

# Coagulation Cascade

How enzymatic amplification produces a fibrin-stabilized hemostatic plug

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**Tissue factor → thrombin → cross-linked fibrin**

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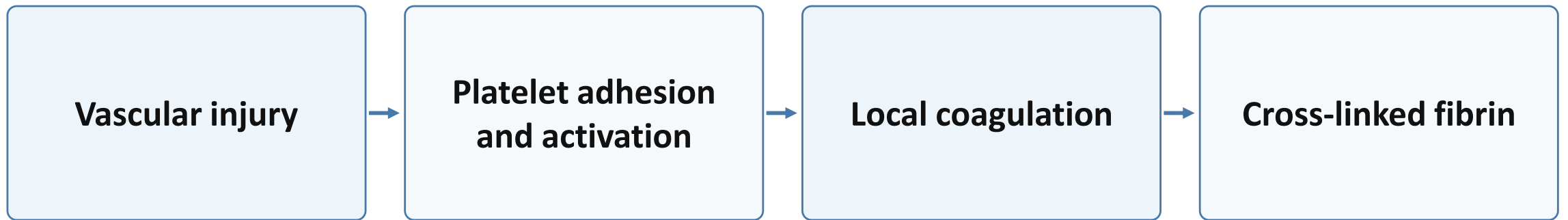
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# Learning objectives

- Explain how plasma zymogens, cofactors, and membrane surfaces generate thrombin.
- Differentiate laboratory intrinsic/extrinsic pathways from coagulation in vivo.
- Relate thrombin, endothelial anticoagulants, and fibrinolysis to clot localization.
- Interpret the logic of PT/PTT and selected factor-deficiency phenotypes.

# Hemostasis proceeds from injury to stable clot



Platelets make the provisional plug; Fibrin stabilizes it.

# Primary and secondary hemostasis

## Platelet-centered response

- Adhesion to exposed subendothelial matrix
- Activation and aggregation
- Forms an initial plug

## Coagulation-centered response

- Sequential protease activation
- Thrombin generation
- Fibrin formation and cross-linking

The pathways cooperate at the same wound; They are not isolated events.

# What is the coagulation cascade?

## Definition

- A sequence of amplifying enzymatic reactions.
- Most participating factors circulate as inactive plasma proteins.
- Proteolytic activation ultimately yields insoluble fibrin.
- Local injury exposes the normally hidden initiator, tissue factor.

# Zymogens versus tissue factor

## Circulating zymogens

- Usually inactive before injury
- Become proteolytically active
- Represent most clotting factors

## Tissue factor (TF)

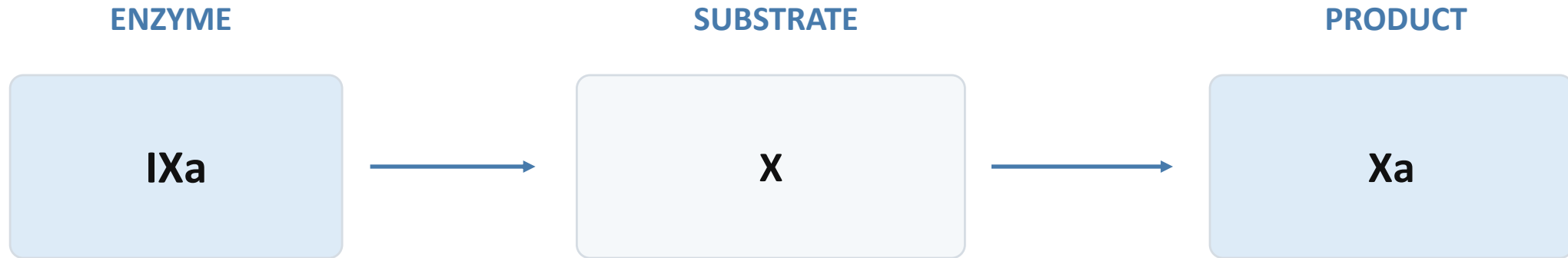
- Cell-associated initiator
- Already expressed within vessel wall tissues
- Exposed to blood after injury

Coagulation begins when a tissue-localized trigger meets circulating factors.

## Reading coagulation-factor notation

- Roman numerals identify clotting factors (II, VII, IX, X).
- An appended “a” denotes an activated factor (Xa, IXa, IIa).
- Factor II = prothrombin; Factor IIa = thrombin.
- Cofactors such as VIIIa and Va accelerate reactions rather than acting as the principal proteases.

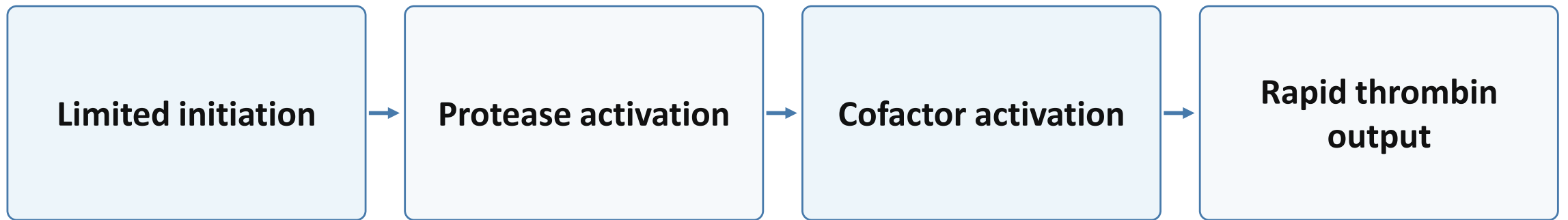
# An enzyme–substrate–cofactor reaction



**Required accelerator/support: VIIIa**

Assembly on an appropriate phospholipid membrane is critical.

# Amplification is built into the cascade



The final fibrin response exceeds the initial triggering signal.

# Two views of coagulation

## Laboratory model

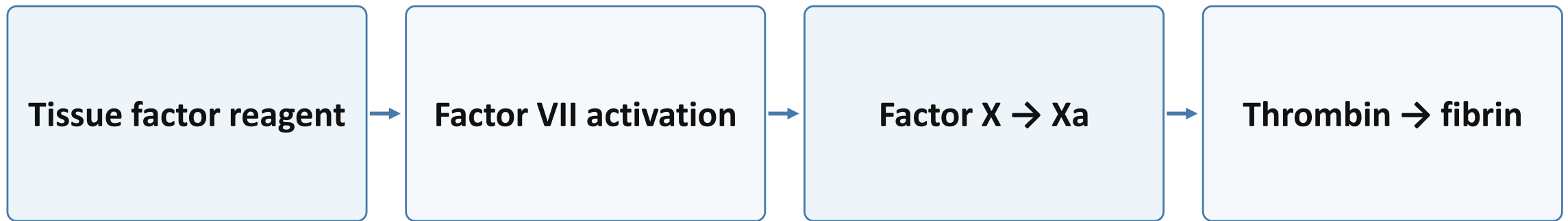
- Intrinsic and extrinsic entry routes
- Defined reagent-triggered reactions
- Useful for PT and PTT interpretation

## Physiologic model

- Tissue factor is the major initiator
- TF–VIIa and IXa–VIIIa are central
- Thrombin provides positive feedback

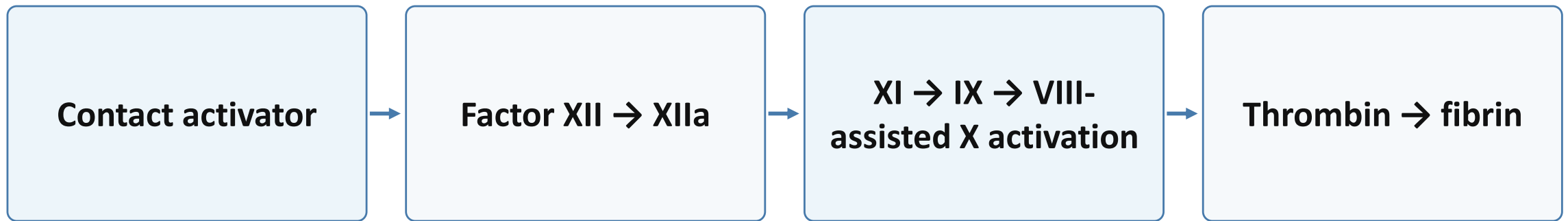
The assay diagram is not a literal map of clotting within a vessel.

# The laboratory extrinsic pathway



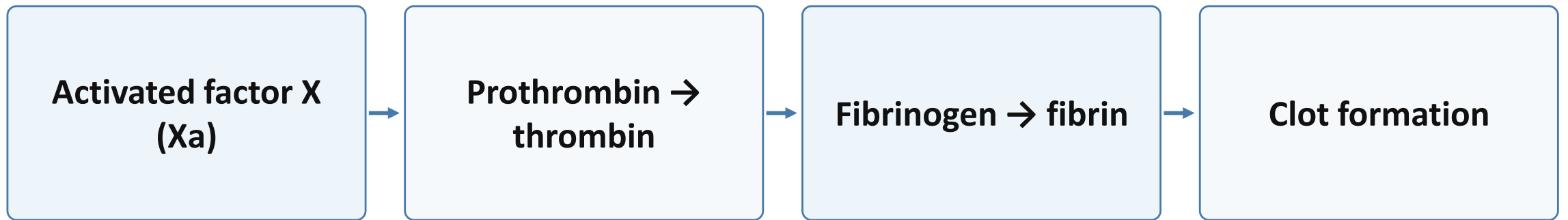
Measured through the prothrombin time (PT).

# The laboratory intrinsic pathway



Measured through the partial thromboplastin time (PTT).

# The shared laboratory pathway

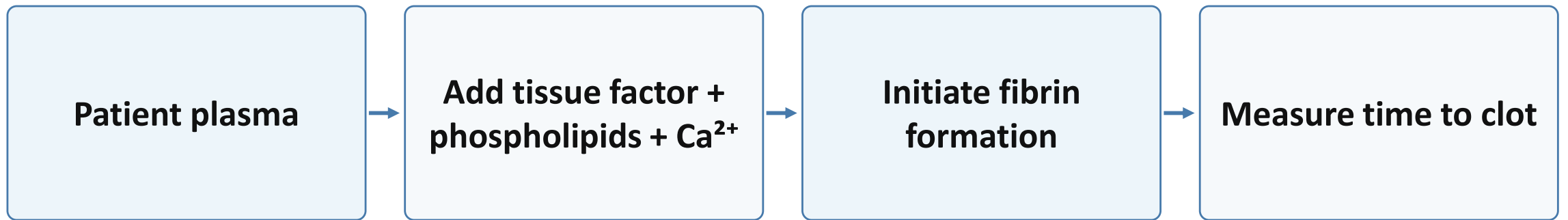


PT and PTT share the downstream conversion to fibrin.

## PT tests the extrinsic and common pathways

- Assesses factors VII, X, V, II (prothrombin), and fibrinogen.
- Plasma receives tissue factor, phospholipids, and calcium.
- Clot-formation time reflects function of the assayed factor system.
- PT is a laboratory assessment—not a direct recording of coagulation in vivo.

# PT assay: Sequence of events

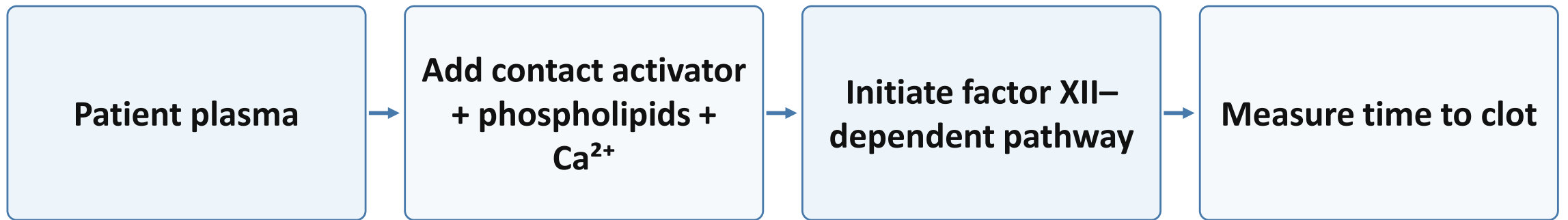


The initiating reagent defines the assay pathway.

## PTT tests the intrinsic and common pathways

- Assesses XII, XI, IX, VIII, X, V, II, and fibrinogen.
- Negatively charged particles activate contact-dependent clotting.
- Phospholipids and calcium support downstream reactions.
- The measured endpoint is formation of a fibrin clot.

## PTT assay: Sequence of events



Contact activation in vitro should not be mistaken for physiologic initiation.

## PT and PTT: Pathway coverage

| Assay | Initiating trigger         | Factors assessed                        |
|-------|----------------------------|-----------------------------------------|
| PT    | Tissue factor              | VII, X, V, II, fibrinogen               |
| PTT   | Negatively charged surface | XII, XI, IX, VIII, X, V, II, fibrinogen |

Both assays test functional ability to reach fibrin formation.

## Why PT/PTT do not recreate hemostasis in vivo

- Reagents impose distinct activation routes absent from ordinary vascular injury.
- Physiologic clotting is localized to injury-associated cell membranes.
- Tissue factor initiates most in-vivo coagulation.
- Clinical factor deficiencies expose limitations of the simplified pathway diagram.

# Factor deficiencies challenge the assay model

## Greater bleeding impact

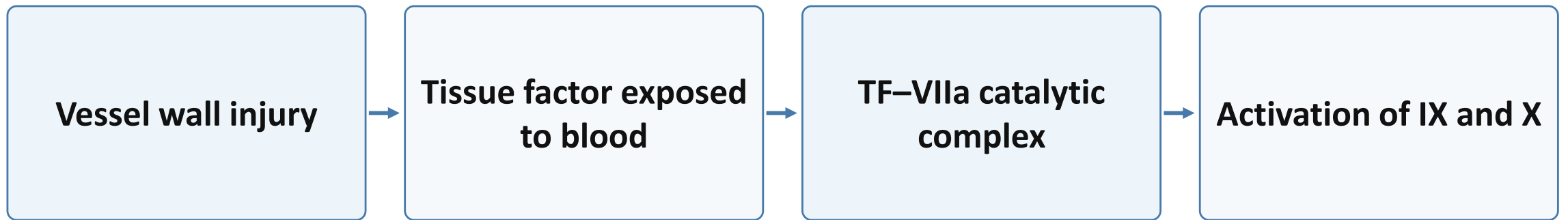
- Deficiencies of V, VII, VIII, IX, or X
- Moderate-to-severe bleeding can occur
- Supports key physiologic roles

## Factor XI deficiency

- Often a milder bleeding phenotype
- Thrombin can activate XI by feedback
- XI may have additional roles in thrombosis

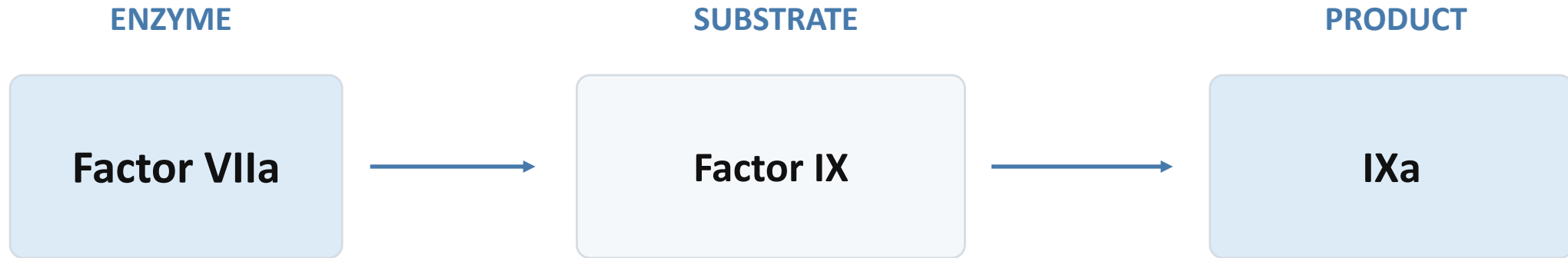
Laboratory pathway placement alone does not predict bleeding severity.

# Physiologic initiation starts at tissue injury



The major physiologic entry point differs from contact activation.

# Tissue factor and factor VIIa initiate clotting



**Required accelerator/support: Tissue factor (TF)**

The TF–VIIa complex is especially important for producing IXa in vivo.

## TF–VIIa has two downstream routes

### Direct route

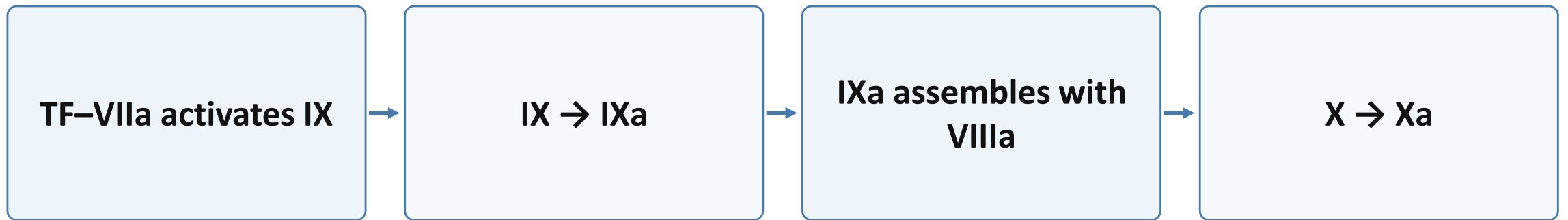
- TF–VIIa activates  $X \rightarrow Xa$
- Generates an initiating thrombin signal
- Does not eliminate need for amplification

### Indirect route

- TF–VIIa activates  $IX \rightarrow IXa$
- IXa works with VIIIa
- Prominent route to X activation in vivo

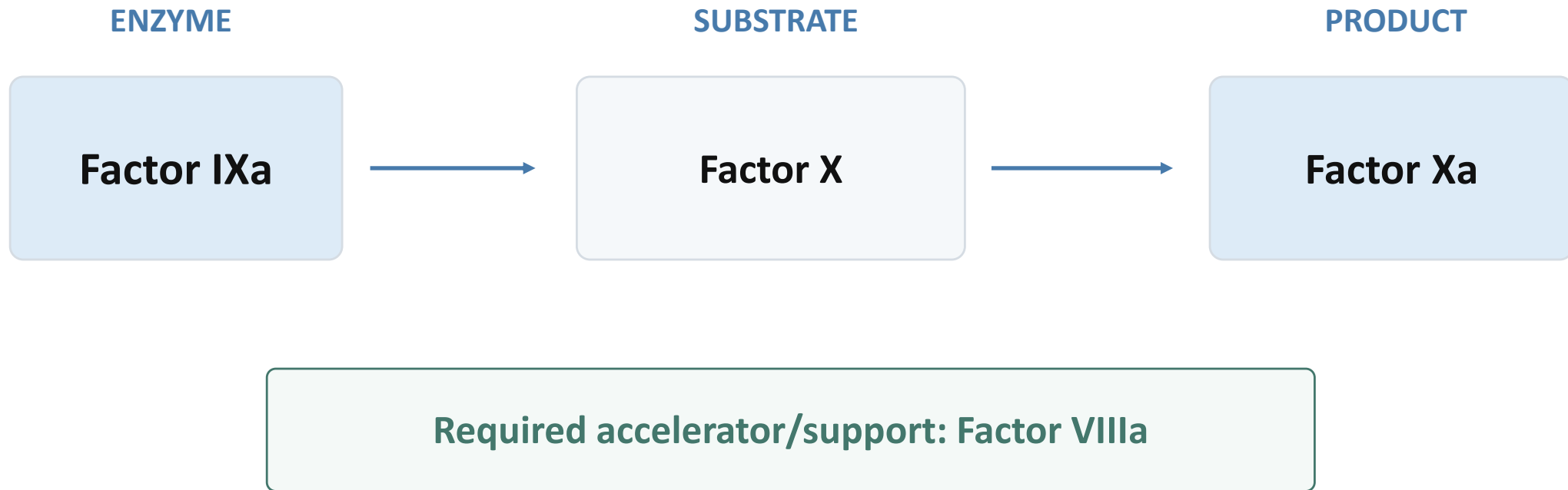
Both paths originate from the tissue factor–VIIa complex.

## Factor IX feeds the propagation system



IXa-VIIIa is a major physiologic activator of factor X.

# Intrinsic tenase activates factor X

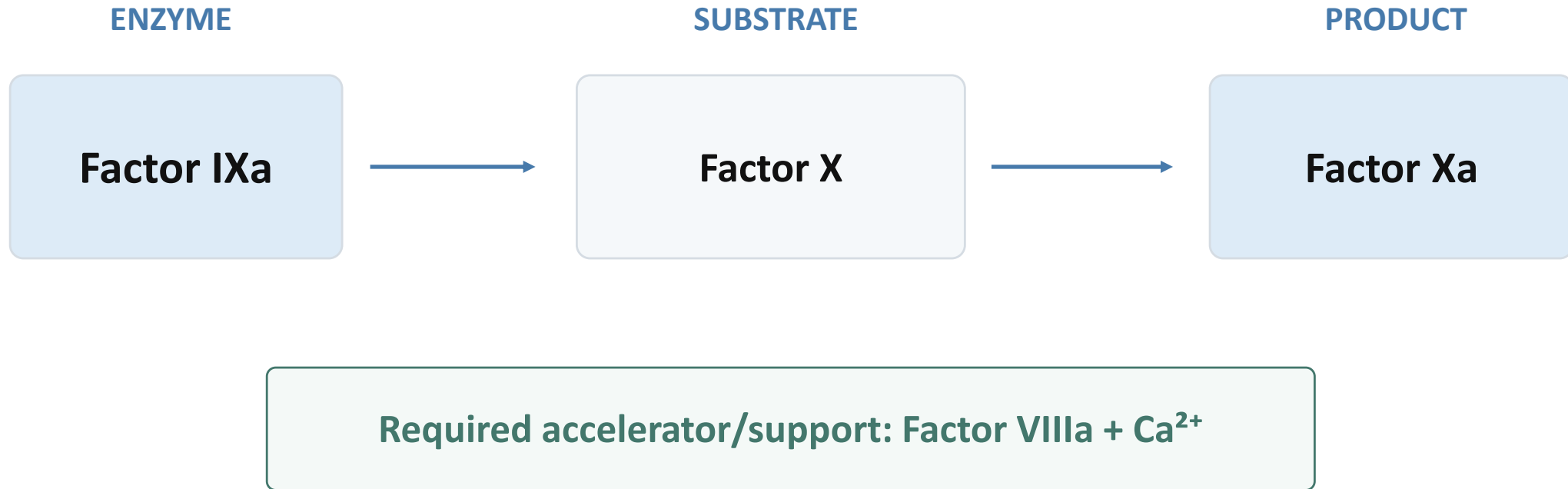


“Tenase” denotes an X-activating enzyme system; The complex resides on a phospholipid surface.

## Activated platelet membranes provide a platform

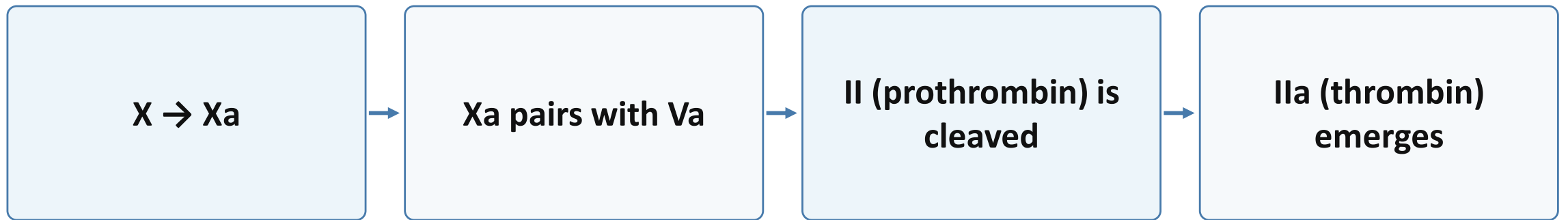
- Activated platelets expose negatively charged phospholipid surfaces.
- Clotting proteins assemble into membrane-associated reaction complexes.
- The same injury that activates platelets also concentrates coagulation.
- Spatial organization enhances local conversion of substrates.

# Calcium stabilizes membrane-associated reactions



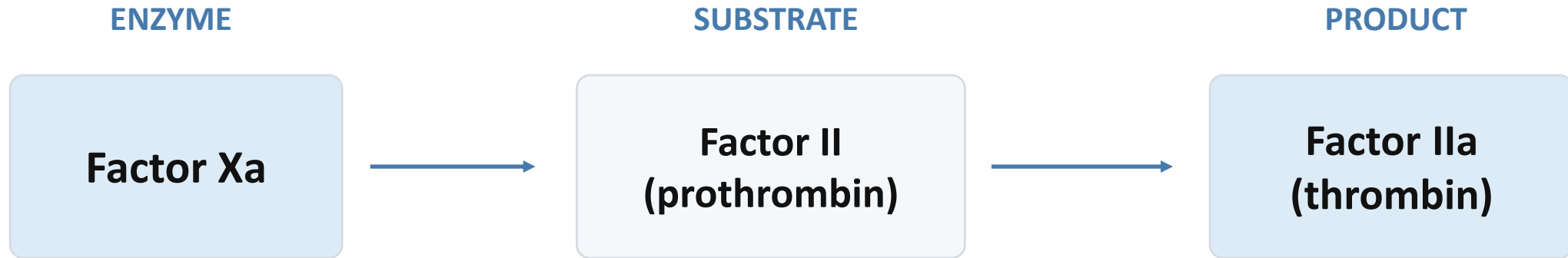
Calcium ions help hold the enzyme, substrate, and cofactor together on the phospholipid membrane.

## From factor Xa to thrombin



The Xa–Va reaction complex links upstream activation to the central effector.

# The prothrombinase reaction



**Required accelerator/support: Factor Va**

Factor Va accelerates thrombin generation on the membrane surface.

# Tenase and prothrombinase

## Tenase complex

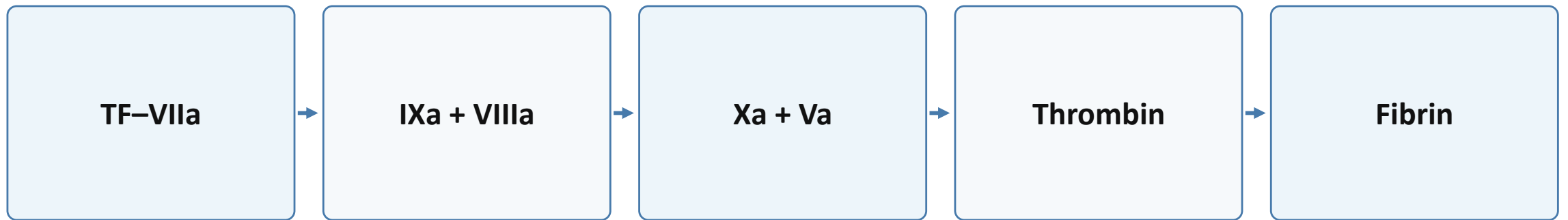
- Protease IXa
- Cofactor VIIIa
- Substrate X  $\rightarrow$  product Xa

## Prothrombinase complex

- Protease Xa
- Cofactor Va
- Substrate II  $\rightarrow$  product IIa

Both use membrane association and calcium to organize enzymatic activation.

# The central propagation sequence

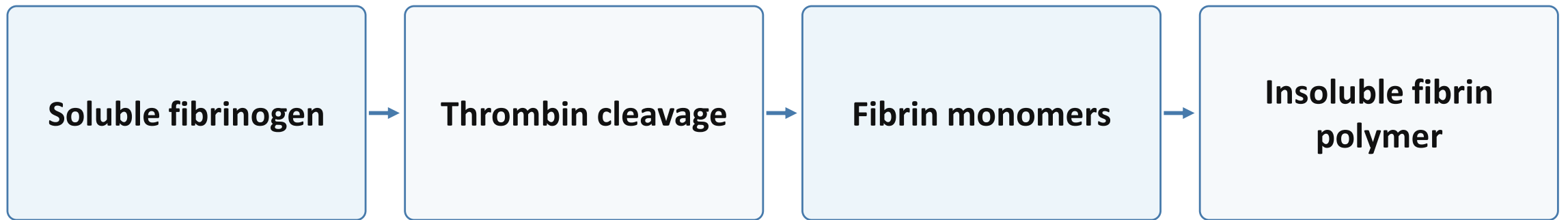


A simplified physiologic sequence; TF-VIIa can also activate factor X directly.

# Why thrombin is the central effector

- Thrombin (IIa) converts fibrinogen into fibrin.
- It reinforces its own production by activating several factors.
- It strongly activates platelets through PAR-1.
- It signals to endothelial and inflammatory cells.

# Thrombin converts fibrinogen to fibrin



Fibrin deposition provides the scaffold for secondary hemostasis.

# Fibrin assembly and fibrin stabilization

## Polymer formation

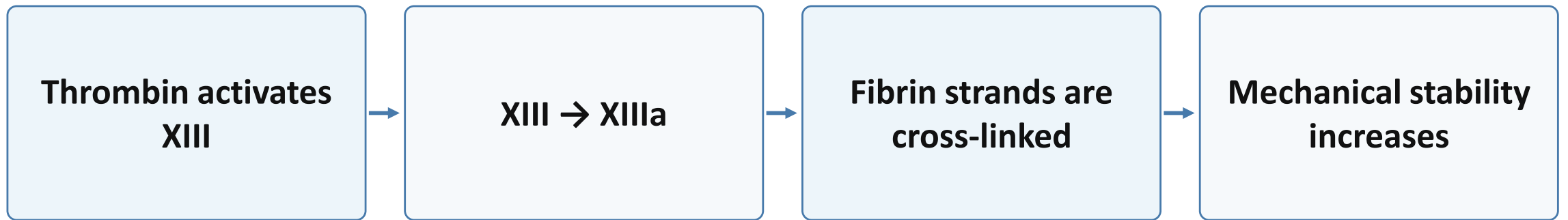
- Thrombin releases fibrin monomers
- Monomers assemble into fibrils
- Produces an insoluble fibrin network

## Covalent cross-linking

- Thrombin activates factor XIII
- Factor XIIIa cross-links fibrin
- Stabilizes the final hemostatic plug

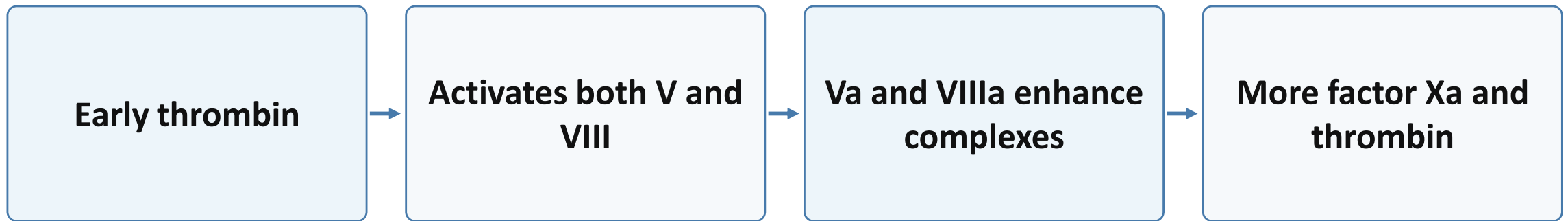
Polymerization and XIII-mediated cross-linking are distinct steps.

## Factor XIII strengthens the clot



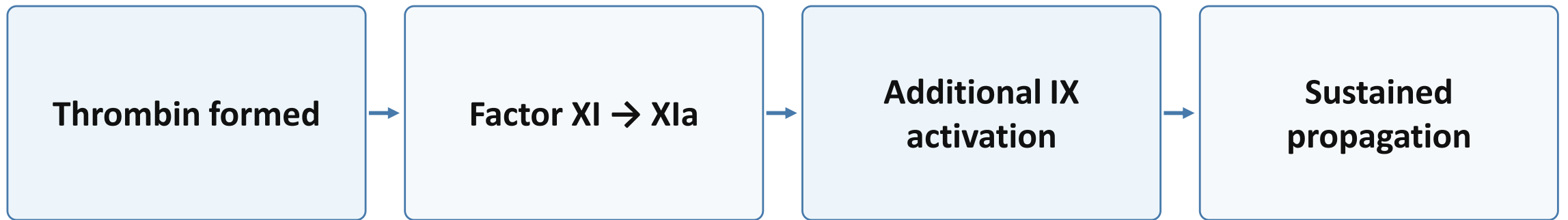
Final clot stabilization depends on more than thrombin-mediated fibrin release.

# Thrombin activates its own cofactors



This positive feedback is a major amplification mechanism.

## Thrombin can activate factor XI



Feedback activation helps explain how XI participates despite limited in-vivo initiation.

# Initiation and amplification answer different questions

## Initiation

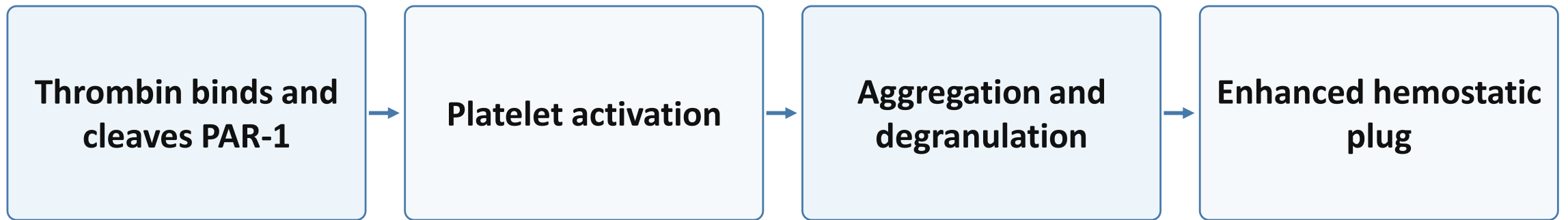
- Where does clotting begin?
- Tissue factor is exposed at injury
- TF–VIIa starts downstream proteolysis

## Amplification

- How does output become large?
- IXa–VIIIa and Xa–Va complexes
- Thrombin activates V, VIII, and XI

Separating the two phases makes the cascade easier to interpret.

# Thrombin activates platelets through PAR-1



PAR-1 links enzymatic coagulation to primary hemostasis.

# Platelets and coagulation reinforce one another

## Platelets support coagulation

- Provide phospholipid reaction surfaces
- Release calcium during activation
- Concentrate clot formation at injury

## Coagulation supports platelets

- Thrombin activates PAR-1
- Induces aggregation/degranulation
- Fibrin consolidates platelet plug

Primary and secondary hemostasis form an interdependent system.

## Thrombin signals beyond the clot

- Protease-activated receptors occur on endothelium and inflammatory cells.
- Thrombin signaling may promote leukocyte responses.
- The source links these effects to tissue repair and angiogenesis.
- These cellular effects are distinct from thrombin's direct fibrin-forming activity.

# Thrombin has hemostatic and cellular outputs

## Direct clotting functions

- Fibrinogen → fibrin
- XIII → XIIIa
- Activation of V, VIII, and XI

## Cell signaling functions

- Platelet activation via PAR-1
- Endothelial responses
- Inflammatory-cell activation

One protease integrates hemostasis and injury responses.

## Thrombin can switch to anticoagulant signaling

- On intact endothelium, thrombin can bind thrombomodulin.
- The thrombin–thrombomodulin system activates protein C.
- This suppresses factors Va and VIIIa with protein S as cofactor.
- The switch restricts extension beyond injured tissue.

## How a clot stays confined to injury

- Tissue factor exposure is concentrated at the wounded vessel wall.
- Activated platelet membranes localize major enzyme complexes.
- Neighboring intact endothelium presents anticoagulant safeguards.
- Fibrinolysis limits clot size and supports later dissolution.

## Blood flow reduces activated-factor persistence

- Flowing blood dilutes and washes activated proteins from injury sites.
- The liver removes circulating activated coagulation factors.
- These processes complement endothelial anticoagulant mechanisms.
- Flow-based removal alone is not the entire control system.

## Membrane dependence is a spatial safeguard

- Several major enzyme complexes require anionic phospholipids.
- These surfaces are enriched on platelets activated at vascular injury.
- Coagulation becomes markedly more effective at appropriate local surfaces.
- This helps confine reactions even while zymogens circulate throughout plasma.

# Intact versus activated endothelium

## Intact endothelium

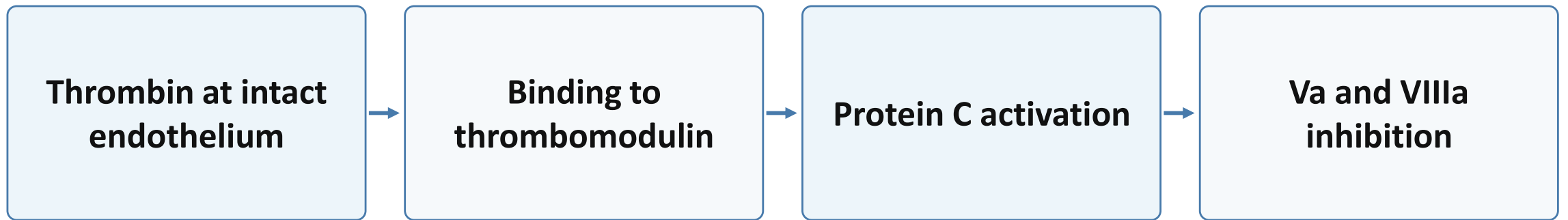
- Shields blood from tissue factor
- Presents anticoagulant proteins
- Supports fibrinolysis

## Injured / activated endothelium

- Barrier protection is disrupted
- Antithrombotic phenotype can diminish
- Favors local clot formation

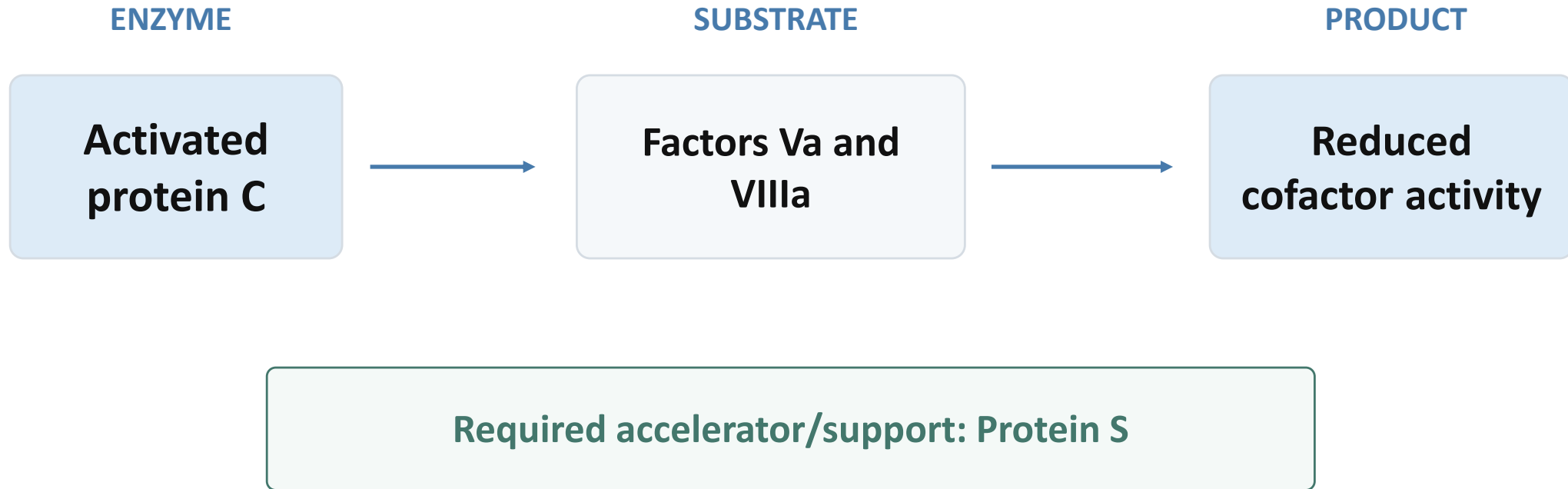
The endothelial state strongly influences clot growth or dissolution.

# Thrombomodulin changes thrombin's substrate



EPCR binds protein C and assists its activation at the endothelial surface.

# Activated protein C attenuates propagation

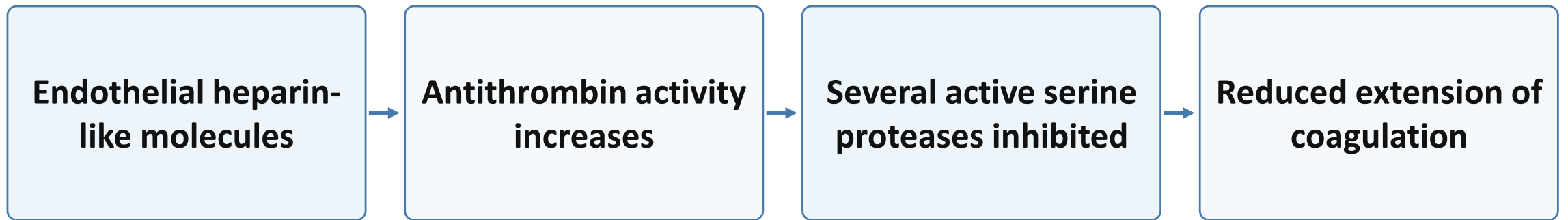


Inactivation of cofactors diminishes both tenase and prothrombinase efficiency.

## Protein S cooperates with activated protein C

- Protein S functions as a cofactor for activated protein C.
- Its best-established pathway here is suppression of Va and VIIIa.
- The source also discusses additional candidate anticoagulant actions.
- Protein S deficiency may increase propensity to inappropriate clot formation.

# Endothelial heparin-like molecules stimulate antithrombin



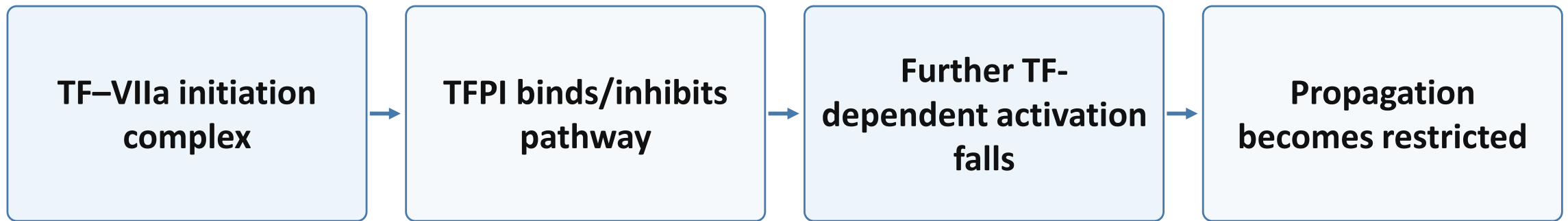
The heparin class of drugs exploits the same antithrombin-related mechanism.

## Antithrombin targets multiple active factors

| Primary inhibitor | Coagulation targets | Effect                              |
|-------------------|---------------------|-------------------------------------|
| Antithrombin      | IIa (thrombin)      | Limits fibrin production            |
| Antithrombin      | IXa and Xa          | Restrains propagation               |
| Antithrombin      | XIa and XIIa        | Restrains upstream serine proteases |

Endothelial heparin-like molecules potentiate antithrombin activity.

## Tissue factor pathway inhibitor restrains initiation



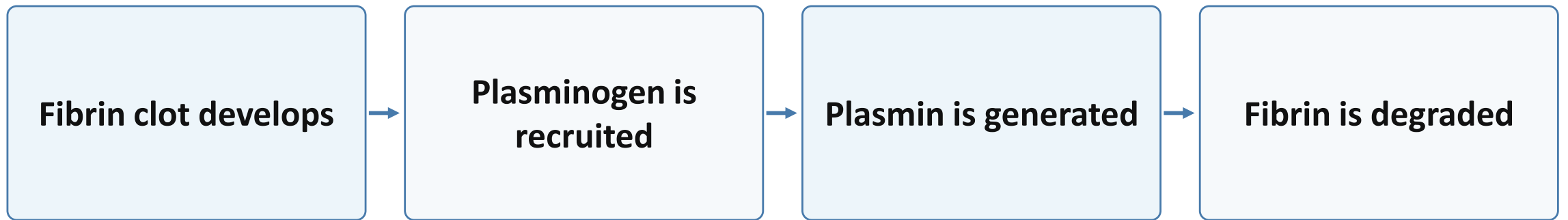
The source identifies protein S as a TFPI cofactor.

## Three endothelial anticoagulant strategies

| Mechanism                    | Key mediator                             | Principal action                |
|------------------------------|------------------------------------------|---------------------------------|
| <b>Cofactor inactivation</b> | Thrombomodulin / EPCR /<br>protein C / S | Inhibit Va and VIIIa            |
| <b>Protease inhibition</b>   | Heparin-like molecules /<br>antithrombin | Inhibit IIa, IXa, Xa, XIa, XIIa |
| <b>Initiation inhibition</b> | TFPI                                     | Oppose TF–VIIa complexes        |

Different brakes operate at different levels of the cascade.

## Coagulation triggers its counter-process

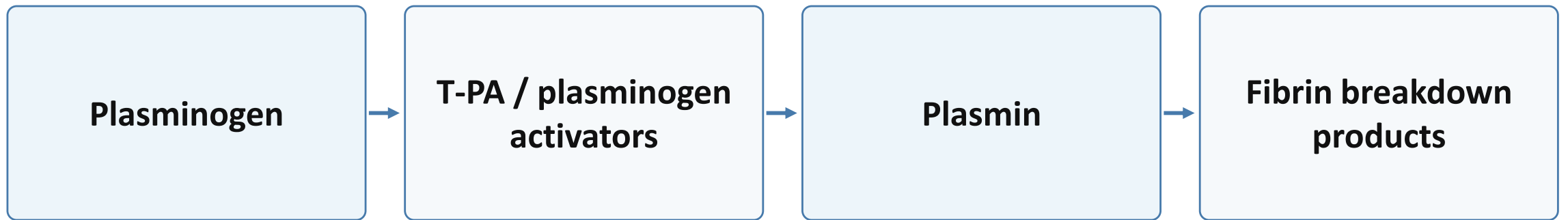


Fibrinolysis both limits clot size and supports later dissolution.

## T-PA localizes plasmin generation

- Endothelium is the main source of tissue plasminogen activator (t-PA).
- T-PA acts most effectively when bound to fibrin.
- It converts circulating plasminogen to plasmin.
- The localization helps focus fibrinolysis at fibrin-rich sites.

# The fibrinolytic protease is plasmin



Plasmin opposes persistent fibrin and can interfere with fibrin polymerization.

# Fibrinolysis is also regulated

## Promote fibrin breakdown

- T-PA: Activates plasminogen
- Plasmin: Cleaves fibrin
- Fibrin binding localizes activity

## Restrain excess breakdown

- $\alpha_2$ -antiplasmin inhibits free plasmin
- PAI opposes plasminogen activators
- Prevents indiscriminate proteolysis

Fibrinolysis requires negative regulation as well as activation.

## D-dimer reflects fibrin turnover

- Fibrin breakdown produces circulating degradation products.
- D-dimer is a fibrin-derived breakdown marker.
- The source associates elevated D-dimer with several thrombotic states.
- It is not a direct readout of which coagulation initiation pathway was used.

# Normal hemostasis versus pathological thrombosis

## Normal local response

- Triggered at vascular injury
- Confined by endothelial inhibitors
- Eventually remodeled by fibrinolysis

## Pathologic extension

- Inhibition becomes inadequate
- Activated factors are insufficiently constrained
- Clot can propagate inappropriately

The physiologic cascade must be balanced, not merely switched on.

# A functional map of the cascade

| Functional stage | Major factor(s)                 | Biologic purpose               |
|------------------|---------------------------------|--------------------------------|
| Initiation       | TF–VIIa                         | Activate IX and X              |
| Amplification    | IXa–VIIIa, Xa–Va, thrombin      | Increase thrombin output       |
| Clot formation   | Ila, fibrinogen                 | Generate fibrin polymers       |
| Stabilization    | XIIIa                           | Cross-link fibrin              |
| Containment      | Protein C/S, antithrombin, TFPI | Restrict excessive propagation |

This is a functional synthesis, not an additional literal laboratory pathway.

## Clinical reasoning: What does PTT test?

**A laboratory activates plasma with a negatively charged reagent and records time to fibrin formation. Which pathway is deliberately initiated?**

- A. Tissue-factor pathway only
- B. Contact/intrinsic pathway
- C. Fibrinolysis
- D. Platelet adhesion alone

**Answer: B. Contact/intrinsic pathway**

PTT includes XII, XI, IX, VIII and the common-pathway factors.

## Clinical reasoning: Factor XI deficiency

**Why can a factor XI deficiency cause less bleeding than the classical intrinsic pathway diagram might suggest?**

- A. Factor XI makes fibrin directly
- B. In-vivo coagulation is principally TF-initiated
- C. Factor XI is identical to tissue factor
- D. PTT never involves factor XI

**Answer: B. In-vivo coagulation is principally TF-initiated**

Thrombin feedback can activate XI; Laboratory pathway placement does not equal physiologic primacy.

## Clinical reasoning: Stabilize the fibrin network

**A clot contains fibrin monomers but needs covalent cross-linking. Which factor does thrombin activate to support this step?**

- A. Factor XII
- B. Factor VII
- C. Factor XIII
- D. Protein S

**Answer: C. Factor XIII**

Factor XIIIa covalently cross-links fibrin after thrombin has generated fibrin monomers.

## Clinical reasoning: Confining a clot

**Which mechanism most directly inactivates the propagation cofactors Va and VIIIa at adjacent intact endothelium?**

- A. T-PA alone
- B. Activated protein C with protein S
- C. TF–VIIa
- D. Fibrinogen

**Answer: B. Activated protein C with protein S**

Thrombin–thrombomodulin shifts thrombin activity toward protein C activation.

## Coagulation: Integrated synthesis

- TF–VIIa is the major in-vivo initiator, with IXa–VIIIa central to X activation.
- Xa–Va generates thrombin; Thrombin produces and stabilizes fibrin.
- Platelets, calcium, and phospholipid surfaces organize the cascade locally.
- Intact endothelium and fibrinolysis prevent unlimited clot propagation.

## Selected reading

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 4: Hemodynamic Disorders, Thromboembolic Disease, and Shock.

See the source discussion of coagulation, endothelial anticoagulants, and the fibrinolytic system.