

Normal Hemostasis

Platelet adhesion and activation • fibrin reinforcement • endothelial regulation

Mechanisms and clinicopathologic correlations

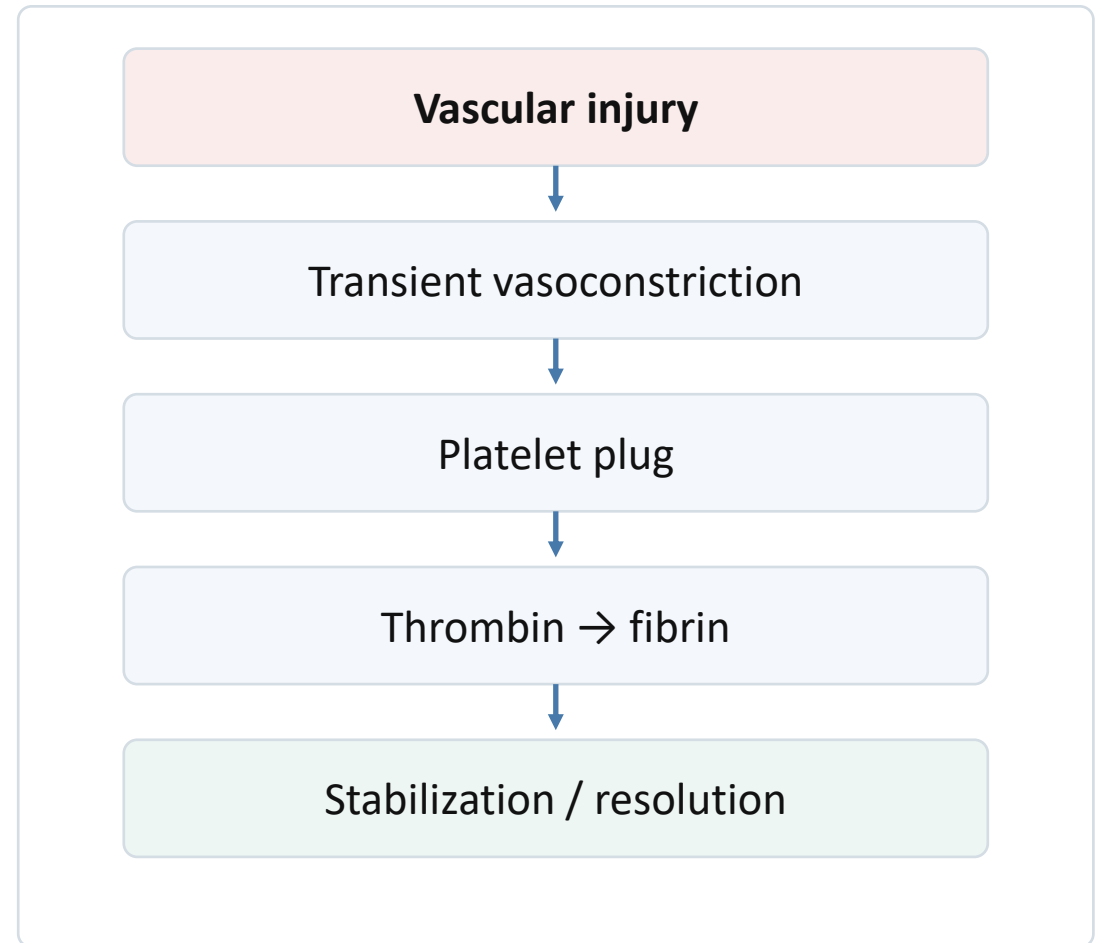
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Learning goals

- Describe the four overlapping phases after vascular injury.
- Explain platelet adhesion, activation, recruitment and aggregation.
- Link thrombin and fibrin deposition to plug stabilization.
- Identify how intact endothelium limits and resolves clotting.



Hemostasis is localized clot formation

- Hemostasis limits blood loss at the site of vascular injury.
- Platelets, clotting factors and the vessel wall act as an integrated system.
- The intended product is a stable local plug—not generalized coagulation.

Platelets

Adhesion →
aggregation

Coagulation

Thrombin →
fibrin

Endothelium

Switch +
localization

Localized, stable hemostatic plug

Three participants perform different tasks

- Platelets provide immediate adhesion, a cellular plug and a catalytic surface.
- Coagulation proteins generate thrombin and polymerized fibrin.
- Endothelium determines whether clotting proceeds, remains localized or resolves.

Platelets

Adhesion →
aggregation

Coagulation

Thrombin →
fibrin

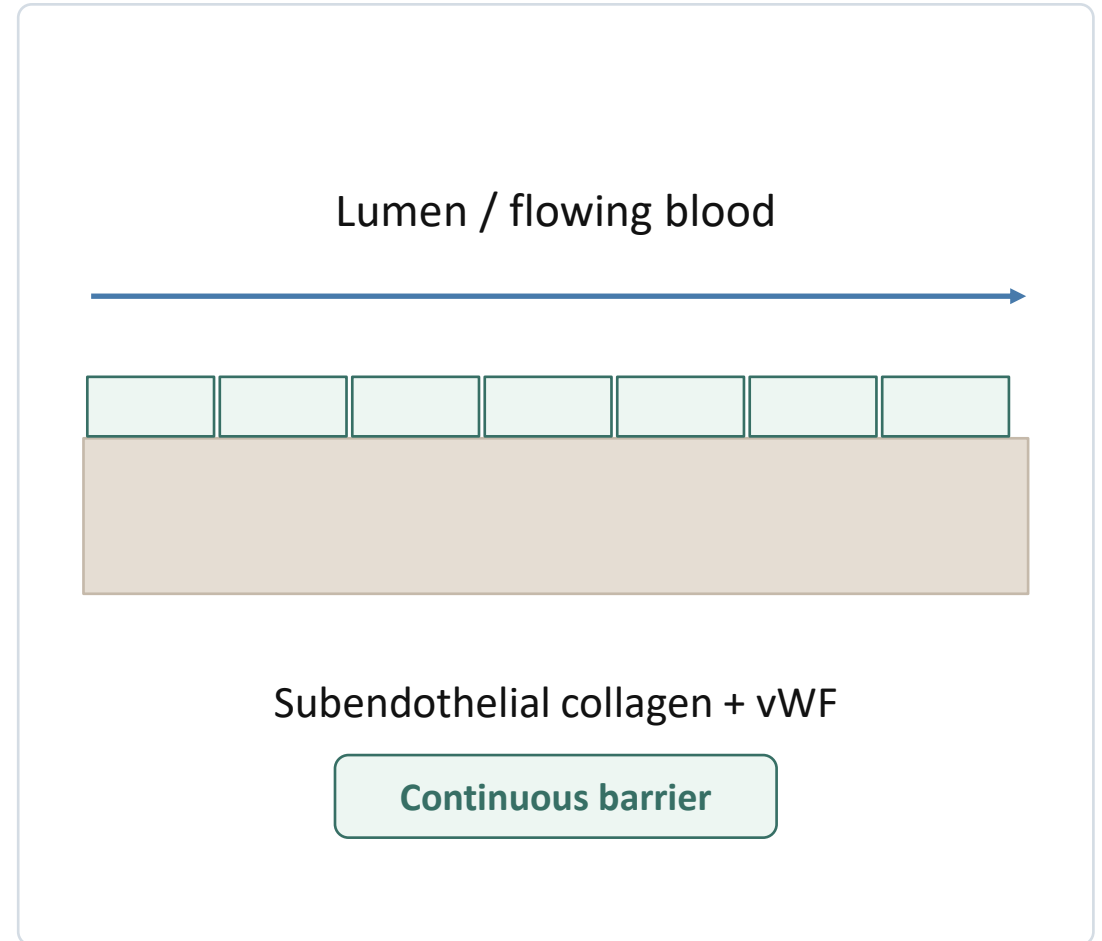
Endothelium

Switch +
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Localized, stable hemostatic plug

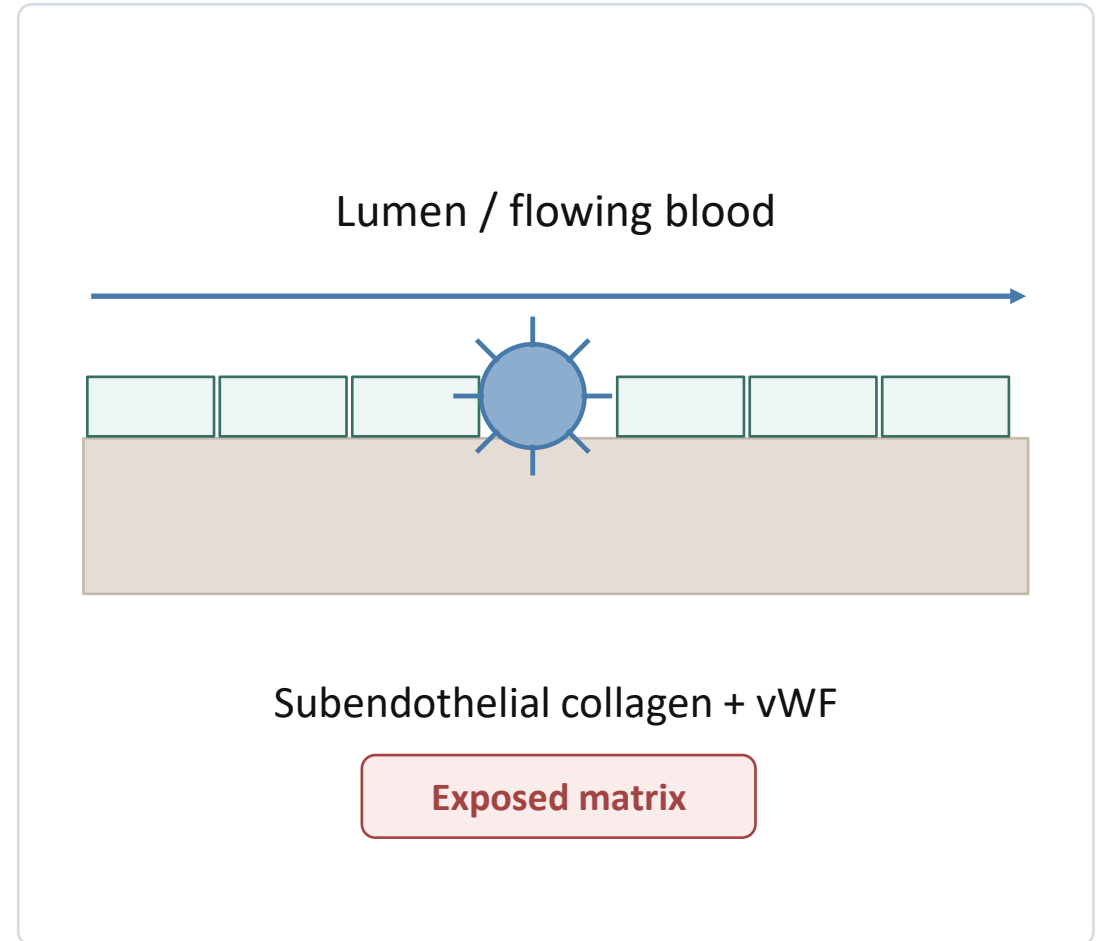
Intact endothelium separates blood from matrix

- Circulating platelets ordinarily do not contact subendothelial collagen or vWF.
- An uninterrupted endothelial barrier also shields blood from vessel-wall tissue factor.
- Barrier loss is a powerful spatial cue for hemostasis.



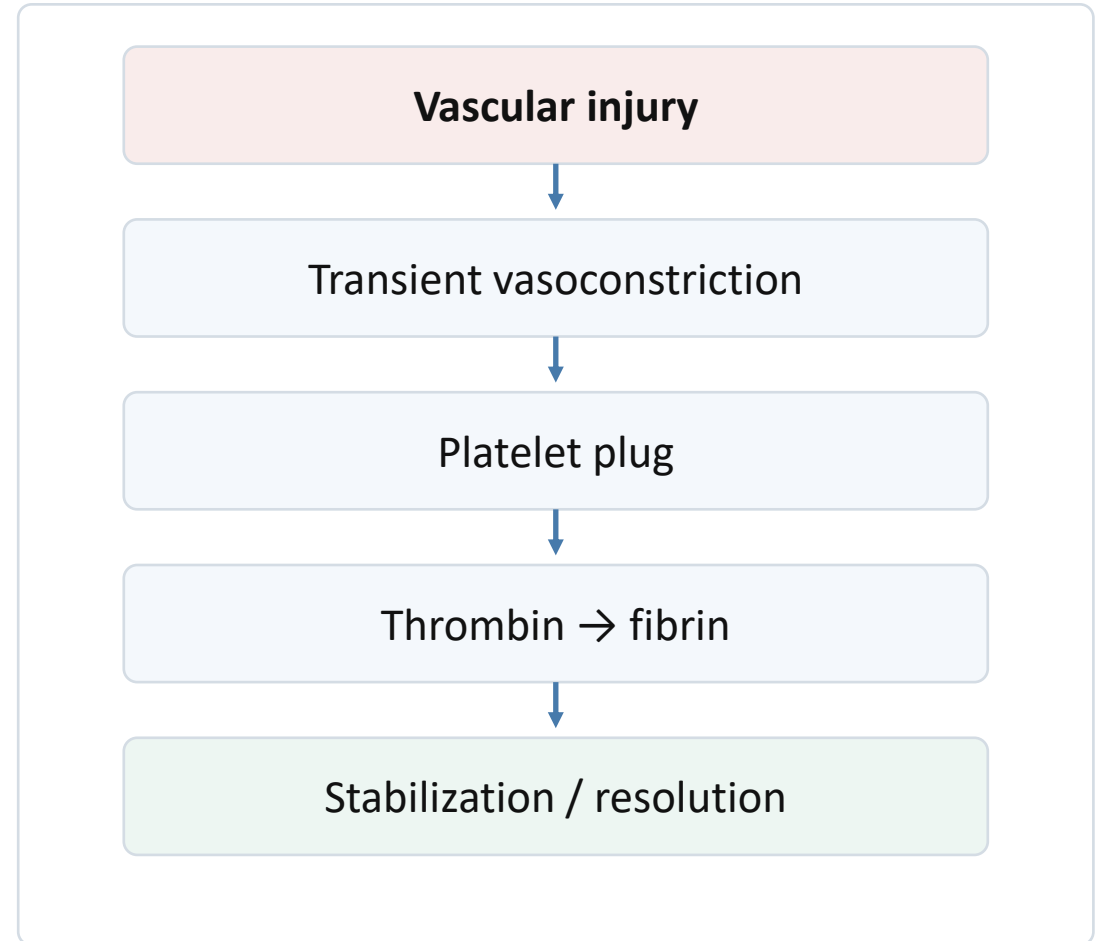
A vascular breach changes local exposure

- Injury uncovers extracellular matrix and subendothelial vWF.
- Platelet-adhesive surfaces and tissue factor become accessible at the same lesion.
- The injury site coordinates primary and secondary hemostasis.



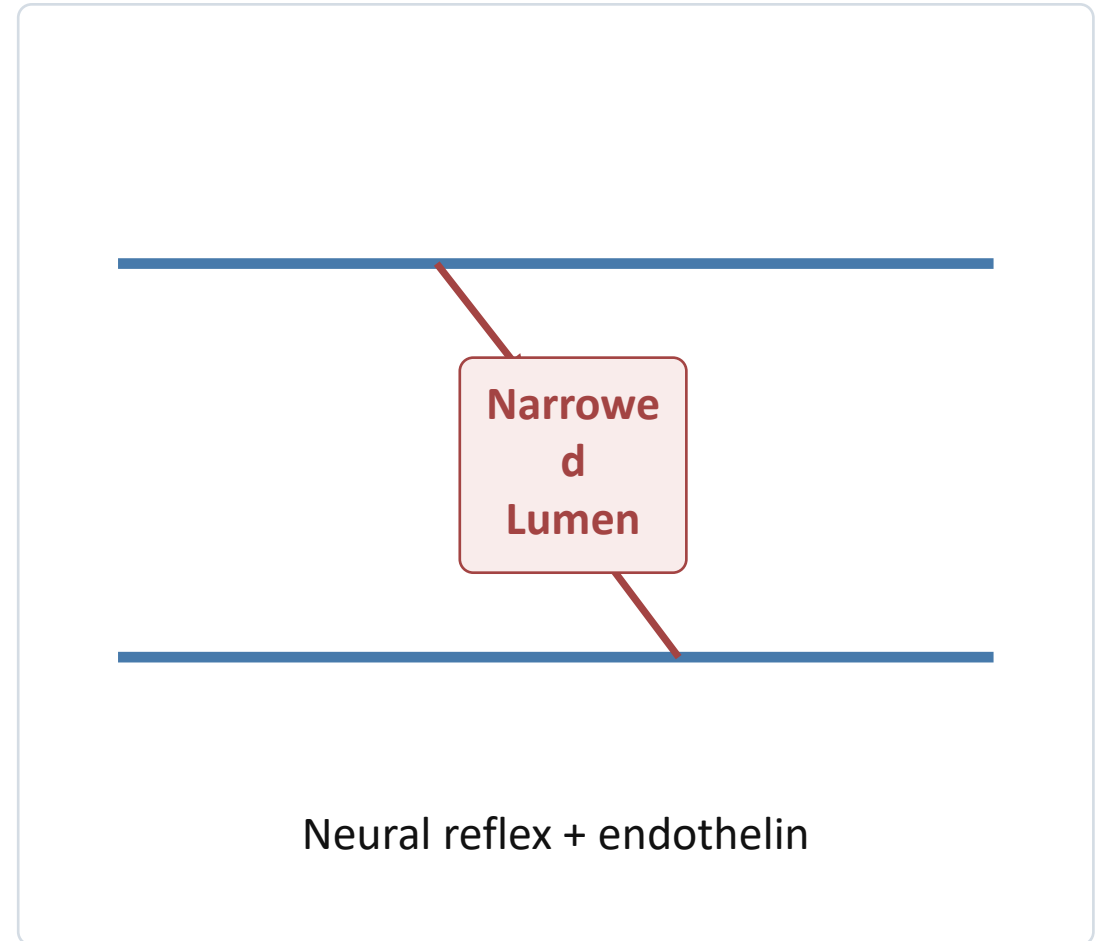
Four processes overlap after injury

- Transient vasoconstriction reduces local blood flow.
- Platelets assemble the primary plug while tissue factor drives thrombin production.
- Fibrin stabilizes the plug; Counterregulation later promotes resolution.



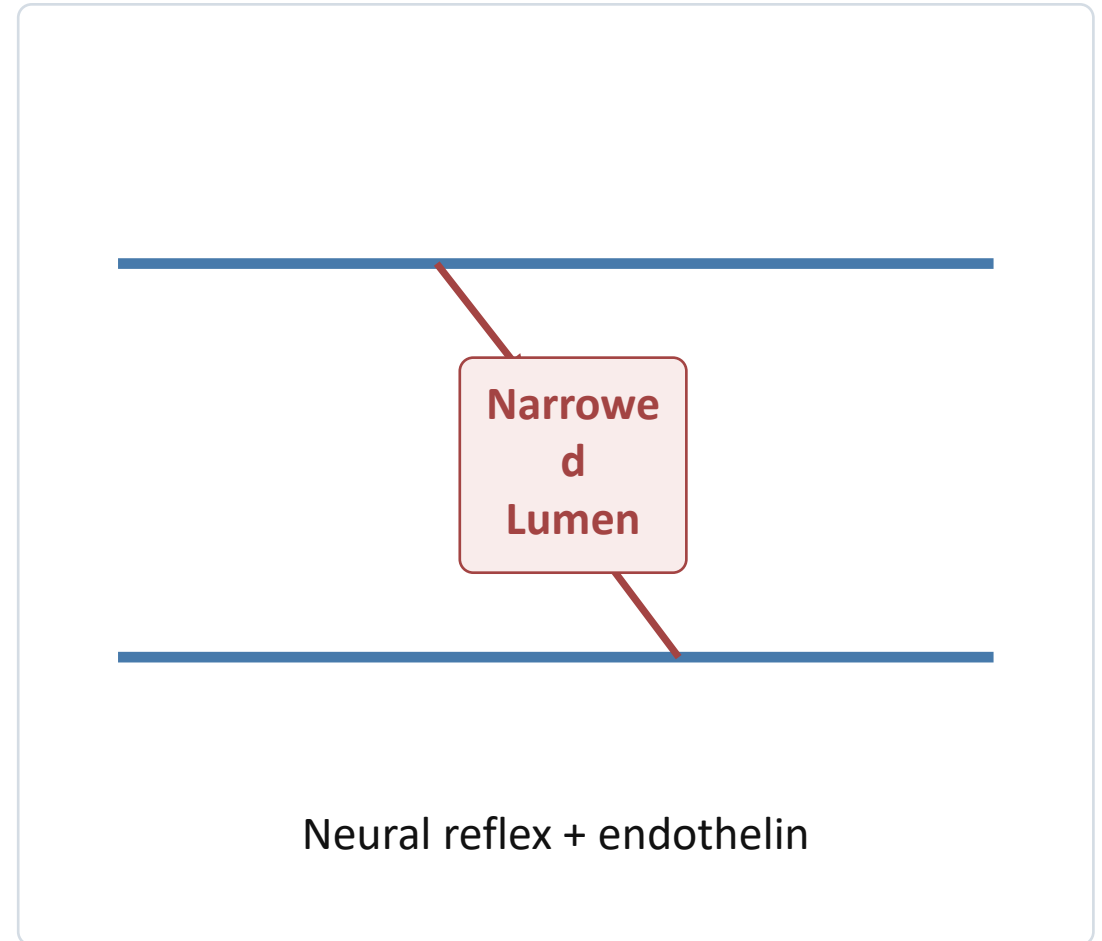
Vasoconstriction is the immediate response

- Arterioles constrict within moments after vessel injury.
- The reduced lumen temporarily limits blood delivery to the lesion.
- This buys time for platelet and coagulation-factor responses.



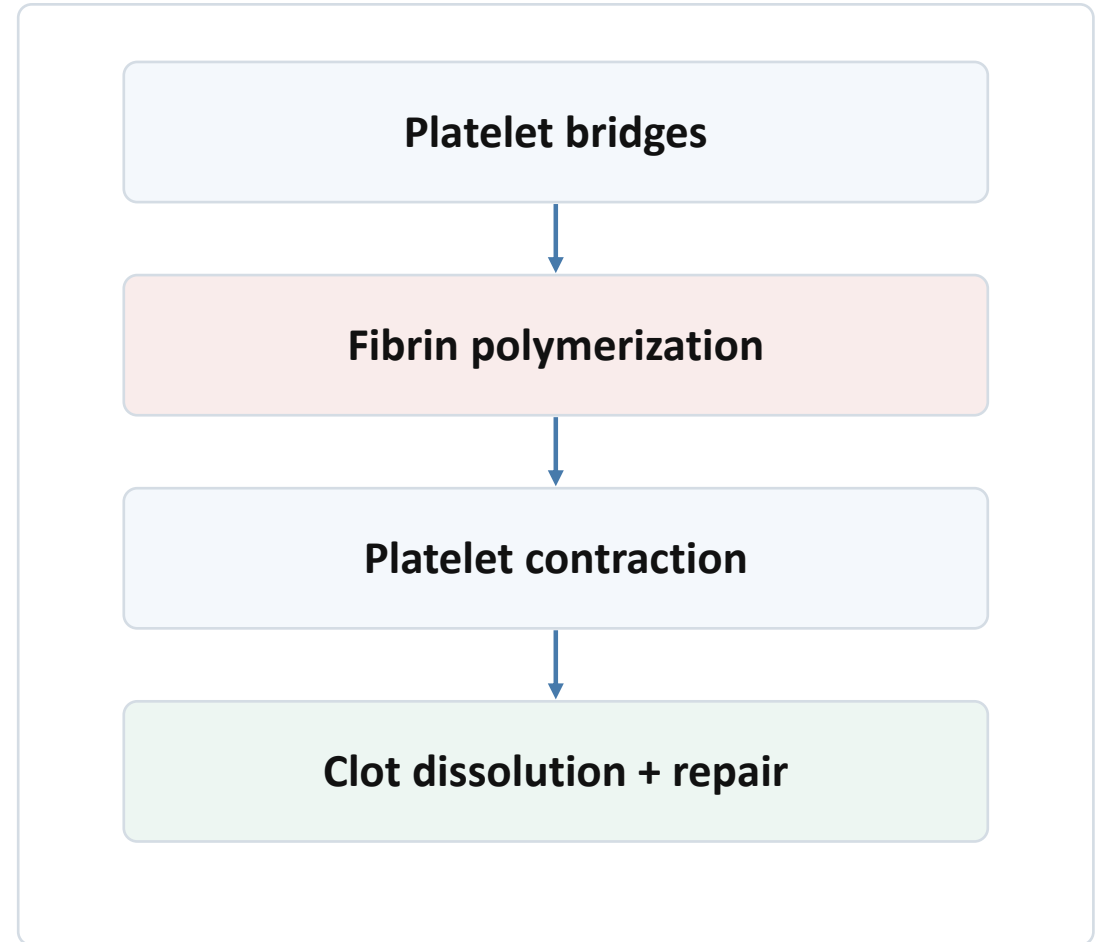
Neural reflexes and endothelin narrow vessels

- Reflex neurogenic mechanisms contribute to early vasoconstriction.
- Locally released endothelial endothelin can augment the response.
- The effect is short-lived and cannot independently provide lasting hemostasis.



Why vasoconstriction alone is insufficient

- Vessel narrowing is transient, so flow can return before tissue repair.
- Without platelet and fibrin plug formation, bleeding can resume.
- Hemostasis therefore requires rapid cellular and enzymatic reinforcement.



Primary and secondary hemostasis are coupled

- Primary: Adhesion and aggregation form a platelet-rich initial seal.
- Secondary: Thrombin converts fibrinogen to fibrin, reinforcing that seal.
- They are overlapping biochemical programs, not isolated compartments.

Primary

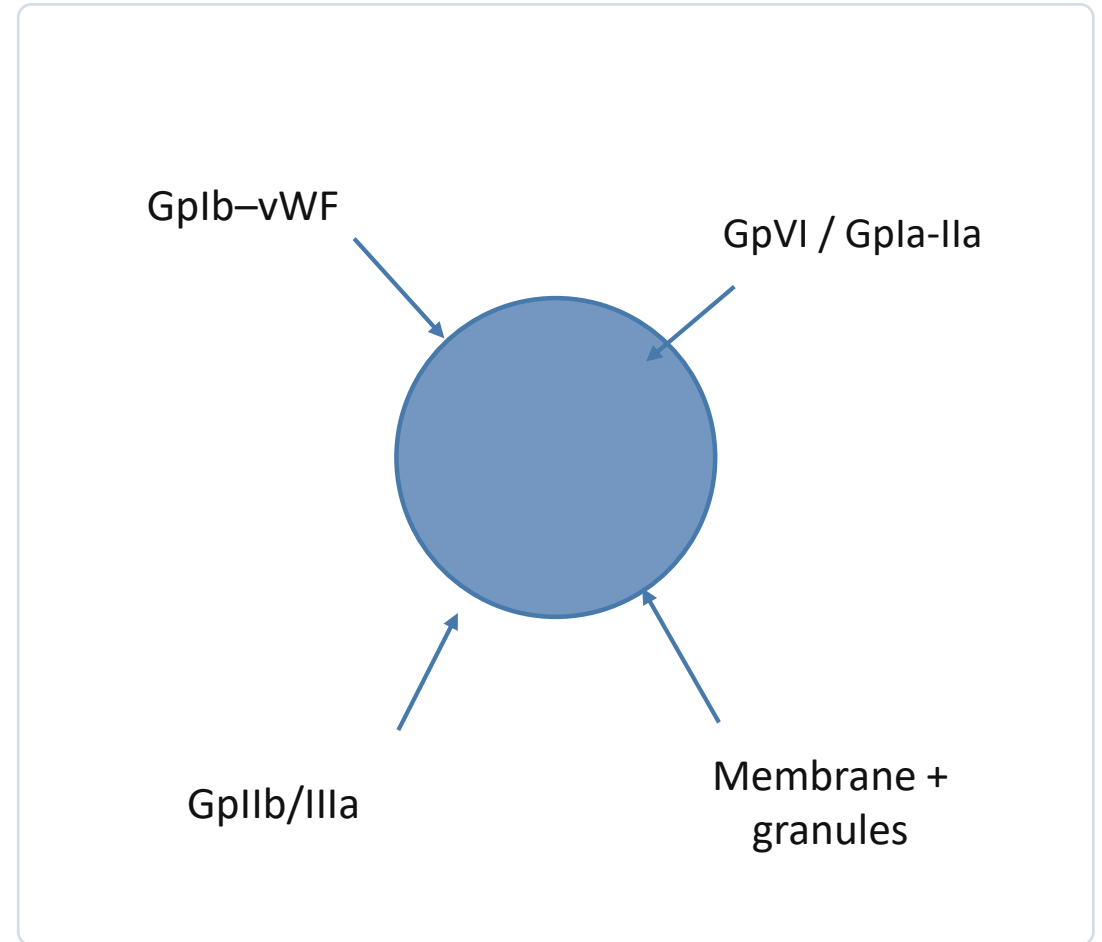
Platelets adhere, activate and bridge through fibrinogen.

Secondary

Thrombin generation polymerizes fibrin around the platelet mass.

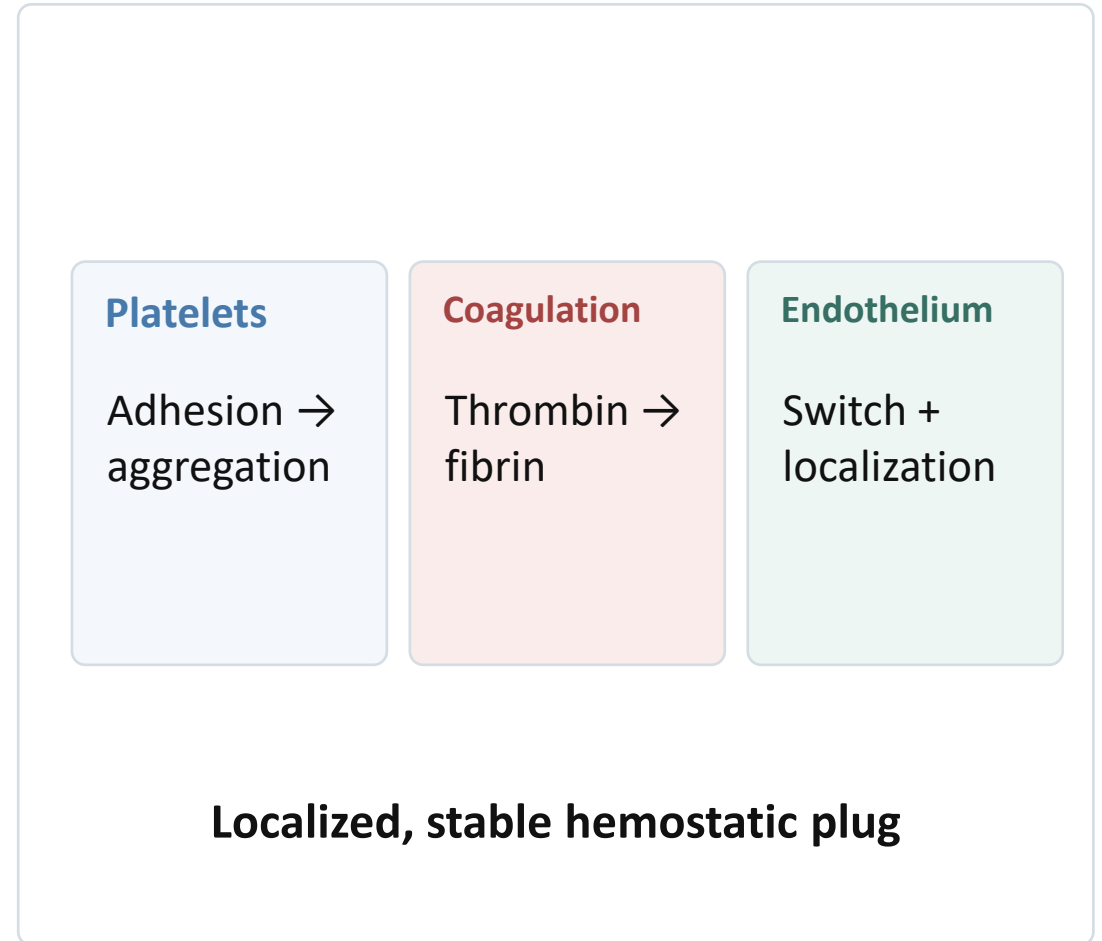
Platelets arise from megakaryocytes

- Platelets are anucleate circulating cell fragments released from marrow megakaryocytes.
- Their resting shape is a small disk; Activation rapidly changes their form.
- Specialized receptors, granules and cytoskeleton determine function.



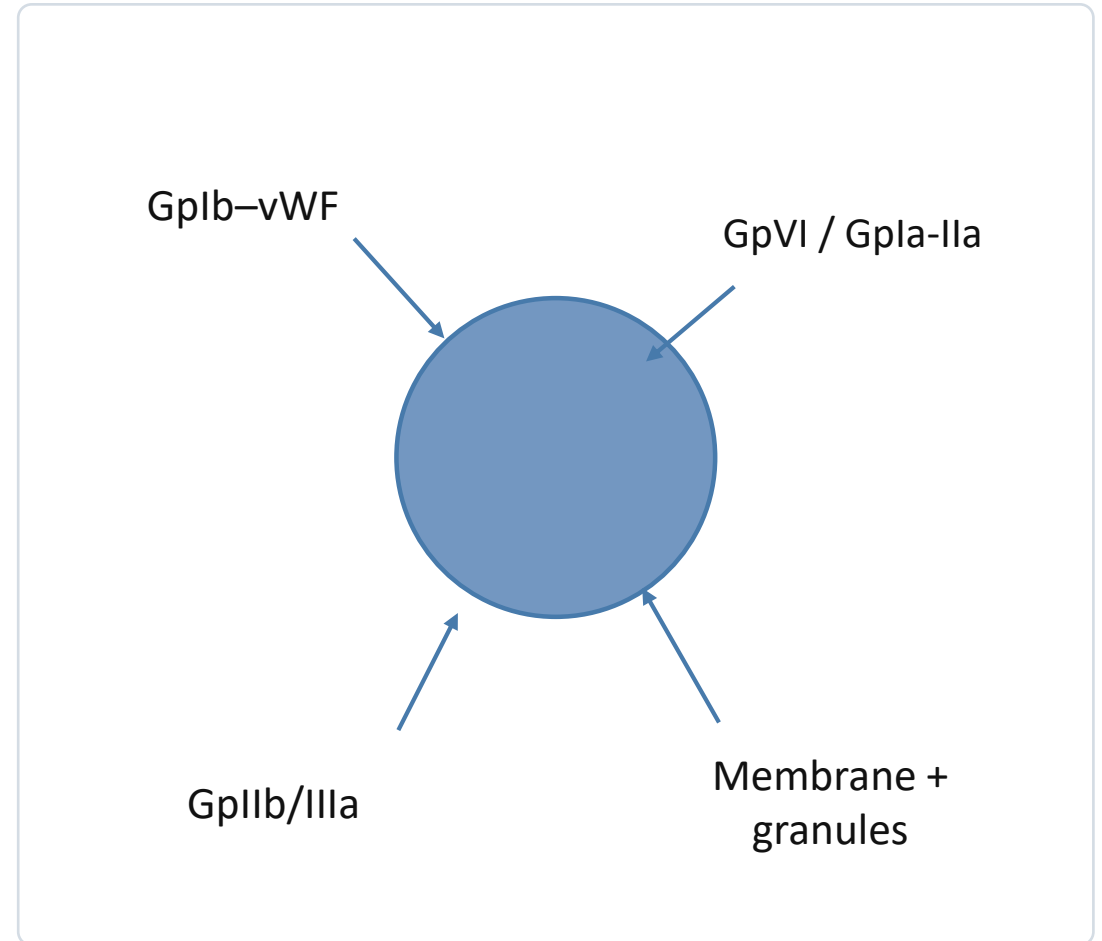
Platelets serve two hemostatic roles

- An adhesive/aggregating surface rapidly seals small vascular defects.
- Activated platelets concentrate coagulation reactions on membrane phospholipids.
- Thus, platelet dysfunction impairs both the initial plug and its fibrin reinforcement.



Each platelet receptor has a distinct ligand

- GpIb binds von Willebrand factor, permitting adhesion to exposed matrix.
- GpVI and GpIa/IIa recognize collagen.
- Activated GpIIb/IIIa binds fibrinogen, supporting platelet-to-platelet linkage.



α -granules carry adhesive and repair proteins

- Contents include fibrinogen, vWF and coagulation factors V and XI.
- Also contain fibronectin, platelet factor 4, PDGF and TGF- β .
- Their release supplies local proteins relevant to coagulation and wound repair.

α -granules

VWF · fibrinogen ·
factors V/XI
PF4 · PDGF · TGF- β

Dense granules

ADP · ATP · Ca²⁺
Serotonin ·
epinephrine

Dense granules supply rapid soluble signals

- Dense granules contain ADP, ATP and ionized calcium.
- Serotonin and epinephrine are also present.
- Released ADP recruits and activates additional platelets near the injury.

α -granules

VWF · fibrinogen ·
factors V/XI
PF4 · PDGF · TGF- β

Dense granules

ADP · ATP · Ca²⁺
Serotonin ·
epinephrine

Granule cargo links aggregation and repair

- Dense-granule ADP supports self-amplifying recruitment.
- α -granule proteins supply adhesive/coagulation components and repair signals.
- Granule secretion is part of platelet activation, not a late bystander event.

Dense-granule emphasis

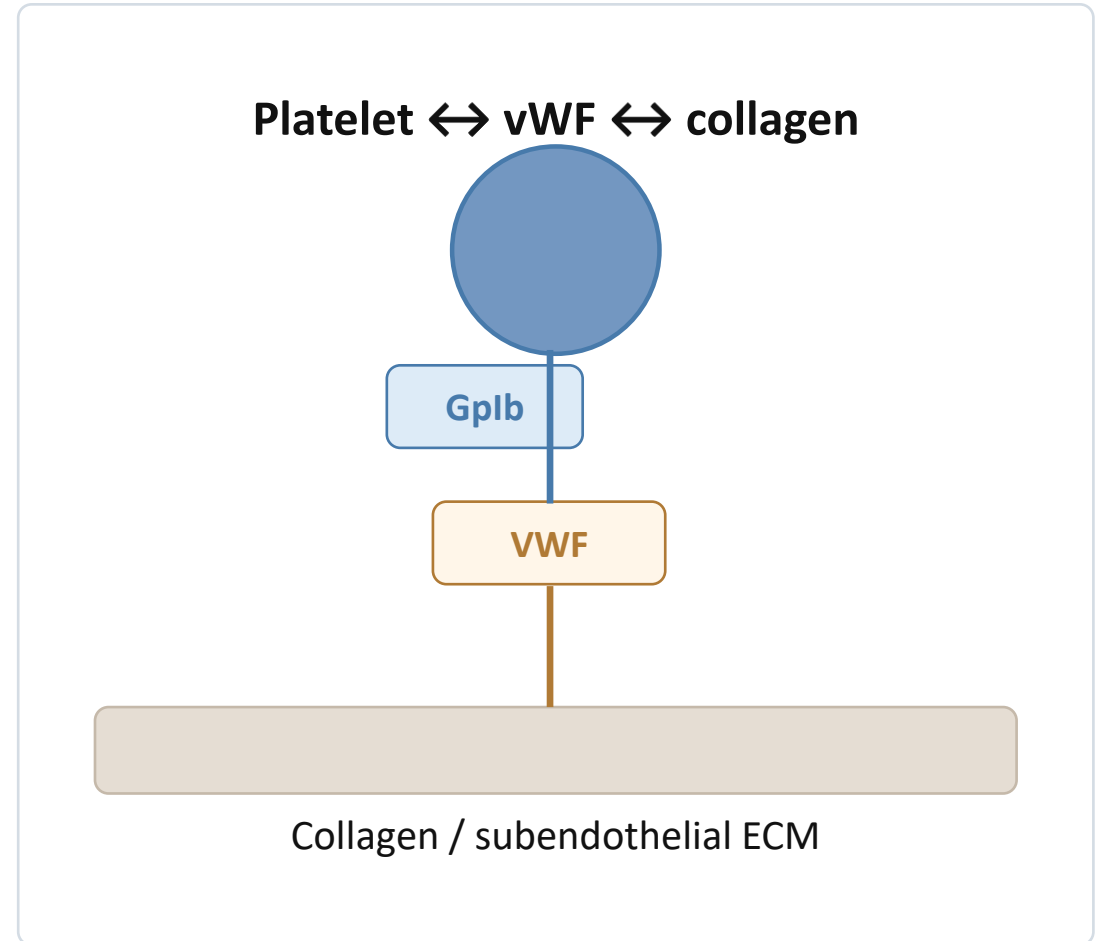
Rapid small-molecule release: ADP and Ca^{2+} .

α -granule emphasis

Adhesive proteins, coagulation components and growth factors.

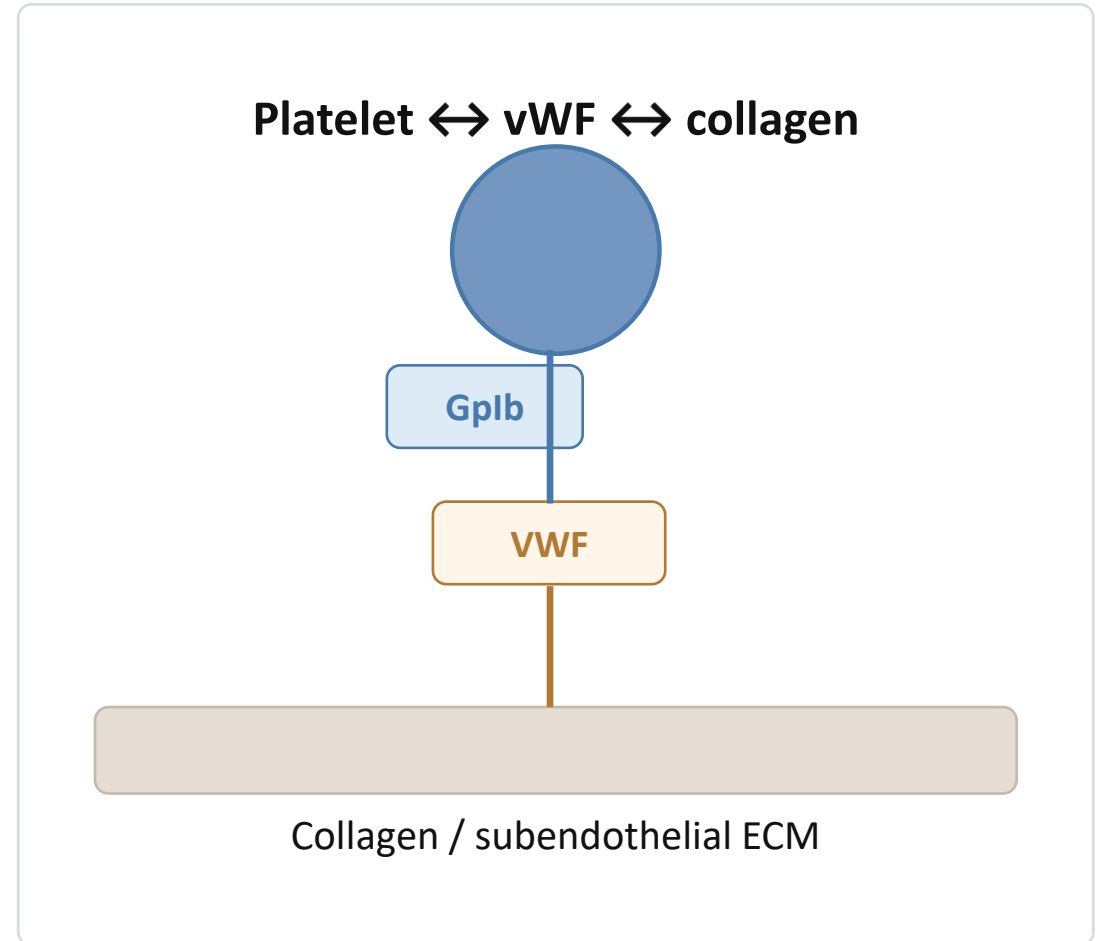
Adhesion begins at exposed matrix

- Endothelial disruption brings circulating platelets into contact with the ECM.
- Subendothelial collagen and vWF provide adhesion substrates.
- This initial tethering initiates activation and plug development.



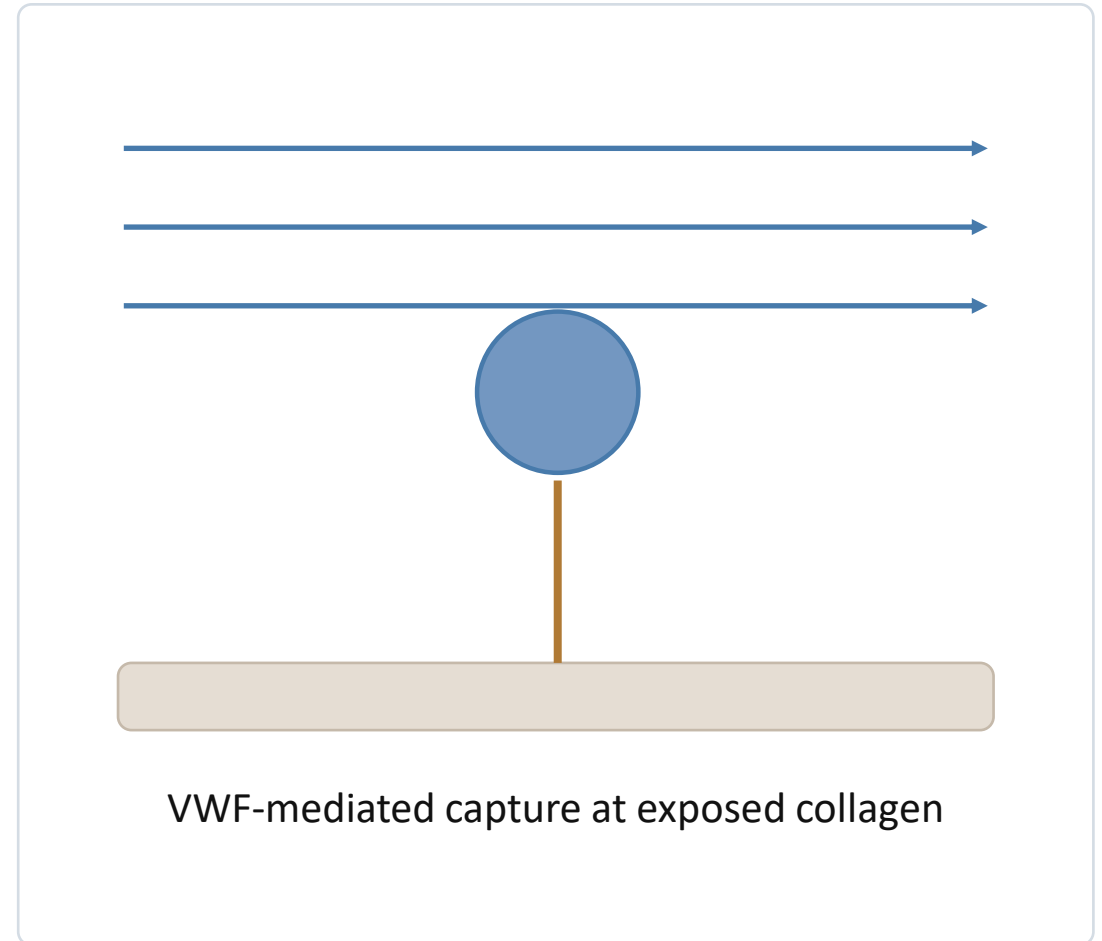
VWF bridges platelet GpIb to collagen

- VWF associates with exposed subendothelial collagen.
- Its platelet-binding interaction with GpIb captures platelets at the lesion.
- The bridging molecule and its platelet receptor are both essential to normal adhesion.



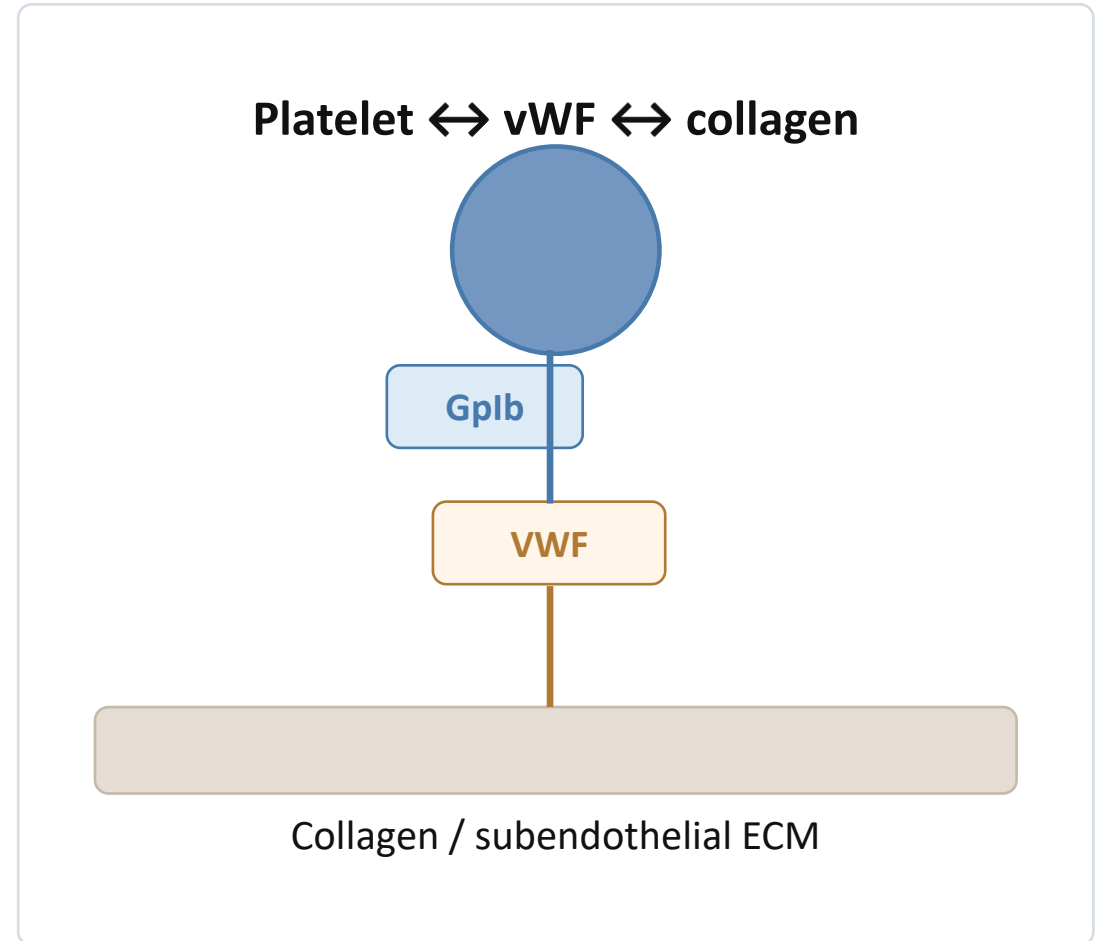
VWF is especially important under high shear

- High-shear blood flow favors the vWF-dependent adhesion mechanism.
- VWF simultaneously interacts with collagen and platelets, serving as a tether.
- This explains why defects can particularly compromise rapid platelet capture.



Platelets also engage collagen directly

- GpVI and the GpIa/IIa complex are platelet collagen receptors.
- Direct collagen interaction complements GpIb–vWF tethering.
- Several receptor–ligand pairs cooperate rather than representing one exclusive route.



Adhesion and aggregation use different bridges

- Adhesion links a platelet to the exposed vessel wall.
- Aggregation links platelets to each other.
- VWF/GpIb primarily mediates wall tethering; Fibrinogen/GpIIb-IIIa mediates interplatelet bridges.

Adhesion

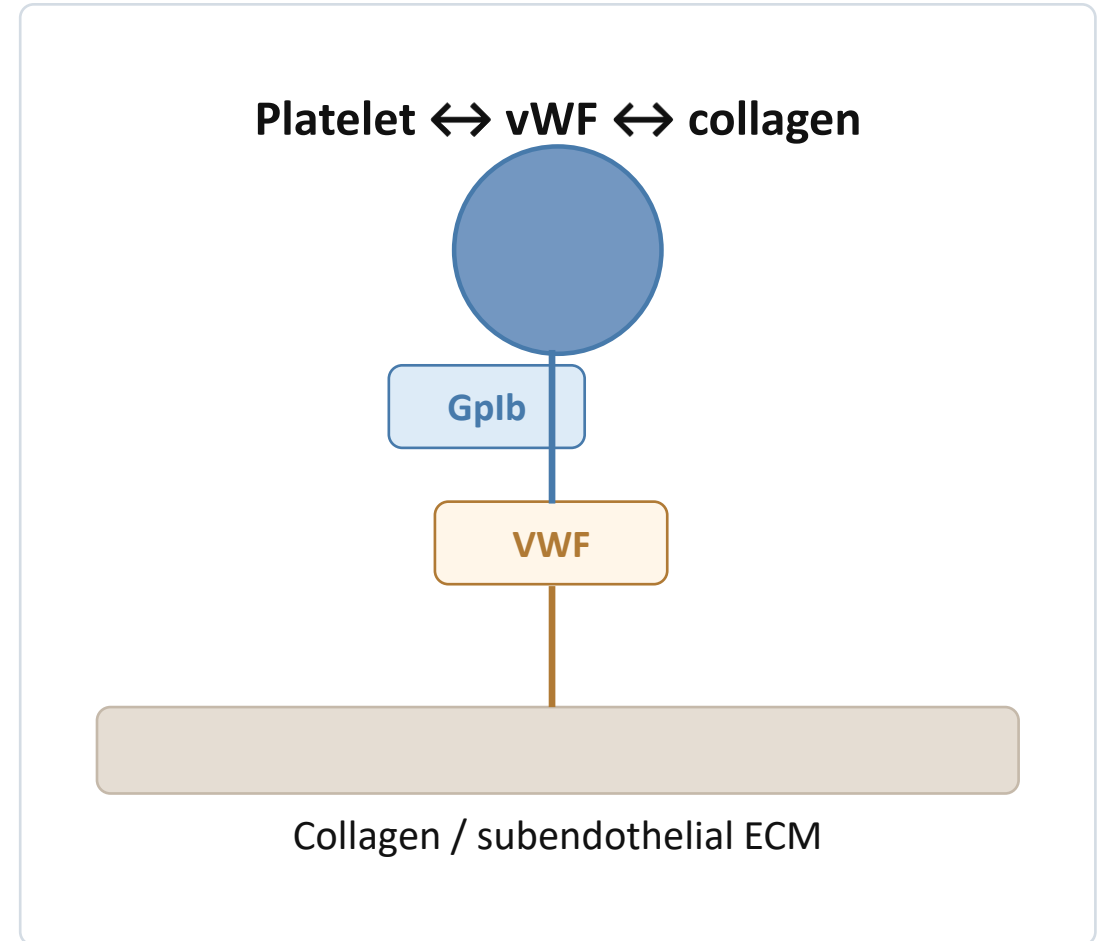
Platelet GpIb ↔
vWF ↔ matrix
collagen.

Aggregation

Platelet GpIIb/IIIa
↔ fibrinogen ↔
adjacent platelet.

Von Willebrand disease illustrates failed tethering

- Genetic deficiency of vWF impairs platelet–matrix adhesion.
- The resulting defect is in primary hemostatic plug formation.
- The disorder illustrates the functional importance of a plasma–matrix bridging protein.



Bernard–Soulier syndrome localizes to GpIb

- GpIb is the platelet receptor for von Willebrand factor.
- Inherited deficiency of GpIb disrupts the same adhesion interface from the platelet side.
- Distinct molecular lesions can impair the same hemostatic step.

VWF defect

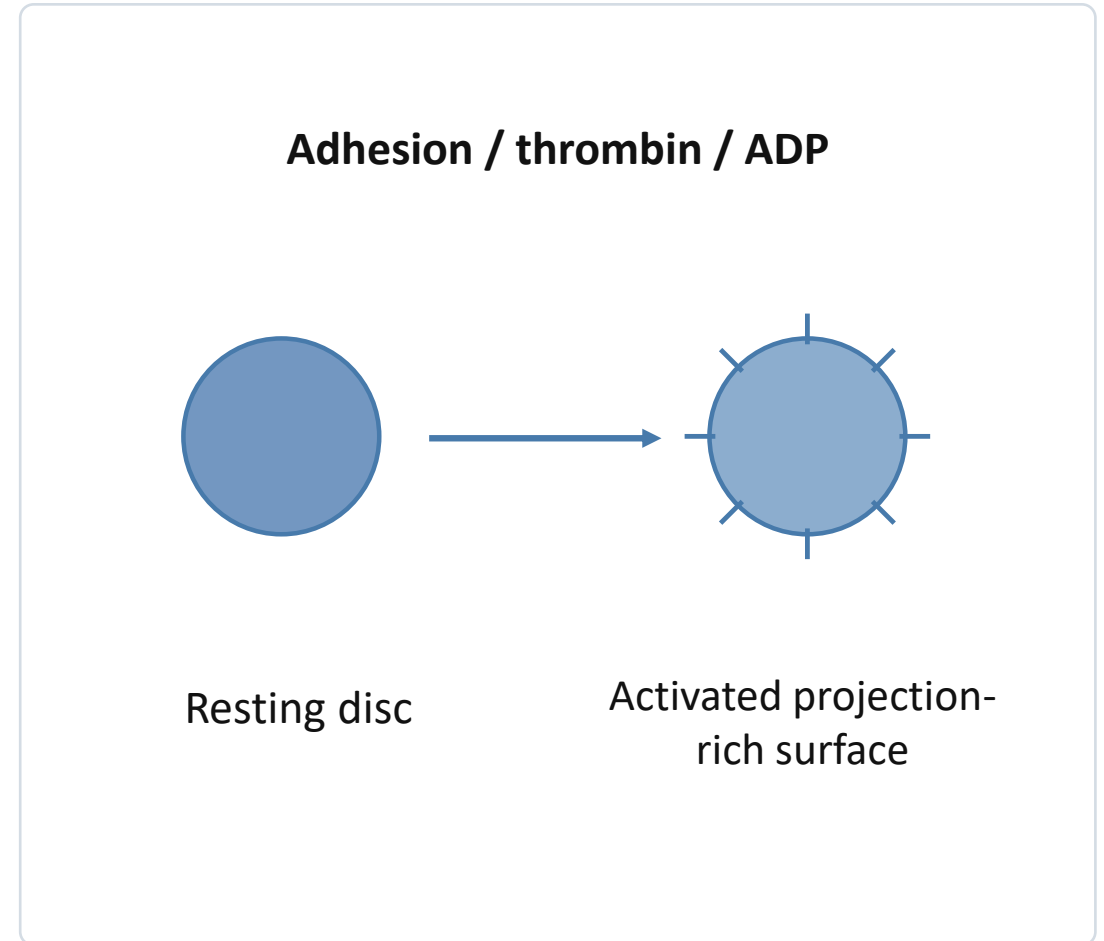
Bridge protein
unavailable or
dysfunctional.

GpIb defect

Platelet receptor for
that bridge is
deficient.

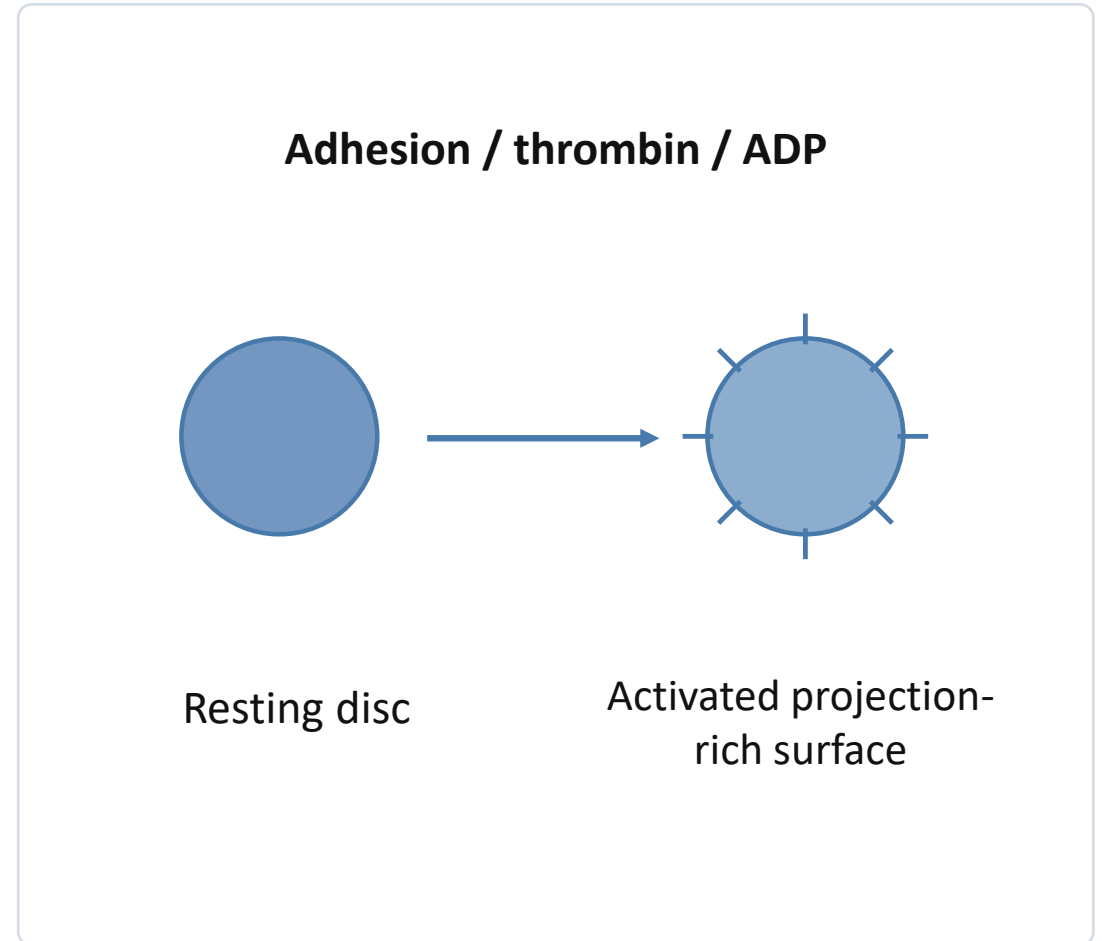
Adherent platelets undergo activation

- Adhesion rapidly initiates shape change and granule secretion.
- Membrane receptor conformations and lipid distribution also change.
- These linked transformations prepare platelets for recruitment and coagulation.



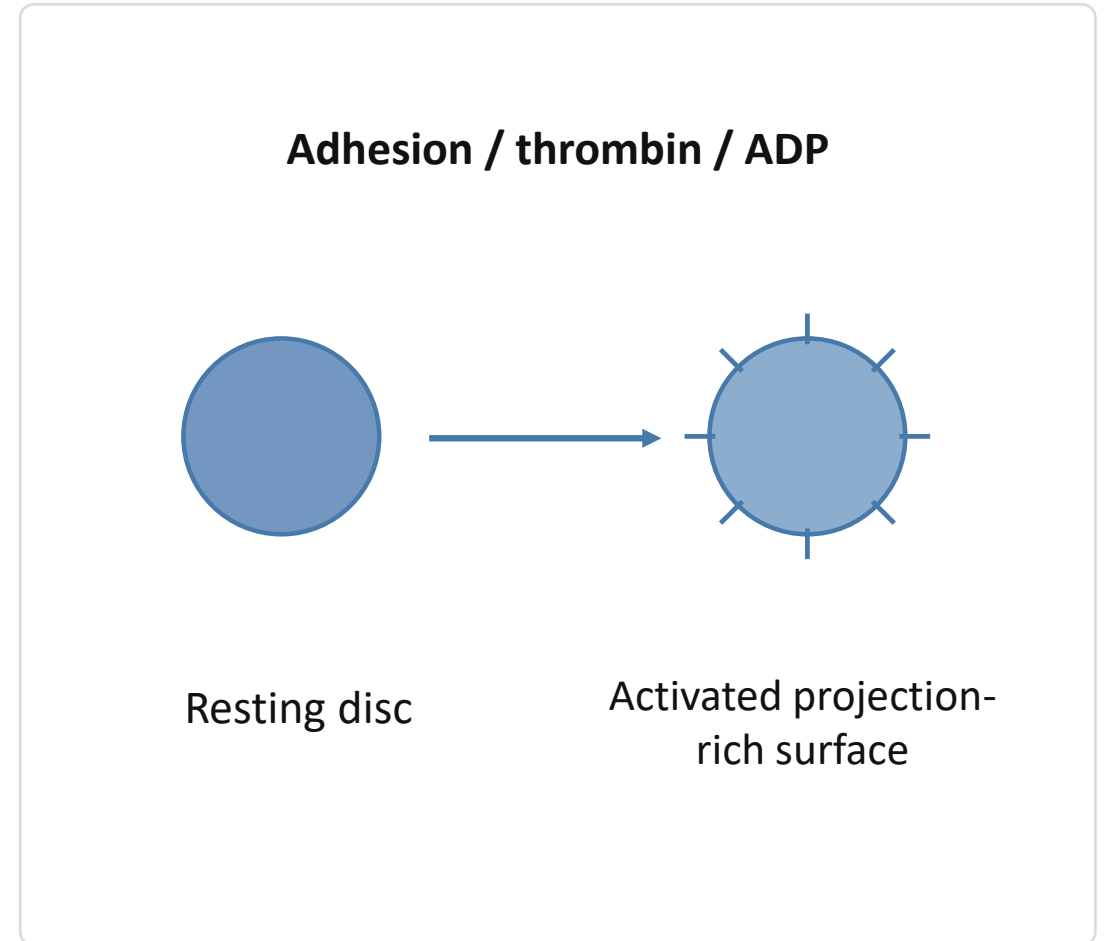
Activation converts disks into spiky cells

- Resting platelets are relatively smooth, rounded disks.
- Activated platelets develop projecting processes and markedly greater surface area.
- Shape remodeling increases their interaction with the local plug and matrix.



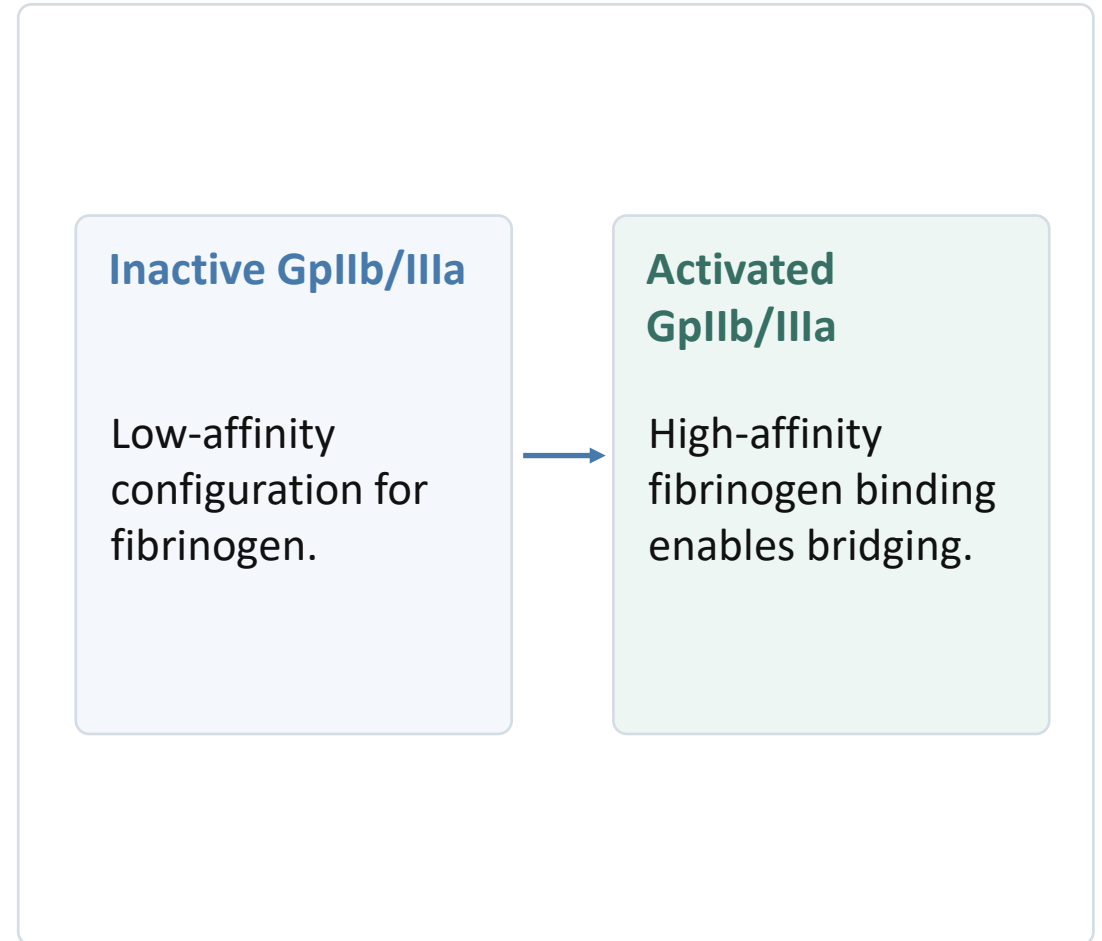
Platelet cytoskeleton drives mechanical change

- The contractile cytoskeleton underlies shape remodeling.
- Later contraction pulls aggregated elements into a more consolidated plug.
- Platelet function is therefore both biochemical and mechanical.



Activated GpIIb/IIIa binds fibrinogen

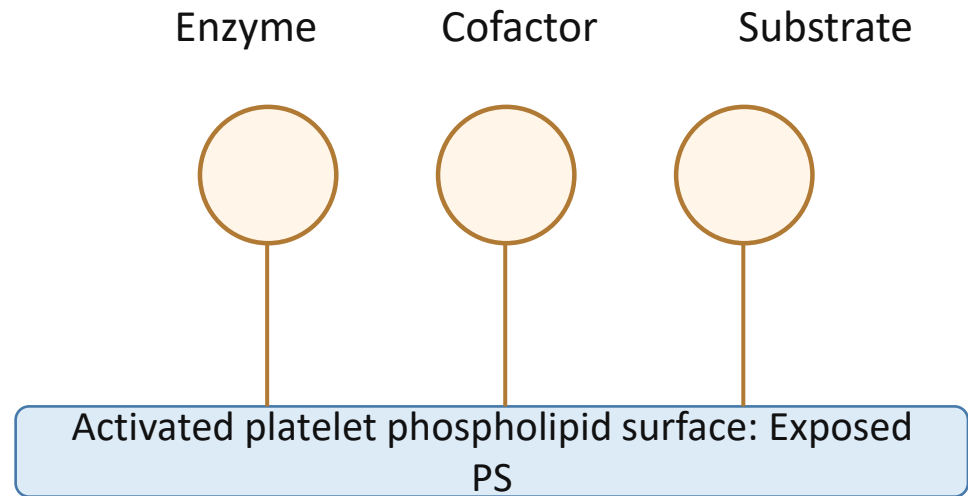
- Activation alters the conformation of GpIIb/IIIa.
- The altered receptor has increased affinity for circulating fibrinogen.
- This transition enables fibrinogen to link neighboring platelets.



Phosphatidylserine exposes a catalytic surface

- Activation translocates negatively charged phospholipids, especially PS, outward.
- These membrane lipids concentrate calcium-dependent coagulation-factor complexes.
- The activated platelet thus accelerates local thrombin production.

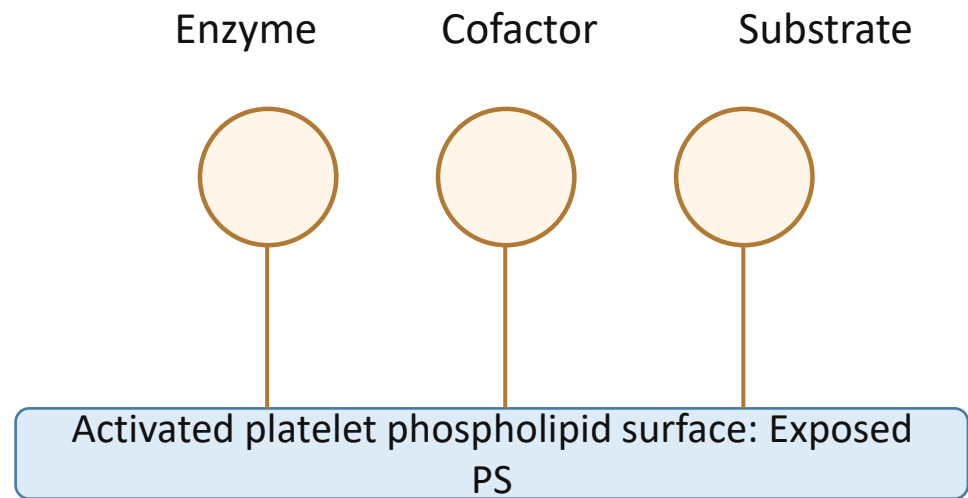
Ca²⁺ supports membrane assembly



Calcium supports assembly of coagulation complexes

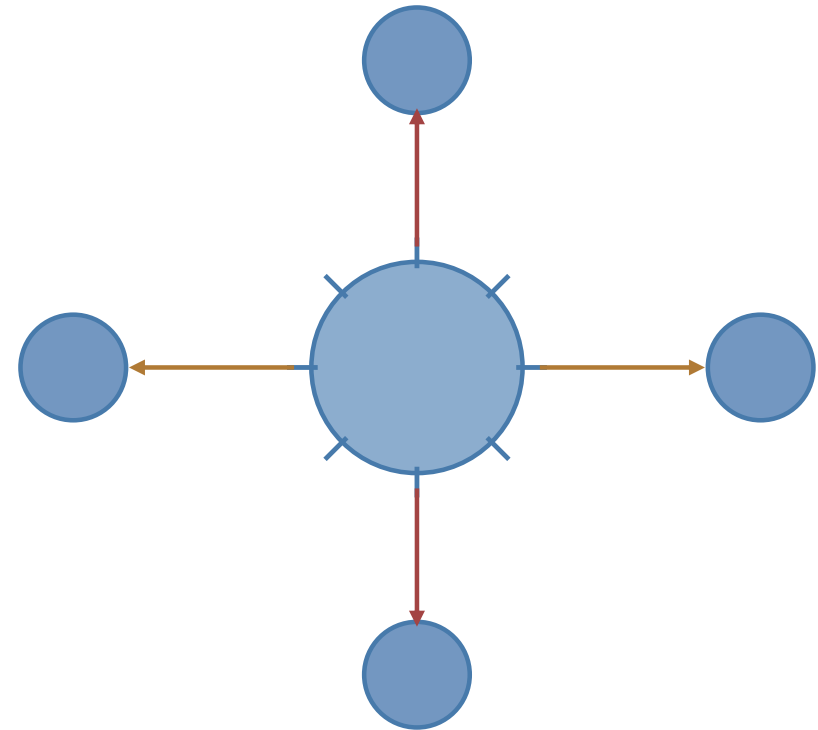
- Several coagulation reactions occur on a negatively charged lipid surface.
- Calcium helps organize membrane-bound proteins within those complexes.
- Platelet-derived calcium and surface exposure couple primary to secondary hemostasis.

Ca²⁺ supports membrane assembly



ADP is a platelet recruitment signal

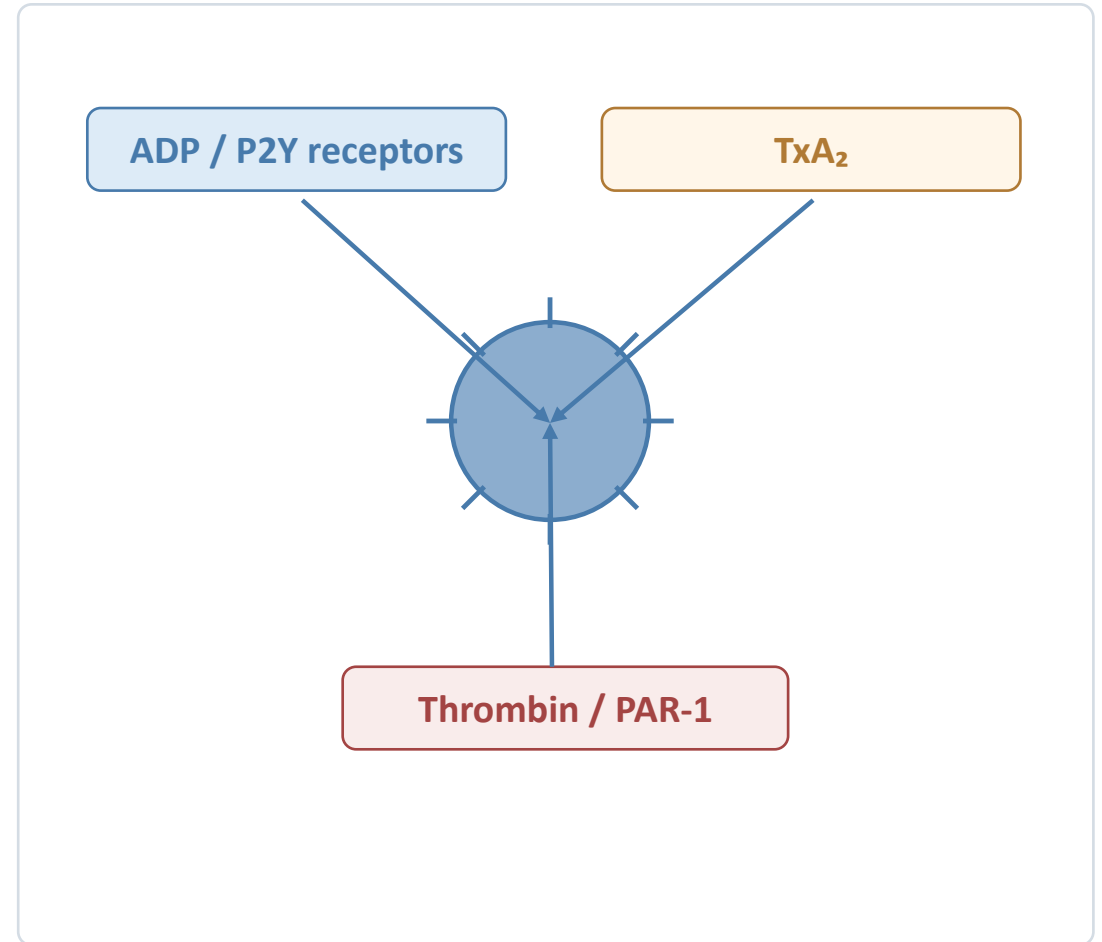
- ADP is released from dense granules of activated platelets.
- Nearby platelets respond and themselves release additional granule contents.
- This amplifying cycle expands the primary plug locally.



ADP + TxA₂ recruit neighboring platelets

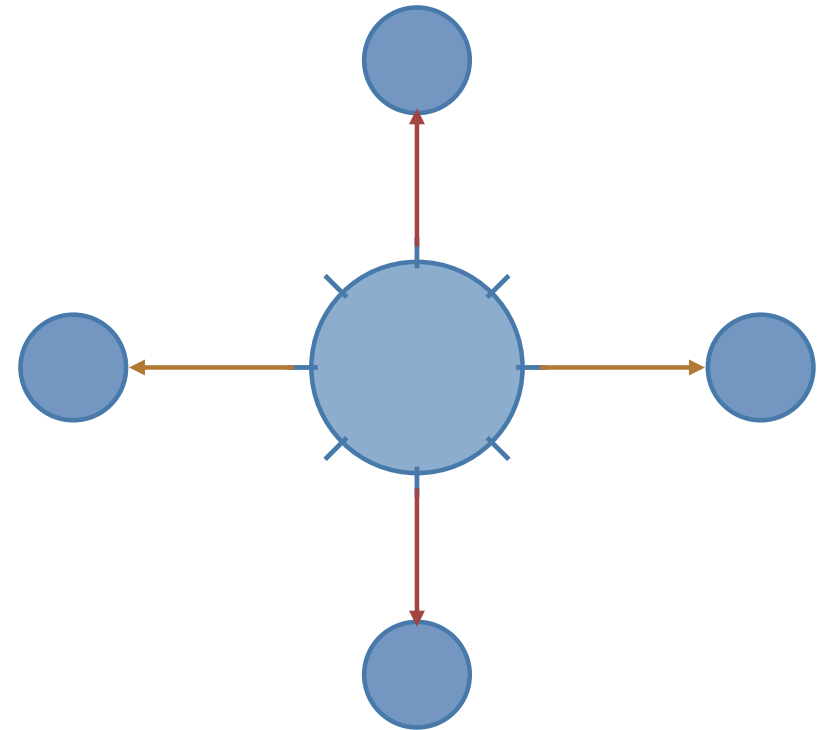
ADP stimulates P2Y₁ and P2Y₁₂ receptors

- Platelets carry both P2Y₁ and P2Y₁₂ G-protein–coupled receptors.
- ADP binding contributes to platelet activation and recruitment.
- P2Y₁₂ antagonism interrupts an established amplification pathway.



Recruitment turns a few adherent cells into a plug

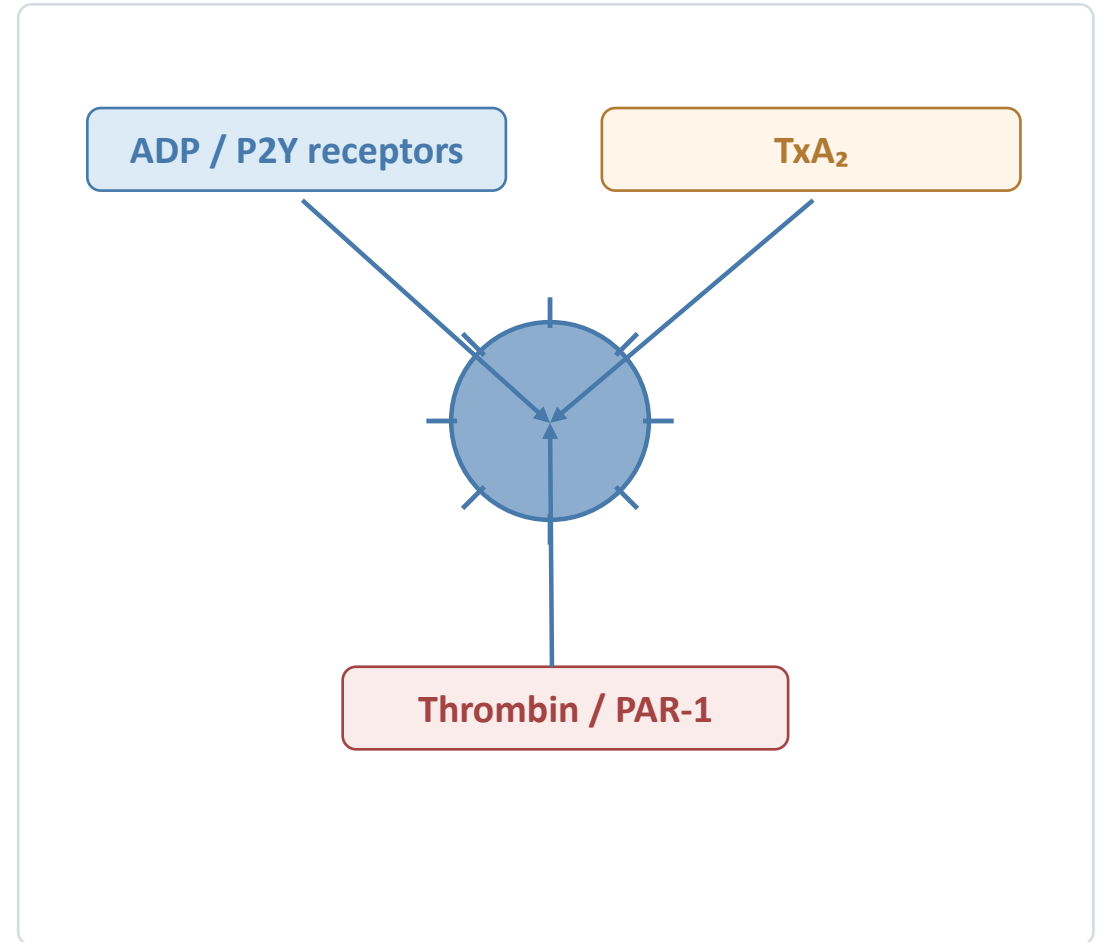
- Initially, only a small number of platelets contact the vessel-wall lesion.
- ADP secretion promotes successive rounds of platelet activation.
- Platelet mass accumulates rapidly through nearby recruitment and aggregation.



ADP + TxA₂ recruit neighboring platelets

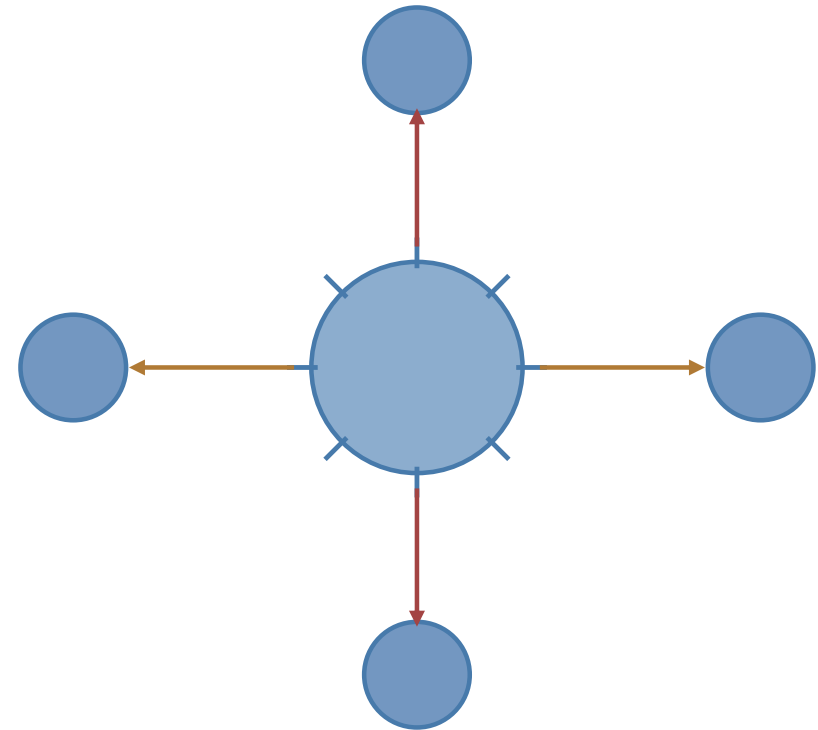
Thrombin activates platelets through PAR-1

- Thrombin cleaves and activates the platelet PAR-1 receptor.
- PAR-1 is a protease-activated G-protein–coupled receptor.
- This establishes a direct feedback link from coagulation to platelet activation.



Activated platelets produce thromboxane A₂

- Platelet activation induces synthesis of thromboxane A₂ (TxA₂).
- TxA₂ strongly promotes platelet aggregation and recruitment.
- Its local signaling cooperates with ADP and thrombin.



ADP + TxA₂ recruit neighboring platelets

Aspirin interrupts TxA₂-dependent aggregation

- Aspirin inhibits platelet cyclooxygenase required for TxA₂ synthesis.
- Reduced TxA₂ signaling attenuates platelet aggregation.
- The mild bleeding defect illustrates pharmacologic inhibition of primary hemostasis.

Without aspirin

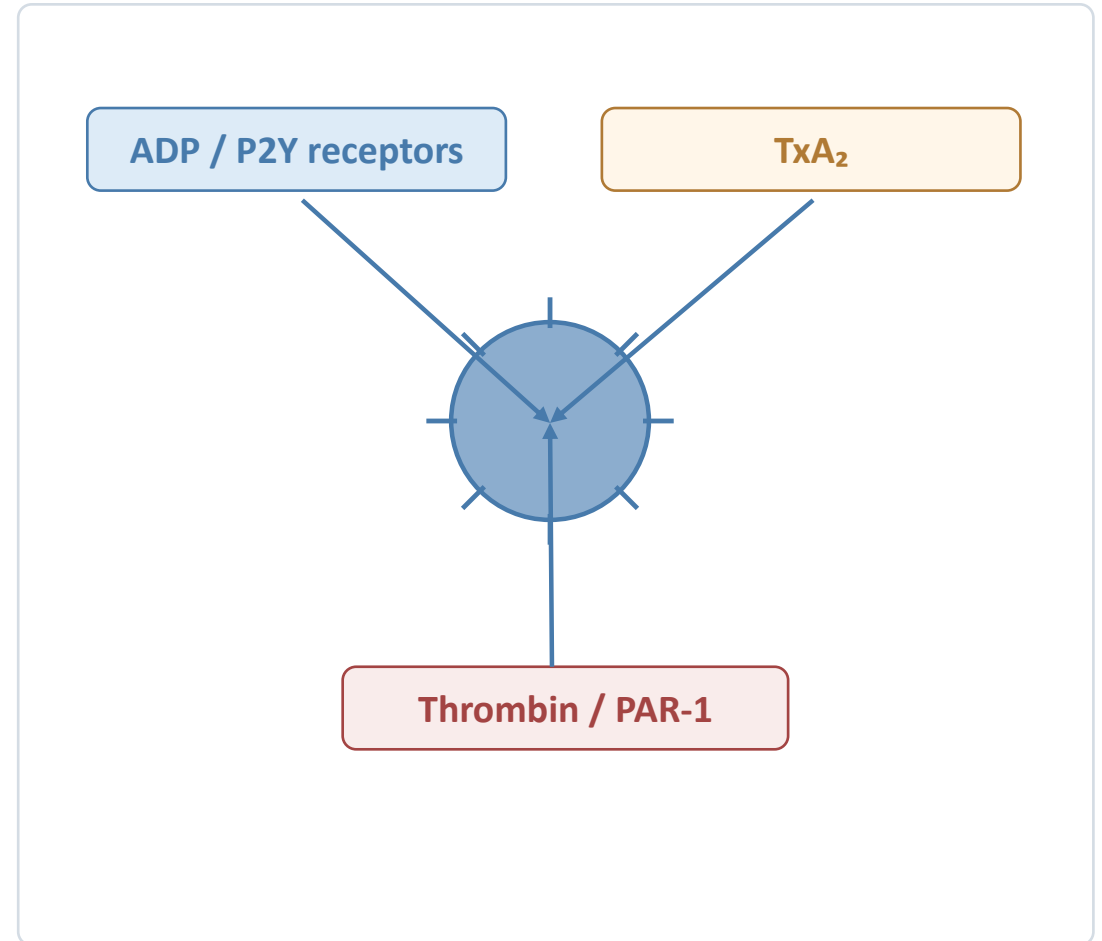
Cyclooxygenase activity permits TxA₂ synthesis.

With aspirin

Cyclooxygenase inhibition decreases TxA₂-dependent recruitment.

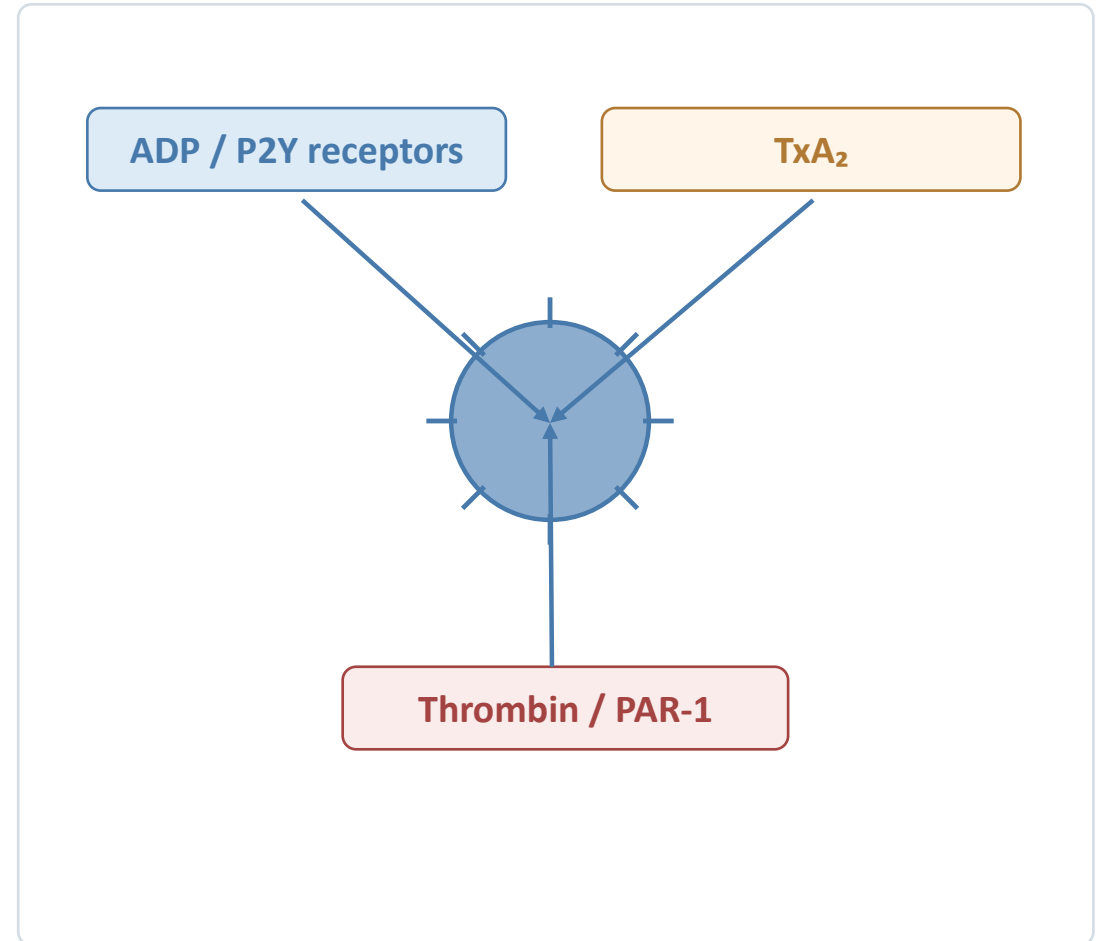
Antiplatelet therapies target amplification nodes

- P2Y₁₂ antagonists interrupt the ADP recruitment pathway.
- PAR-1 antagonism interferes with thrombin-dependent platelet activation.
- These targets act downstream of initial matrix exposure.



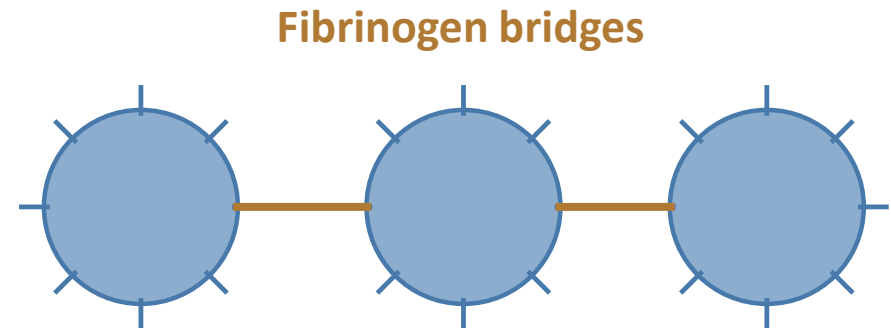
Three signals reinforce platelet activation

- ADP secretion recruits additional responsive platelets.
- TxA₂ synthesis sustains platelet activation and aggregation.
- Thrombin generation provides a simultaneous coagulation-to-platelet feedback loop.



Fibrinogen forms bridges between platelets

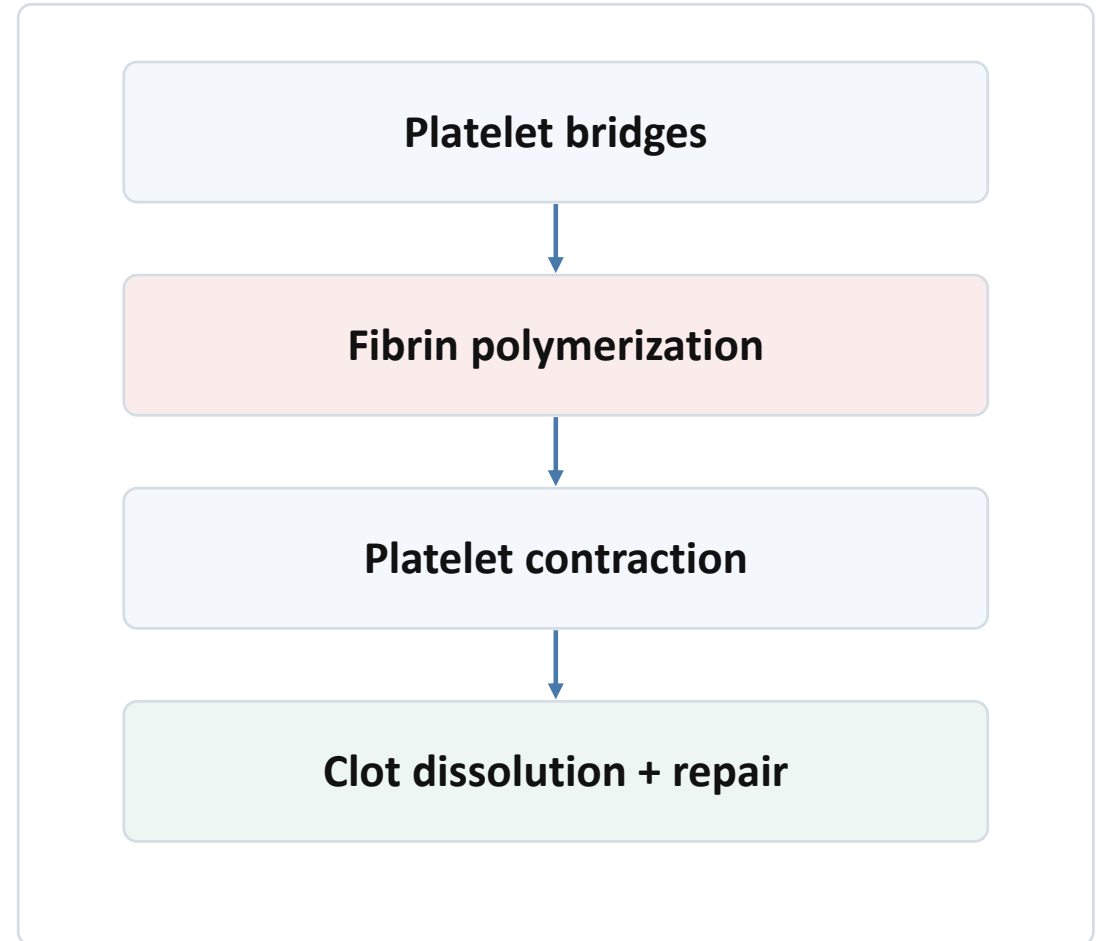
- Activated GpIIb/IIIa binds fibrinogen with high affinity.
- A fibrinogen molecule can bridge receptors on adjacent platelets.
- Multiple bridges establish the primary platelet aggregate.



GpIIb/IIIa binding on neighboring platelets

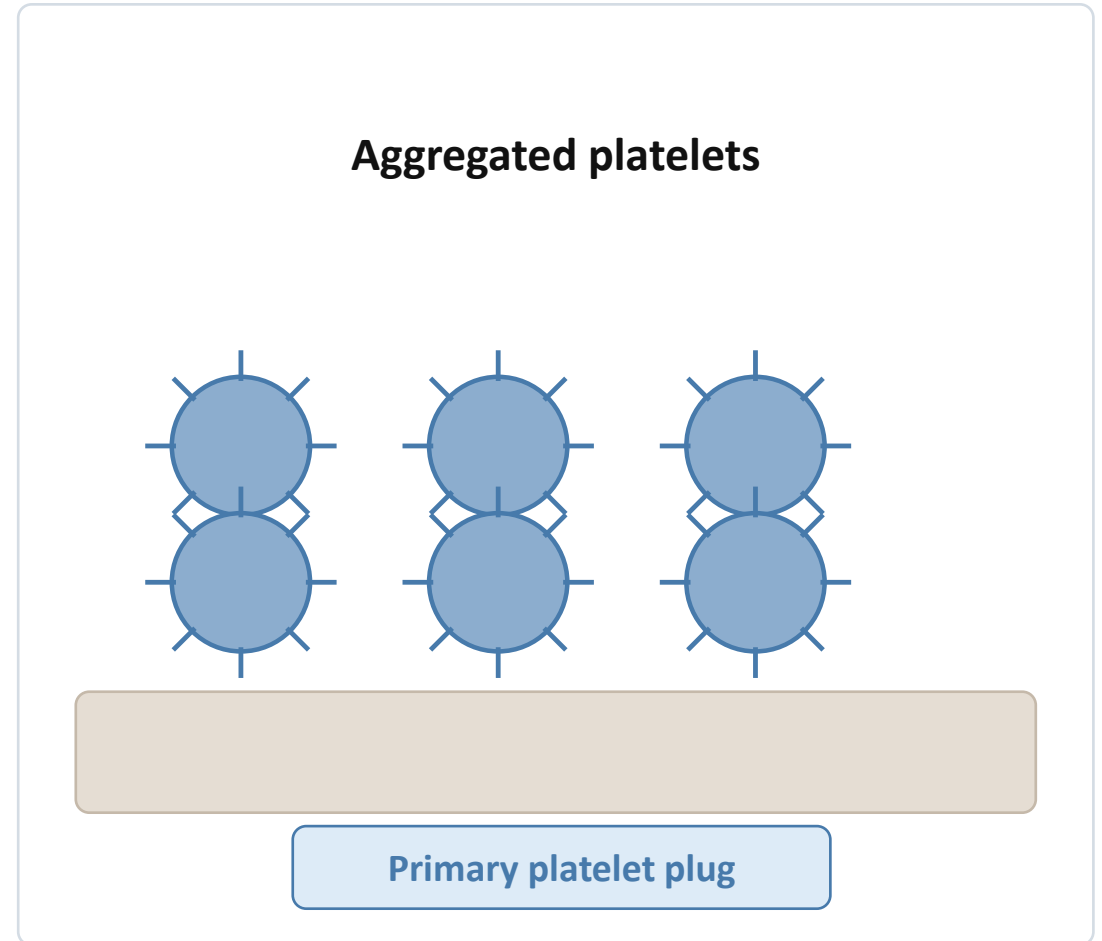
The initial platelet aggregate is reversible

- Early aggregation may disperse before the plug matures.
- Concomitant thrombin generation amplifies platelet activation.
- Stable platelet contraction and fibrin deposition help make the plug definitive.



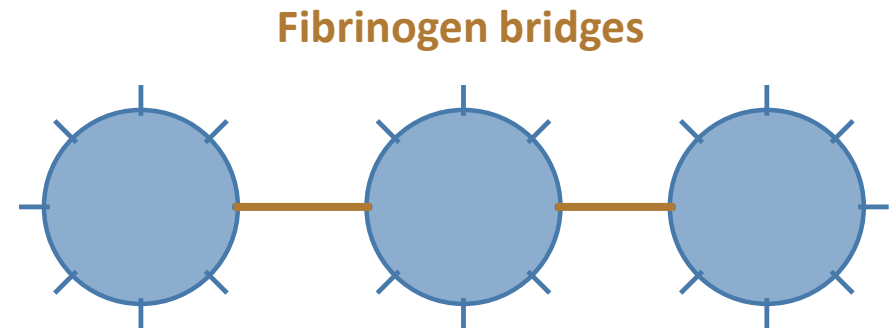
Thrombin stabilizes platelet aggregation

- Thrombin induces additional platelet aggregation through PAR-1.
- It also promotes irreversible platelet contraction.
- Its role extends beyond fibrin formation to direct modification of the platelet plug.



Glanzmann thrombasthenia demonstrates bridge failure

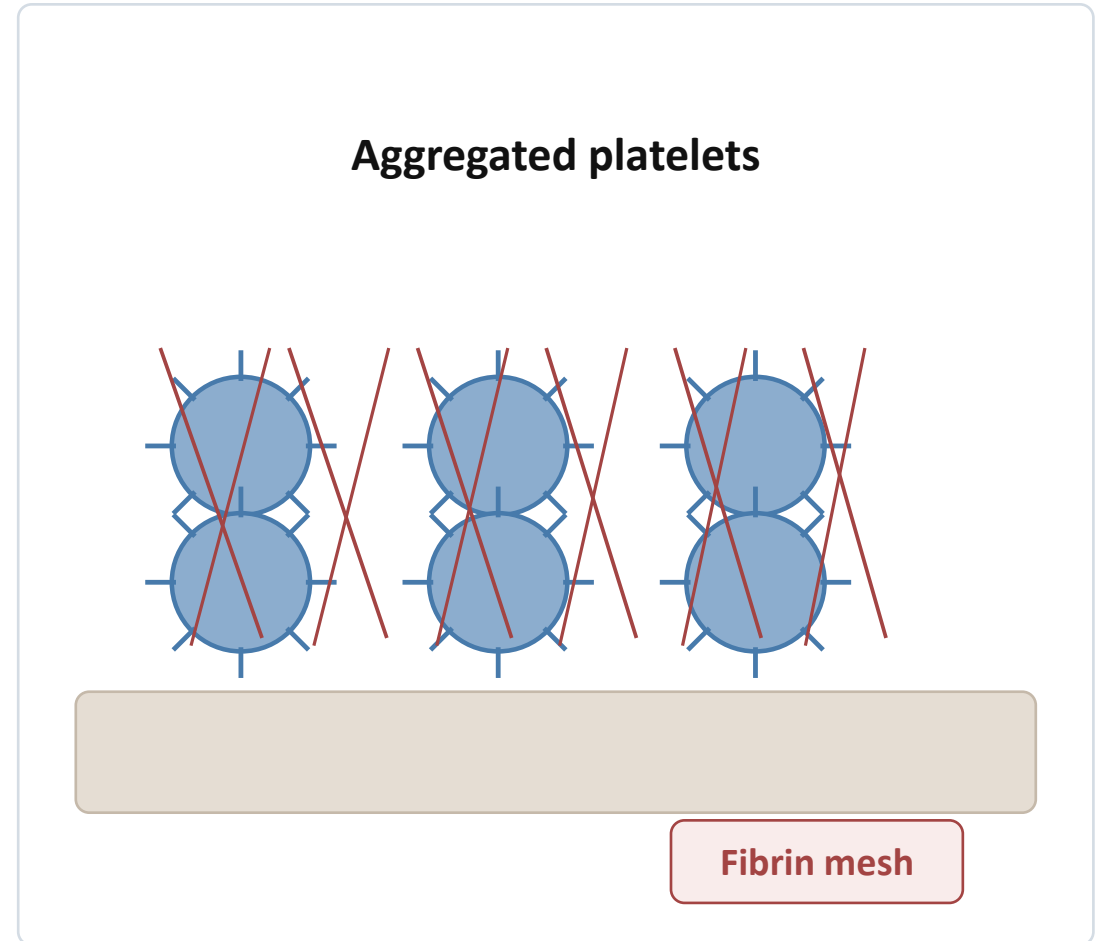
- Inherited GpIIb/IIIa deficiency impairs fibrinogen-mediated aggregation.
- Platelets may encounter the wound but cannot efficiently connect to one another.
- The defect is mechanistically distinct from impaired vWF/Gplb adhesion.



GpIIb/IIIa binding on neighboring platelets

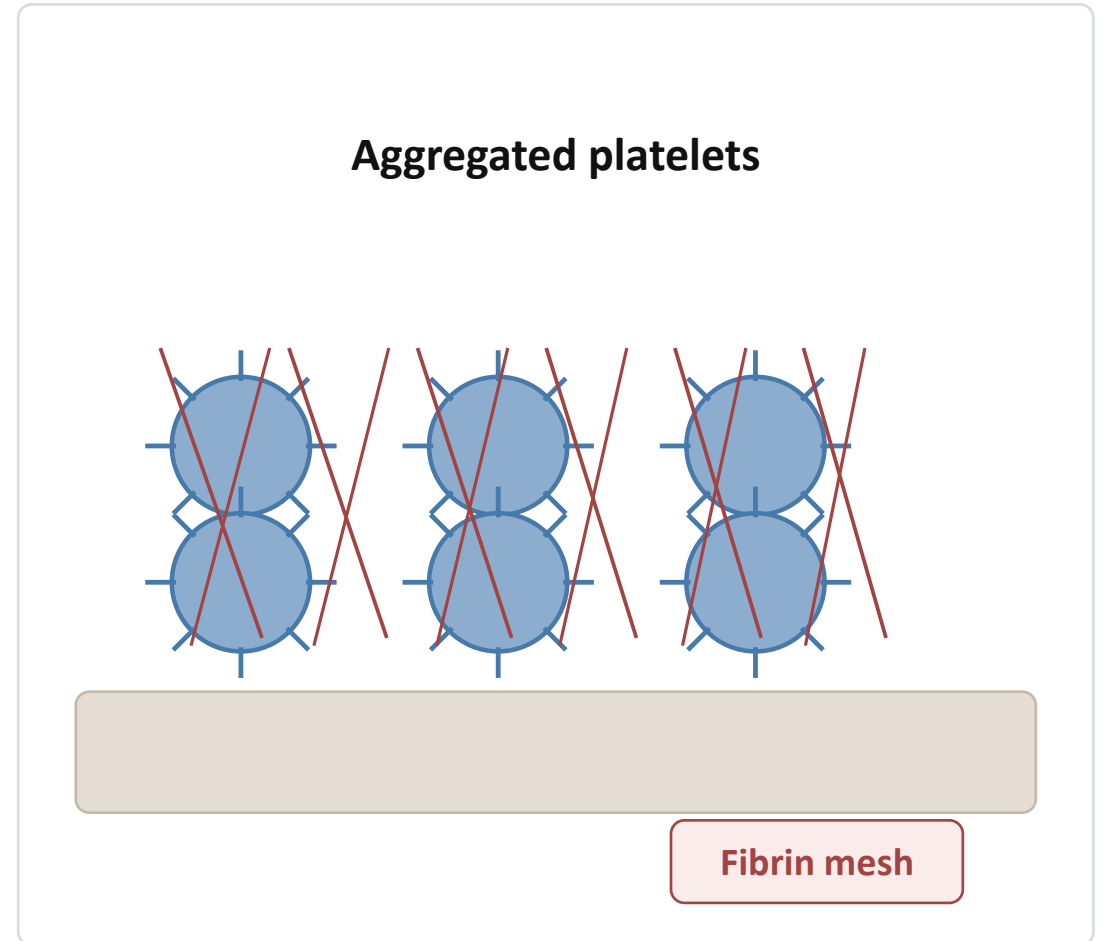
Platelet contraction consolidates the aggregate

- The activated platelet cytoskeleton pulls the aggregated cell mass together.
- Contraction makes the plug more compact and stable.
- In parallel, fibrin deposition strengthens the architecture.



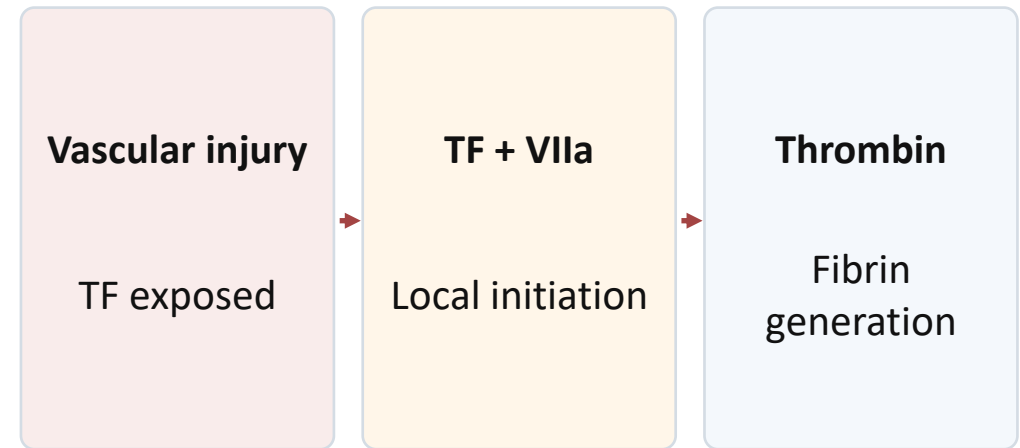
Other blood cells can become trapped in plugs

- Entrapped red cells and leukocytes are found within hemostatic plugs.
- Activated platelet P-selectin supports leukocyte adhesion.
- These cellular elements accompany the platelet–fibrin scaffold rather than defining its initiation.



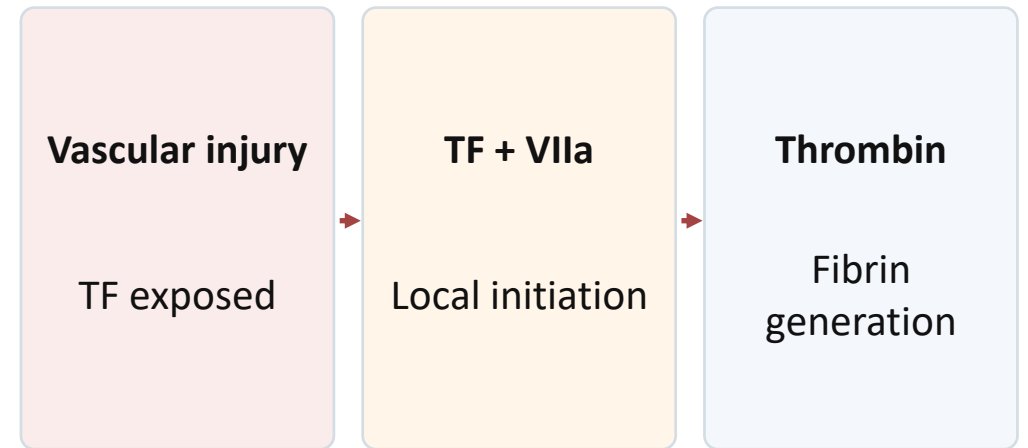
Exposed tissue factor initiates secondary hemostasis

- Tissue factor is a membrane-bound vessel-wall procoagulant glycoprotein.
- Smooth muscle cells and fibroblasts normally express TF beneath the endothelium.
- Injury exposes TF to circulating blood, initiating local coagulation.



Tissue factor and factor VII launch thrombin generation

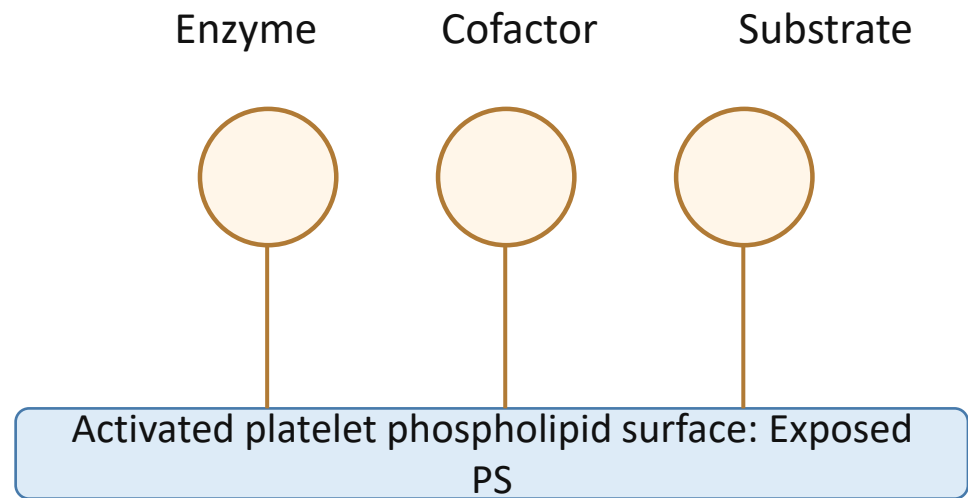
- TF binds and activates factor VII at the injured site.
- A cascade of proteolytic factor activations culminates in thrombin.
- Tissue factor is the major in-vivo trigger; Details of factor networks belong to the adjacent cascade topic.



Activated platelet surfaces accelerate clotting

- Coagulation steps assemble enzyme, substrate and cofactor on platelet phospholipids.
- Calcium supports efficient assembly of these membrane-localized complexes.
- Clotting reactions consequently intensify where platelets have been activated.

Ca²⁺ supports membrane assembly

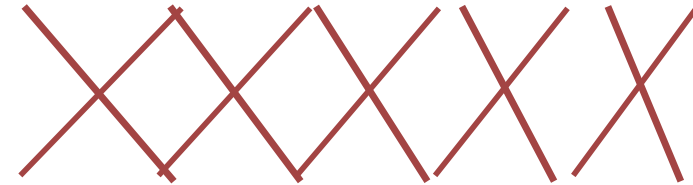


Thrombin converts fibrinogen into fibrin

- Thrombin proteolytically cleaves soluble plasma fibrinogen.
- The fibrin monomers polymerize into an insoluble fibrillar network.
- Fibrin physically cements the aggregated platelet plug.

Soluble fibrinogen → Fibrin monomers

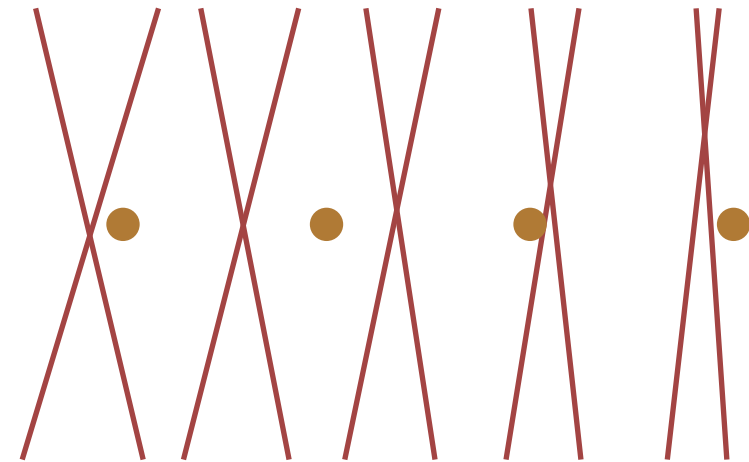
Thrombin



Insoluble polymerized network

Factor XIIIa cross-links polymerized fibrin

- Thrombin activates factor XIII in the coagulation pathway.
- Factor XIIIa establishes covalent cross-links within the fibrin network.
- Cross-linking strengthens the fibrin component of the hemostatic plug.



Factor XIIIa establishes covalent cross-links

Thrombin couples fibrin formation and platelet activity

- One thrombin output is fibrinogen cleavage and stabilization of fibrin.
- Another is platelet activation through PAR-1.
- Amplification of coagulation factors further sustains the local response.

Coagulation output

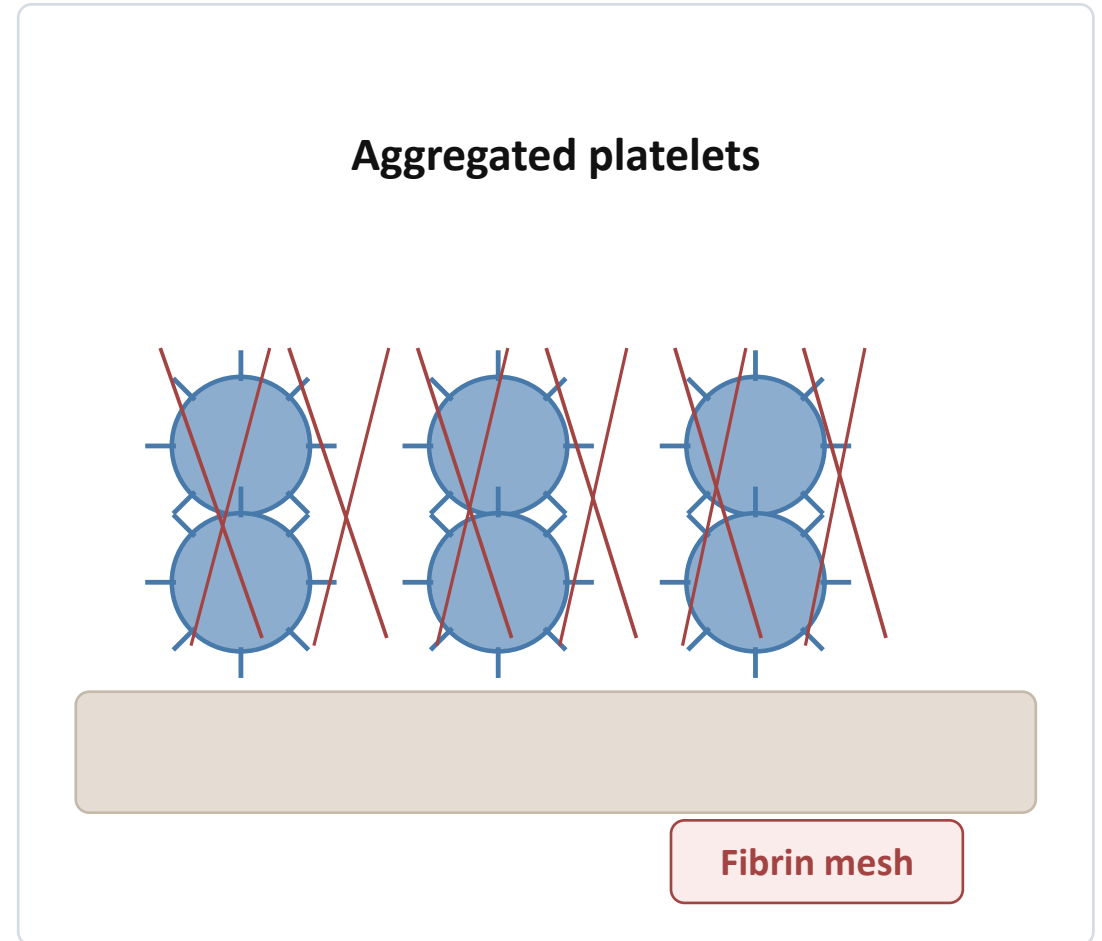
Fibrin polymerization and factor XIII activation.

Platelet output

PAR-1 signaling, aggregation and contraction.

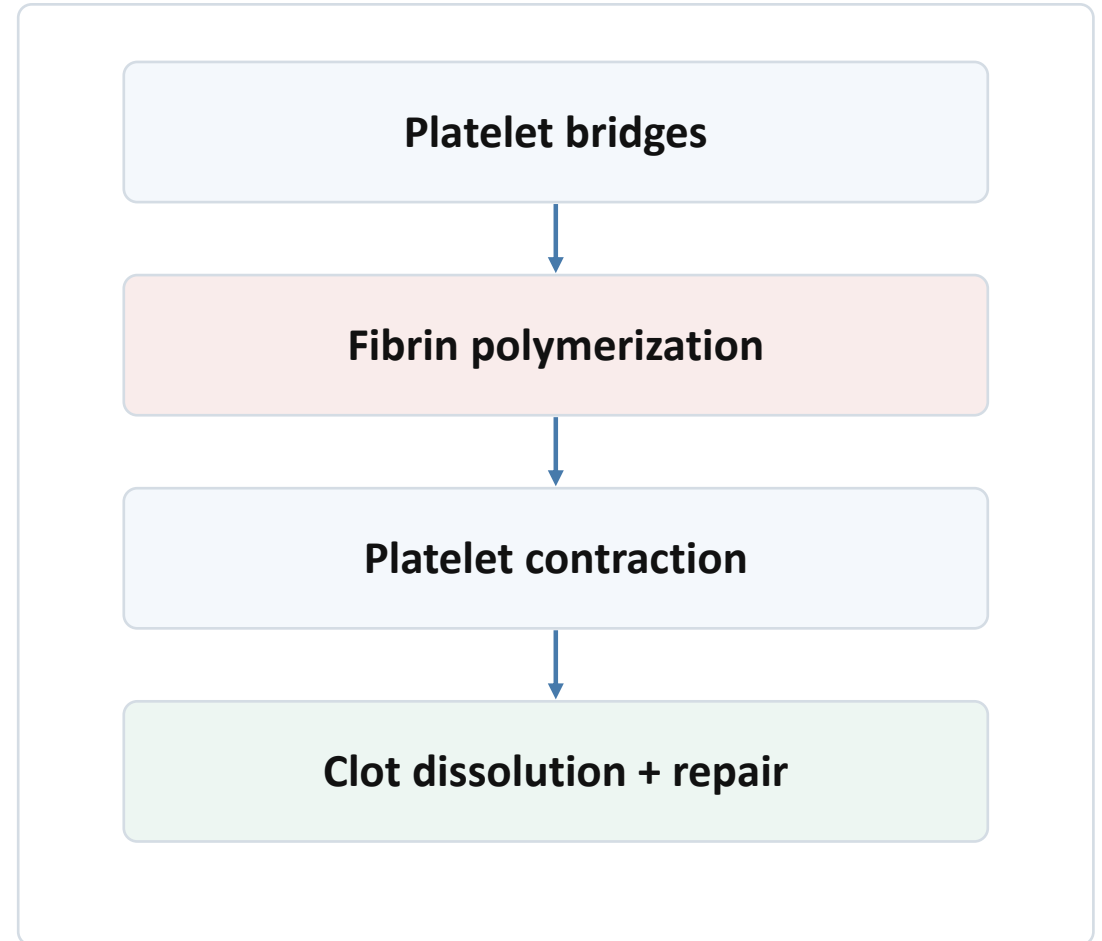
The definitive plug is platelet–fibrin composite

- Platelets seal the breach rapidly through adhesion and aggregation.
- Fibrin polymers create a reinforcing mesh around the platelet aggregate.
- A stable secondary plug resists renewed bleeding during tissue repair.



Clot contraction and fibrin create mechanical stability

- Contractile platelets draw the aggregate into a compact mass.
- An insoluble, cross-linked fibrin mesh reinforces that mass.
- The clot is a temporary protective structure while the vessel heals.



Endothelium functions as a hemostatic switch

- Uninjured endothelium actively prevents platelet activation and coagulation.
- Injury or activation shifts the local surface toward a procoagulant phenotype.
- This spatial contrast helps localize the plug to the injured region.

Intact endothelium

PGI₂ · NO · ADP
degradation
Thrombomodulin ·
EPCR
Antithrombin
activation · TFPI · t-
PA

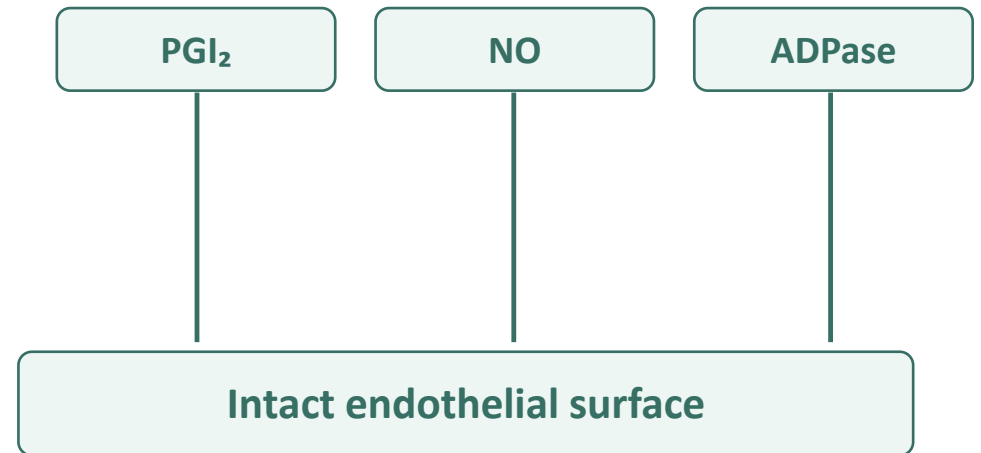
Injured / activated

Matrix and tissue
factor exposed
Platelet recruitment
and coagulation
become favored

Three endothelial factors restrain platelets

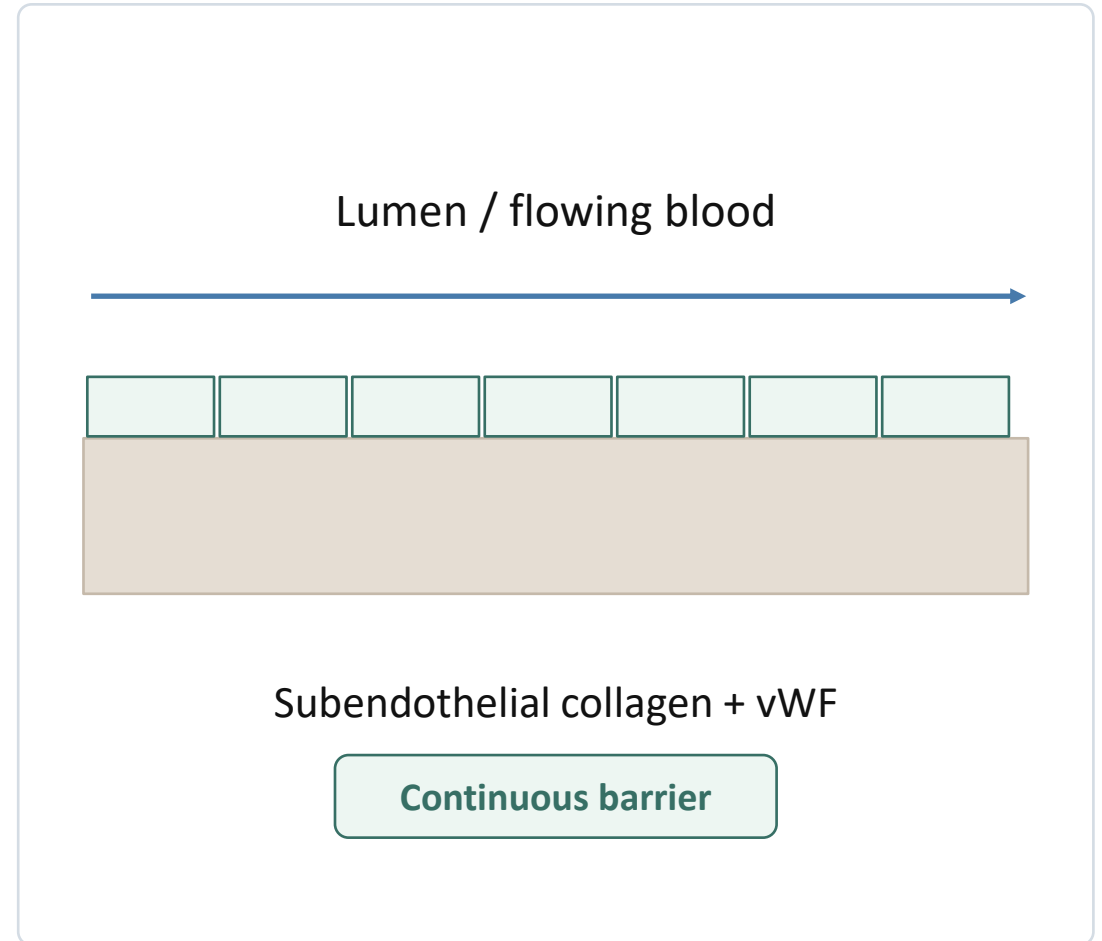
- Prostacyclin (PGI_2) opposes platelet activation and aggregation.
- Nitric oxide (NO) also inhibits platelet activity.
- Endothelial ADPase removes extracellular ADP, interrupting recruitment.

Net effect: Platelet activation is restrained



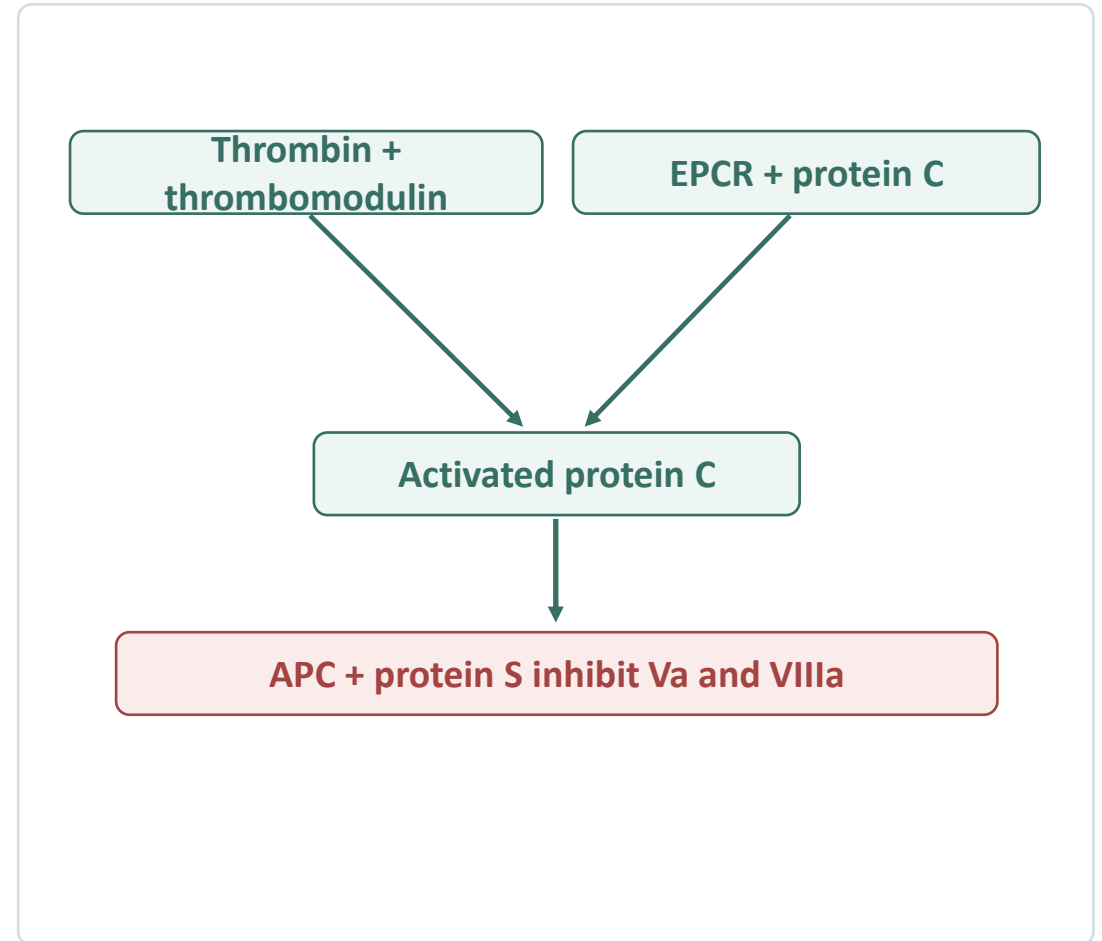
A continuous endothelial barrier is itself protective

- Intact endothelial cells shield circulating platelets from subendothelial vWF and collagen.
- They also prevent exposure of vessel-wall tissue factor to blood.
- Physical separation works alongside active molecular anticoagulants.



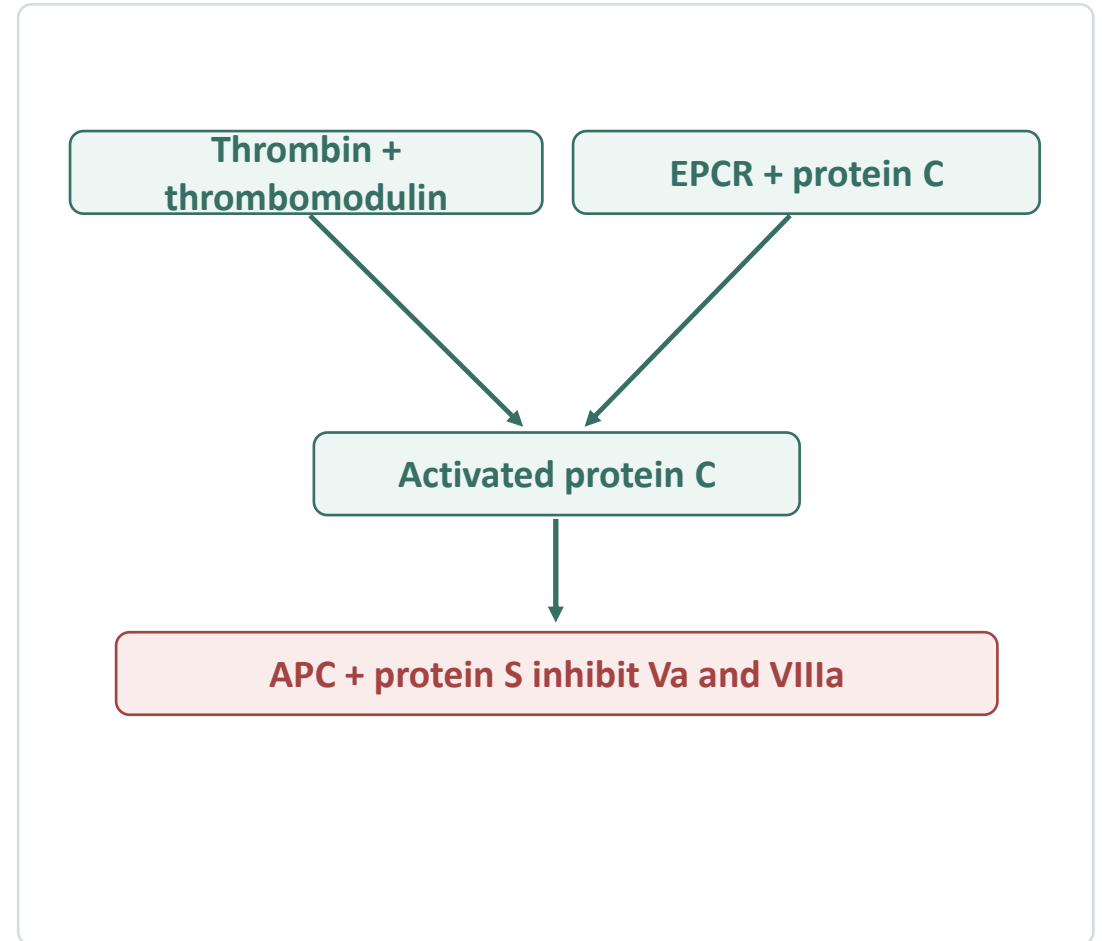
Endothelium shifts thrombin toward anticoagulation

- Thrombin binds endothelial thrombomodulin near intact vessel surfaces.
- Endothelial protein C receptor (EPCR) presents protein C.
- In this context, thrombin activates the protein C anticoagulant pathway.



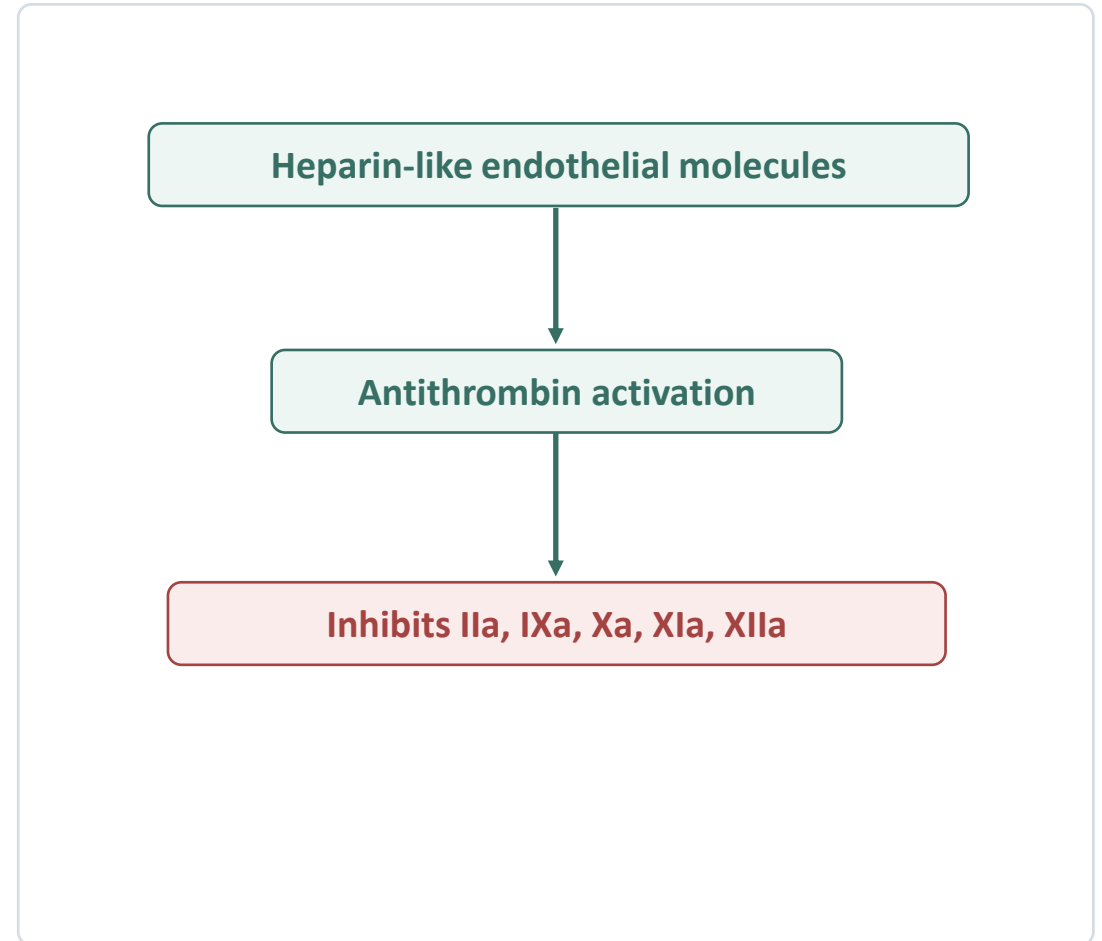
Activated protein C and protein S inhibit Va and VIIIa

- Protein C is converted to an active protease in the endothelial complex.
- Protein S supports its anticoagulant activity.
- The protein C–protein S system inactivates procoagulant cofactors Va and VIIIa.



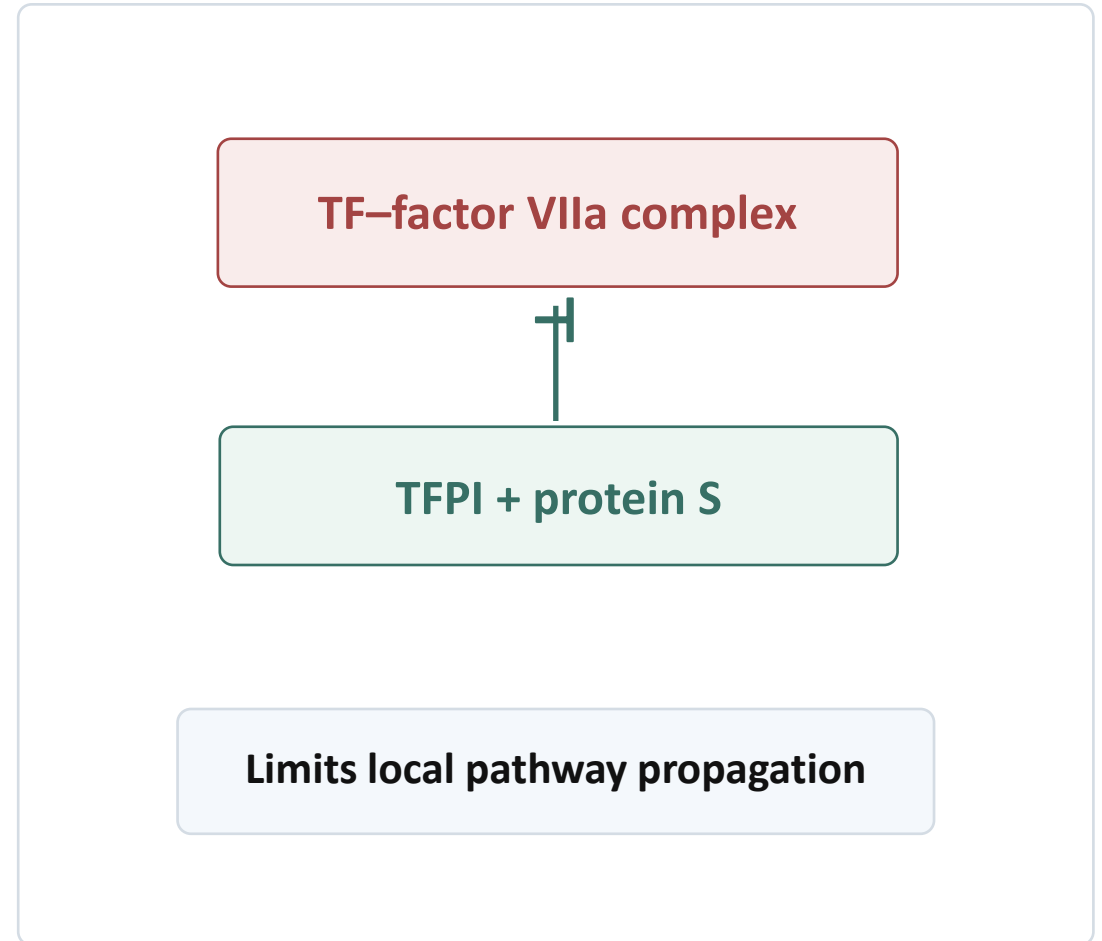
Heparin-like endothelial molecules support antithrombin

- Surface heparin-like molecules enhance antithrombin activity.
- Antithrombin inhibits thrombin and several activated clotting factors.
- This restrains coagulation as blood flows away from the injured focus.



TFPI restricts tissue-factor pathway activity

- Endothelial tissue factor pathway inhibitor (TFPI) inhibits TF–VIIa complex activity.
- Protein S acts as a cofactor for TFPI-mediated inhibition.
- TFPI complements protein C and antithrombin in limiting propagation.



Clotting stays local through redundant safeguards

- Activated platelet surfaces favor coagulation at the vessel-wall breach.
- Blood flow dilutes activated proteins; Liver clearance further removes them.
- Adjacent intact endothelium supplies inhibitors that restrict clot extension.

Prohemostatic

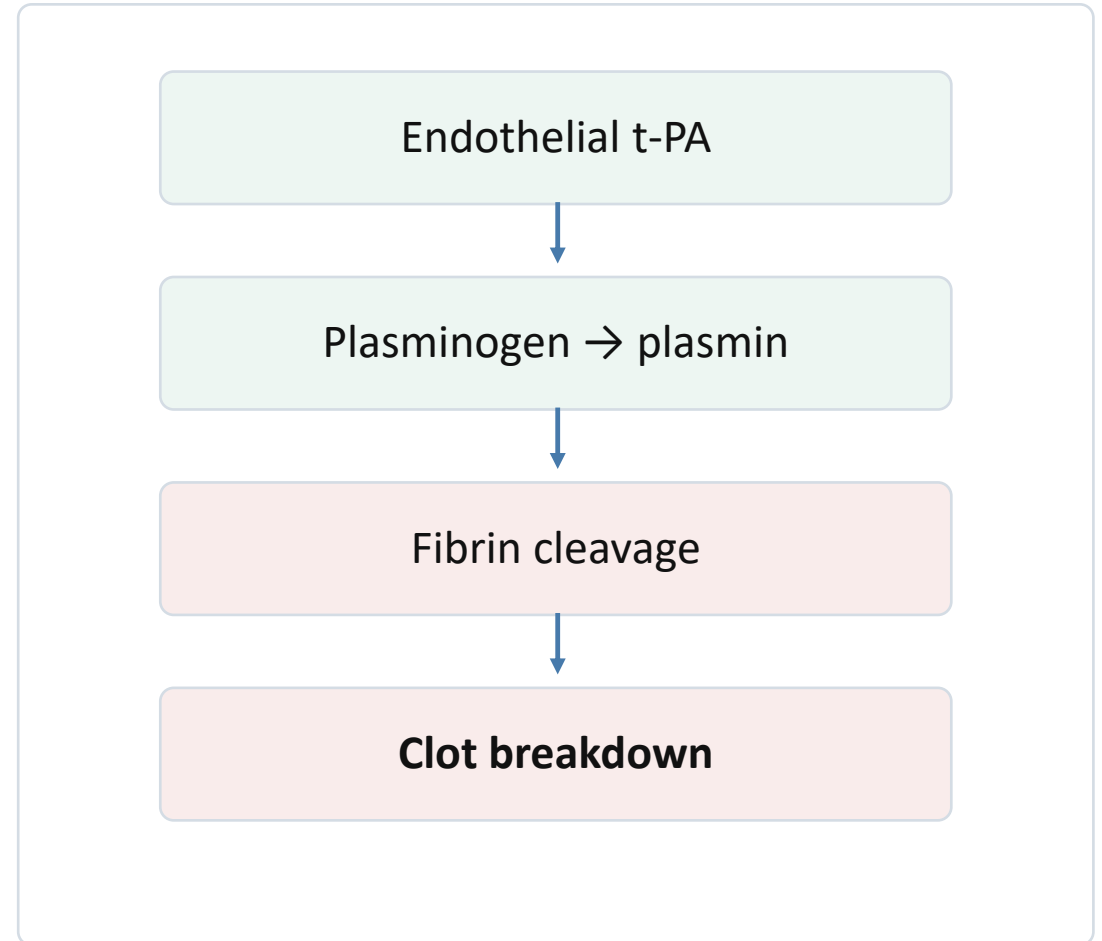
Matrix/vWF
exposure
Platelet activation
TF → thrombin
Fibrin formation

Restraining

NO / PGI₂ / ADPase
Protein C /
antithrombin / TFPI
T-PA → plasmin

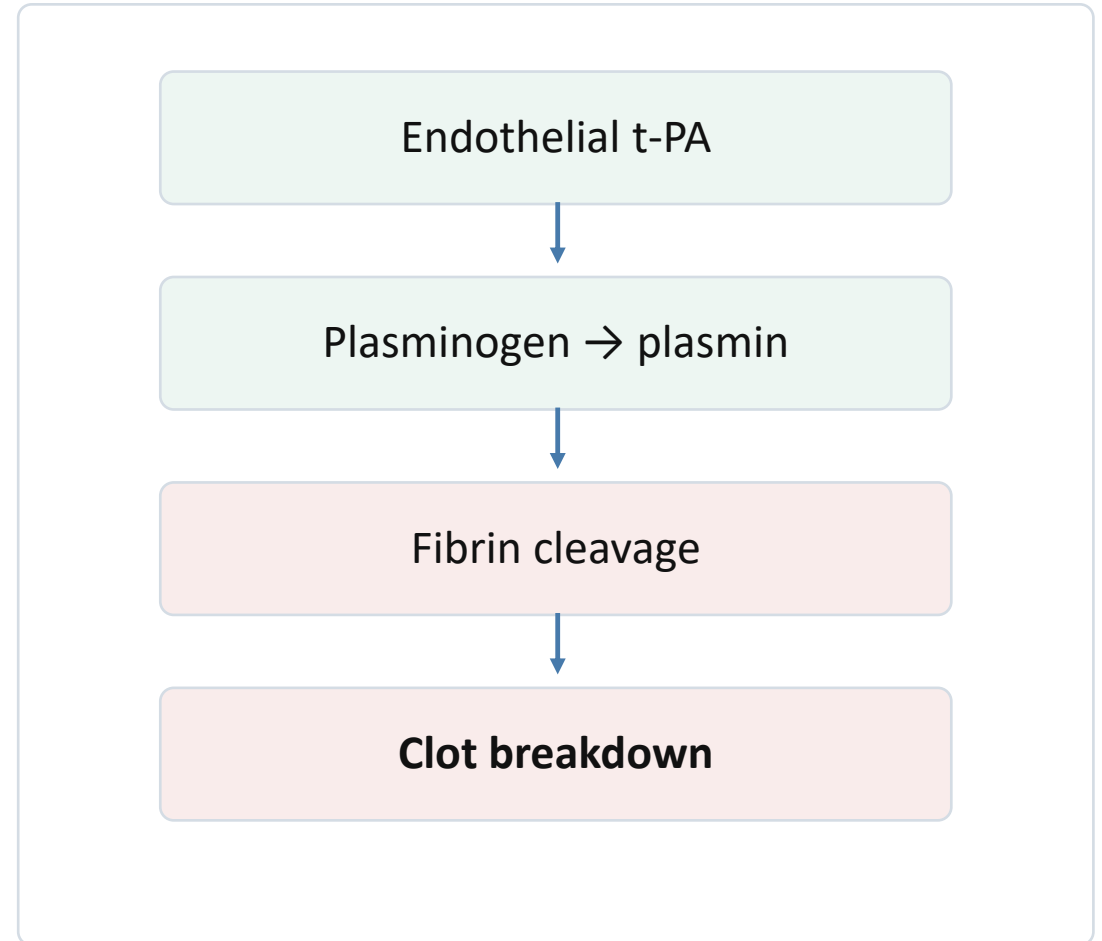
Coagulation also triggers clot-removal pathways

- The fibrinolytic response begins in parallel with clot formation.
- Endothelial tissue plasminogen activator (t-PA) converts plasminogen to plasmin.
- Plasmin mediates enzymatic breakdown of the fibrin scaffold.



Plasmin cleaves fibrin during resolution

- Plasmin degrades polymerized fibrin and limits further polymerization.
- This helps constrain clot size and later remove the temporary plug.
- Fibrin-derived breakdown products reflect the substrate being degraded.



Plasmin activity is also counterregulated

- Circulating α_2 -antiplasmin rapidly inhibits free plasmin.
- Plasminogen activator inhibitors (PAI) limit activator activity.
- These brakes help prevent indiscriminate dissolution away from the clot.

Generate plasmin

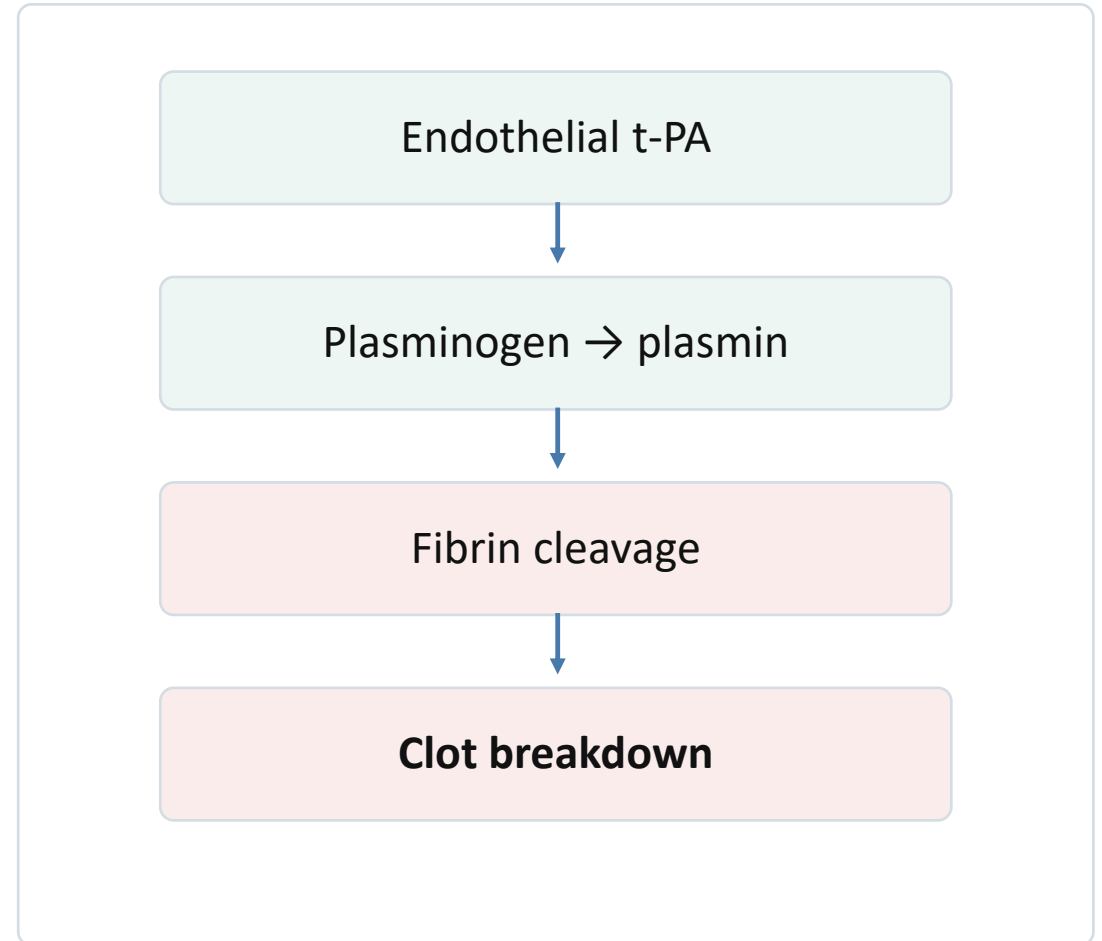
Endothelial t-PA
activates
plasminogen on
fibrin.

Limit proteolysis

α_2 -antiplasmin
neutralizes free
plasmin; PAI checks
activation.

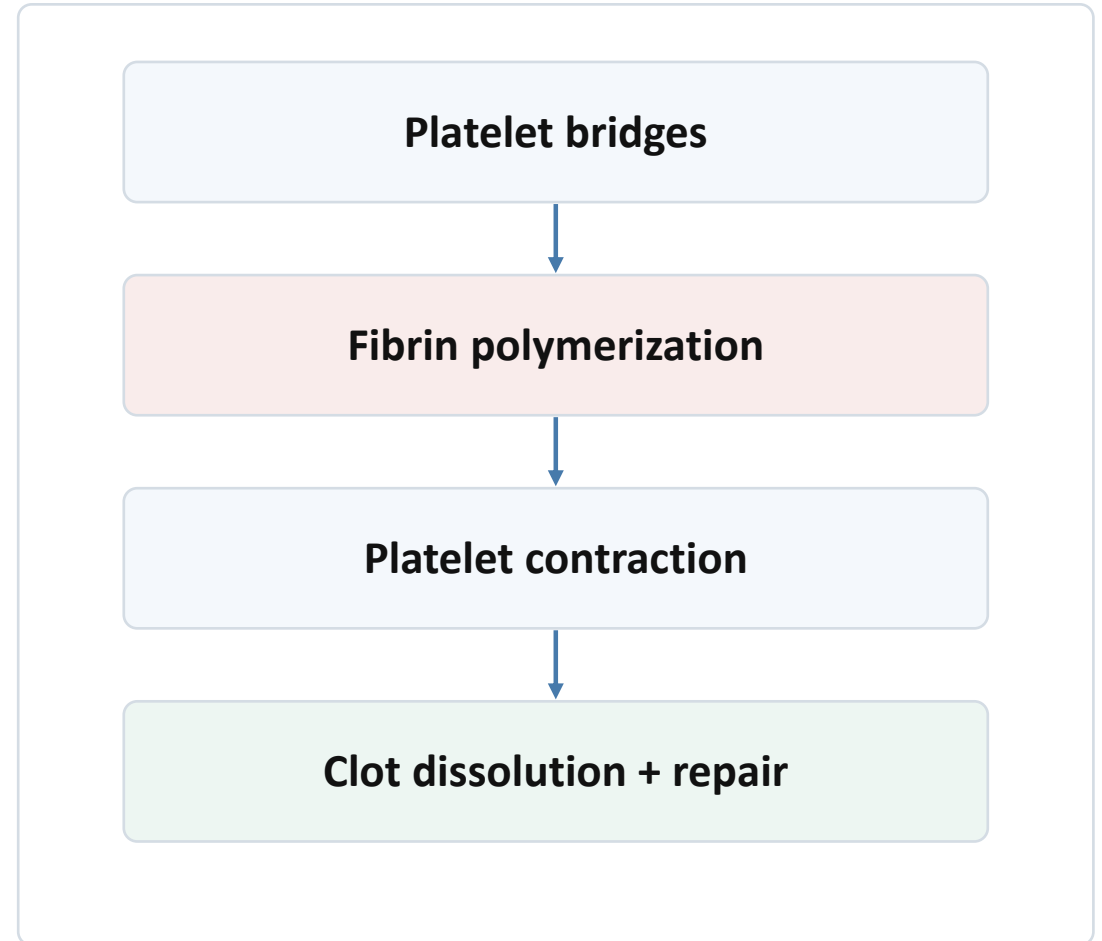
Fibrin localization focuses t-PA activity

- T-PA is most active when bound to fibrin.
- Its localization concentrates plasmin generation near the clot substrate.
- This feature supports targeted fibrinolysis rather than generalized proteolysis.



Clot resorption is linked to vessel repair

- The protective plug must persist long enough to prevent recurrent hemorrhage.
- Fibrinolysis then dismantles its fibrin component.
- Hemostasis therefore includes both construction and regulated removal.



Primary defects produce a characteristic bleeding pattern

- Defects in platelet function or vWF often cause skin or mucosal bleeding.
- Petechiae/purpura, epistaxis and heavy menstrual bleeding are examples.
- Coagulation-factor defects more often produce deep soft-tissue or joint bleeding.

Primary hemostasis defect

Mucocutaneous bleeding
Petechiae or purpura
Epistaxis /
menorrhagia

Coagulation-factor defect

Bleeding into soft tissues or joints
Hemarthrosis may occur

Clinical reasoning: Identify the failed interface

- A patient has recurrent mucosal bleeding after minor trauma.
- One candidate mechanism is defective vWF–GpIb-dependent adhesion.
- Another is impaired GpIIb/IIIa–fibrinogen aggregation; Which step distinguishes them?

Candidate A

Failure to tether circulating platelets to the vessel wall.

Candidate B

Failure to bridge platelets into a growing aggregate.

Clinical reasoning: Distinct step, similar phenotype

- VWF/GpIb defects interfere with platelet–matrix tethering.
- GpIIb/IIIa defects interfere with platelet–platelet aggregation.
- Both compromise formation of a satisfactory primary plug despite different receptors.

Platelet–wall bridge

VWF / GpIb /
collagen: Adhesion.

Platelet–platelet bridge

Fibrinogen /
activated GpIIb/IIIa:
Aggregation.

The hemostatic balance has two equally necessary sides

- Injury exposes vWF, collagen and tissue factor to initiate clot formation.
- Normal endothelium restrains platelet recruitment and procoagulant proteases.
- Fibrinolysis resolves the plug after its protective function is served.

Prohemostatic

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Mechanistic synthesis: a stable clot with defined borders

- Vasoconstriction briefly limits blood delivery; platelet adhesion starts the seal.
- ADP, TxA₂ and thrombin amplify aggregation; fibrin stabilizes the structure.
- Endothelial anticoagulants and t-PA prevent unchecked persistence and propagation.

