Hemodynamic Disorders III

Haemostasis (coagulation factors and endothelium)

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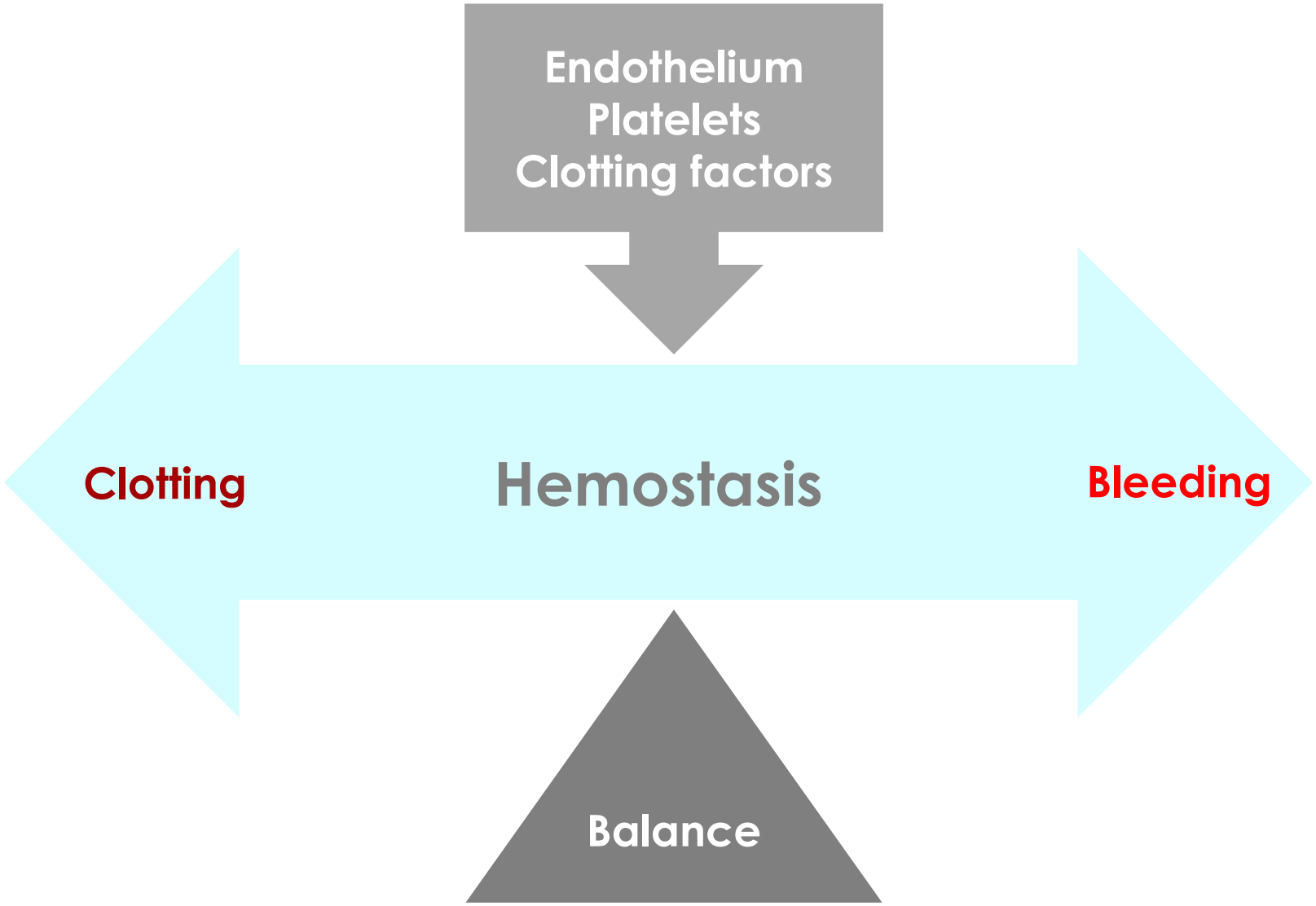
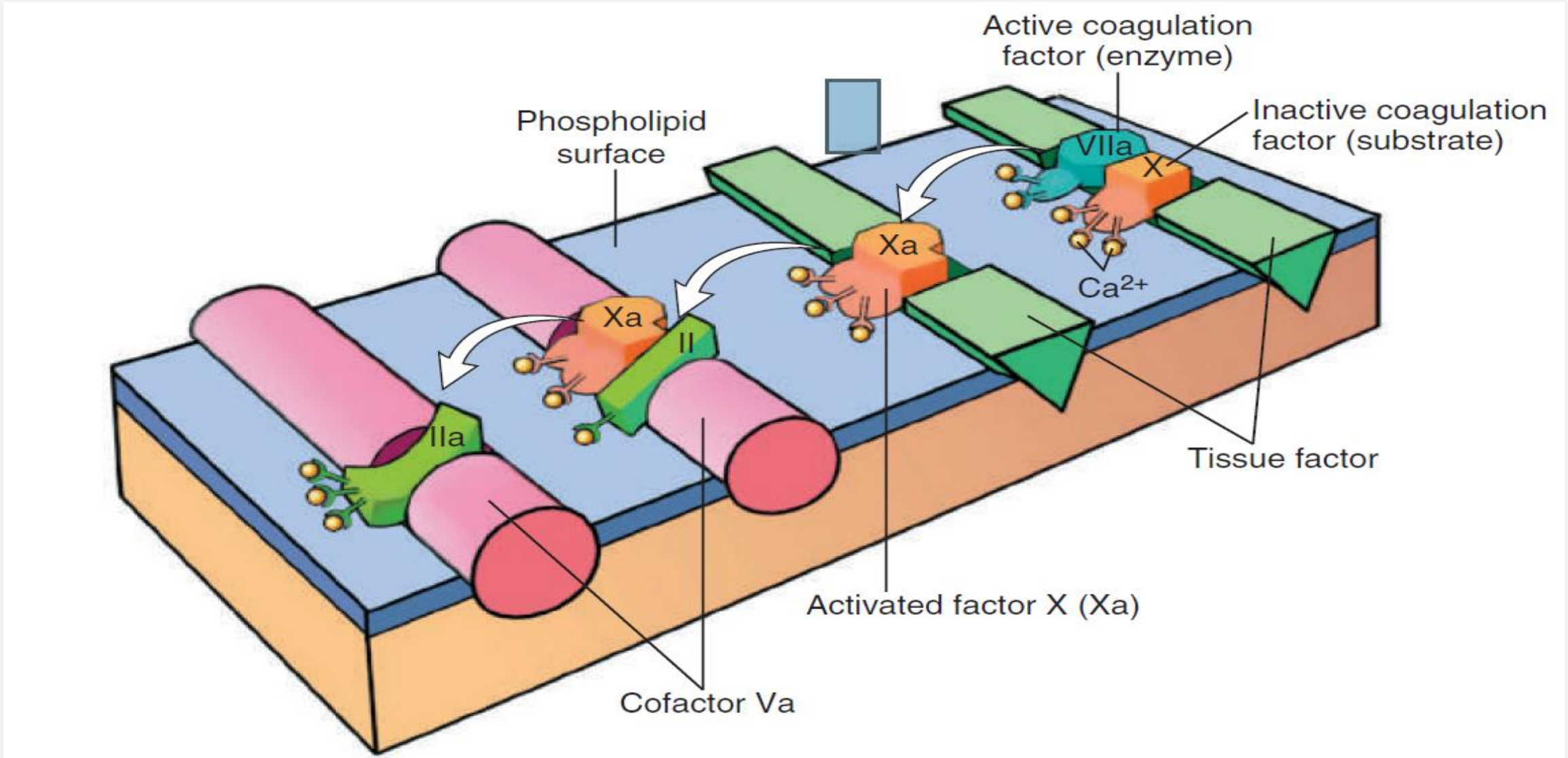

Endothelium
Platelets
Clotting factors
Clotting
Hemostasis
Bleeding
Balance

Coagulation Cascade

- **It is a series of amplifying enzymatic reactions that lead to the deposition of an insoluble fibrin clot.**
- In each reaction step there is : an **enzyme** (an **activated coagulation** factor), a **substrate** (an **inactive proenzyme** form of a coagulation factor), and a **cofactor (a reaction accelerator).**
- These components are assembled on **a negatively charged phospholipid surface**, which is provided by activated platelets.
- Assembly of reaction complexes also depends on **calcium**, which binds to γ-carboxylated glutamic acid residues that are present in **factors II, VII, IX, and X.**
- The enzymatic reactions that produce γ-carboxylated glutamic acid use **vitamin K as a cofactor.**
- These reactions are antagonized by drugs such as Coumadin (warfarin), a widely used **anti-coagulant.**


Active coagulation factor (enzyme)
Inactive coagulation factor (substrate)
Phospholipid surface
VIIa
X
Xa
Ca^{2+}
Xa
II
IIa
Tissue factor
Activated factor X (Xa)
Cofactor Va

Blood Clotting Factors

Factor Number	Common Name
I	Fibrinogen
II	Prothrombin
III	Tissue Factor
IV	Ca2+
Va	Proaccelerin
VII	Proconvertin
VIII	Antihemophilic Factor
IX	Christmas Factor
X	Stuart Factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin Stabilizing Factor

- Usually referred to by number (except prothrombin, Ca+2, TF and fibrinogen)
- Numbers written as Roman numerals
- 12 known procoagulants
- Activated when collagen, tissue factor or negatively charged surfaces are exposed

Based on assays performed in clinical laboratories, the coagulation cascade has traditionally been divided into the *extrinsic* and *intrinsic* pathways

The *prothrombin time* (PT)

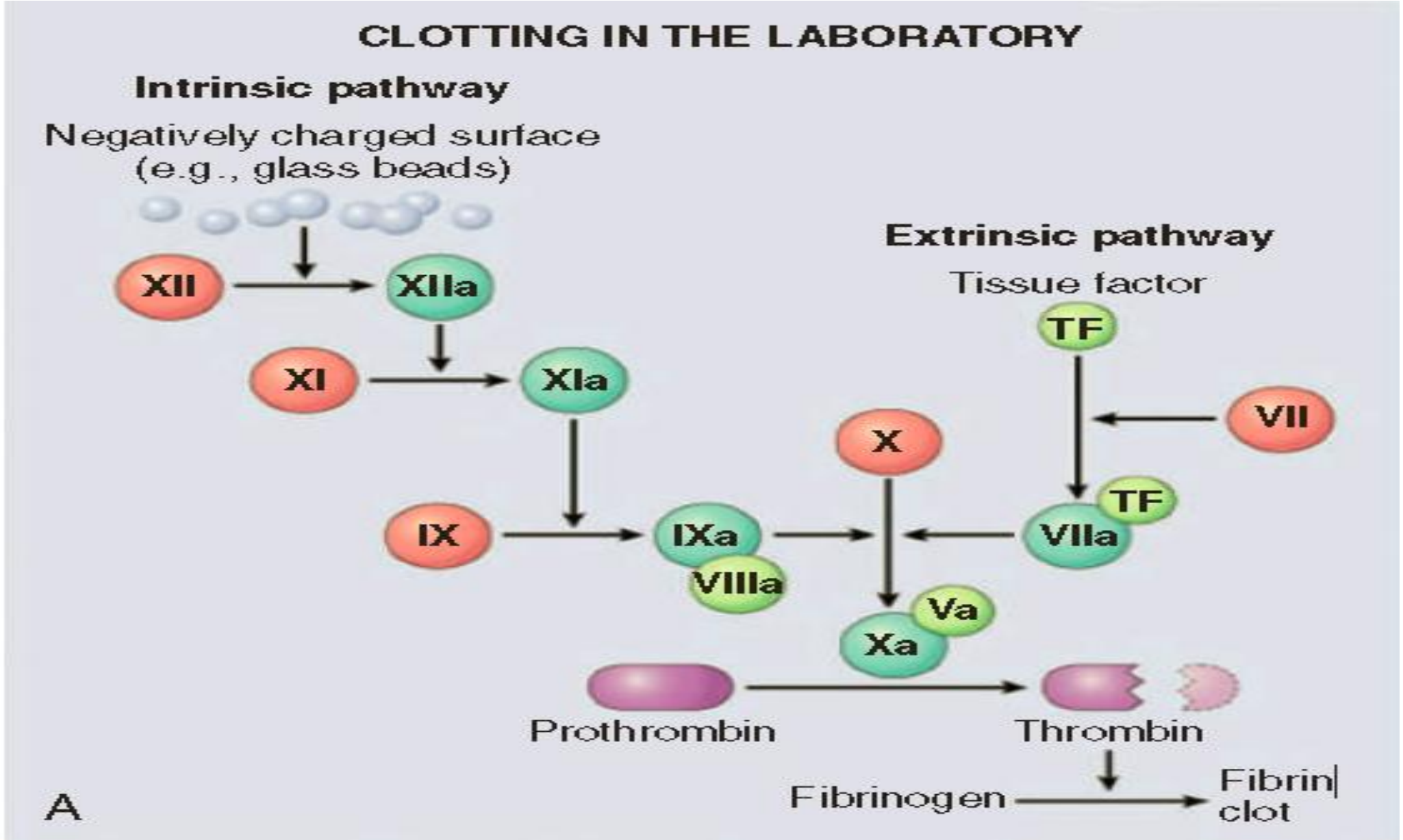
Assess proteins in the extrinsic pathway (factors VII, X, V,II (prothrombin), and fibrinogen).

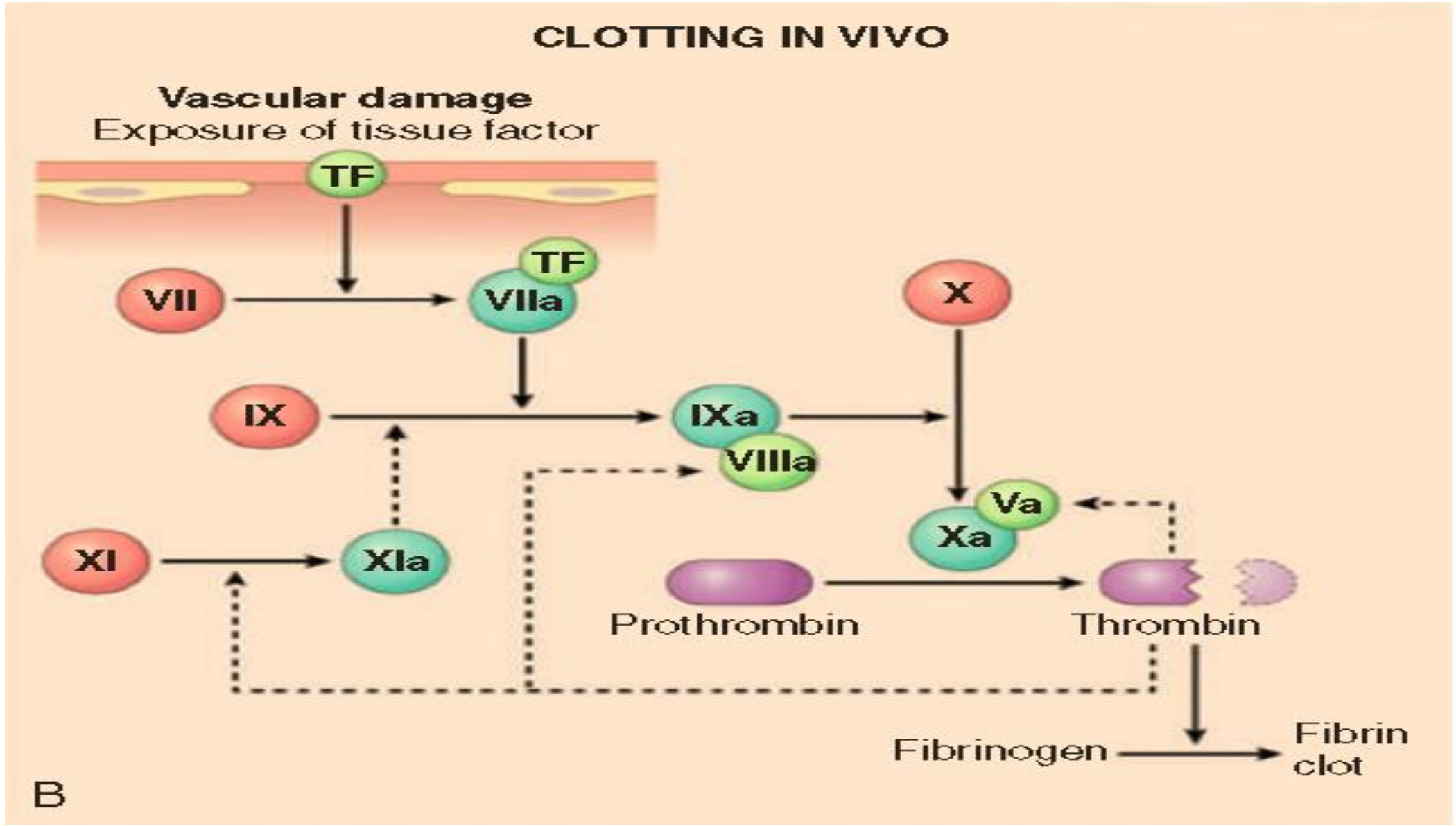
tissue factor, phospholipids, and calcium are added to plasma and the time for a fibrin clot to form is recorded.

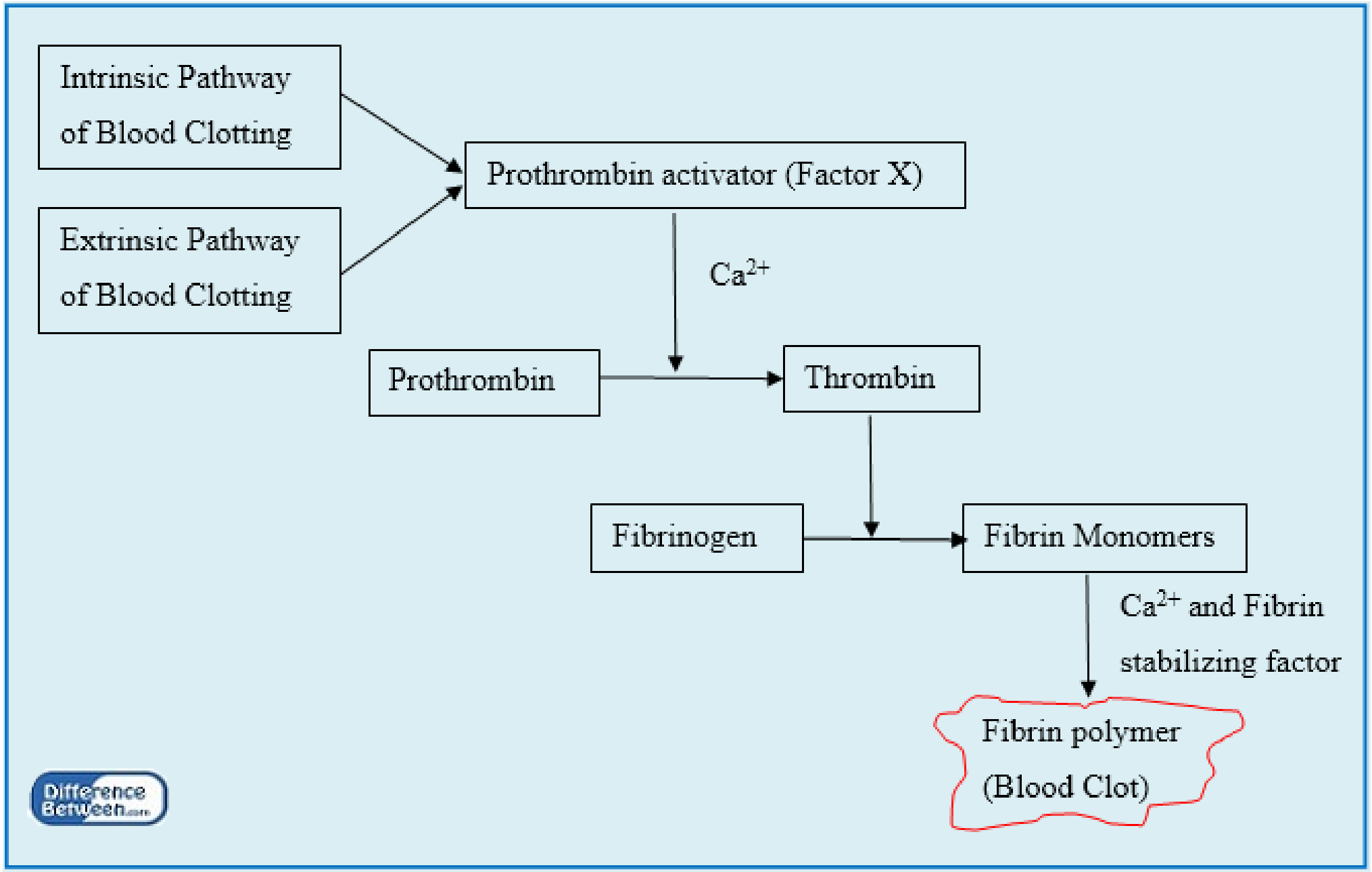
The partial thromboplastin time (PTT)

Screens the function of the proteins in the intrinsic pathway (factors XII, XI, IX, VIII, X, V, II, and fibrinogen).

addition of negative charged particles (e.g., ground glass) that activate factor XII (Hageman factor) together with phospholipids and calcium.


CLOTTING IN THE LABORATORY
Intrinsic pathway
Negatively charged surface
(e.g., glass beads)
XII
XIIa
XI
XIa
IX
IXa
VIIIa
Extrinsic pathway
Tissue factor
TF
VII
X
TF
VIIa
Va
Xa
Prothrombin
Thrombin
Fibrinogen
Fibrin clot
A


CLOTTING IN VIVO
Vascular damage
Exposure of tissue factor
TF
VII
TF
VIIa
X
IX
IXa
VIIIa
Va
Xa
XI
XIa
Prothrombin
Thrombin
Fibrinogen
Fibrin clot
B


Intrinsic Pathway of Blood Clotting
Extrinsic Pathway of Blood Clotting
Prothrombin activator (Factor X)
Ca^{2+}
Prothrombin
Thrombin
Fibrinogen
Fibrin Monomers
Ca^{2+} and Fibrin stabilizing factor
Fibrin polymer (Blood Clot)

Common pathway

Xa with V, Calcium and phospholipid convert prothrombin (II) to thrombin (IIa)

"Prothrombinase complex" occurs on platelet surface

Thrombin has many substrates both procoagulant (positive feedback loop) and anticoagulant (negative feedback)

Extrinsic pathway

Precipitating event is exposure of tissue factor to blood

Tissue factor is a membrane protein which acts as cofactor for VIIa

Phospholipid, tissue factor and VIIa cleaves X → Xa

Intrinsic pathway

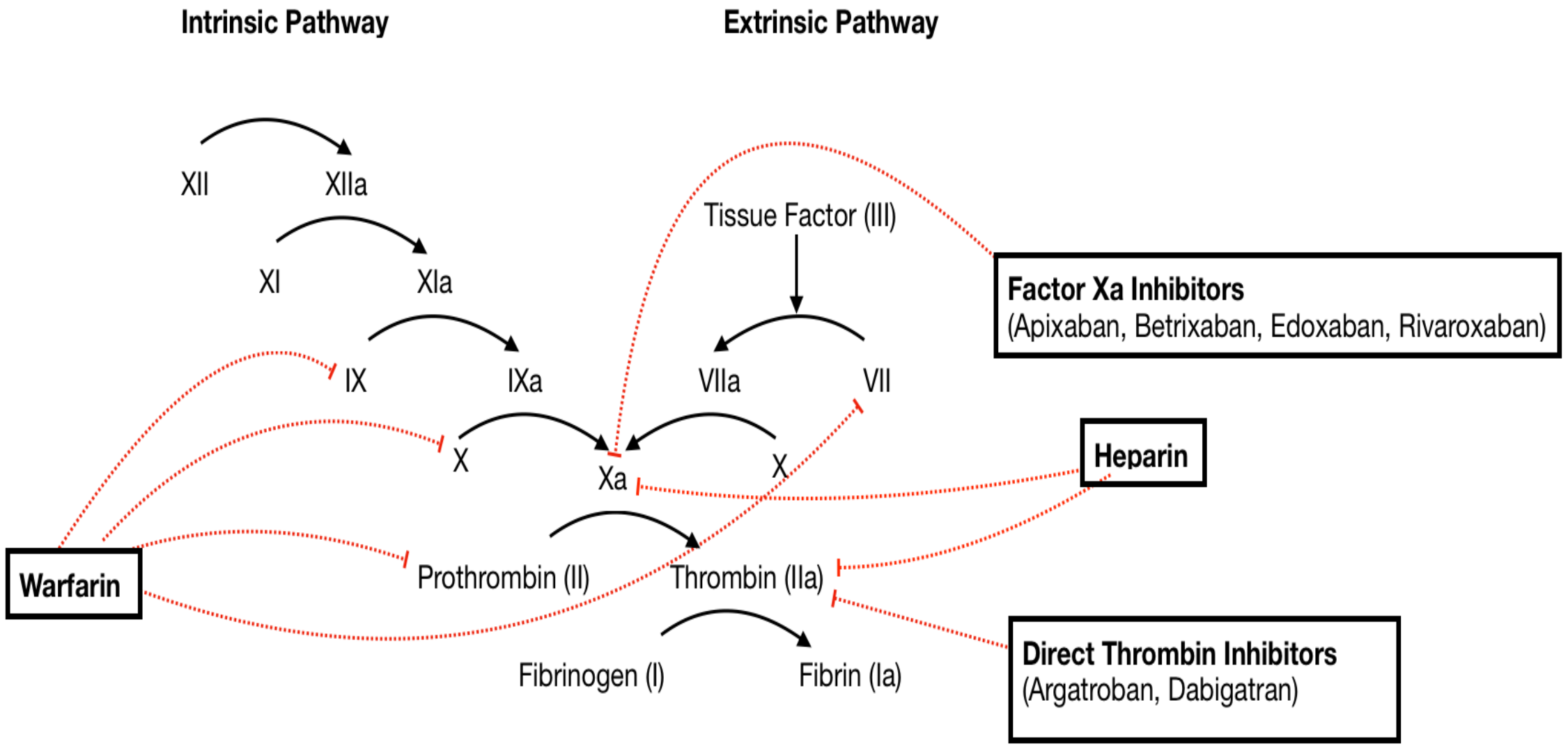
Independent of VII

Contact activation of XII activates XI

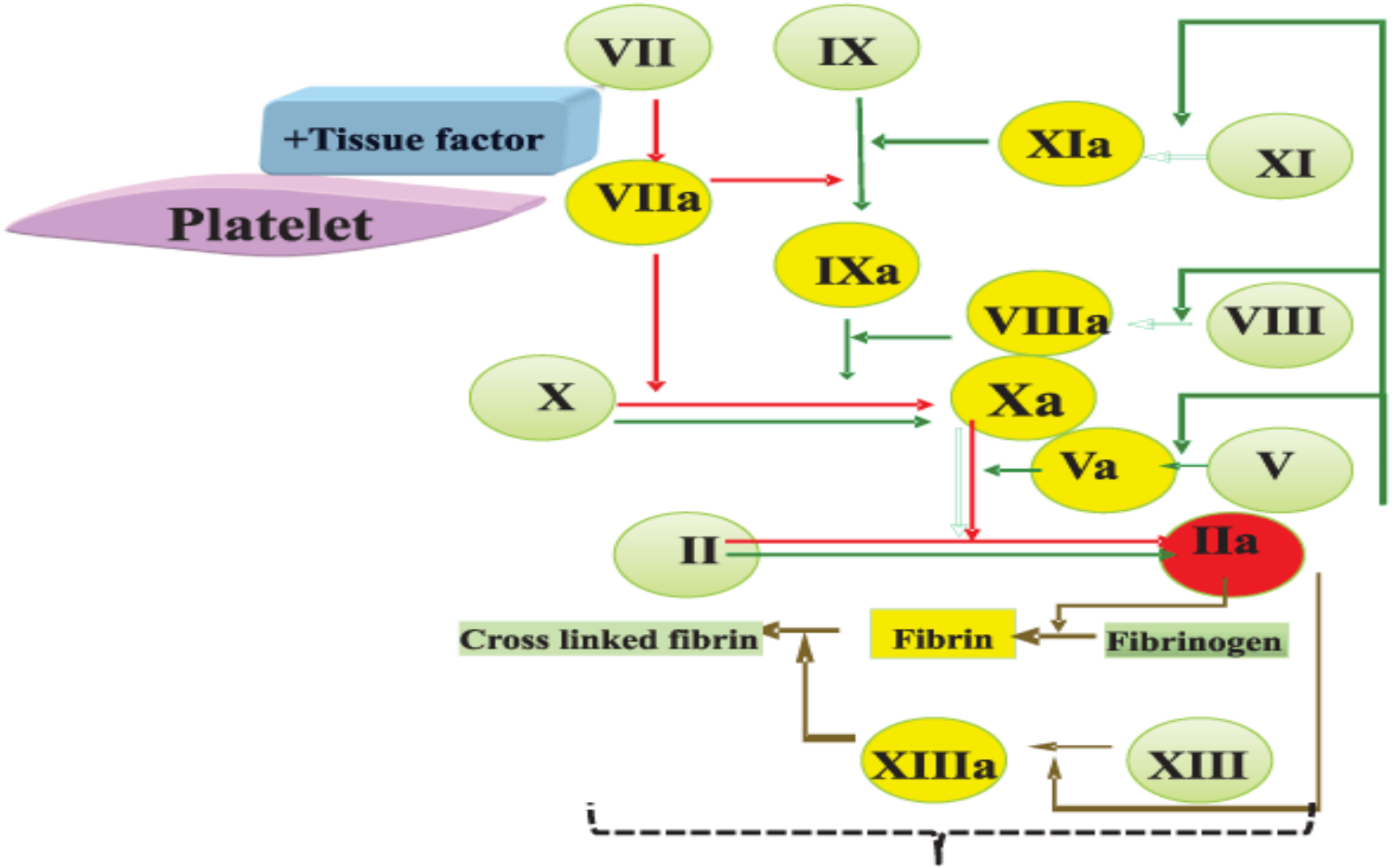
In lab =contact to negatively charged surfaces (kaolin, celite, silica)

XIa activates IX

IXa with VIII can activate X


Intrinsic Pathway
Extrinsic Pathway
XII
XIIa
XI
XIa
IX
IXa
X
Xa
Tissue Factor (III)
VIIa
VII
X
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
Factor Xa Inhibitors
(Apixaban, Betrixaban, Edoxaban, Rivaroxaban)
Heparin
Warfarin
Direct Thrombin Inhibitors
(Argatroban, Dabigatran)

- **Deficiencies of factors V, VIII, IX, X and VII are associated with moderate to severe bleeding disorders.**
- **Prothrombin** deficiency is likely **incompatible with life**.
- In contrast, **factor XI deficiency** is only associated with **mild bleeding,** and individuals with **factor XII deficiency do not bleed** and in fact may be susceptible to thrombosis.
- Based on the effects of various factor deficiencies in humans, it is believed that**, in vivo, factor VIIa/tissue factor complex is the most important activator of factor IX and that factor IXa/factor VIIIa complex is the most important activator of factor X**.
- The mild bleeding tendency seen in patients with factor XI deficiency is likely explained by the ability of thrombin to activate factor XI (as well as factors V and VIII), a feedback mechanism that amplifies the coagulation cascade.

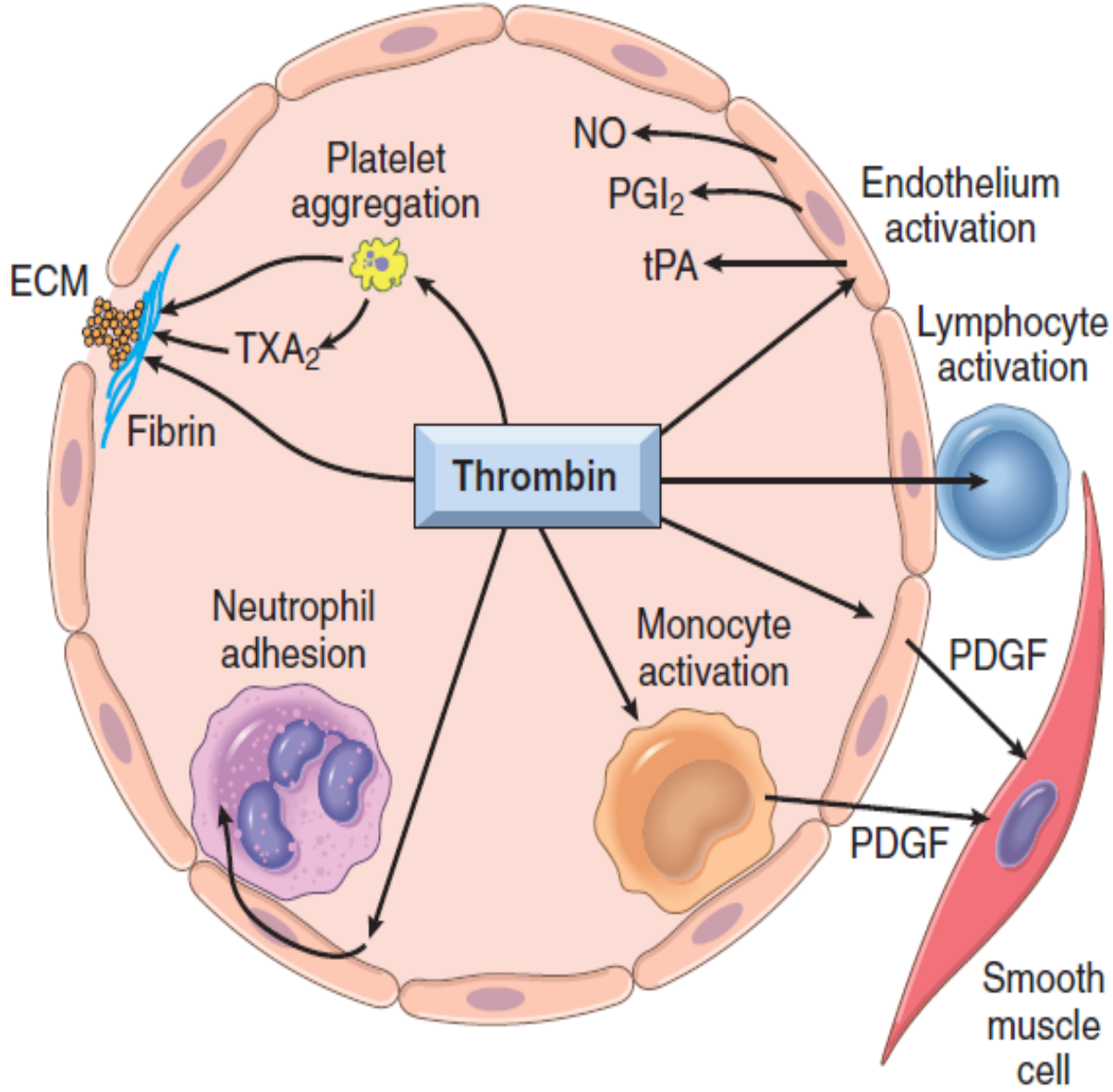


https://www.omicsonline.org/articles-images/2157-7412-S1-005-g001.html

Thrombin

factor IIa

Among the coagulation factors, thrombin is the most important, because its various enzymatic activities control diverse aspects of hemostasis and link clotting to inflammation and repair.



Among thrombin's most important activities:

- ***Conversion of fibrinogen into crosslinked fibrin* monomers, directly**, that polymerize into an insoluble fibril.

- **Amplifies the coagulation process**, not only by activating factor XI, but also by activating two critical **cofactors factors V and VIII**. It also stabilizes the secondary hemostatic plug by activating **factor XIII**, which covalently crosslinks fibrin.

- ***Platelet activation***. Thrombin is a potent inducer of platelet activation and aggregation through **its ability to activate PARs** (protease-activated receptors)

- ***Proinflammatory effects***. PARs also are expressed on inflammatory cells, endothelium, & other cell types, so activation of these receptors mediate proinflammatory effects that contribute to tissue repair and angiogenesis.

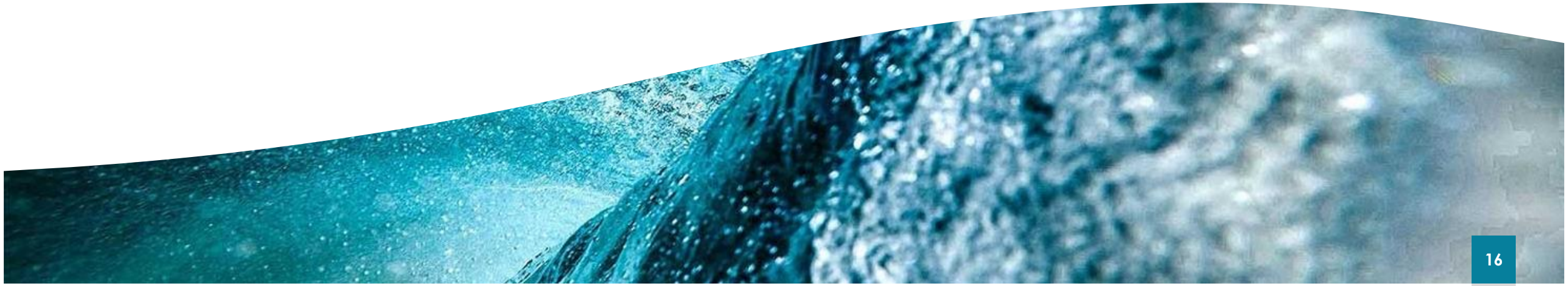
- ***Anti-coagulant effects:*** *in* normal endothelium, changes from a procoagulant to an anticoagulant (prevents clots from extending beyond the site of the vascular injury).

Factors That Limit Coagulation

Once initiated, coagulation must be restricted to the site of vascular injury to prevent harmful consequences:

+ One limiting factor is **simple dilution**; blood flowing past the site of injury washes coagulation factors.

+ Second is the **requirement for negatively charged phospholipids**, mainly provided by platelets.



Cont ..Factors That Limit Coagulation

+ Activation od *fibrinolytic cascade* that limits the size of the clot & contributes to its later dissolution.

plasmin: enzyme that breaks down fibrin & interferes with its polymerization.

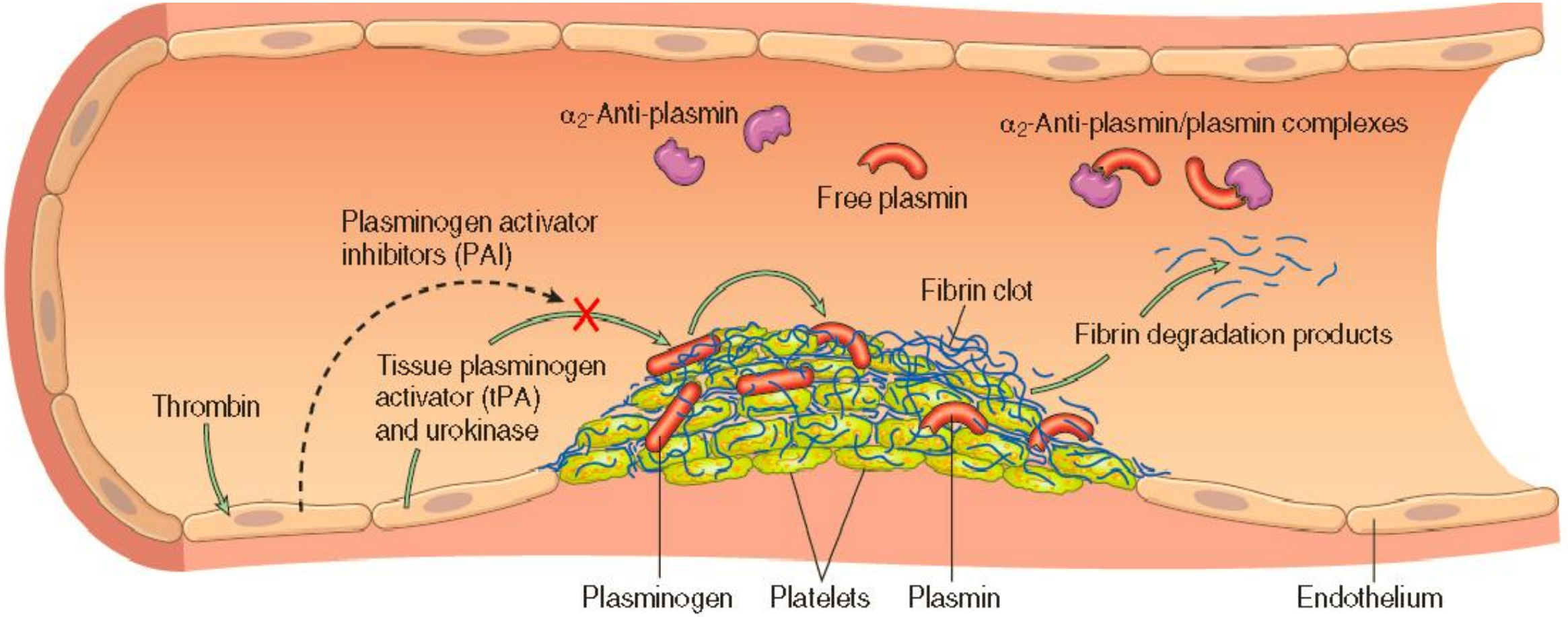
*An elevated level of breakdown products of fibrinogen (fibrin split products **mostly D-dimers**) are a useful clinical markers of several thrombotic states.*

Plasmin is generated by enzymatic catabolism of the inactive circulating **precursor *plasminogen:***

+ *by* a factor XII–dependent pathway (Remember: XII deficiency & thrombosis)

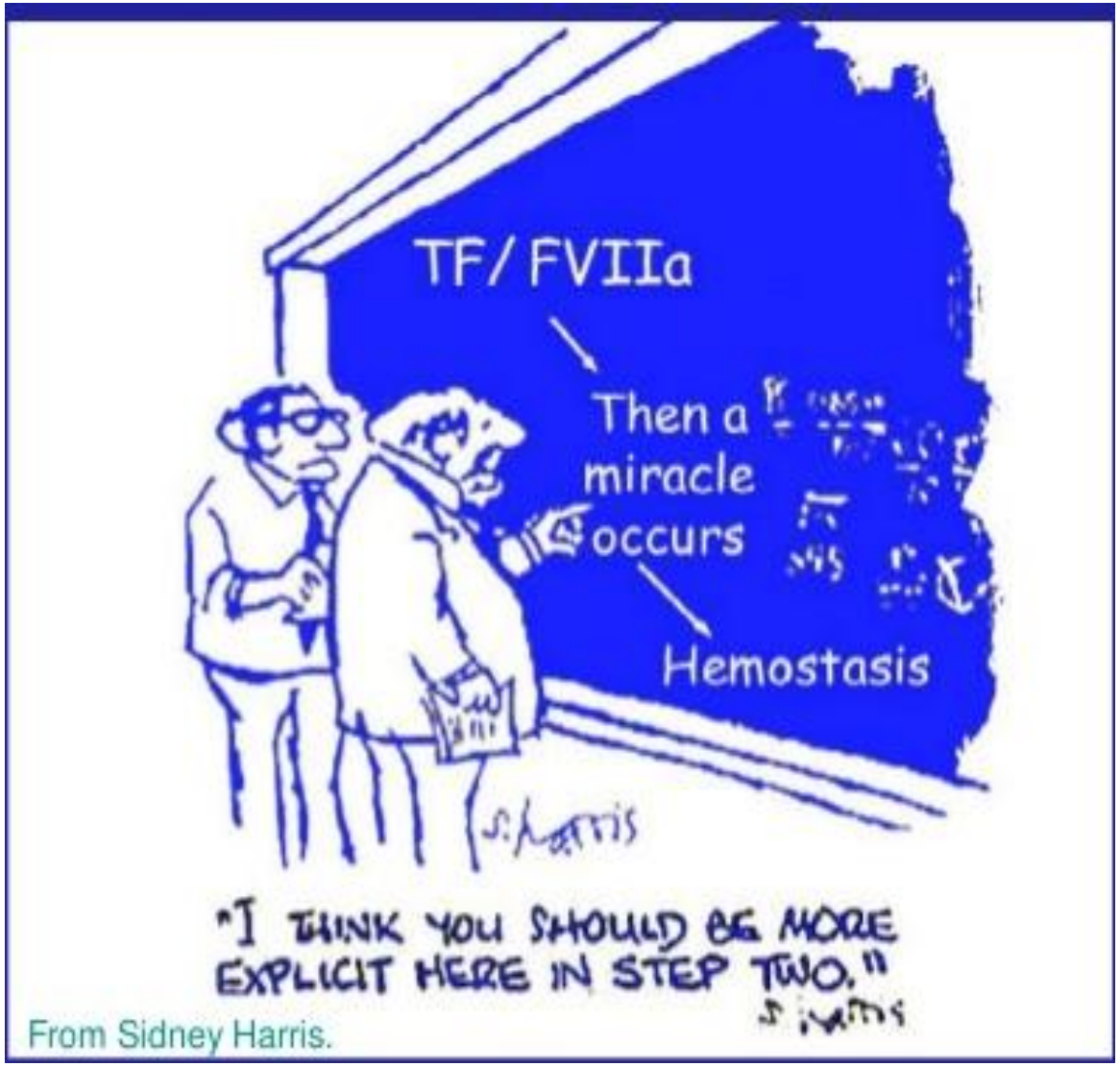
+ or by plasminogen activators. **The most important plasminogen activator is t-PA**; it is synthesized principally by endothelium.

- Fibrinolytic activity is largely confined to sites of recent thrombosis→ plasmin is tightly controlled by counter regulatory factors such as **a2-plasmin inhibitor.**


α2-Anti-plasmin
α2-Anti-plasmin/plasmin complexes
Free plasmin
Plasminogen activator inhibitors (PAI)
Fibrin clot
Fibrin degradation products
Tissue plasminogen activator (tPA) and urokinase
Thrombin
Plasminogen
Platelets
Plasmin
Endothelium

Site	Thrombogenic	Antithrombogenic
Vessel wall	Exposed endothelium	Heparin
	TF	Thrombomodulin
	Collagen	Tissue plasminogen activator
Circulating elements	Platelets	Antithrombin
	Platelet activating factor	Protein C and S
	Clotting factor	Plasminogen
	Prothrombin	
	Fibrinogen	
	vWF	

vWF – Von Willebrand factor; TF – Tissue factor



Endothelium

+ The balance between the anticoagulant & procoagulant activities of endothelium often determines whether clot formation, propagation, or dissolution occurs.

+ **Normal** endothelial cells express a multitude of factors that inhibit the procoagulant activities of platelets & coagulation factors & that augment fibrinolysis, they act in concert to prevent thrombosis & to limit clotting to sites of vascular damage.

The antithrombotic properties of endothelium:

- **Platelet inhibitory effects.**

+ Intact endothelium serves as a barrier that shields platelets from **subendothelial vWF & collagen**

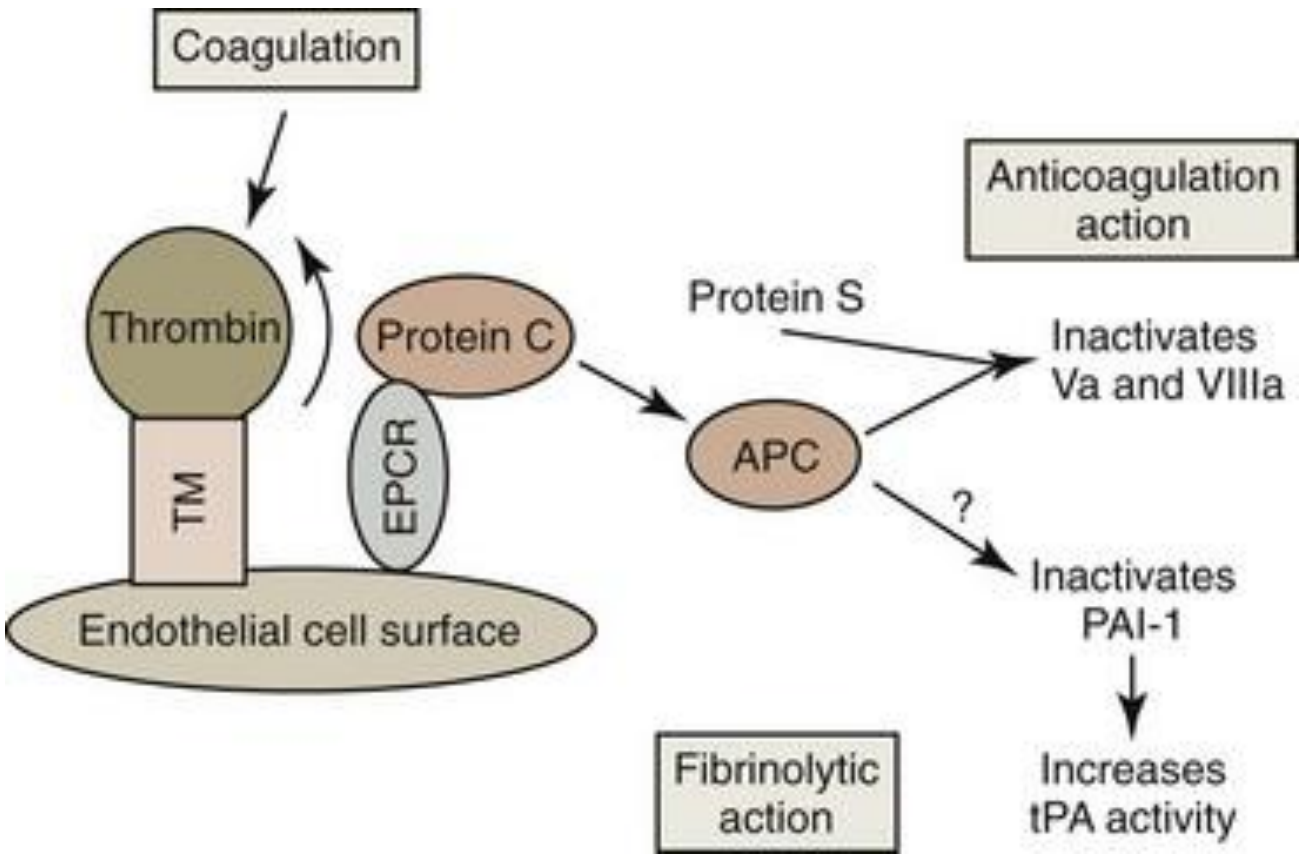
+ Releases factors that inhibit platelet activation and aggregation; ***prostacyclin (PGI2), nitric oxide (NO),*** **and** ***adenosine diphosphatase*** (degrades ADP)

+ Endothelial cells bind and alter the activity of thrombin, which is one of the most potent activators of platelets.

- **Anticoagulant effects.**

+ intact endothelium shields coagulation factors from tissue factor in vessel walls.

+ expresses multiple factors that actively oppose coagulation; **thrombomodulin, endothelial protein C receptor, heparin-like molecules, and tissue factor pathway inhibitor**.



+ Thrombomodulin and endothelial protein C receptor bind thrombin and protein C, respectively, in a complex on the endothelial cell surface.

+ thrombin loses its ability to activate coagulation factors and platelets.

+ thrombin cleaves & activates protein C instead,
Protein C: a vitamin K–dependent protease that requires a cofactor → protein S.

+Activated **protein C/protein S complex is a potent inhibitor of coagulation factors Va and VIIIa**.

Cont.. The antithrombotic properties of endothelium:

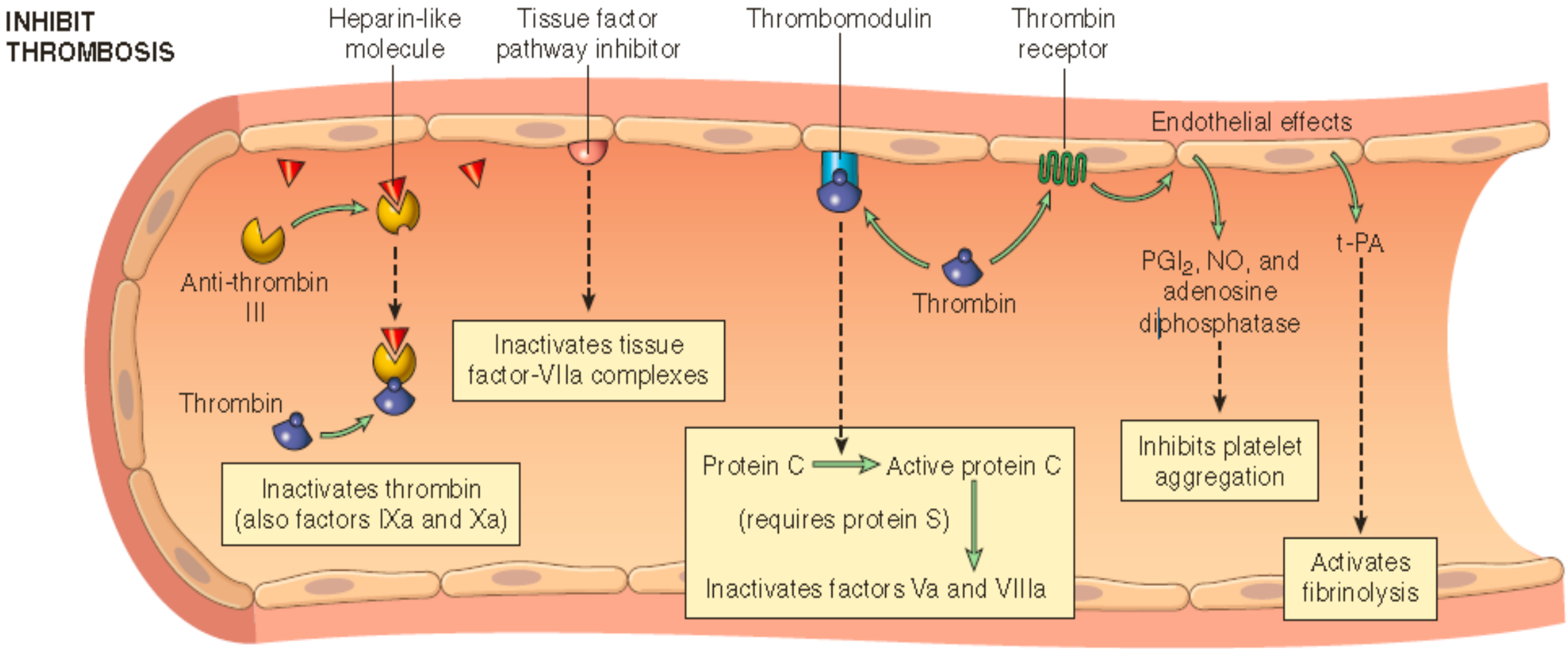
+ Heparin-like molecules on endothelium surface bind and activate **antithrombin III, which then inhibits thrombin and factors IXa, Xa, XIa, and XIIa.**

The clinical utility of heparin and related drugs is based on their ability to stimulate antithrombin III activity.

+ Tissue factor pathway inhibitor (TFPI), like protein C, requires protein S as a cofactor, to bind and inhibit tissue factor/factor VIIa complexes.

- ***Fibrinolytic effects.***

Normal endothelial cells synthesize t-PA, as a key component of the fibrinolytic pathway.


INHIBIT THROMBOSIS
Heparin-like molecule
Tissue factor pathway inhibitor
Thrombomodulin
Thrombin receptor
Endothelial effects
Anti-thrombin III
Thrombin
Inactivates tissue factor-VIIa complexes
Thrombin
Inactivates thrombin (also factors IXa and Xa)
Protein C
Active protein C
(requires protein S)
Inactivates factors Va and VIIIa
Thrombin
PGI2, NO, and adenosine diphosphatase
Inhibits platelet aggregation
t-PA
Activates fibrinolysis

THANK YOU