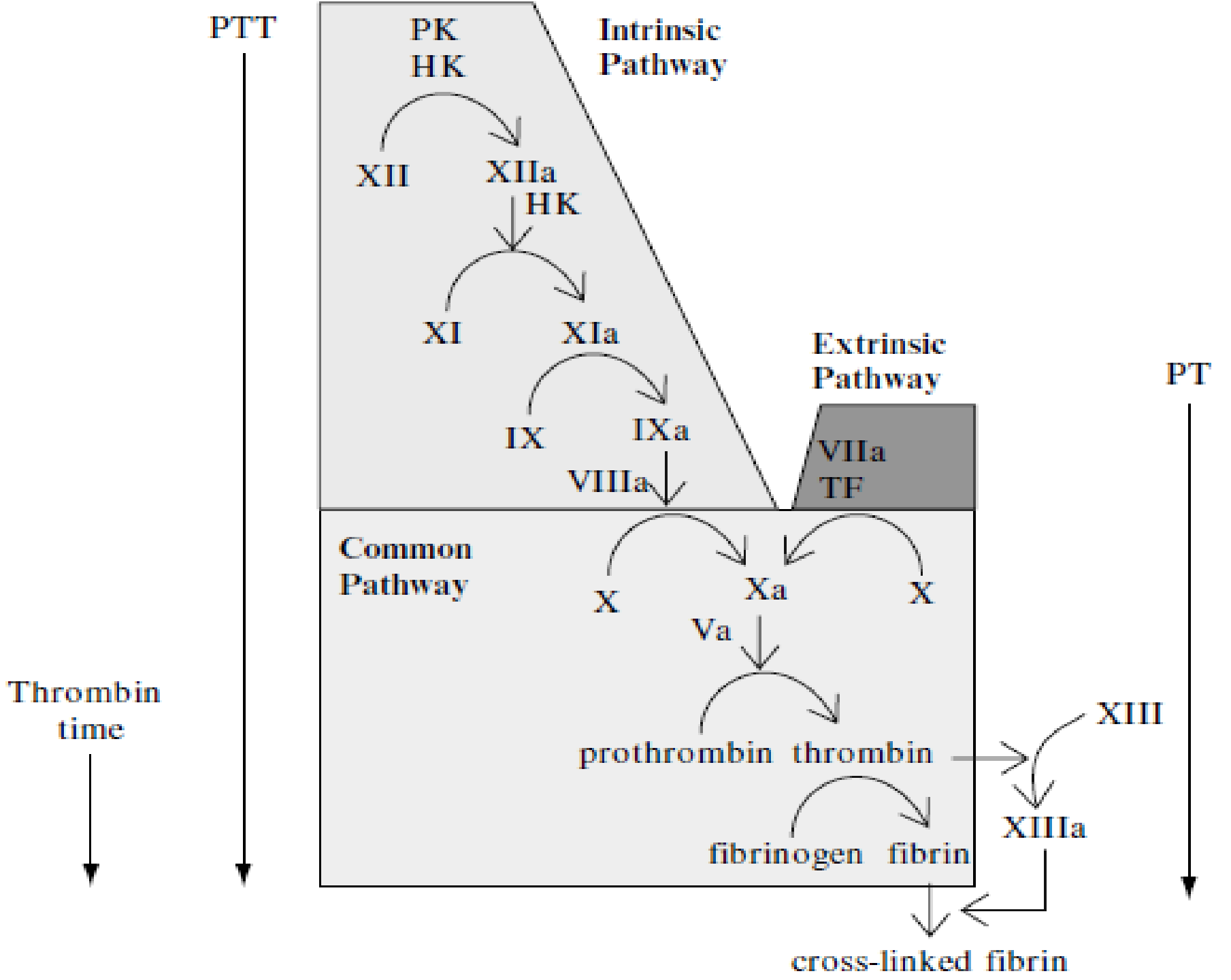

PTT
PK
HK
Intrinsic
Pathway
XII
XIIa
HK
XI
XIa
IX
IXa
VIIIa
Extrinsic
Pathway
VIIa
TF
PT
Common
Pathway
X
Xa
X
Va
Thrombin
time
prothrombin
thrombin
XIII
XIIIa
fibrinogen
fibrin
cross-linked fibrin

Table 11-9. Genetics, Prevalence, Coagulation Studies, and Symptoms of Inherited Coagulation Factor Deficiencies

Factor deficiency	Genetics	Est. Prevalence	BT	APTT	PT	Associated with bleeding episodes
Afibrinogenemia	AR	1:1 million	N	P	P	++
Dysfibrinogenemia	AR		N	N/P	P	+/−
II	AR	1:2 million	N	P	P	++
V (parahemophilia)	AR	1:1 million	N	P	P	++
VII	AR	1:500,000	N	N	P	+
VIII (hemophilia A)	XLR	1:10,000	N	P	N	+++
von Willebrand disease		1:1,000				
Type 1	AD		N/P	N/P	N	+
Type 2	AD		P	N/P	N	++
Type 3	AR		P	P	N	++
IX (hemophilia B)	XLR	1:60,000	N	P	N	+++
X	AR	1:1 million	N	P	P	++
XI (hemophilia C)	AR	1:1 million	N[a]	P	N	+
XII	AD		N	P	N	−
XIII	AR	1:1 million	N	N	N	+[c]

- Hemophilia A (factor VlIl deficiency) and hemophilia B (factorIX deficiency) are the most common and serious congenital coagulation factor deficiencies.

Clinical Course of Hemophilia

- Hemophilia should be suspected when unusual bleeding is encountered in a male patient. Clinical presentations of hemophilia A and hemophilia B are indistinguishable.
- The frequency and severity of bleeding in hemophilia are usually related to the plasma levels of factor VIII or IX .
- The median age for first bleeding episode is 10 months, corresponding to the age at which the infant becomes mobile.

CLINICAL MANIFESTATIONS

Neither factor VlIl nor factor IX crosses the placenta; Only approximately 2% of neonates with hemophilia sustain intracranial hemorrhages and 30% of male infants with hemophilia bleed with circumcision.

CLINICAL MANIFESTATIONS

- Even in patients with severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age.
- the hallmark of hemophilia is hemarthrosis.

Table 11-11. Relationship of Factor Levels to Severity of Clinical Manifestations of Hemophilia A and B

Type	Percentage factor VIII/IX	Type of hemorrhage
Severe	<1	Spontaneous; hemarthroses and deep soft tissue hemorrhages
Moderate	1–5	Gross bleeding following mild to moderate trauma; some hemarthrosis; seldom spontaneous hemorrhage
Mild	5–25	Severe hemorrhage only following moderate to severe trauma or surgery
High-risk carrier females	Variable	Gynecologic and obstetric hemorrhage common, other symptoms depend on plasma factor level.

Table 11-12. Common Sites of Hemorrhage in Hemophilia

- Hemarthrosis
- Intramuscular hematoma
- Hematuria
- Mucous membrane hemorrhage
  - Mouth
  - Dental
  - Epistaxis
  - Gastrointestinal
- High-risk hemorrhage
  - Central nervous system
    - Intracranial
    - Intraspinal
  - Retropharyngeal
  - Retroperitoneal
  - Hemorrhage causing compartment syndrome/nerve compression
    - Femoral (iliopsoas muscle)
    - Sciatic (buttock)
    - Tibial (calf muscle)
    - Perineal (anterior compartment of leg)
    - Median and ulnar nerve (flexor muscles of forearm)

Table 11-13. Incidence of Severity and Clinical Manifestations of Hemophilia

Severity	Severe	Moderate	Mild
Incidence			
Hemophilia A	70%	15%	15%
Hemophilia B	50%	30%	20%
Bleeding manifestations			
Age of onset	≤1 year	1–2 years	2 years–adult
Neonatal hemorrhages			
Following circumcision	Common	Common	None
Intracranial	Occasionally	Rare	Rare
Muscle/joint hemorrhage	Spontaneous	Following minor trauma	Following trauma
CNS hemorrhage	High risk	Moderate risk	Rare[a]
Postsurgical hemorrhage	Common	Common	Rare[a]
Oral hemorrhage[b]	Common	Common	Rare[a]

[a]FVIII, >25; FIX, >15.

[b]Following trauma or tooth extraction.

Treatment

- Factor replacement therapy is the mainstay of hemophilia treatment. The degree of factor correction required to achieve hemostasis is largely determined by the site and nature of the particular bleeding episode.
- Strategies for hemophilia care include on demand treatment of acute bleeding episodes or, for severe hemophilia patients, prophylactic administration of clotting factor concentrate to maintain trough factor levels >1% augmented with on-demand treatment of breakthrough bleeding episodes.

Ancillary Therapy

- DDAVP
- In hemophilia A patients (DDAVP) increases plasma FVIII levels 2.5- to 6-fold. It is commonly used to treat selected hemorrhagic episodes in mild hemophilia A patients. When used intravenously the dose is 0.3 µg/kg administered in 25–50 mL normal saline over 15–20 minutes. Subcutaneous DDAVP is as effective as intravenous DDAVP, facilitating treatment of very young patients with limited venous access.
- Concentrated intranasal DDAVP (Stimate), available as a 1.5-mg/mL preparation,has approximately two thirds the effect of intravenous DDAVP.

Table 11-15. Treatment of Bleeding Episodes

Type of hemorrhage	Hemostatic factor level	Hemophilia A	Hemophilia B	Comment/ adjuncts
Hemarthrosis	30–50% minimum	FVIII 20–40 U/kg q12–24h as needed; if joint still painful after 24 h, treat for further 2 days	FIX 30–40 U/kg q24h as needed; if joint still painful after 24 h, treat for further 2 days	Rest, immobilization, cold compress, elevation.
Muscle	40–50% minimum, for iliopsoas or compartment syndrome, 100%, then 50–100% × 2–4 days	20–40 U/kg q12–24h as needed For iliopsoas or compartment syndrome, initial dose is 50 U/kg	40–60 U/kg q24h as needed For iliopsoas or compartment syndrome, initial dose is 60–80 U/kg	Calf/forearm bleeds can be limb threatening. Significant blood loss can occur with femoral-retroperitoneal bleed.
Oral mucosa	Initially 50%, then EACA at 50 mg/kg q6h × 7 days usually suffices	25 U/kg	50 U/kg	Antifibrinolytic therapy is critical. Do not use with PCC or APCC.
Epistaxis	Initially 30–40%, use of EACA 50 mg/kg q6h until healing occurs may be helpful	15–20 U/kg	30–40 U/kg	Local measures: pressure, packing.
Gastrointestinal	Initially 100%, then 50% until healing occurs	FVIII 50 U/kg, then 25 U/kg q12h	FIX 100 U/kg, then 50 U/kg q day	Lesion is usually found, endoscopy is recommended, antifibrinolytic therapy may be helpful.

Table 11-15. (*Continued*)

Type of hemorrhage	Hemostatic factor level	Hemophilia A	Hemophilia B	Comment/ adjuncts
Hematuria	Painless hematuria can be treated with complete bed rest and vigorous hydration for 48 hrs. For pain or persistent hematuria 100%	FVIII 50 units/kg; if not resolved, 30–40 U/kg q day until resolved	FIX 80–100 units/kg; if not resolved, then 30–40 U/kg q day until resolved	Evaluate for stones or urinary tract infection. Lesion may not be found. Prednisone 1–2 mg/kg/d × 5–7 days may be helpful. Avoid antifibrinolytics.
Central nervous system	Initially 100%, then 50–100% for 14 days	50 U/kg, then 25 U/kg q12h	80–100 U/kg, then 50 U/kg q24h	Treat presumptively before evaluating, hospitalize. Lumbar puncture requires prophylactic factor coverage.
Retroperitoneal retropharyngeal	Initially 80–100%, then 50–100% until complete resolution	FVIII 50 units/kg, then 25 U/kg q12h until resolved	FIX 100 U/kg, then 50 U/kg q24h until resolved	Hospitalize.
Trauma or surgery	Initially 100%, then 50% until wound healing is complete	50 U/kg, then 25 U/kg q12h	100 U/kg, then 50 U/kg q24h	Evaluate for inhibitor prior to elective surgery.

Ancillary Therapy

- Antifibrinolytic Therapy
- Antifibrinolytic drugs inhibit fibrinolysis by preventing activation of the proenzyme plasminogen to plasmin.
- Tranexamic acid (Cyklokapron):
- 20–25 mg/kg (maximum, 1.5 g) orally or
- 10 mg/kg(maximum, 1.0 g) intravenously every 8 hours.

THANK YOU