

Hemostasis, Hemorrhagic Disorders, and Thrombosis

Physiologic mechanisms • bleeding phenotypes • thrombus formation

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Learning objectives

- Sequence normal hemostasis from vascular injury to fibrin stabilization and clot removal.
- Connect platelet receptors, tissue factor, thrombin, and endothelial regulators to their functions.
- Distinguish typical patterns of bleeding caused by platelet, coagulation, or vascular defects.
- Explain thrombosis through Virchow triad, hypercoagulability, morphology, and clinical outcomes.

One system, two pathological extremes

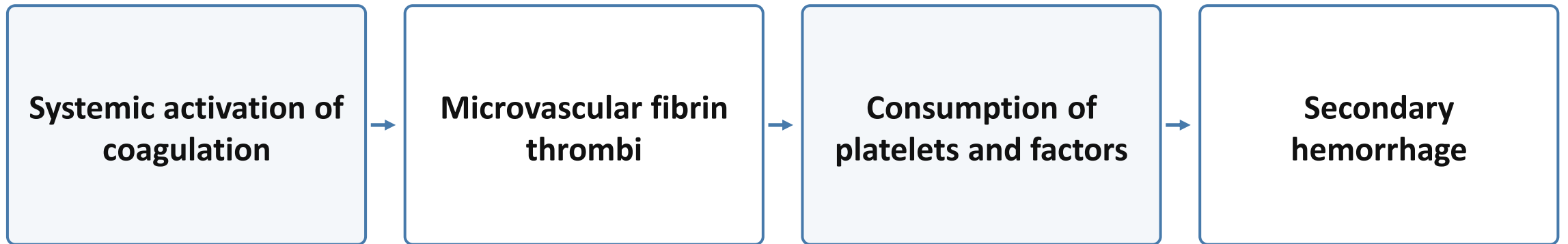
Insufficient hemostasis

- Deficient platelets, coagulation factors, or vessel integrity
- Spontaneous or provoked bleeding
- Risk: Blood loss or vital-organ hemorrhage

Excessive or misplaced coagulation

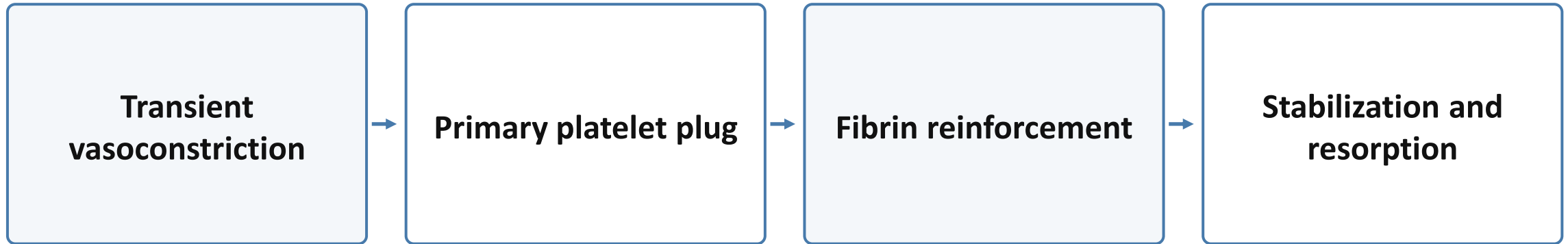
- Clots form within intact vessels or heart chambers
- Thrombi obstruct flow or embolize
- Risk: Tissue ischemia and infarction

Why bleeding and clotting can coexist



Disseminated intravascular coagulation is a key example of this paradox.

The four phases of normal hemostasis

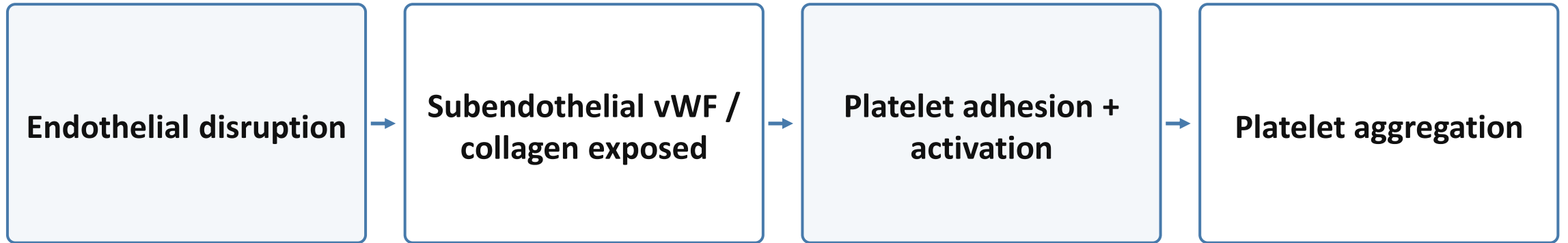


Hemostasis is spatially restricted: Clotting is encouraged at an injury, not throughout the circulation.

Vasoconstriction immediately reduces blood loss

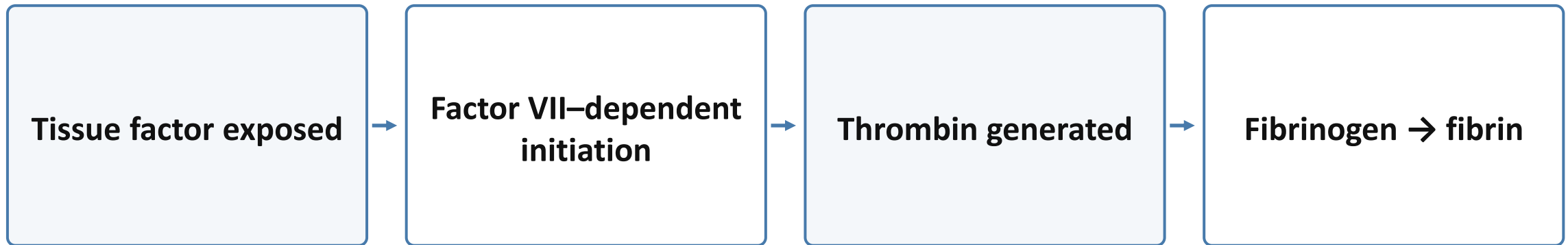
- Arteriolar contraction is the earliest reaction to vascular injury.
- Neurohumoral reflexes and local endothelin contribute to the response.
- The effect is transient and cannot alone provide durable hemostasis.
- Platelet activation and coagulation must follow to prevent renewed bleeding.

Primary hemostasis creates a platelet plug



The initial platelet plug develops within minutes and needs later fibrin reinforcement.

Secondary hemostasis reinforces the plug



Fibrin forms a meshwork that consolidates the primary platelet aggregate.

Clot stabilization does not end regulation

- Platelets contract through their cytoskeleton and compact the plug.
- Factor XIII–dependent cross-linking strengthens the fibrin network.
- Endothelial counterregulatory processes confine coagulation to injured tissue.
- Subsequent fibrinolysis and tissue repair enable clot resorption.

Three cellular and molecular partners

Platelets + coagulation proteins

- Platelets adhere and build the primary plug
- Membrane phospholipids support factor complexes
- Thrombin produces fibrin and activates platelets

Vascular endothelium

- Normal surface inhibits platelet activation and clotting
- Injured or activated cells become prothrombotic
- T-PA contributes to localized clot dissolution

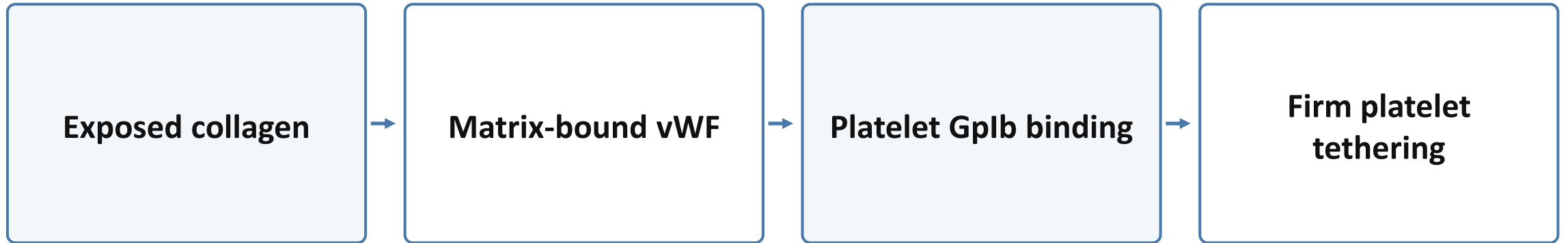
Platelets are specialized anucleate fragments

- Bone marrow megakaryocytes release platelets into the bloodstream.
- They normally circulate as small discoid, anucleate fragments.
- Receptors, cytoskeletal machinery, and cytoplasmic granules support rapid responses.
- Activated platelets provide a phospholipid surface for enzyme complexes.

Adhesion and aggregation use different receptors

Receptor	Major ligand	Function
GpIb	Von Willebrand factor	Adhesion
GpVI; GpIa/IIa	Collagen	Adhesion
GpIIb/IIIa	Fibrinogen	Aggregation

VWF bridges exposed collagen to GpIb

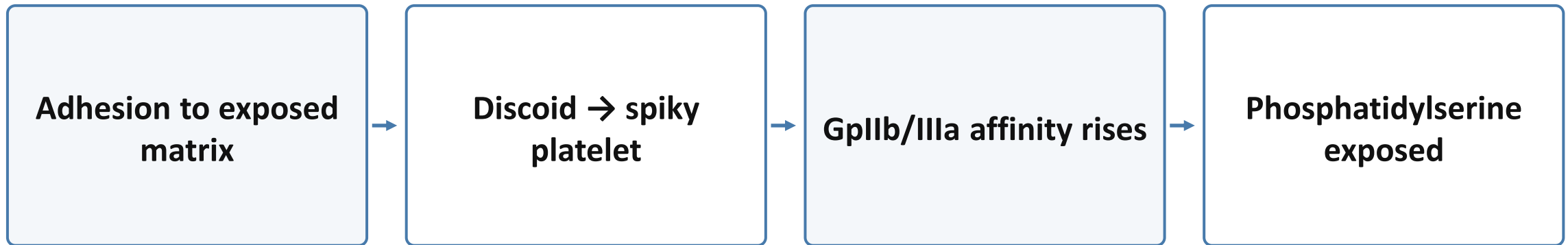


This adhesive bridge is particularly important where shear forces are high.

Collagen is also a direct platelet ligand

- GpVI and GpIa/IIa mediate platelet binding to exposed collagen.
- The receptor pathways complement vWF–GpIb-mediated tethering.
- Both platelet receptors and matrix ligands are required for normal adhesion.
- Inherited deficiencies illustrate how failures in adhesion cause bleeding.

Platelet activation changes shape and surface



The new membrane surface supports assembly of calcium-dependent coagulation complexes.

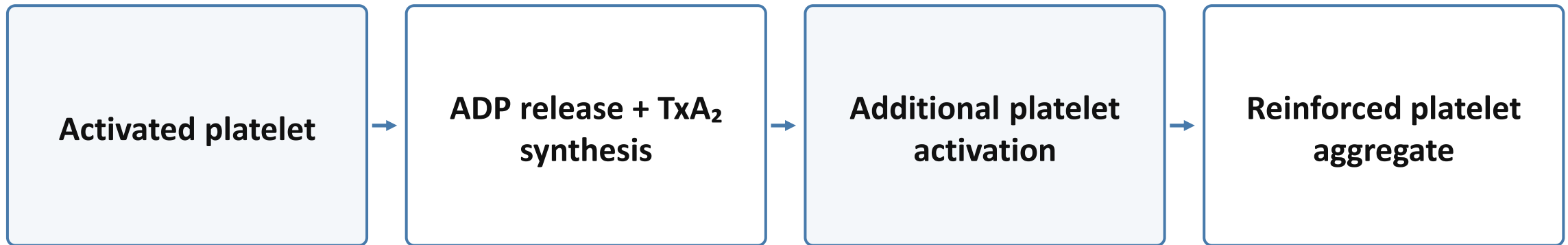
Alpha granules provide adhesive and repair proteins

- α -granules contain fibrinogen, vWF, and coagulation-related proteins.
- Platelet factor 4 binds heparin and is relevant to immune-mediated HIT.
- Fibronectin and platelet-derived growth factor contribute to repair responses.
- P-selectin is present in granule membranes and appears at the surface after activation.

Dense granules amplify platelet recruitment

- Dense granules contain ADP, ATP, calcium, serotonin, and epinephrine.
- Released ADP stimulates neighboring platelets through purinergic receptors.
- Calcium supports membrane-associated coagulation reactions.
- This release reaction helps turn local adhesion into a growing platelet plug.

ADP and thromboxane recruit more platelets

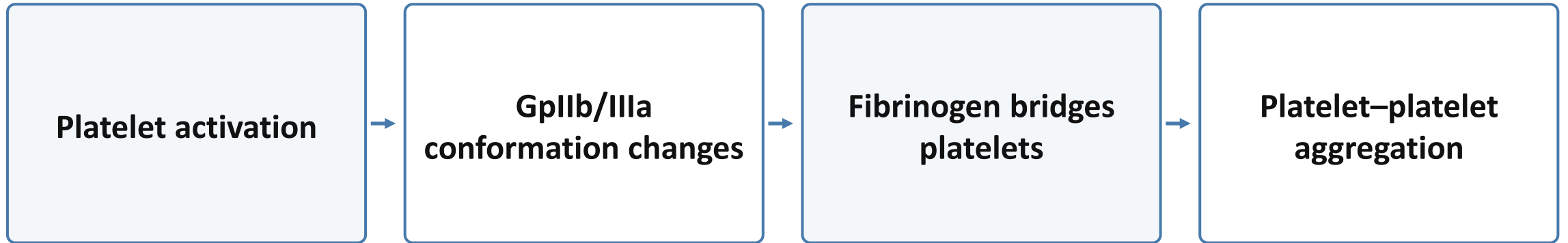


ADP acts through P2Y receptors; Thromboxane A₂ is generated through cyclooxygenase-dependent signaling.

Thrombin links coagulation to platelet signaling

- Thrombin activates platelets by proteolytically switching on PAR-1.
- Platelet degranulation and aggregation therefore reinforce thrombin generation.
- Activated platelet membranes promote additional coagulation reactions.
- The platelet–thrombin feedback loop rapidly consolidates the plug.

GpIIb/IIIa enables platelet aggregation



Fibrinogen forms bridges between receptors on adjacent activated platelets.

Inherited defects map to distinct functions

Molecular defect	Impaired step	Named disorder
VWF	Adhesion	Von Willebrand disease
GpIb	Adhesion	Bernard–Soulier syndrome
GpIIb/IIIa	Aggregation	Glanzmann thrombasthenia

Drug effects reveal platelet pathways

Cyclooxygenase inhibition

- Aspirin reduces thromboxane A₂ synthesis
- Platelet aggregation is impaired
- The mechanism produces a mild bleeding tendency

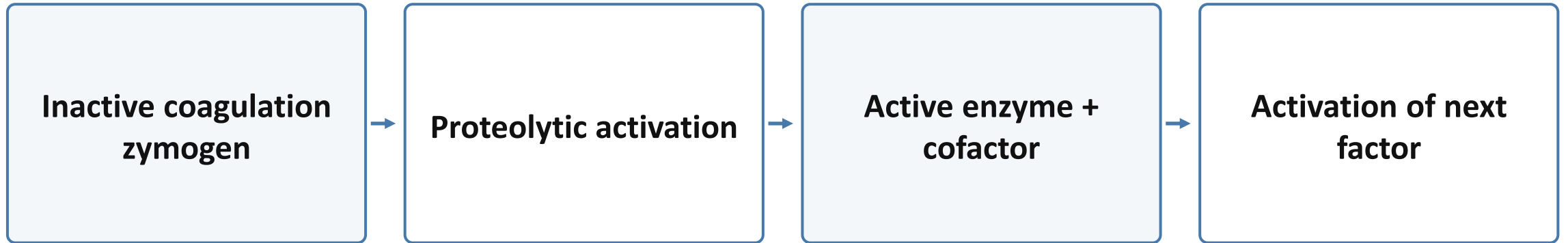
P2Y₁₂ or PAR-1 antagonism

- P2Y₁₂ blockade limits ADP-dependent signaling
- PAR-1 antagonism interferes with thrombin signaling
- Both target recruitment or activation pathways

Platelet surfaces localize coagulation

- Activated platelets expose negatively charged phospholipids.
- Calcium bridges coagulation proteins to these surfaces.
- Local assembly concentrates factors and accelerates enzymatic reactions.
- Restriction of this surface to activated cells helps confine clot formation.

Coagulation is an amplifying protease network



The result is highly amplified thrombin generation and insoluble fibrin deposition.

The laboratory pathways are not the in vivo map

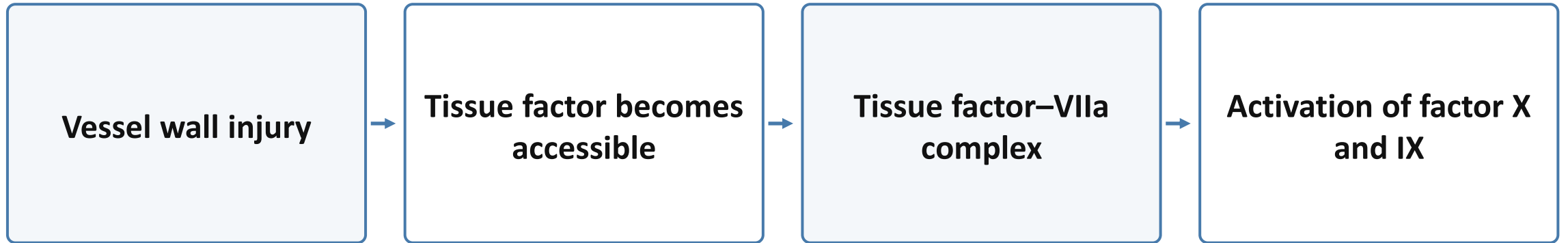
Laboratory assay model

- Contact activation defines the intrinsic arm
- Added tissue factor activates the extrinsic arm
- Both feed a common pathway in test conditions

Coagulation in vivo

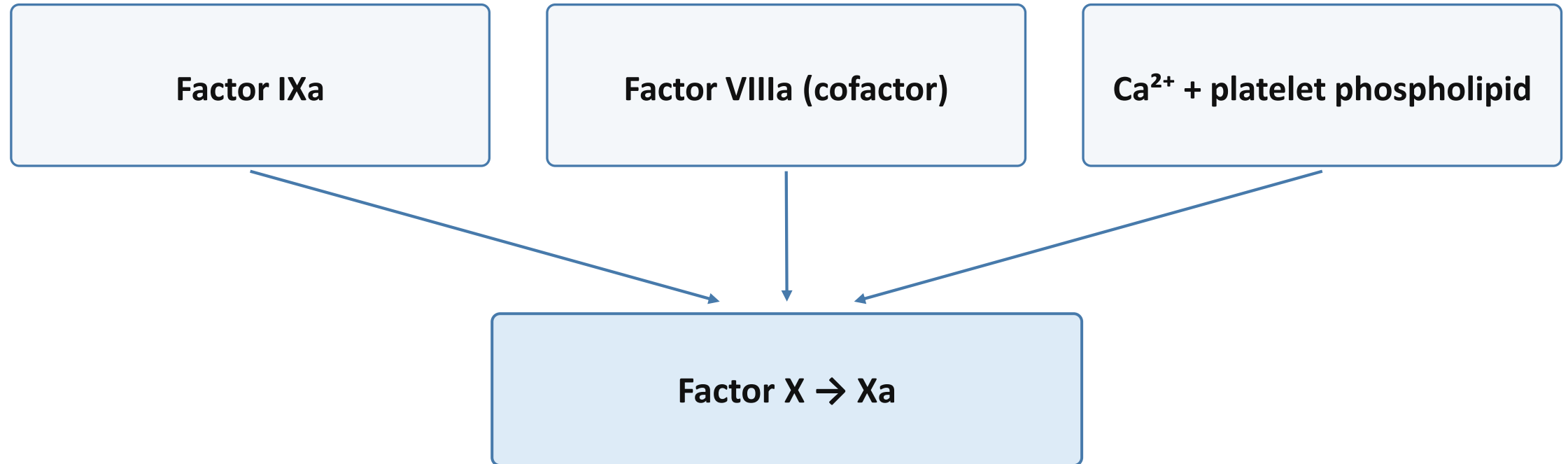
- Exposed tissue factor is the major initiating trigger
- TF–VIIa activates factors X and IX
- IXa–VIIIa efficiently activates factor X

Tissue factor initiates physiologic clotting



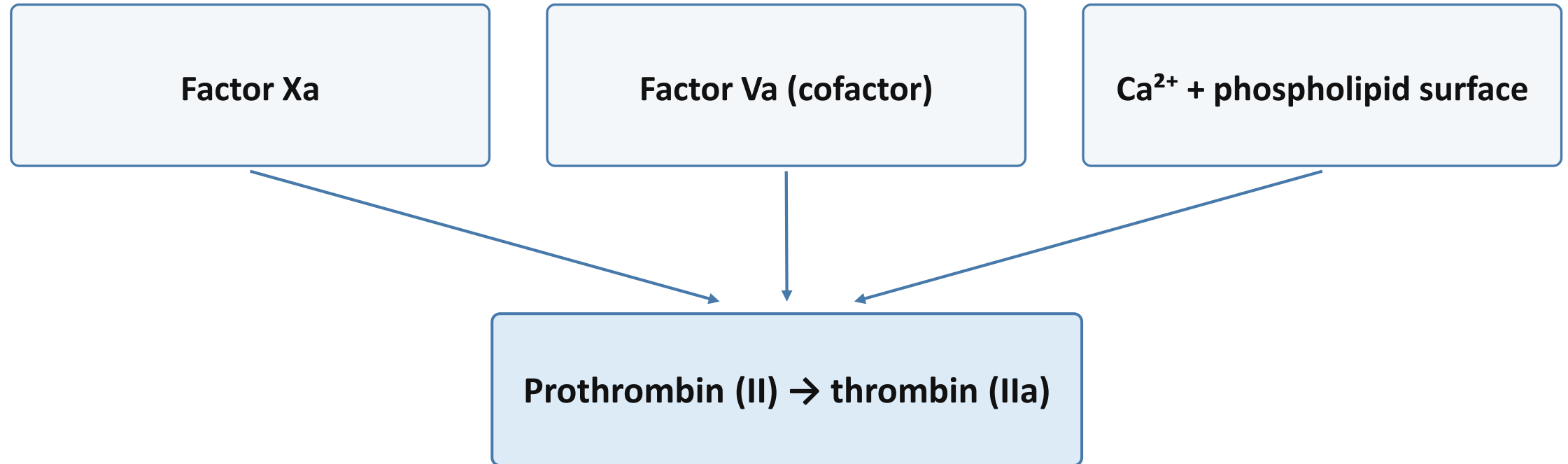
Tissue factor normally resides in cells shielded from circulating blood.

The intrinsic tenase complex activates factor X



The factor IXa–VIIIa complex is a major physiologic route to generating factor Xa.

Prothrombinase generates thrombin

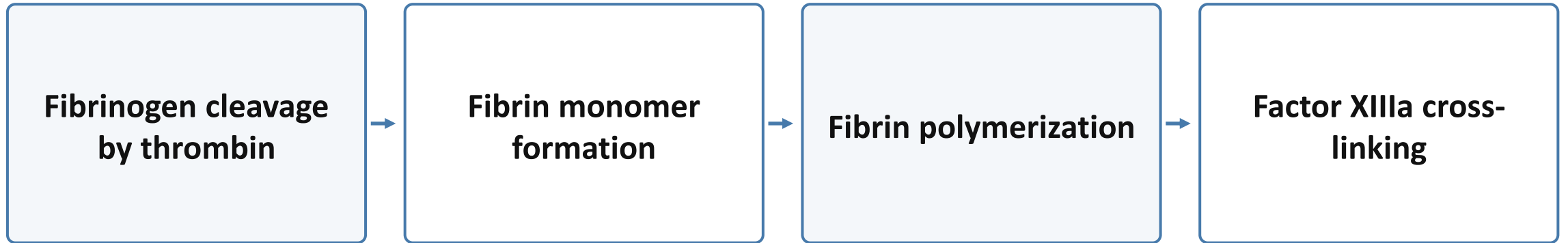


Coagulation factor complexes use an enzyme, a substrate, a cofactor, and a catalytic surface.

Thrombin is the central effector

- Converts soluble fibrinogen into insoluble fibrin monomers.
- Amplifies coagulation through factors V, VIII, and XI.
- Activates factor XIII to cross-link fibrin.
- Stimulates platelets and selected inflammatory cells through PAR signaling.

Fibrin polymerization creates mechanical stability



A cross-linked fibrin mesh strengthens the initially fragile platelet aggregate.

Thrombin coordinates clotting and inflammation

Hemostatic actions

- Generates fibrin and activates factor XIII
- Amplifies coagulation factors
- Promotes platelet activation and aggregation

Cellular actions

- Acts via protease-activated receptors
- Activates endothelial and inflammatory responses
- Contributes to repair-associated signaling

PT and PTT interrogate laboratory pathways

Test	Principal pathway interrogated	Interpretive limit
PT	Tissue factor–initiated and common factors	Does not duplicate all in vivo reactions
PTT / aPTT	Contact-initiated and common factors	Contact system is less central in vivo

Clotting must stay at the site of injury

- Flow dilutes activated factors and allows their clearance by the liver.
- Coagulation complexes require localized membrane phospholipid surfaces.
- Intact adjacent endothelium expresses potent anticoagulant activities.
- Fibrinolysis limits clot size and later assists resorption.

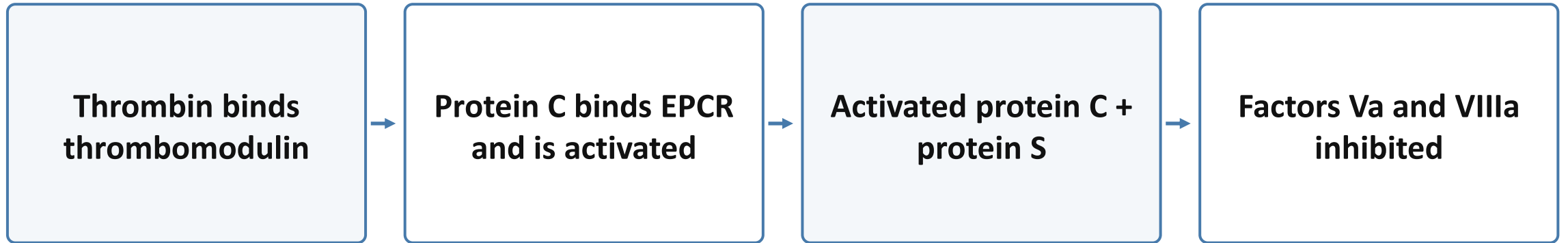
Resting endothelium suppresses platelet activation

- An intact monolayer separates platelets from subendothelial vWF and collagen.
- Prostacyclin (PGI₂) and nitric oxide inhibit platelet activation.
- Endothelial ADPase limits activation by degrading ADP.
- These actions collectively prevent unnecessary platelet adherence.

Endothelial proteins restrain coagulation

Regulatory axis	Main effect
Thrombomodulin + EPCR	Shift thrombin to protein C activation
Heparin-like molecules + antithrombin	Inhibit thrombin and activated factors
Tissue factor pathway inhibitor	Restrict TF–VIIa–dependent initiation

Activated protein C inactivates cofactors



Normal endothelium redirects thrombin from procoagulant to anticoagulant activity.

Antithrombin and TFPI block amplification

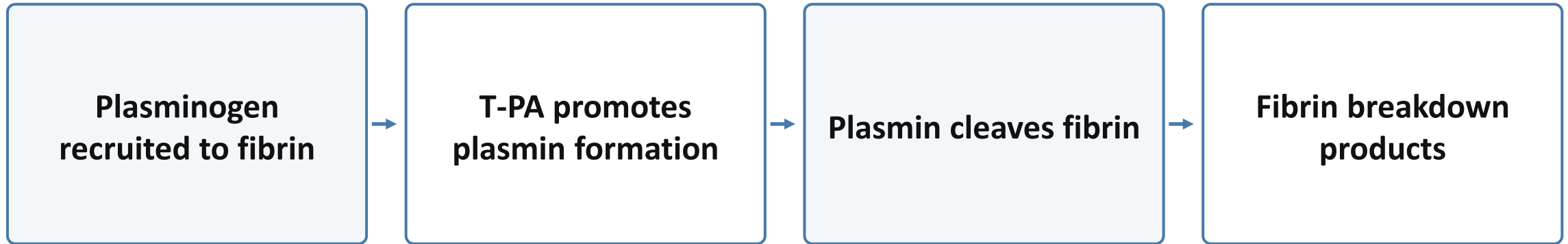
Antithrombin

- Activity enhanced by endothelial heparin-like molecules
- Inhibits thrombin and factors IXa, Xa, XIa, XIIa
- Basis for pharmacologic heparin action

Tissue factor pathway inhibitor

- Endothelial anticoagulant regulator
- Inhibits the tissue factor–VIIa pathway
- Restrains propagation of TF-initiated coagulation

Plasmin degrades fibrin



Fibrin-derived D-dimers indicate breakdown of cross-linked fibrin, but are not specific for a single cause.

Fibrinolysis is spatially controlled

- Endothelium produces tissue plasminogen activator (t-PA).
- T-PA acts especially efficiently when associated with fibrin.
- α_2 -antiplasmin rapidly inhibits free plasmin.
- Plasminogen activator inhibitors attenuate clot lysis.

Endothelial activation reverses the balance

Resting endothelium

- PGI₂, NO, ADPase suppress platelets
- Protein C pathway, antithrombin, TFPI oppose coagulation
- T-PA favors fibrinolysis

Activated or injured endothelium

- Reduced thrombomodulin and anticoagulant activities
- Procoagulant activation, tissue factor access
- PAI release and reduced t-PA inhibit fibrinolysis

Bleeding can reflect three distinct defects

Vessel wall defect

Platelet / vWF defect

Coagulation factor defect

Different defective components produce different anatomic patterns of hemorrhage.

Primary hemostatic defects favor mucosal bleeding

- Typical manifestations include petechiae and purpura.
- Epistaxis, gastrointestinal bleeding, and heavy menstruation are characteristic.
- Platelet number or function may be abnormal; VWF deficiency is another cause.
- Very severe thrombocytopenia can cause catastrophic intracranial bleeding.

Coagulation factor defects favor deep bleeding

- Hematomas may develop in muscles and other soft tissues.
- Hemarthrosis after minor trauma is characteristic of severe hemophilia.
- Deep tissue bleeding reflects an inadequate stable fibrin clot.
- Severe deficiencies can also produce intracranial hemorrhage.

Vascular fragility produces purpura and bruising

- Disorders of small vessels may produce palpable purpura.
- Vasculitis and amyloidosis are examples of vascular disease.
- Scurvy predisposes to vessel fragility.
- Ecchymoses and soft tissue hematomas may occur without a primary factor deficiency.

Bleeding morphology has useful terminology

Finding	Definition
Petechiae	Minute hemorrhages, typically 1–2 mm
Purpura	Larger skin / mucosal hemorrhages, ≥ 3 mm
Ecchymoses	Bruises measuring approximately 1–2 cm
Hematoma	Localized palpable collection of extravasated blood

The bleeding pattern guides mechanism

Typical presentation	Most suggestive defect
Petechiae + epistaxis	Primary hemostasis / vessel wall
Hemarthrosis + muscle hematoma	Coagulation factor deficiency
Palpable purpura	Small-vessel inflammatory injury
Massive rupture-related bleed	Large-vessel structural failure

Three variables determine hemorrhage severity

Volume of blood lost

Rate of blood loss

Anatomic location

A small intracranial bleed may be more dangerous than a larger superficial hemorrhage.

Intracranial hemorrhage is a special emergency

- The rigid skull limits accommodation of increased intracranial volume.
- Rising pressure can compromise cerebral perfusion.
- Severe hemorrhage can cause brainstem herniation.
- Both platelet and coagulation defects can produce fatal intracranial bleeding.

Chronic external bleeding depletes body iron

Repeated external blood loss

- Loss of erythrocytes and their iron stores
- Examples: Heavy menstruation, gastrointestinal bleeding
- May cause iron deficiency anemia

Bleeding retained in tissues

- Blood remains in body spaces or tissues
- Iron can be recovered and recycled
- Not equivalent to chronic external iron loss

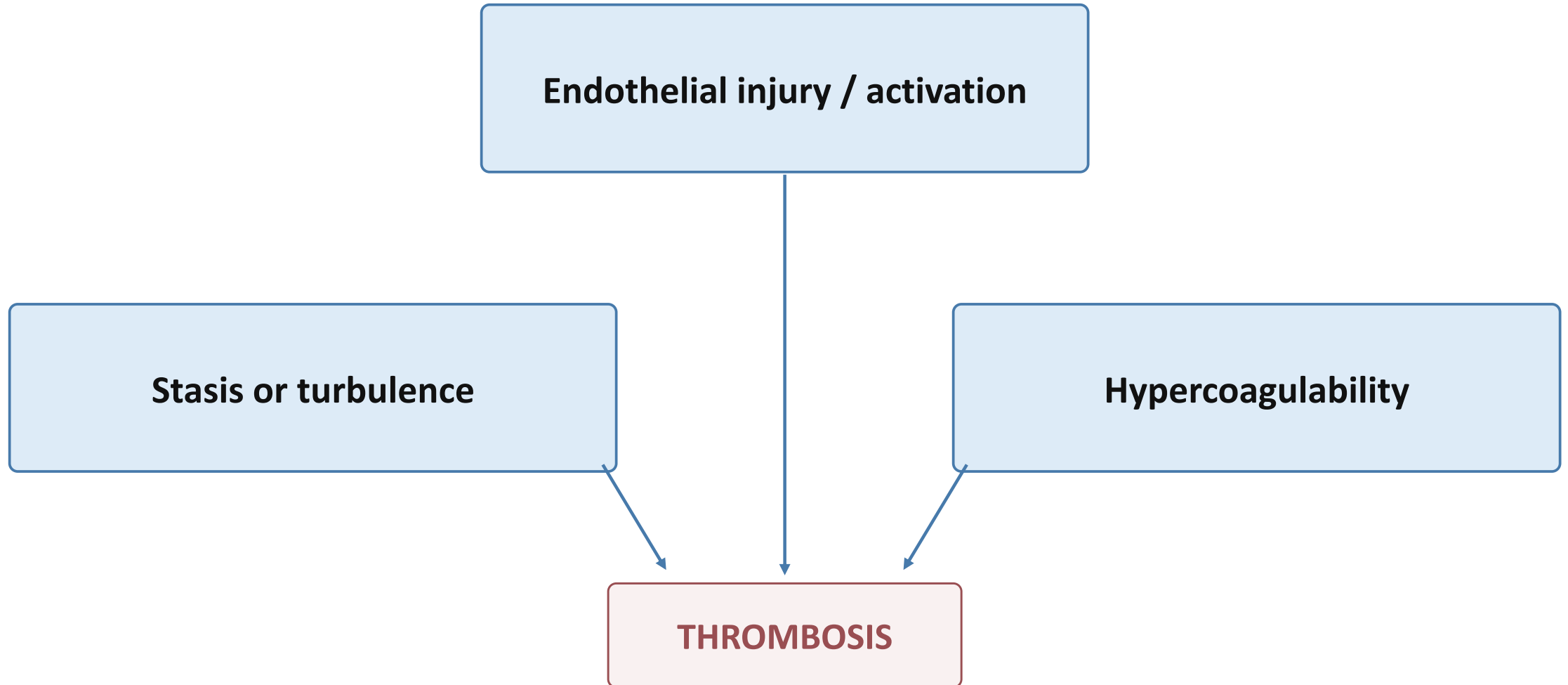
Hemostatic stress can unmask mild defects

- Some bleeding tendencies are inconspicuous in everyday life.
- Surgery, childbirth, dental work, menstruation, or trauma may reveal them.
- Von Willebrand disease is a common inherited example.
- Aspirin exposure and uremia are acquired causes of impaired platelet function.

Thrombosis means pathologic intravascular clotting

- A thrombus forms within intact blood vessels or cardiac chambers.
- It differs from a localized hemostatic plug at a site of vascular injury.
- Thrombi can obstruct blood flow or release emboli.
- Arterial and venous thrombosis differ in their dominant pathophysiology.

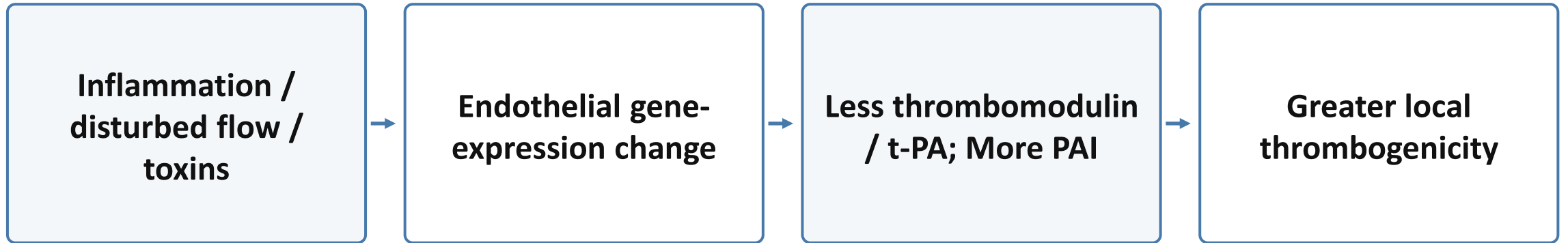
Virchow triad provides a causal framework



Endothelial injury promotes arterial thrombosis

- Loss of endothelial integrity exposes vWF, collagen, and tissue factor.
- Platelet adhesion is especially important under high-shear arterial flow.
- Plaque rupture and vascular injury can trigger an arterial thrombus.
- Inflammatory endothelial activation can be prothrombotic without overt denudation.

Endothelial dysfunction is an active phenotype



Endothelial activation links inflammatory and metabolic insults to clot formation.

Laminar flow separates platelets from the wall

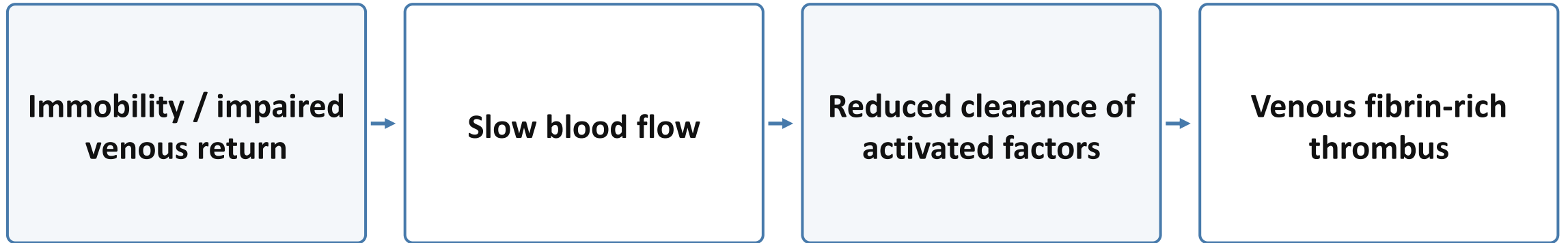
Physiologic laminar flow

- Blood cells predominantly occupy a central stream
- A plasma layer separates cells from the endothelium
- Activated coagulation factors are diluted and washed away

Stasis or turbulence

- Platelets contact the endothelium more readily
- Activated factors accumulate locally
- Endothelium may become activated or injured

Stasis especially favors venous thrombosis



Turbulence is particularly important in arteries and the heart; Stasis is dominant in many veins.

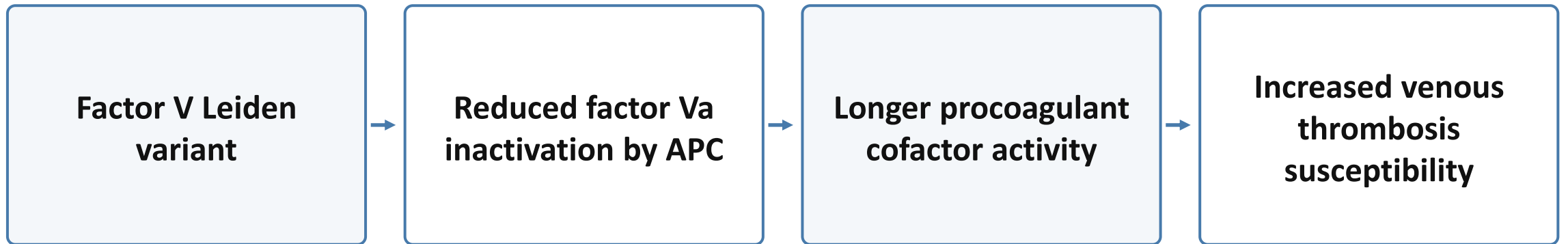
Common flow disturbances have specific settings

Hemodynamic problem	Illustrative setting
Turbulence	Atherosclerotic plaque; Stenotic arterial segment
Chamber stasis	Atrial fibrillation; Poorly contracting ventricle
Venous stasis	Prolonged bed rest; Reduced muscle pumping
Local stasis	Aneurysmal vessel dilation

Hypercoagulability is a systemic predisposition

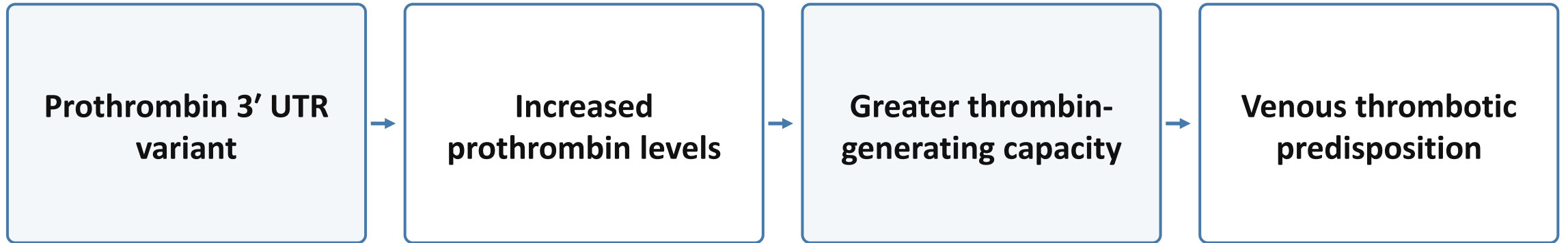
- An increased tendency to clot is often caused by altered coagulation proteins.
- Inherited thrombophilias include common variants and rare anticoagulant deficiencies.
- Acquired states include immobilization, malignancy, surgery, pregnancy, and immune syndromes.
- Hypercoagulability is particularly important in venous thrombosis.

Factor V Leiden resists activated protein C



The mutation removes a natural anticoagulant feedback mechanism.

Prothrombin G20210A increases substrate supply

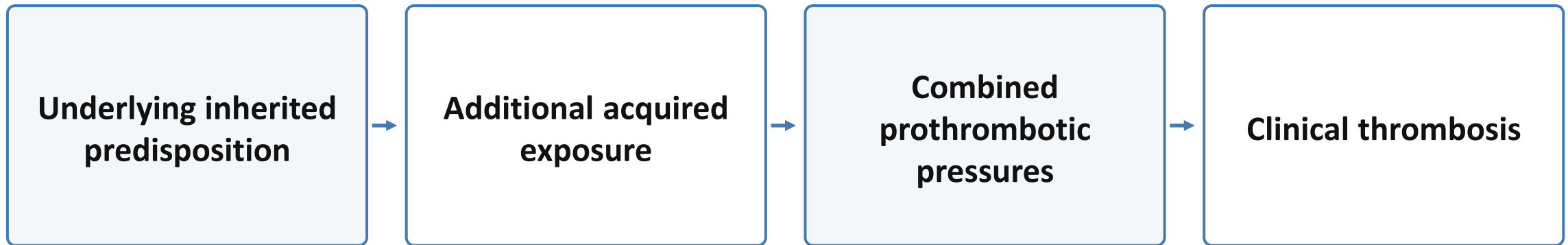


Factor V Leiden and G20210A are distinct molecular mechanisms.

Rare inherited defects affect anticoagulant brakes

Deficiency	Lost protection
Antithrombin	Inhibition of thrombin and activated factors
Protein C	Inactivation of activated cofactors Va and VIIIa
Protein S	Cofactor activity in anticoagulant pathways

Genes and exposures act together



An inherited variant alone does not imply that thrombosis is inevitable.

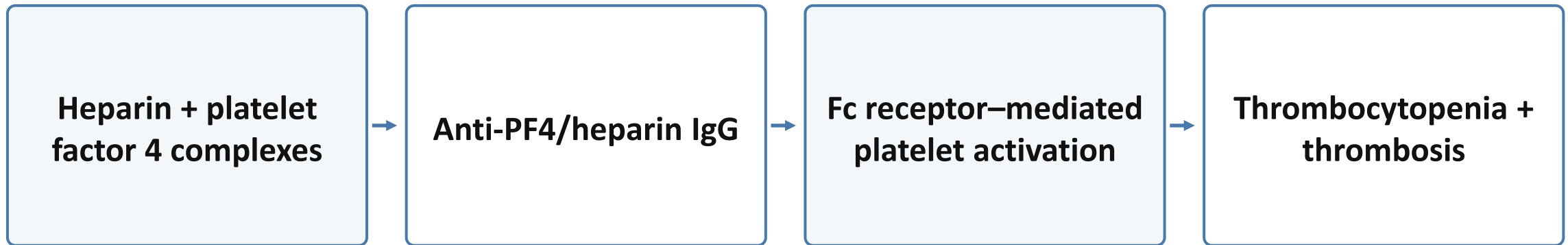
Acquired thrombophilia has multiple mechanisms

Setting	Major mechanistic emphasis
Immobilization / heart failure	Stasis
Surgery / fracture / burns	Injury, tissue procoagulants, inactivity
Pregnancy / oral contraception	Hormonal shifts toward coagulation
Disseminated malignancy	Tumor-related procoagulants, inflammation

Cancer can provoke systemic thrombosis

- Some malignancies release tissue factor or other procoagulants.
- Tumor-associated inflammation contributes to hypercoagulability.
- Disseminated cancer can be associated with migratory thrombophlebitis.
- Trousseau syndrome exemplifies the association between cancer and thrombosis.

Heparin-induced thrombocytopenia is immunologic



Despite falling platelet counts, platelet activation generates substantial thrombotic risk.

HIT: Platelet count and thrombosis diverge

Why platelets fall

- IgG-containing complexes activate platelets
- Antibody-coated activated platelets are removed
- Thrombocytopenia is common

Why clotting rises

- Activated platelets express procoagulant surfaces
- Venous and arterial thrombosis can occur
- Recognition depends on a compatible syndrome and anti-PF4 testing

VITT shares PF4 autoimmunity, not heparin exposure

- Vaccine-induced thrombotic thrombocytopenia has been described rarely after certain adenoviral-vector COVID-19 vaccines.
- Antibodies against PF4 are involved, without requiring exposure to heparin.
- Thromboses may affect cerebral venous sinuses and other venous territories.
- The source describes this as a very rare but potentially life-threatening syndrome.

Antiphospholipid syndrome combines thrombosis and obstetric disease

- Antiphospholipid antibodies are associated with venous or arterial thrombosis.
- Pregnancy manifestations include repeated losses and other placental complications.
- APS may be primary or accompany systemic autoimmune disease, especially SLE.
- Antibody positivity alone does not establish the full clinical syndrome.

APS pregnancy morbidity is not purely thrombotic

Early fetal loss

- Interference with trophoblast growth and differentiation
- Impaired placentation may be central
- Not fully explained by placental vascular thrombosis

Later obstetric complications

- Trophoblast dysfunction remains relevant
- Inflammatory and complement pathways also contribute
- Preeclampsia and preterm birth can occur

Why “lupus anticoagulant” is misleading

In vitro observation

- Antiphospholipid antibodies can prolong PTT
- They interfere with phospholipid-dependent assays
- The historic term “anticoagulant” reflects laboratory testing

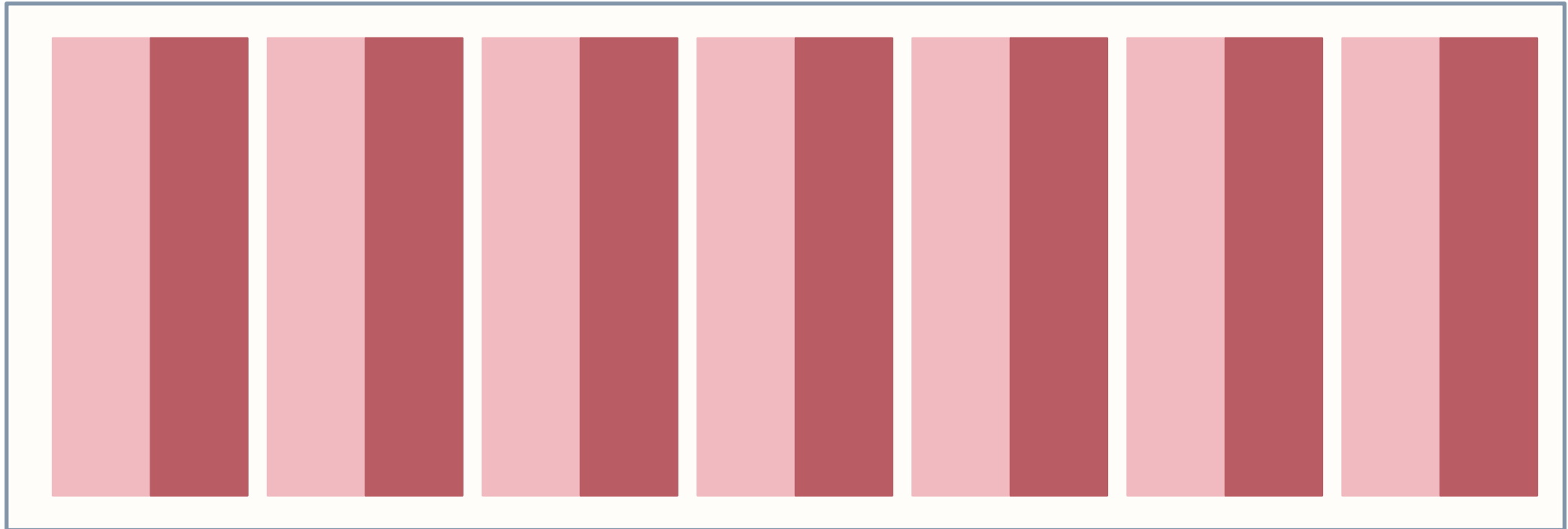
In vivo clinical phenotype

- Patients may have a prothrombotic state
- Thrombosis and pregnancy morbidity define the clinical risk
- Interpret assays with the clinical context

Thrombi contain components of flowing blood

- Thrombi contain platelets, fibrin, erythrocytes, and degenerating leukocytes.
- Their relative proportions depend on flow conditions and location.
- They are attached to the vascular or endocardial surface where they originate.
- Propagation may create an unstable trailing segment.

Lines of Zahn signify formation during flow

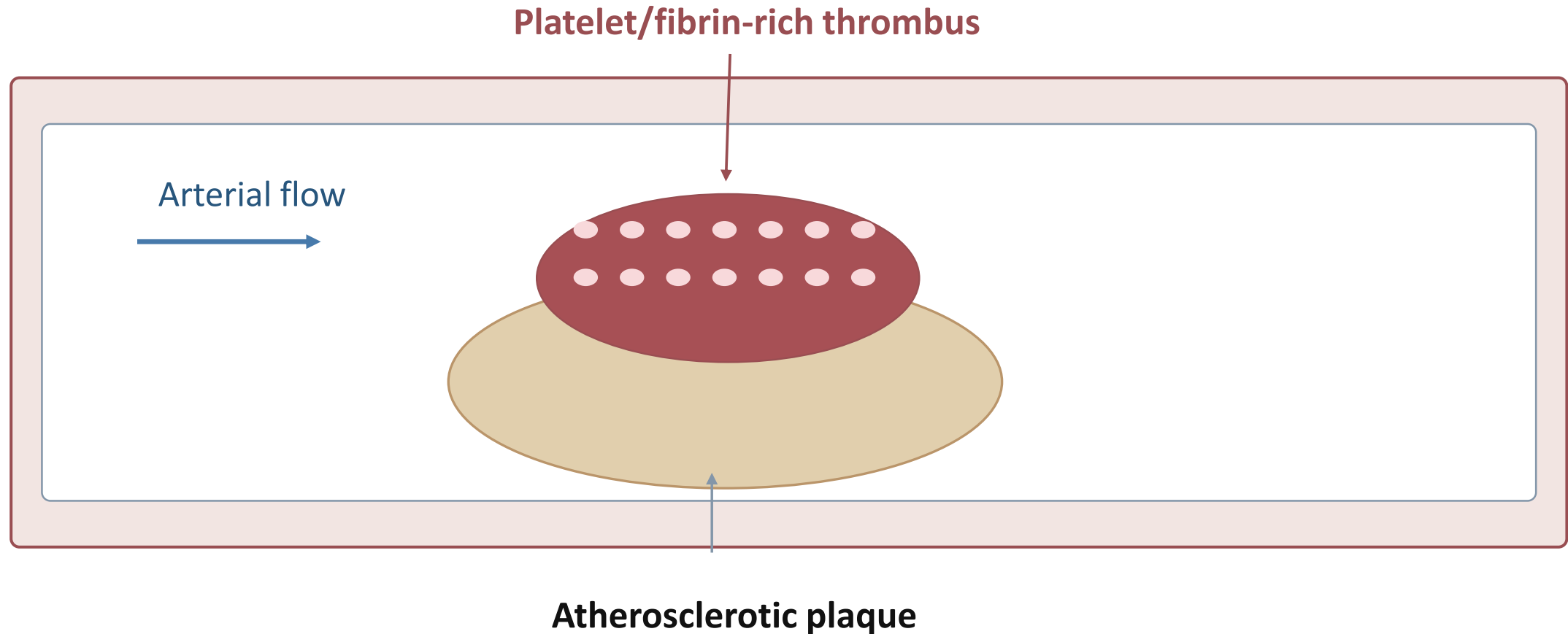


Pale platelet + fibrin layers

Darker erythrocyte-rich layers

Original schematic — not histology

Plaque disruption initiates an arterial thrombus

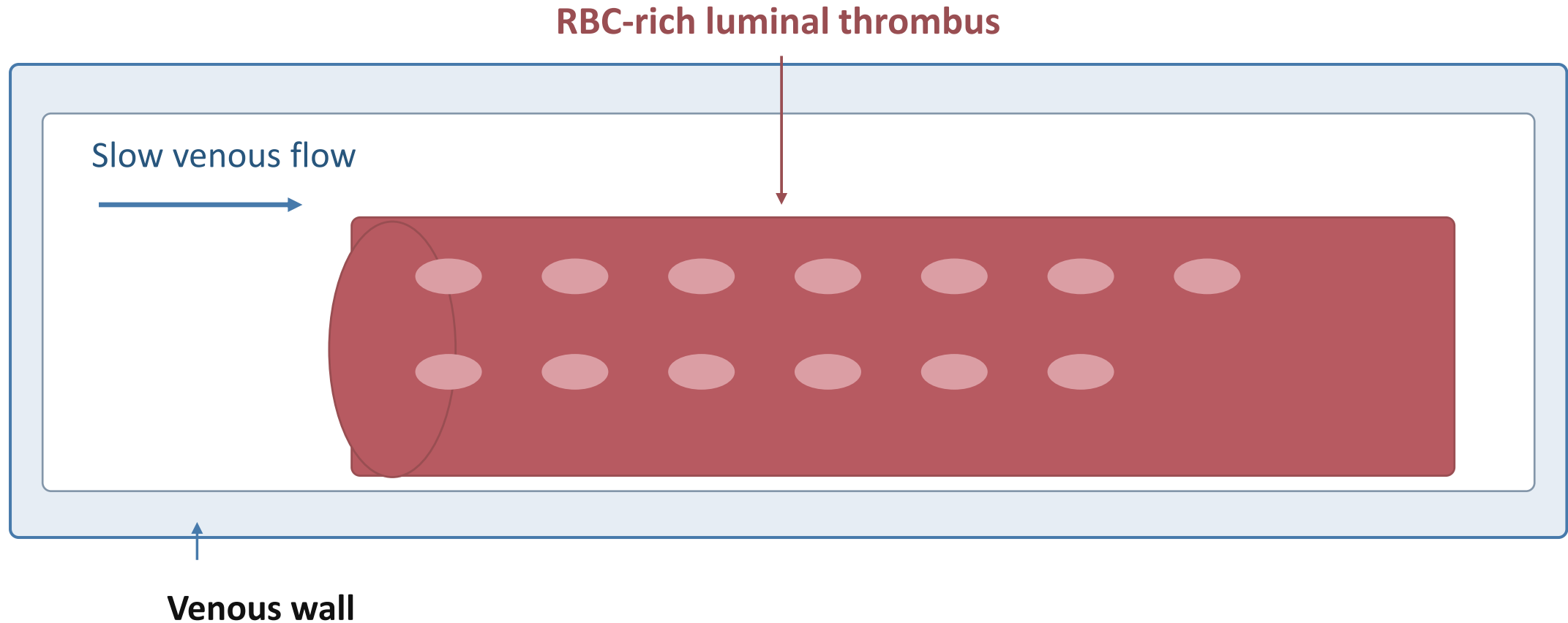


Original vascular schematic — not a gross or histologic specimen

Arterial thrombi commonly relate to endothelial injury

- Arterial thrombi are frequently occlusive.
- Ruptured or eroded atherosclerotic plaques commonly provide the substrate.
- Platelets and fibrin are prominent in these higher-flow environments.
- Coronary, cerebral, and femoral arterial beds are common sites.

A venous thrombus may fill the entire lumen



Original vessel schematic — not a gross or histologic specimen

Venous thrombi are typically red and occlusive

- Venous thromboses often form elongated casts of the venous lumen.
- Sluggish flow favors extensive entrapped red cells with relatively fewer platelets.
- These are called red or stasis thrombi.
- Deep veins of the lower extremities are common sites.

Mural thrombi adhere to the heart or aorta

Cardiac mural thrombi

- Develop at abnormal endocardial surfaces
- Promoted by myocardial infarction, dyskinetic contraction, and arrhythmia
- Can give rise to systemic emboli

Aortic mural thrombi

- May accompany aneurysmal dilatation
- Atherosclerotic ulceration contributes injury and turbulence
- Can provide a source of embolic fragments

Antemortem thrombus versus postmortem clot

Characteristic	Antemortem thrombus	Postmortem clot
Wall attachment	Usually present	Usually absent
Texture	Typically firmer	Gelatinous
Lamination	Lines of Zahn may appear	Generally not laminated
Appearance	Flow-associated layering	Red dependent + yellow “chicken fat”

Valve vegetations are thrombotic masses

- Vegetations are thrombi that form on cardiac valves.
- Infective endocarditis creates microbial-associated, thrombotic masses.
- Nonbacterial thrombotic endocarditis may occur in hypercoagulable states.
- Libman–Sacks vegetations may accompany systemic lupus erythematosus.

Propagation and flow direction matter

Arterial thrombi

- Often begin at injury or turbulence
- May extend retrograde relative to local blood flow
- Growth generally proceeds toward the heart

Venous thrombi

- Typically originate in stasis-prone segments
- Propagate in the direction of venous flow
- Poorly attached regions may detach and embolize

Four possible fates of a thrombus

Propagation

Embolization

Dissolution

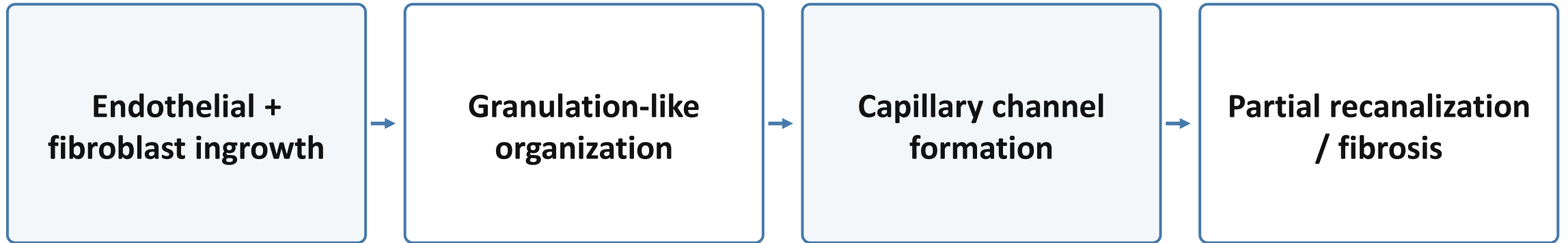
**Organization ±
recanalization**

These outcomes may coexist in a single evolving thrombus.

Clot age influences fibrinolytic dissolution

- Recent thrombi may be largely dissolved through fibrinolysis.
- Older thrombi accumulate dense, cross-linked fibrin.
- Established organized thrombi are less susceptible to dissolution.
- This distinction underlies the importance of timing in thrombolytic therapy.

Organization converts thrombus into tissue



Recanalization may restore part of the lumen, but not necessarily normal vessel structure.

Arterial and venous thrombi create different hazards

Arterial / cardiac thrombi

- Critical-artery occlusion causes tissue ischemia
- Consequences include myocardial and cerebral infarction
- Detached material may cause systemic emboli

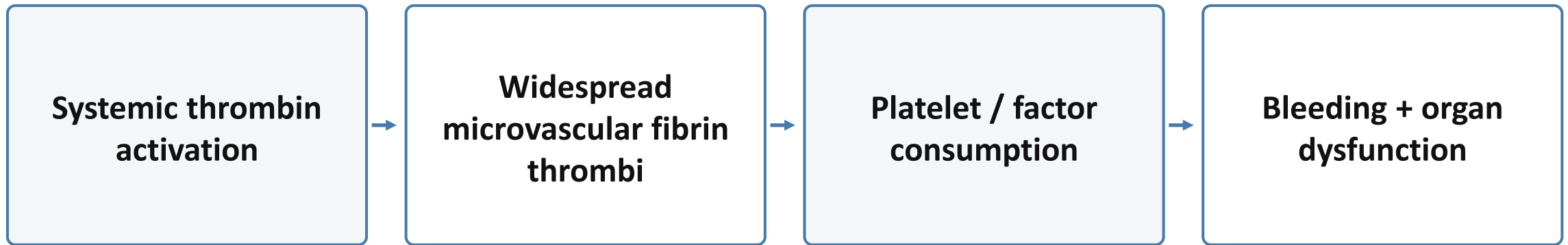
Deep venous thrombi

- Obstruction produces venous congestion and edema
- Deep thrombi may be clinically silent
- Embolization can lead to pulmonary embolism

Deep vein thrombosis may be clinically silent

- Leg DVT can cause swelling, pain, or tenderness.
- Collateral venous channels may limit obvious local symptoms.
- The source notes that many DVTs are asymptomatic until embolization.
- Immobility, cardiac failure, surgery, pregnancy, and cancer raise susceptibility.

Disseminated intravascular coagulation consumes factors



DIC is a secondary syndrome, not one specific primary disease.

Case: Epistaxis, petechiae, and heavy menses

A patient develops frequent epistaxis, petechiae, and excessive menstrual bleeding after minor hemostatic stresses.

Which hemostatic compartment is most likely involved?

Mechanistic interpretation

Primary hemostasis—platelet number/function or vWF-dependent adhesion. The bleeding distribution is more informative here than any single molecular diagnosis.

Case: Spontaneous knee hemarthrosis

A young patient has recurrent bleeding into the knee joint after minimal trauma but lacks prominent petechiae.

What kind of defect should be considered first?

Mechanistic interpretation

A coagulation factor deficiency affecting secondary hemostasis. Hemarthrosis is a characteristic deep-bleeding pattern.

Case: Thrombosis despite thrombocytopenia

Following heparin exposure, platelet counts decrease and the patient develops a new venous thrombus.

What mechanism links low platelet count to new thrombosis?

Mechanistic interpretation

Immune platelet activation by anti-PF4/heparin antibodies can cause both platelet consumption and a strong procoagulant state.

Case: Prolonged immobility and a leg thrombus

A hospitalized patient develops a proximal leg venous thrombosis after prolonged immobilization.

Which Virchow component is especially important?

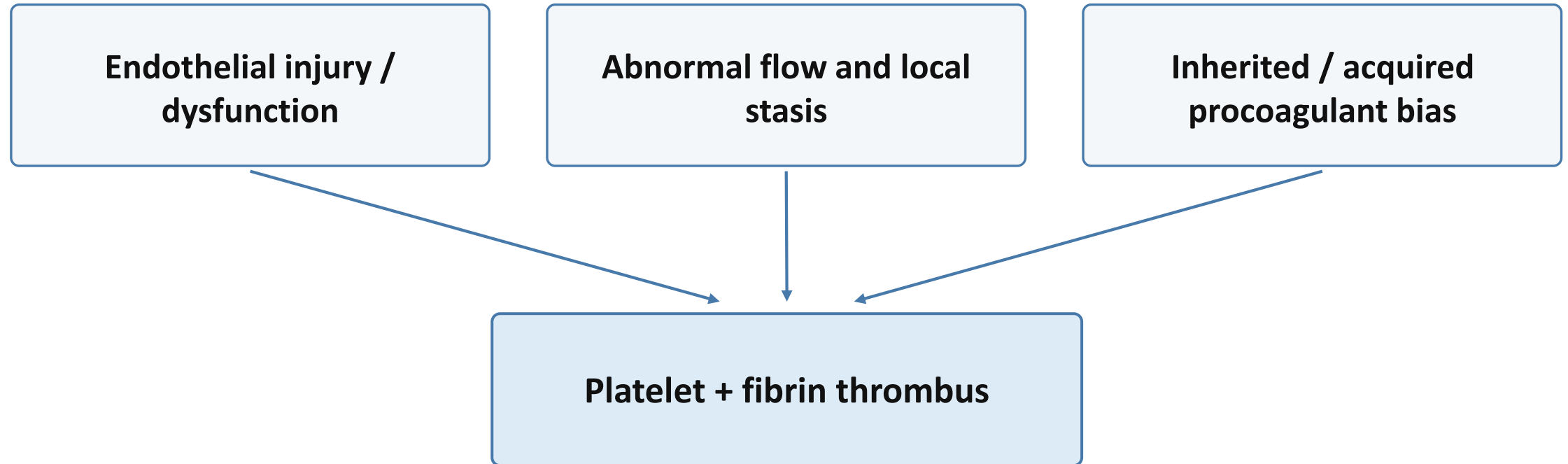
Mechanistic interpretation

Venous stasis: Reduced muscle pumping and slow flow limit the washout of activated coagulation factors; Other factors may also contribute.

Integrate bleeding pattern with the failed step

Impaired step	Clue	Mechanistic interpretation
Platelet adhesion / function	Mucocutaneous bleeding	Poor primary plug formation
Factor-generated fibrin	Deep tissue / joint bleeding	Unstable secondary plug
Vascular integrity	Palpable purpura / ecchymoses	Fragile or inflamed vessel wall
Systemic coagulation activation	Thrombosis plus bleeding	Consumptive coagulopathy

A compact mechanism map of thrombosis



Virchow triad components interact; The dominant contribution depends on the vascular bed.

What a thrombus can ultimately do

**Local growth /
propagation**

Vascular obstruction

**Fragmentation /
embolization**

**Organization /
dissolution**

The dominant clinical consequence depends on location, vascular supply, and embolization.

Integrated core principles

- Normal hemostasis requires a platelet plug, thrombin-mediated fibrin, and endothelial containment.
- Mucosal versus deep-tissue bleeding suggests different failing components.
- Thrombosis results from injury, abnormal flow, hypercoagulability, or their combination.
- Thrombus morphology and location predict obstruction, embolization, and remodeling.

Principal source and coverage

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026)

Hemostasis, Hemorrhagic Disorders, and Thrombosis

Coverage: normal hemostasis, bleeding disorders, and thrombosis

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