

Thrombosis

Mechanisms, morphology, and clinicopathologic consequences

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Learning objectives

- Distinguish pathologic thrombosis from physiologic hemostasis.
- Explain the interacting components of Virchow triad.
- Relate arterial and venous risk factors to thrombus morphology.
- Predict thrombus outcomes and major clinical consequences.

Thrombosis is inappropriate intravascular clot formation

- A thrombus is formed within the circulation or a cardiac chamber during life.
- It may obstruct blood flow at its origin or become a source of emboli.
- The affected vascular bed determines clinical severity.



Intravascular thrombus: Adherent luminal mass

Schematic vessel lumen

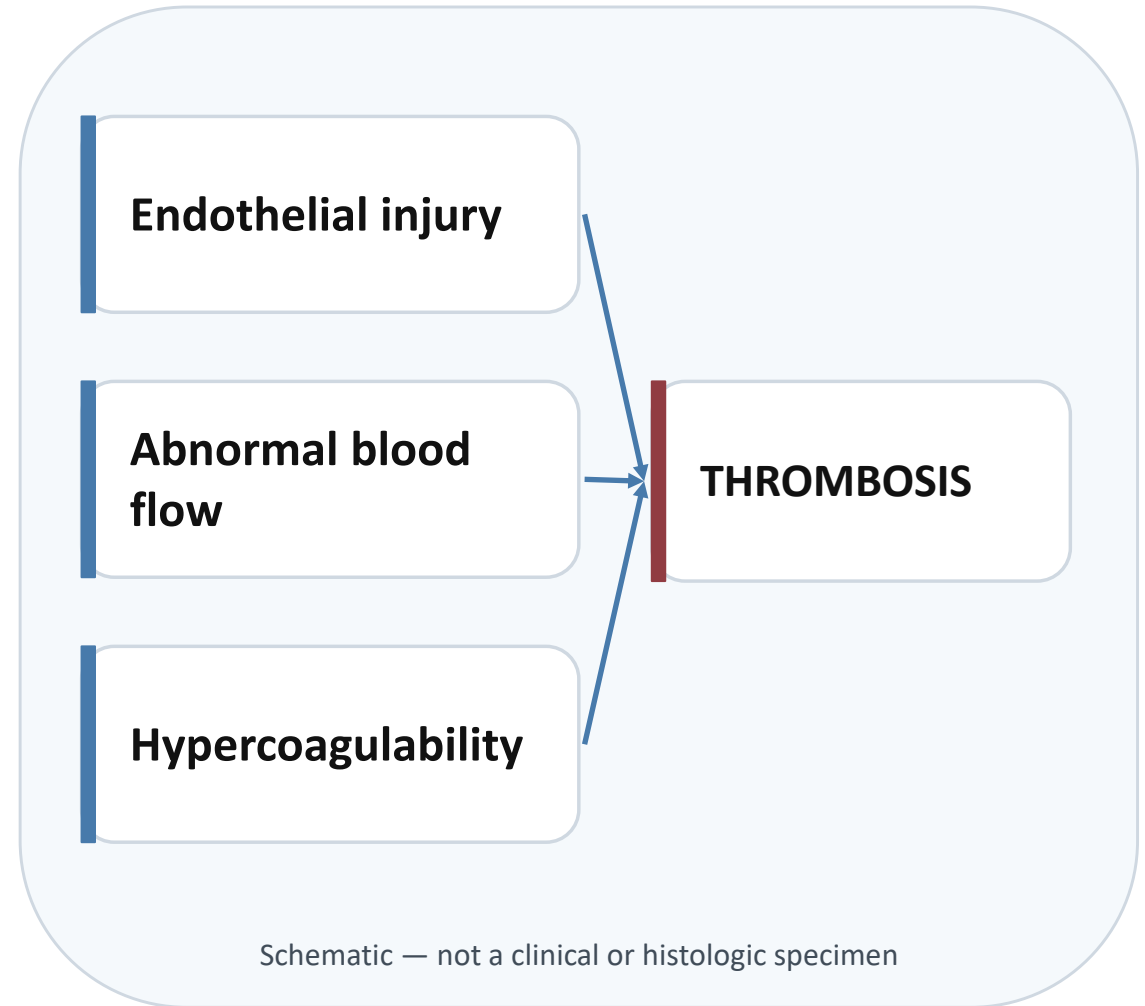
Schematic — not a clinical or histologic specimen

Hemostasis protects; Thrombosis injures

Physiologic hemostasis	Pathologic thrombosis
Activated at a site of vascular injury	Occurs in intact or damaged vessels / cardiac chambers
Limits blood loss	May obstruct vessels or embolize
Spatially limited, regulated response	Unwanted clotting from local/systemic risk factors

Virchow triad: Three principal thrombogenic abnormalities

- Endothelial injury or prothrombotic activation.
- Stasis or turbulent blood flow.
- Hypercoagulability of circulating blood.



The three components reinforce one another

- Endothelial injury changes local flow and coagulation.
- Stasis and turbulence favor endothelial activation.
- Acquired or inherited thrombophilia magnifies local triggers.

Arterial and venous thrombosis arise in different hemodynamic settings

Arteries / heart

High shear, rapid circulation

Endothelial injury and disturbed flow predominate

Platelet-rich lesions common

Veins

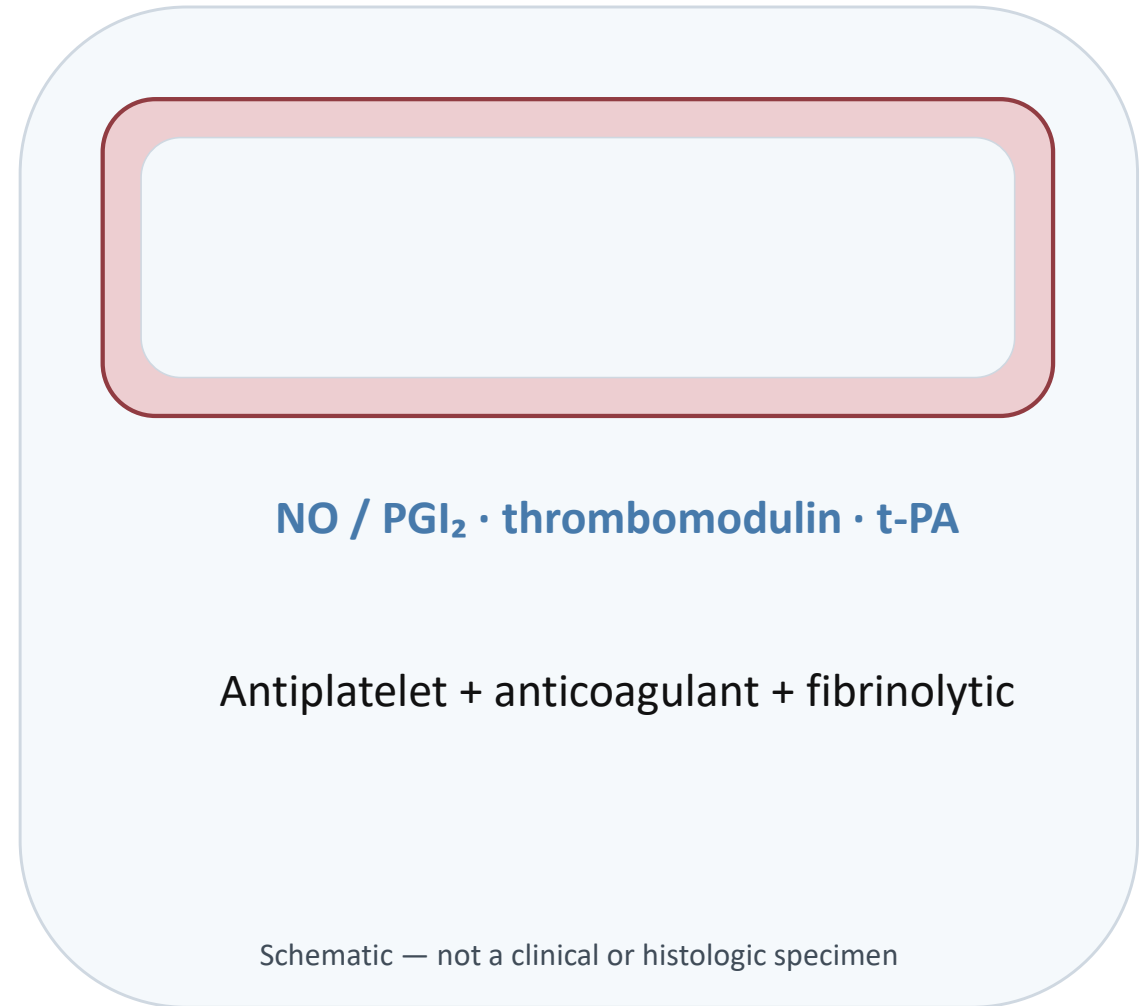
Lower flow velocities and stasis

Stasis and hypercoagulability predominate

Red-cell-rich thrombi common

The intact endothelium is normally antithrombotic

- Healthy endothelium separates blood from thrombogenic subendothelial matrix.
- Antiplatelet, anticoagulant, and fibrinolytic activities oppose unwanted clotting.
- Endothelial activation can reverse this local balance.



Endothelium restrains platelet adhesion and activation

- Prostacyclin (PGI_2) and nitric oxide inhibit platelet activation.
- Adenosine diphosphatase reduces available platelet agonists.
- Exposed von Willebrand factor and collagen promote adhesion after injury.
- Loss of this barrier is particularly important under arterial shear.

Thrombomodulin redirects thrombin toward anticoagulation

- Endothelial thrombomodulin binds thrombin.
- The resulting complex activates protein C.
- Activated protein C, with protein S, suppresses factors Va and VIIIa.

Thrombin + thrombomodulin



Protein C activation



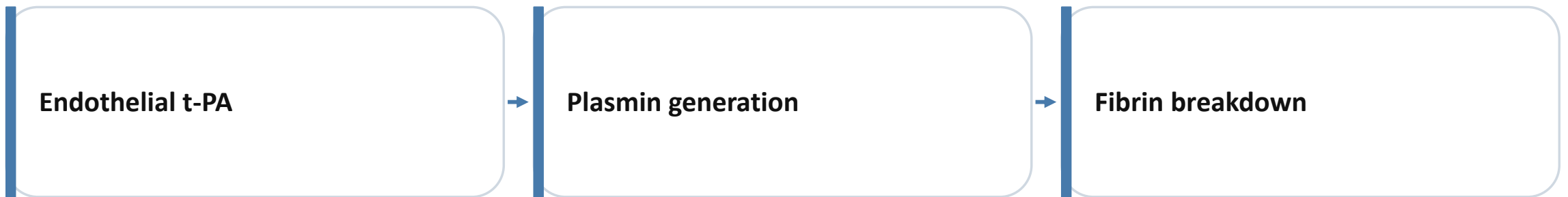
Factor Va / VIIIa inhibition

Protein S is a cofactor of activated protein C

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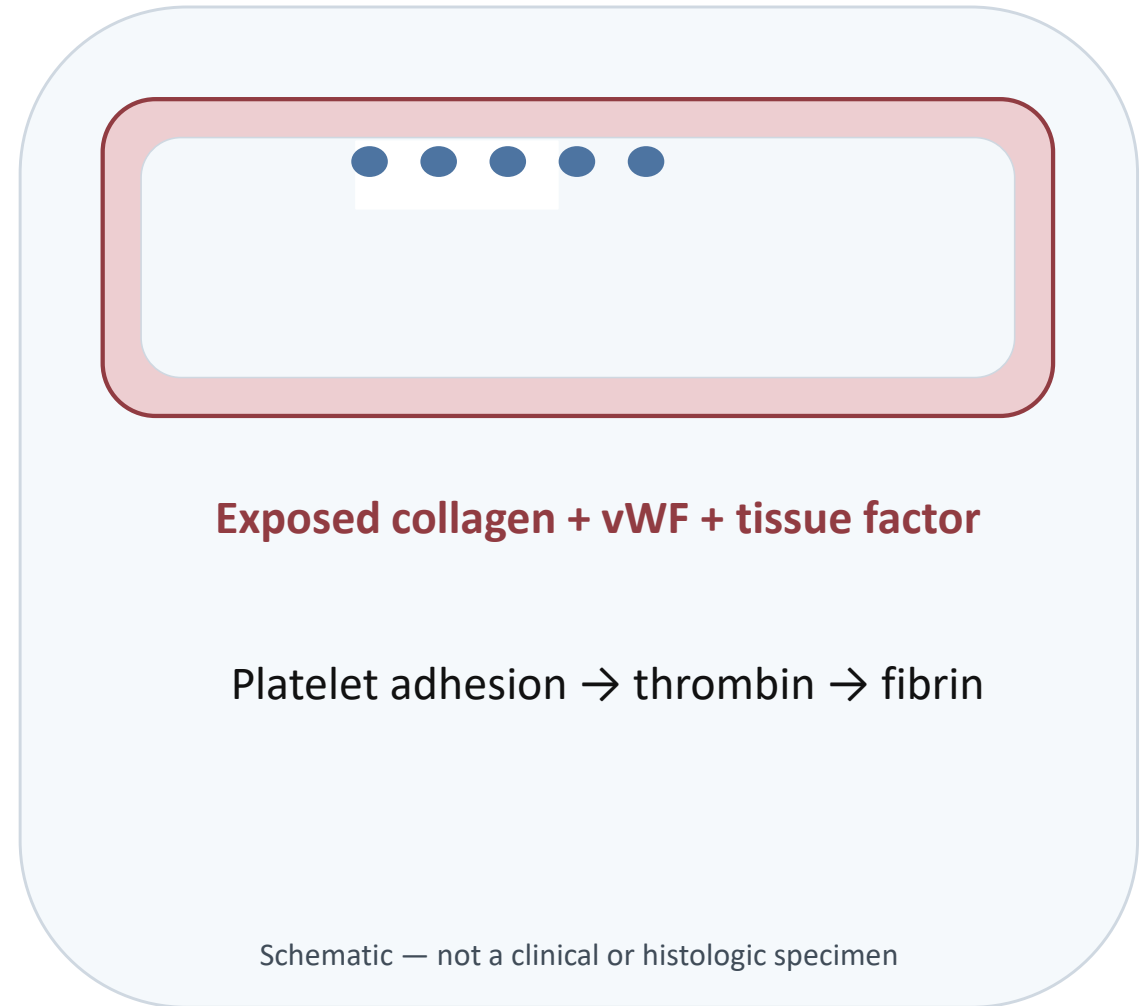
Endothelial regulation also promotes fibrinolysis

- Tissue plasminogen activator (t-PA) drives plasmin generation.
- Plasmin degrades fibrin within a thrombus.
- Plasminogen activator inhibitors (PAIs) limit this pathway.



Severe endothelial injury exposes a thrombogenic surface

- Exposed subendothelial collagen and vWF recruit platelets.
- Tissue factor initiates coagulation and thrombin production.
- Fibrin formation consolidates platelet-rich material.



Endothelial activation is not necessarily endothelial denudation

- Inflammatory mediators can induce a prothrombotic endothelial phenotype.
- The endothelium may remain physically present but become dysfunctional.
- Changes in gene expression shift the balance toward clot formation.

Activated endothelium loses anticoagulant capacity

- Inflammation reduces thrombomodulin expression.
- Anticoagulant pathways, including protein C-related mechanisms, are impaired.
- The net effect favors thrombin activity and coagulation.



↓ **Thrombomodulin and anticoagulant function**

↑ Procoagulant thrombin signaling

Schematic — not a clinical or histologic specimen

Activated endothelium also suppresses fibrin removal

- PAI secretion increases during endothelial activation.
- T-PA expression decreases.
- Reduced fibrinolysis permits persistence of fibrin-rich thrombi.

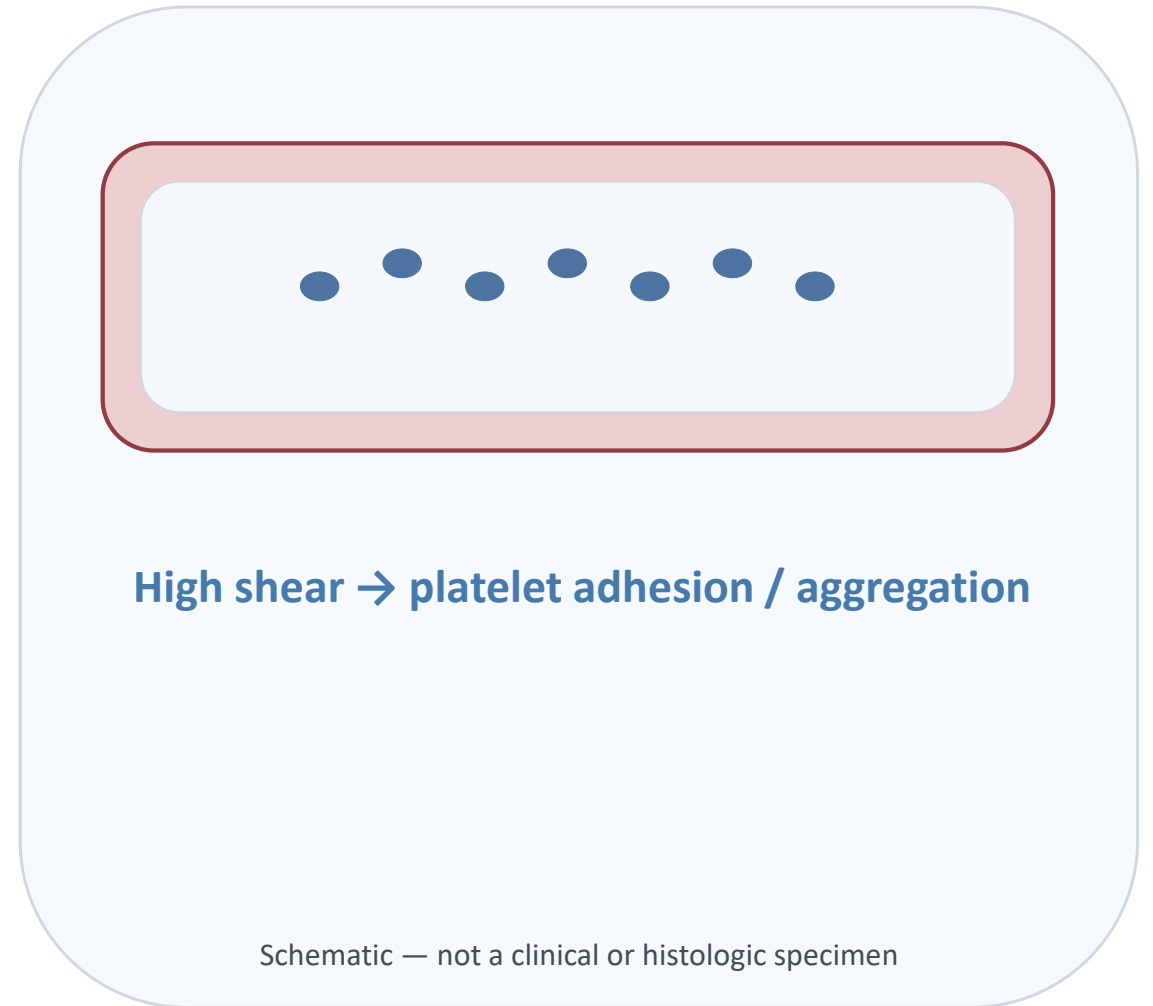


Common endothelial stressors act through different routes

- Physical injury and disturbed flow can directly damage or activate endothelium.
- Infectious agents and inflammatory mediators alter endothelial function.
- Hypercholesterolemia, homocystinemia, and cigarette-smoke toxins are implicated.
- The shared consequence is a more procoagulant vascular surface.

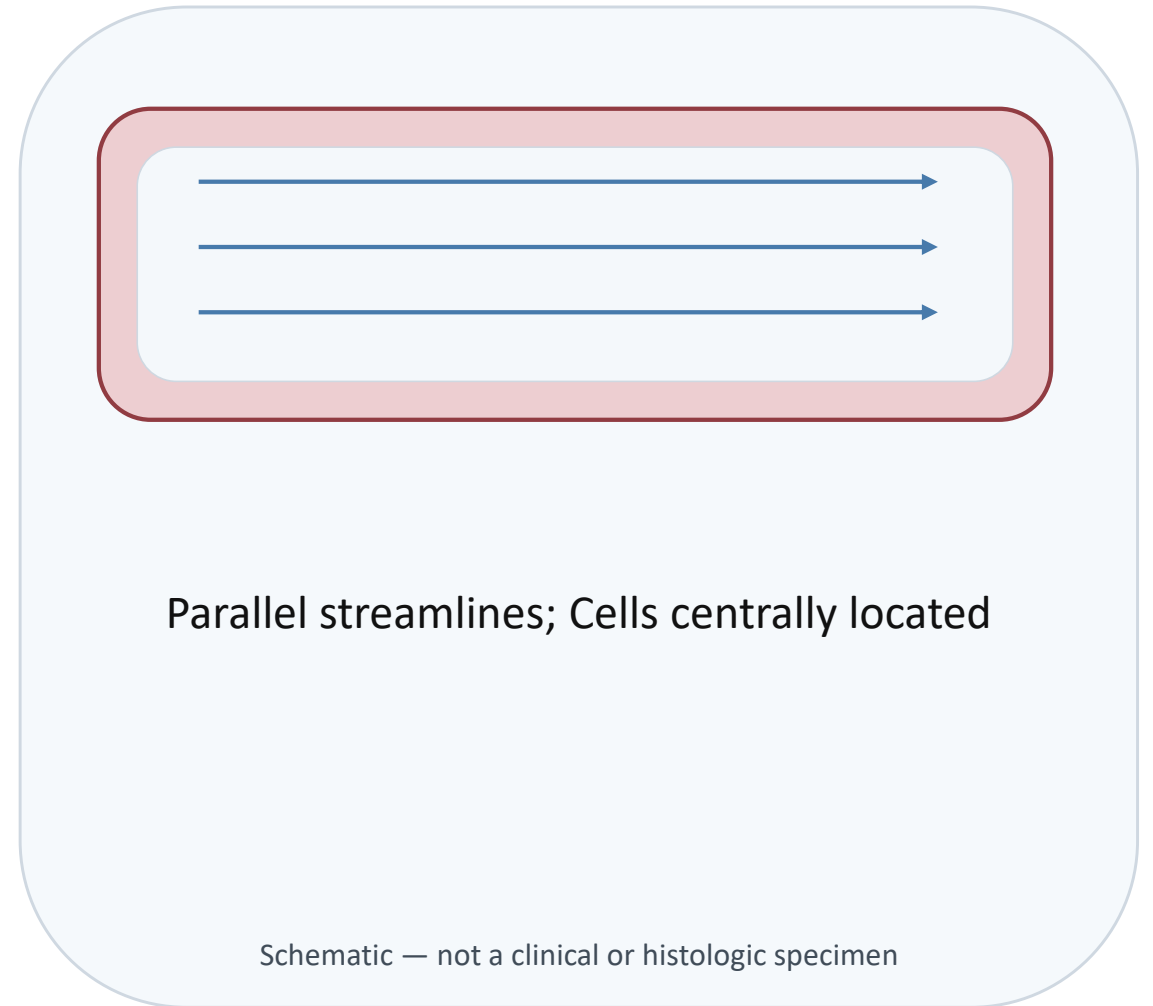
Platelets are central in high-shear arterial thrombosis

- High shear makes platelet adhesion an initiating step in arterial clot formation.
- Platelet activation drives recruitment and aggregation.
- This underpins antiplatelet treatment rationale in coronary disease.



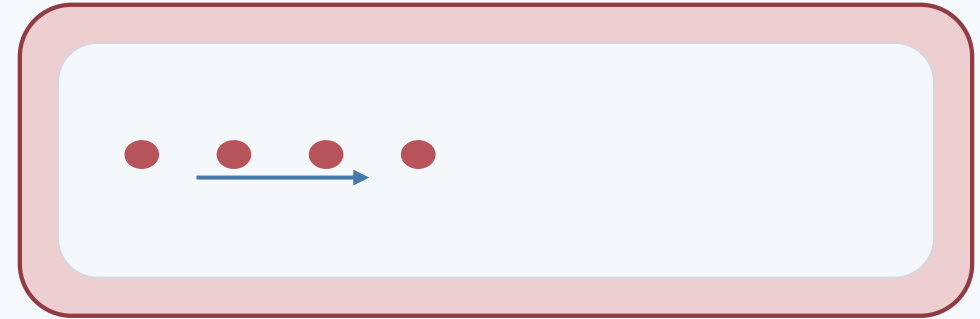
Blood normally moves in organized laminar layers

- Cellular elements tend to flow centrally within the lumen.
- A marginal plasma layer ordinarily separates platelets from endothelium.
- Disrupted flow changes cell–wall contact and local clotting-factor exposure.



Stasis favors thrombosis through several mechanisms

- Slower flow reduces dilution and washout of activated coagulation factors.
- Stasis encourages local accumulation of procoagulant substances.
- Endothelial changes and altered platelet contact may follow.



Impaired washout and accumulation of clotting factors

Schematic — not a clinical or histologic specimen

Turbulence predisposes to arterial and cardiac thrombi

- Disturbed streams create countercurrents and pockets of relative stasis.
- Abnormal shear can injure or activate vascular endothelium.
- Atherosclerotic narrowing and aneurysmal dilation are characteristic settings.

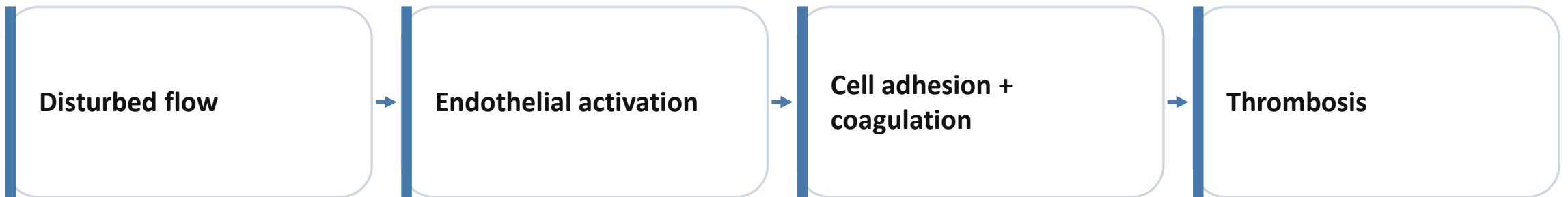


Vortices and disturbed endothelial shear

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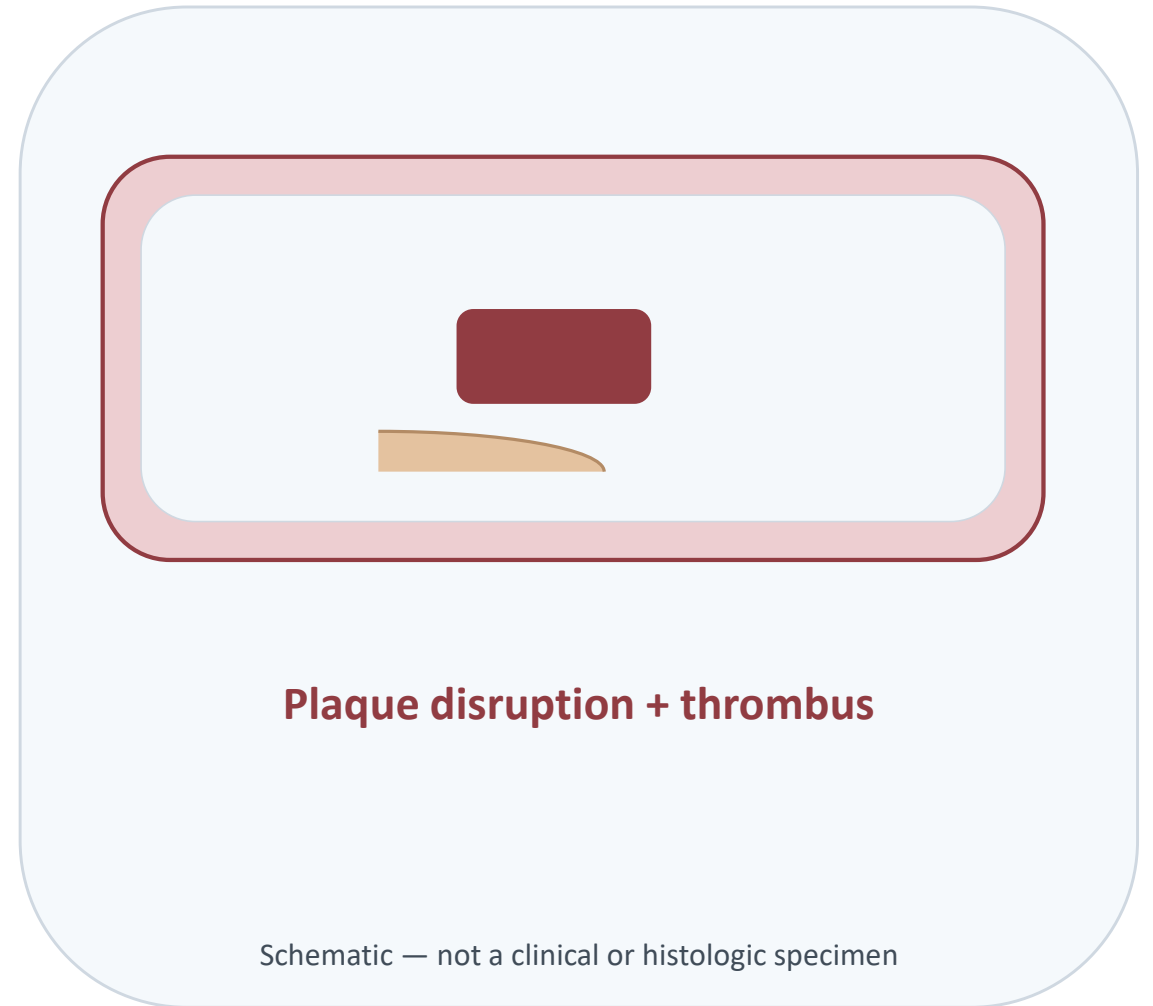
Both abnormal flow patterns amplify endothelial activation

- Stasis and turbulence alter endothelial mechanosignaling.
- Adhesion molecules and proinflammatory mediators are induced.
- Thrombogenic blood elements interact more readily with the vessel surface.



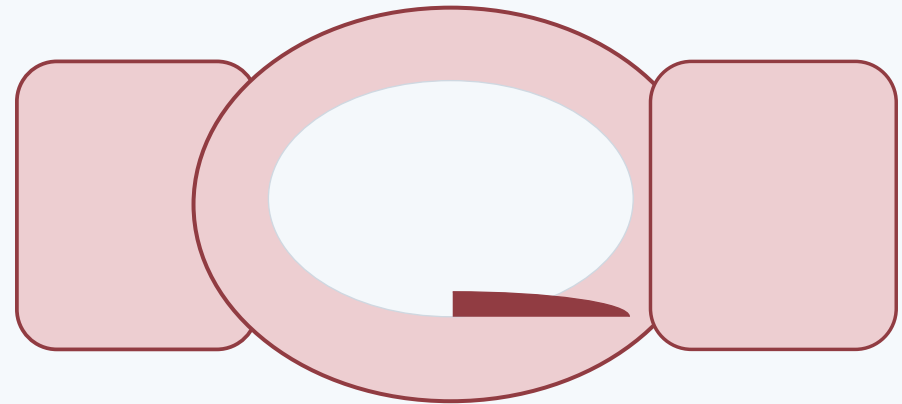
Atherosclerotic plaques combine injury with turbulence

- Plaque ulceration exposes subendothelial thrombogenic material.
- Local luminal narrowing generates disturbed flow.
- The combined mechanism favors occlusive arterial thrombosis.



Aneurysms create regions of sluggish circulation

- Dilated vascular segments permit local stasis.
- Aortic aneurysms can contain mural thrombi.
- The vascular lesion and thrombus may coexist over an extended period.

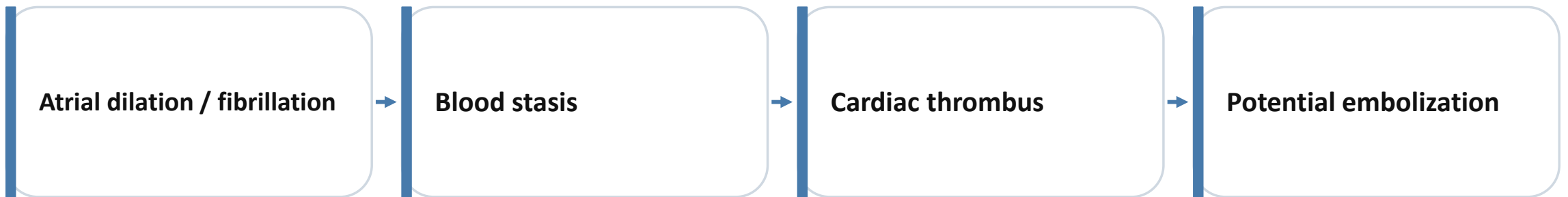


Dilation creates a low-flow recess

Schematic — not a clinical or histologic specimen

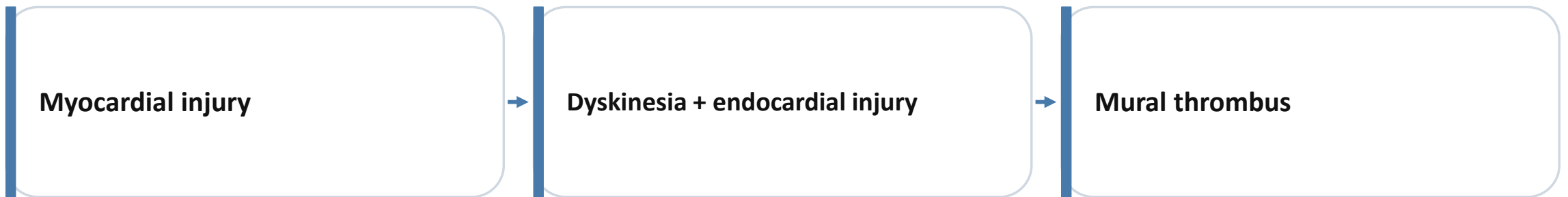
Atrial fibrillation and atrial enlargement promote thrombi

- Reduced coordinated atrial contraction contributes to stasis.
- Left atrial dilation can accentuate the stagnant compartment.
- Mural thrombi can subsequently become an embolic source.



Impaired ventricular contraction promotes mural thrombosis

- Myocardial infarction produces noncontractile or dyskinetic regions.
- Stasis and endocardial injury may coexist over injured myocardium.
- These conditions favor cardiac mural thrombus formation.



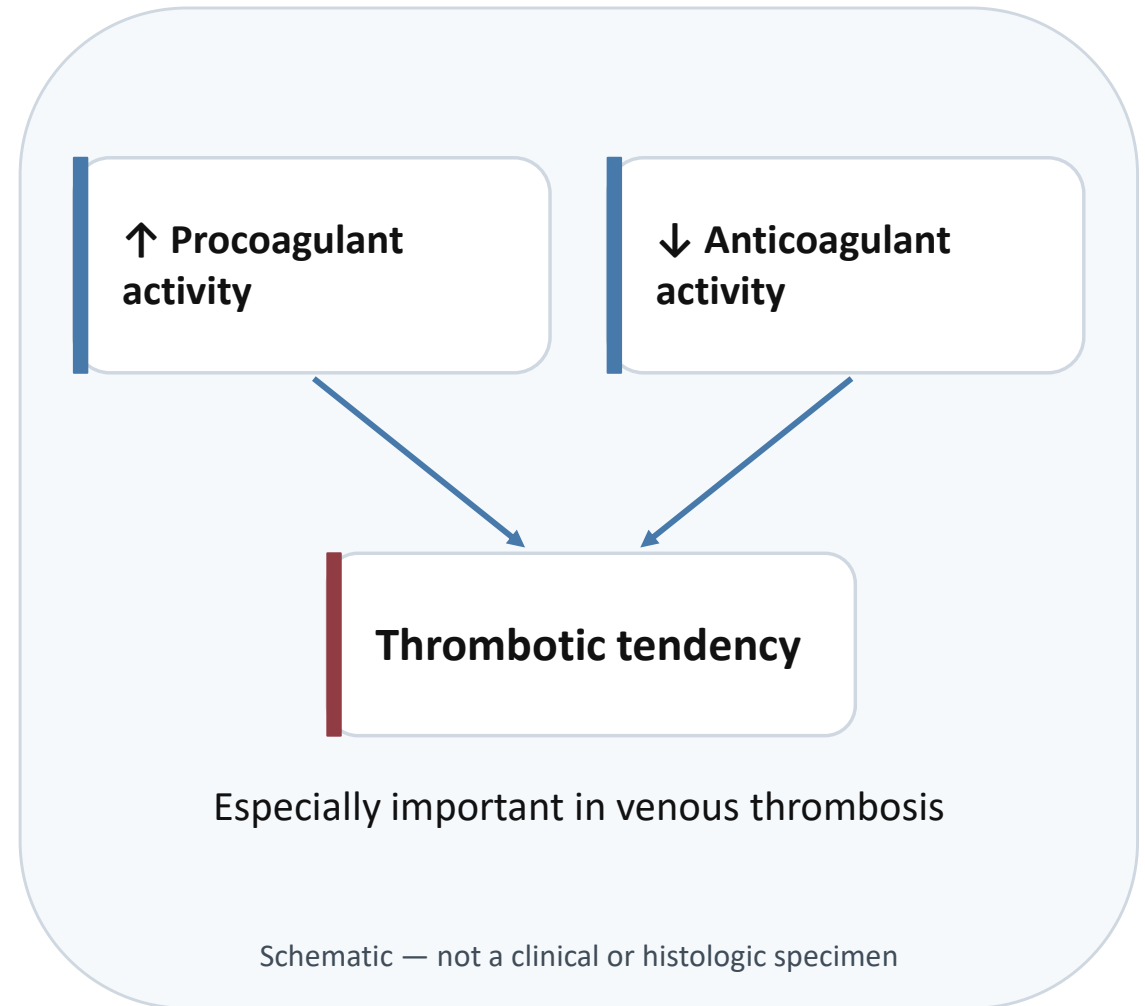
Viscosity and abnormal erythrocytes also disturb flow

Polycythemia vera	Sickle cell disease
Increased viscosity increases flow resistance	Deformed red cells impede small-vessel transit
Small-vessel stasis contributes to risk	Local stasis contributes to thrombosis

Contrast the mechanism, not merely the color or appearance.

Hypercoagulability is an increased tendency of blood to clot

- It often results from abnormalities in coagulation factors or their regulation.
- It is especially important in venous thrombosis.
- Inherited and acquired contributors frequently interact.

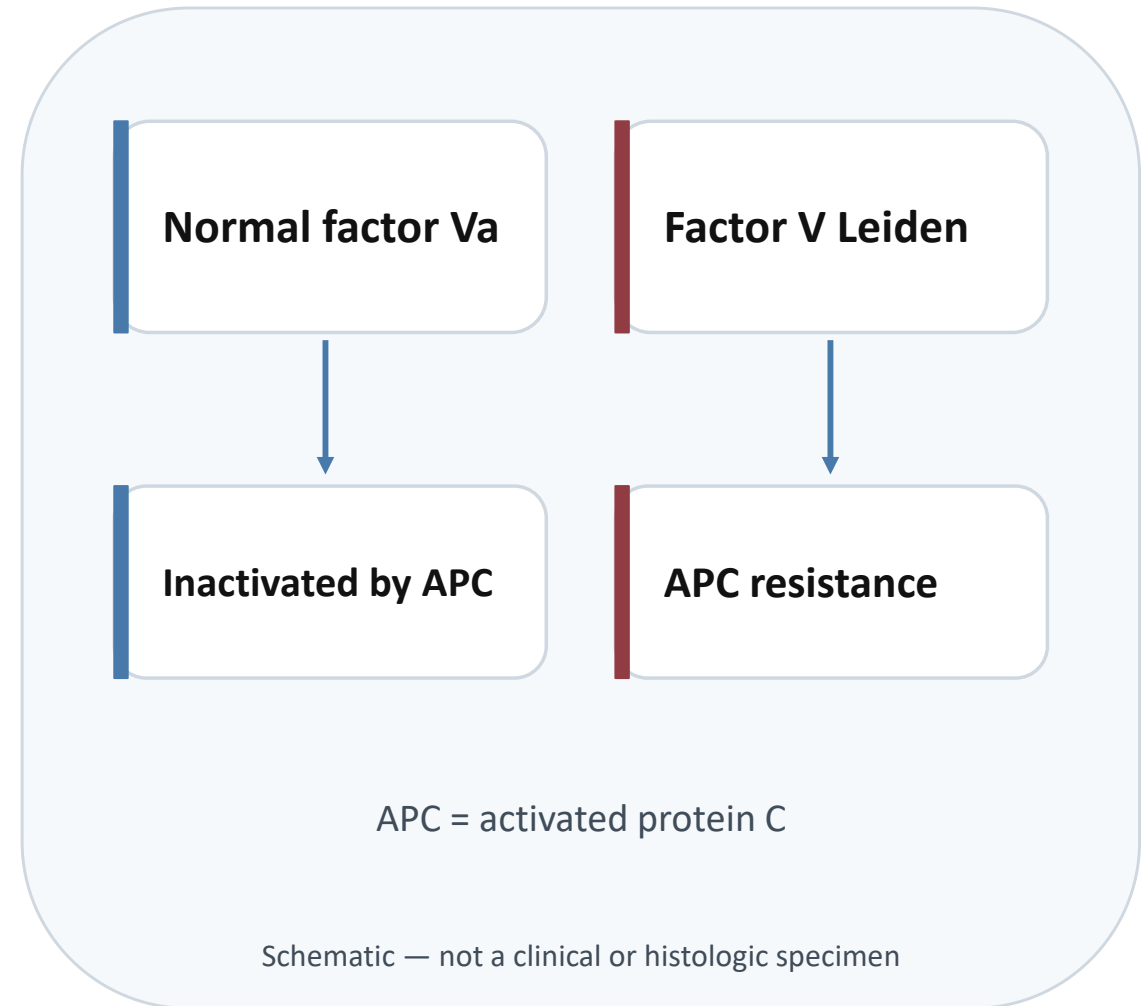


Thrombophilias can be inherited or acquired

Primary (genetic)	Secondary (acquired)
Factor V Leiden	Immobilization; tissue injury
Prothrombin G20210A variant	Malignancy; pregnancy/postpartum
Antithrombin, protein C, protein S deficiency	APS; HIT; cardiac disease

Factor V Leiden impairs physiologic factor V inactivation

- A variant of factor V resists cleavage by activated protein C.
- The impaired negative-feedback pathway permits increased thrombin generation.
- This produces a predisposition to venous thromboembolism.

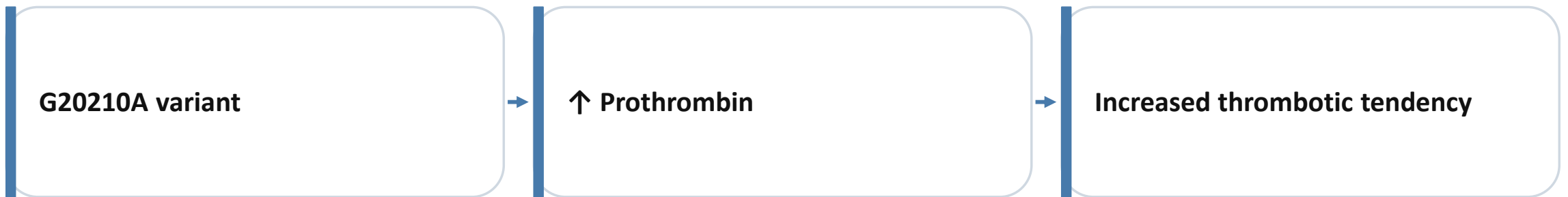


Factor V Leiden has dose-dependent clinical implications

- Heterozygous and homozygous carriers differ in thrombotic risk.
- Not all carriers develop thrombosis.
- Clinical expression is strongly modified by acquired exposures.
- Risk should not be inferred from genotype alone.

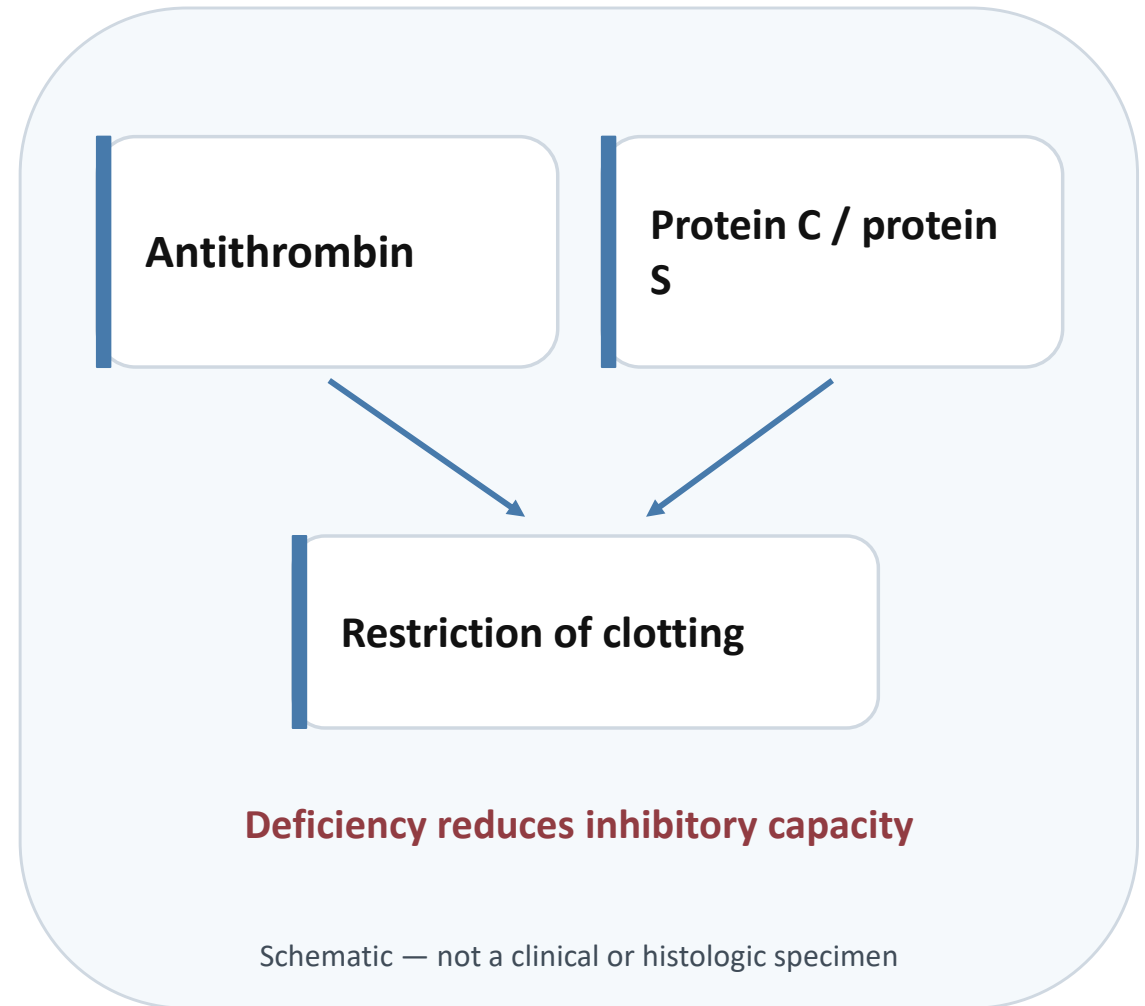
Prothrombin G20210A increases prothrombin availability

- The variant involves the noncoding 3' region of the prothrombin gene.
- Prothrombin expression is increased.
- Greater substrate availability contributes to venous thrombosis risk.



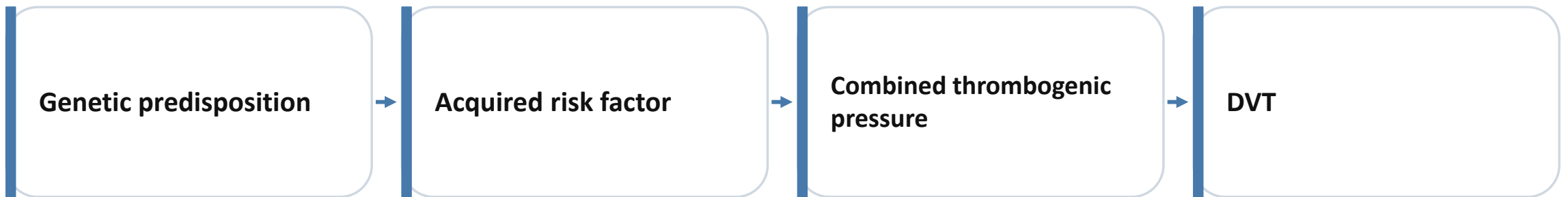
Loss of endogenous anticoagulants predisposes to thrombosis

- Antithrombin restrains activated coagulation proteases.
- Protein C and protein S regulate activated cofactors Va and VIIIa.
- Deficiencies can present as early or recurrent venous thromboembolism.



Inherited thrombophilia acts together with acquired triggers

- A thrombophilic genotype may remain clinically silent for years.
- Bed rest, pregnancy, or other exposures can add venous stasis or hypercoagulability.
- Combined factors may cross the threshold for a thrombotic event.

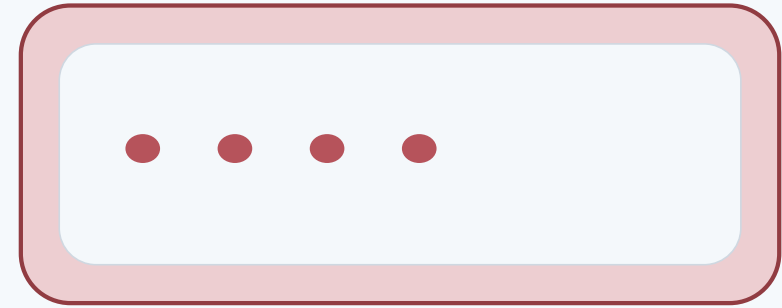


Acquired thrombophilia is usually multifactorial

- Some conditions act mainly through impaired venous return or local injury.
- Hormonal changes may increase procoagulant and reduce anticoagulant synthesis.
- Neoplasms can release thrombogenic substances and induce inflammation.
- Age, smoking, and obesity contribute to overall risk.

Prolonged immobilization removes the leg-muscle pump

- Leg-muscle contraction normally assists venous return.
- Bed rest and prolonged inactivity produce venous stasis.
- Prolonged stasis favors clot formation in lower-limb deep veins.



Reduced muscle contraction → slow venous return

Schematic — not a clinical or histologic specimen

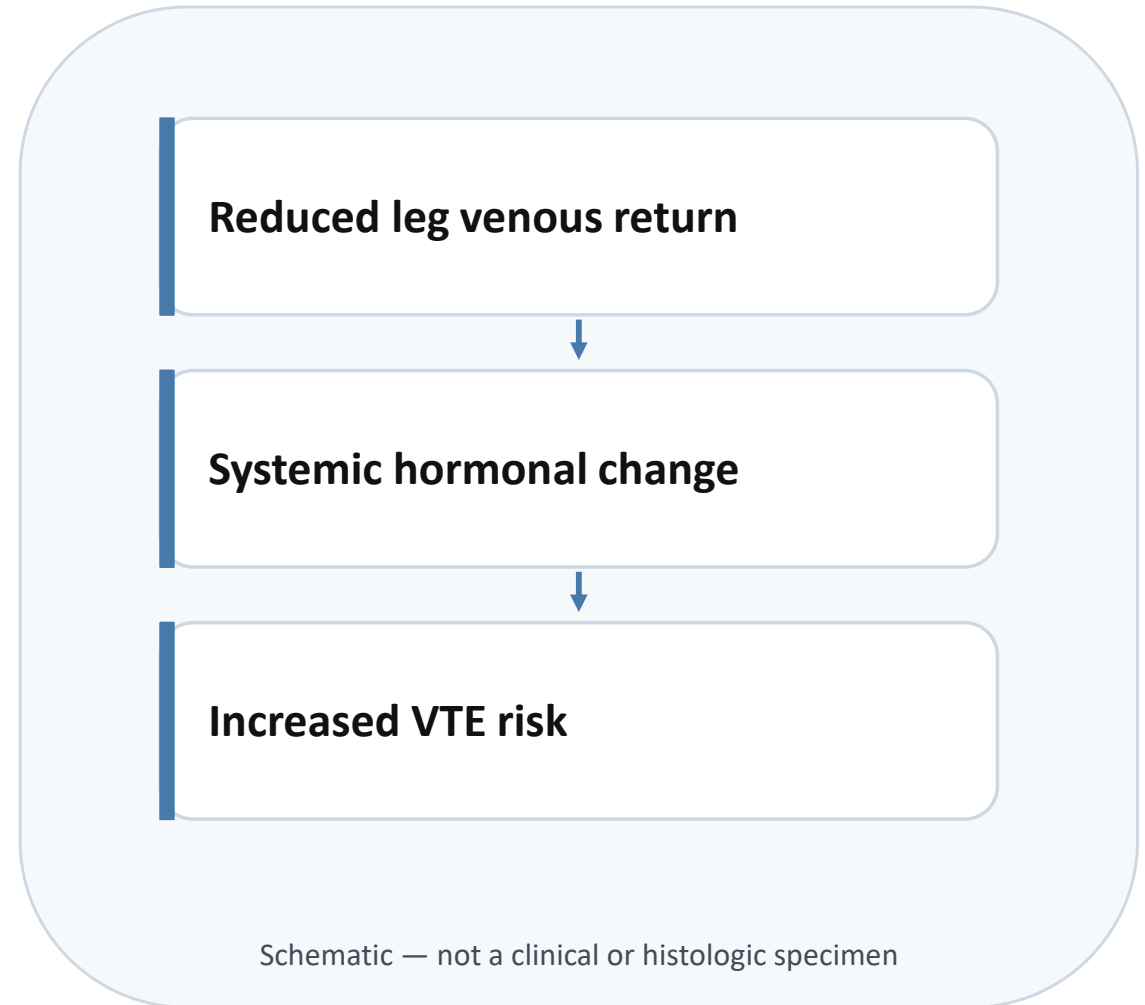
Trauma, surgery, and burns activate multiple elements of the triad

- Tissue injury exposes or releases procoagulant factors.
- Vascular injury and immobility add further prothrombotic pressures.
- Inflammatory responses may compound the local and systemic effects.



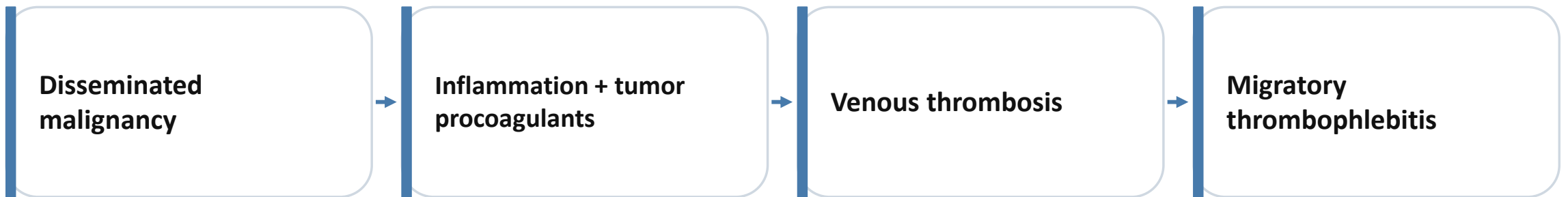
Pregnancy creates both local and systemic thrombotic risk

- Venous return from the lower extremities may be impaired.
- Hormonal changes favor a systemic hypercoagulable state.
- Thrombosis risk extends into the postpartum period.



Malignancy may produce a systemic procoagulant state

- Tumor-associated inflammation supports coagulation activation.
- Tumor tissue factor and mucin contribute to thrombogenic signaling.
- Migratory thrombophlebitis is a classic manifestation (Trousseau syndrome).

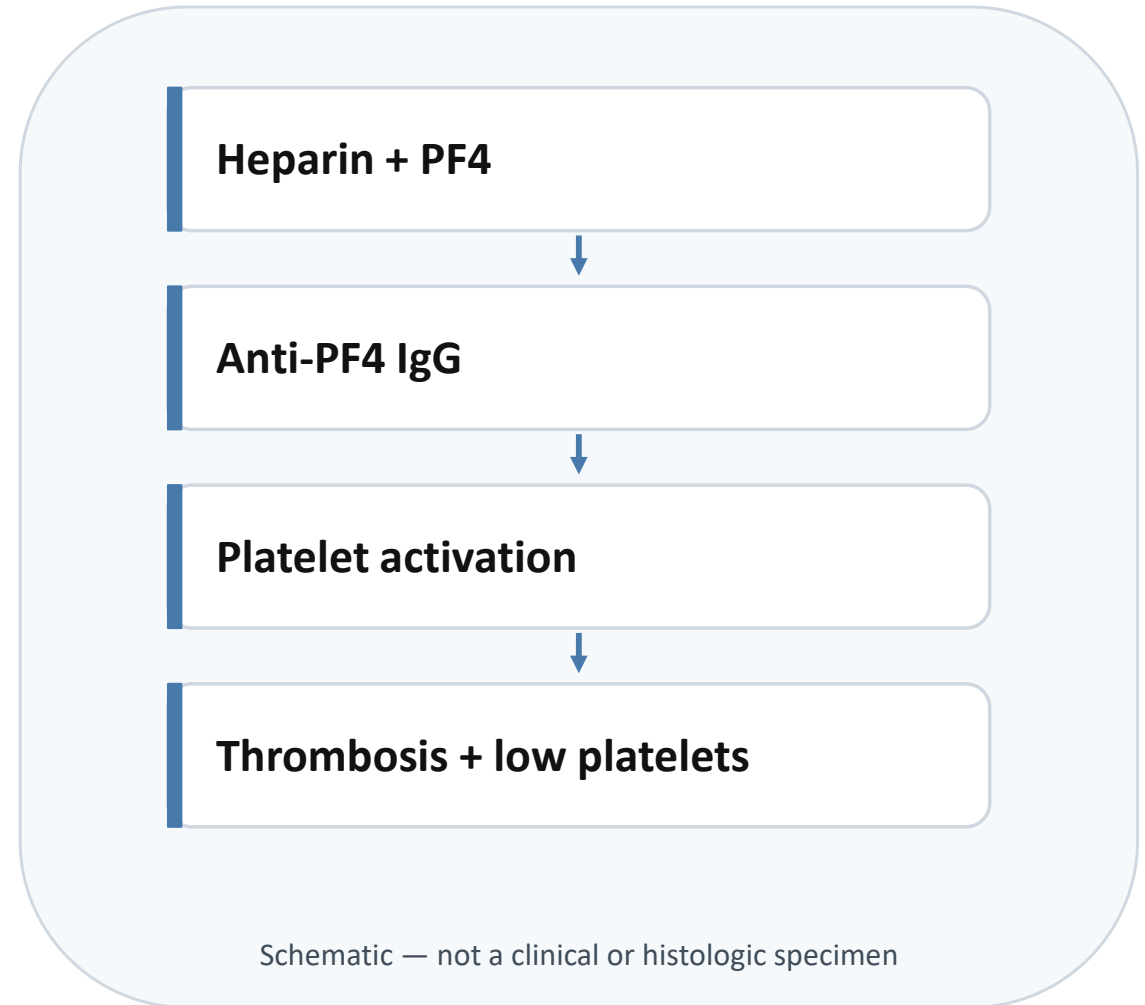


Heparin-induced thrombocytopenia is paradoxically prothrombotic

- Immune complexes recognize platelet factor 4 (PF4) in association with heparin.
- Antibody-mediated platelet activation generates a procoagulant state.
- Despite falling platelets, thrombosis can affect veins or arteries.
- HIT is not merely a low platelet count.

HIT: PF4 antibodies link platelet activation and clearance

- Heparin forms complexes with released PF4.
- IgG recognizing PF4-containing complexes triggers platelet Fc-receptor activation.
- Platelet consumption and thrombin generation occur concurrently.



HIT illustrates thrombosis in the setting of thrombocytopenia

Platelet count	Thrombotic potential
Falls owing partly to immune-mediated clearance	Rises because remaining platelets become activated
Does not quantify the entire clinical danger	Veins and arteries can both be affected

Contrast the mechanism, not merely the color or appearance.

Vaccine-induced thrombotic thrombocytopenia also targets PF4

- VITT after certain adenoviral-vector COVID-19 vaccines.
- Anti-PF4 antibodies can be present without heparin exposure.
- Reported thrombi include cerebral venous sinuses and splanchnic vessels.
- This is distinct from ordinary post-vaccination symptoms.

Antiphospholipid syndrome links autoimmunity to thrombosis

- APS involves antiphospholipid autoantibodies and characteristic clinical disease.
- Venous or arterial thrombosis and obstetric complications are prominent.
- The syndrome may occur with or without systemic autoimmune disease.

Antiphospholipid antibodies



Cellular activation



Thrombosis / pregnancy morbidity

Schematic — not a clinical or histologic specimen

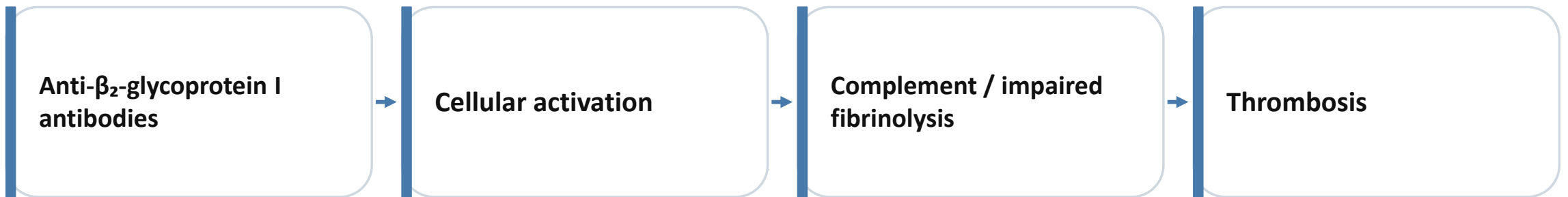
APS may be primary or associated with autoimmune disease

Primary APS	Secondary APS
No accompanying established systemic autoimmune disease	Occurs with autoimmune disease, often SLE
Thrombotic / pregnancy manifestations dominate	Similar APS manifestations plus background autoimmune disease

Contrast the mechanism, not merely the color or appearance.

Anti- β_2 -glycoprotein I participates in APS pathogenesis

- Relevant antibodies recognize phospholipid-associated proteins.
- Endothelial cells, monocytes, neutrophils, and platelets may become activated.
- Complement activation and impaired fibrinolysis further promote thrombosis.

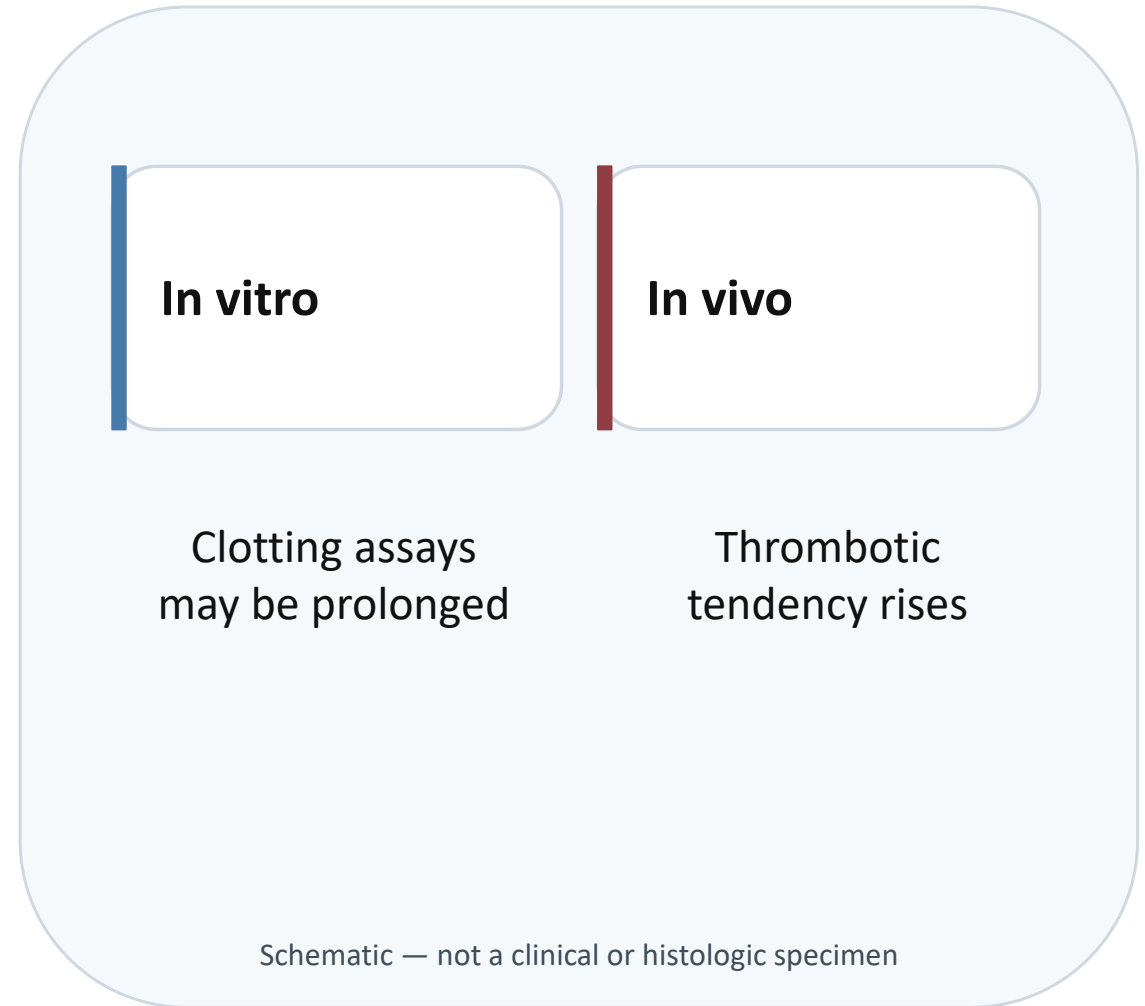


APS pregnancy morbidity is not explained solely by clotting

- Early fetal loss is linked to antibody effects on trophoblast differentiation and placentation.
- Later pregnancy complications may involve trophoblast injury and inflammation.
- A purely vascular-occlusion explanation is therefore inadequate.

The lupus anticoagulant creates an in vitro paradox

- Some antiphospholipid antibodies prolong phospholipid-dependent clotting assays in vitro.
- In patients they are associated with hypercoagulability and thrombosis.
- A prolonged aPTT in this setting does not imply protection from clot formation.

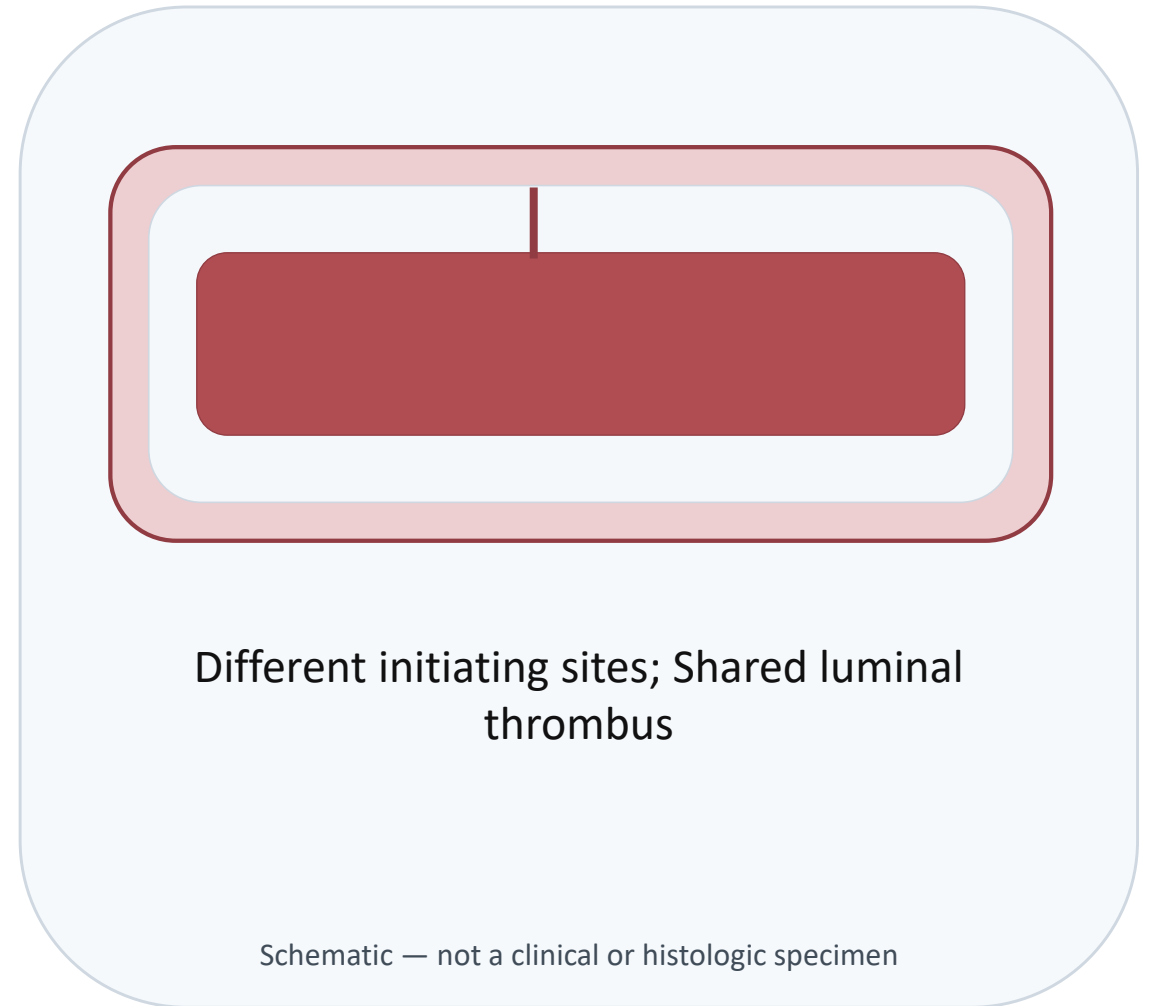


APS clinical manifestations depend on vascular territory

- Recurrent venous thrombosis or pulmonary thromboembolism.
- Stroke, bowel infarction, and renal vascular complications.
- Valvular vegetations and thrombocytopenia.
- Recurrent pregnancy loss or other placental complications.

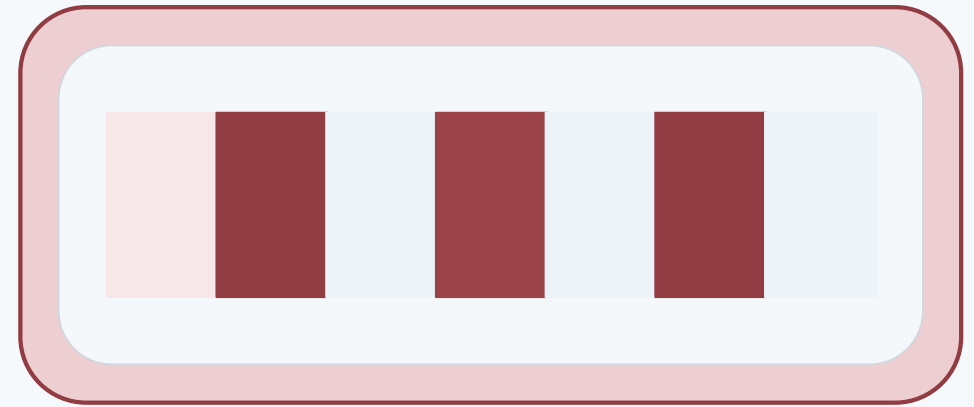
Thrombus morphology depends on its site of formation

- Cardiac and arterial thrombi often begin at injury or turbulence.
- Venous thrombi frequently begin where blood flow stagnates.
- A thrombus is typically attached to vascular or endocardial surfaces.



Lines of Zahn indicate layered deposition during blood flow

- Pale platelet/fibrin layers alternate with darker erythrocyte-rich layers.
- The laminated architecture is evidence of antemortem formation under flow.
- Layering may be evident grossly or microscopically.

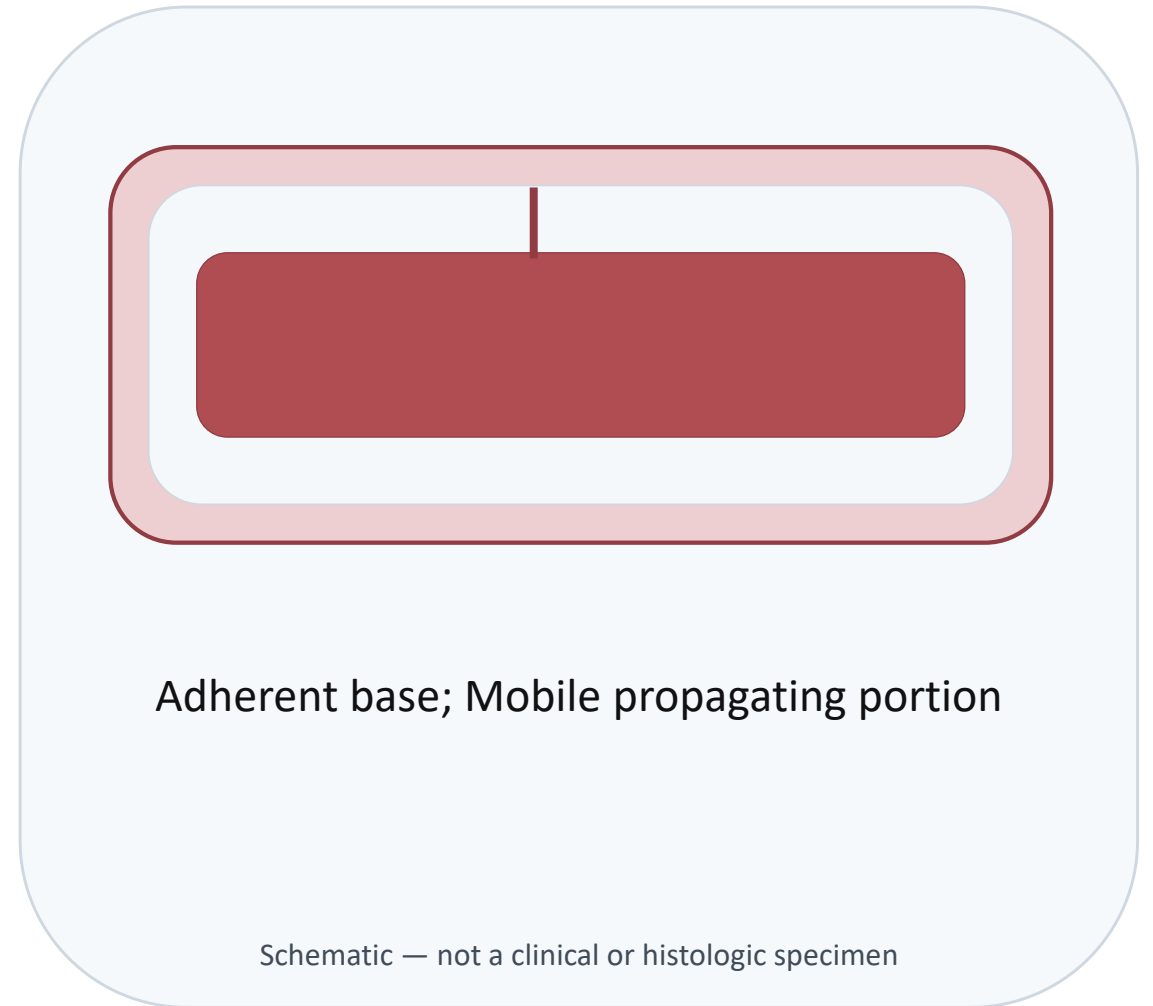


Alternating platelet/fibrin and red-cell layers

Schematic — not a clinical or histologic specimen

Thrombus attachment is a useful morphologic clue

- The point of origin is usually firmly attached to the vessel wall.
- The extending portion may be relatively loosely attached.
- This explains why propagation can increase embolic potential.



Arterial and venous thrombi grow differently

Arterial thrombus

Extends retrograde from initiation site

Growth is commonly toward the heart

Often begins at endothelial injury

Venous thrombus

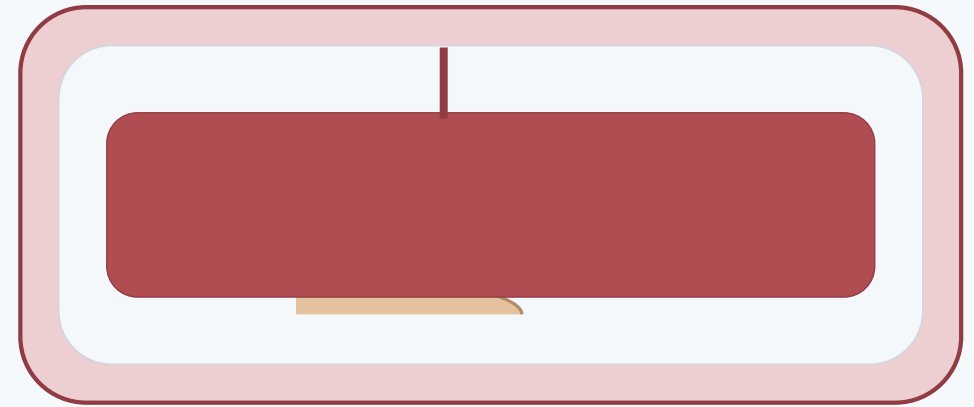
Extends in direction of blood flow

Growth is commonly toward the heart

Often begins with stasis

Arterial thrombi are often platelet-rich and occlusive

- Frequently superimposed on disrupted atherosclerotic lesions.
- Contain platelets, fibrin, trapped red cells, and leukocytes.
- Coronary and cerebral arterial occlusion can rapidly injure vital tissues.

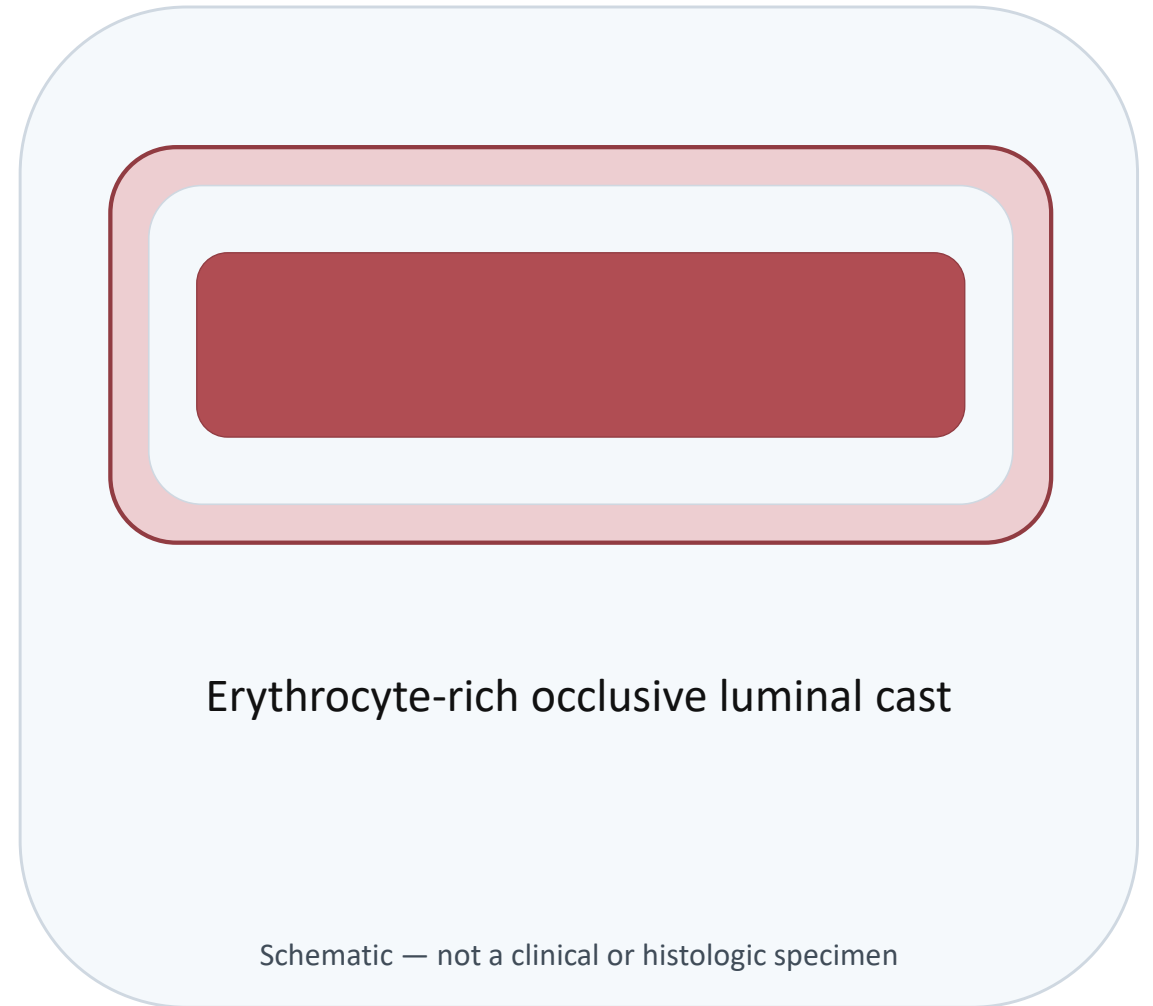


Platelets + fibrin; Often associated with plaque

Schematic — not a clinical or histologic specimen

Venous thrombi commonly form red, occlusive casts

- Slow circulation permits abundant red-cell trapping.
- The thrombus often forms a long cast of the affected venous lumen.
- Focal attachment to the vein wall helps distinguish it from a postmortem clot.



Arterial and venous thrombi: Morphology at a glance

Arterial / cardiac	Venous
Platelet/fibrin prominent	More erythrocytes enmeshed
Frequently friable and occlusive	Usually occlusive long luminal cast
Injury and flow disturbance prominent	Stasis prominent
Ischemic tissue injury often dominant	Congestion and pulmonary embolic risk dominant

Postmortem clots can resemble venous thrombi

Antemortem thrombus	Postmortem clot
Attached at least focally to vessel wall	Usually not firmly attached
May show lines of Zahn	Typically unlaminated
Firm / friable organization varies	Gelatinous “currant jelly” dependent portion
Produced under flowing blood	Can show yellow “chicken-fat” supernatant

Cardiac and aortic mural thrombi reflect local flow defects

- Mural thrombi attach to chamber or aortic walls without necessarily filling the lumen.
- Dyskinesia, myocardial scar, and endocardial injury predispose cardiac sites.
- Aortic atherosclerosis and aneurysm are typical structural substrates.



Adherent mass projecting into cavity or lumen

Schematic — not a clinical or histologic specimen

Valvular vegetations can be infected or sterile

Infective vegetations	Sterile vegetations
Bacterial/fungal colonization on damaged or infected valve	Nonbacterial thrombotic endocarditis with hypercoagulability
Valve damage with platelet/fibrin deposits	Libman–Sacks lesions can occur with SLE

Contrast the mechanism, not merely the color or appearance.

Superficial venous thrombosis mainly produces local effects

- Commonly involves saphenous veins associated with varicosities.
- May produce pain, tenderness, swelling, and congestion.
- Embolization is relatively uncommon compared with proximal DVT.
- Venous drainage impairment can predispose to skin changes and ulceration.

Proximal deep vein thrombosis carries major embolic risk

- Thrombi in popliteal, femoral, or iliac veins may embolize to the lungs.
- DVT can cause pain or swelling, but collateral veins may mask obstruction.
- Absence of symptoms does not exclude clinically important DVT.

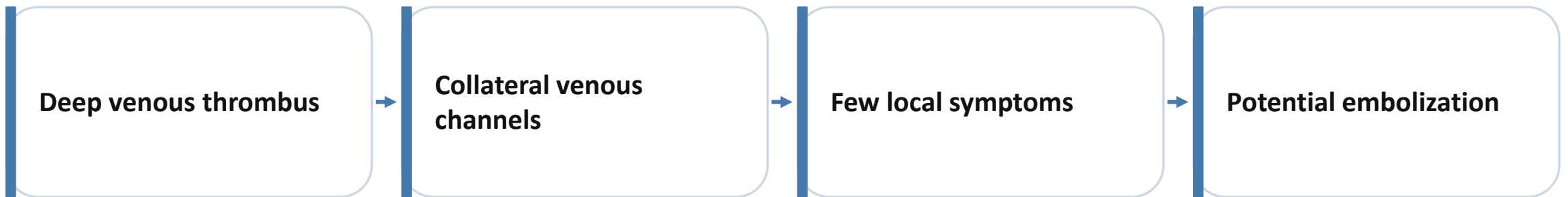


Deep venous obstruction; Possible embolus source

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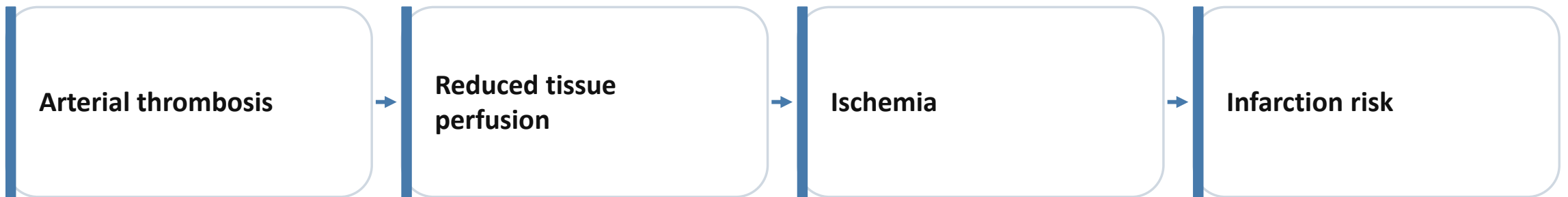
Why a deep venous thrombus can be clinically silent

- Venous collaterals may maintain partial return around an obstructed segment.
- Pain and edema are not obligatory.
- The first recognized complication may be pulmonary thromboembolism.



Arterial occlusion threatens downstream tissue perfusion

- A local arterial thrombus reduces oxygen delivery distal to its site.
- Coronary or cerebral vessel occlusion has serious consequences.
- Arterial fragments can also embolize and produce infarction.



Thrombus fate includes four principal pathways

- Propagation: Growth through further platelet and fibrin deposition.
- Embolization: Detachment and transport to distant vessels.
- Dissolution: Fibrinolytic degradation, particularly in recent thrombi.
- Organization/recanalization: Cellular ingrowth and partial restoration of flow.

Propagation

Embolization

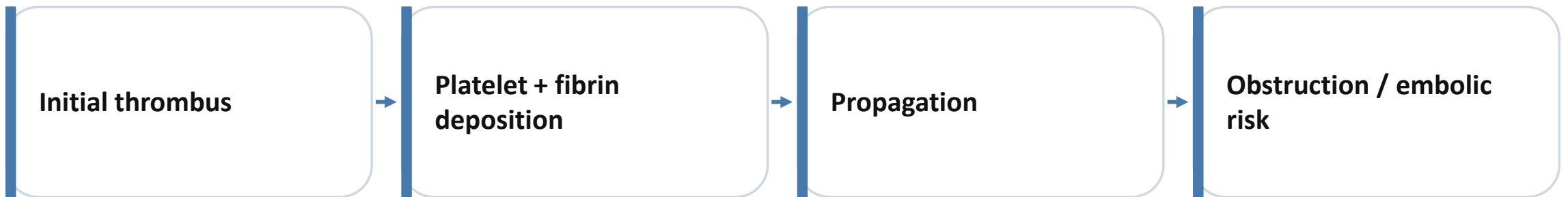
Dissolution

**Organization /
recanalization**

Schematic — not a clinical or histologic specimen

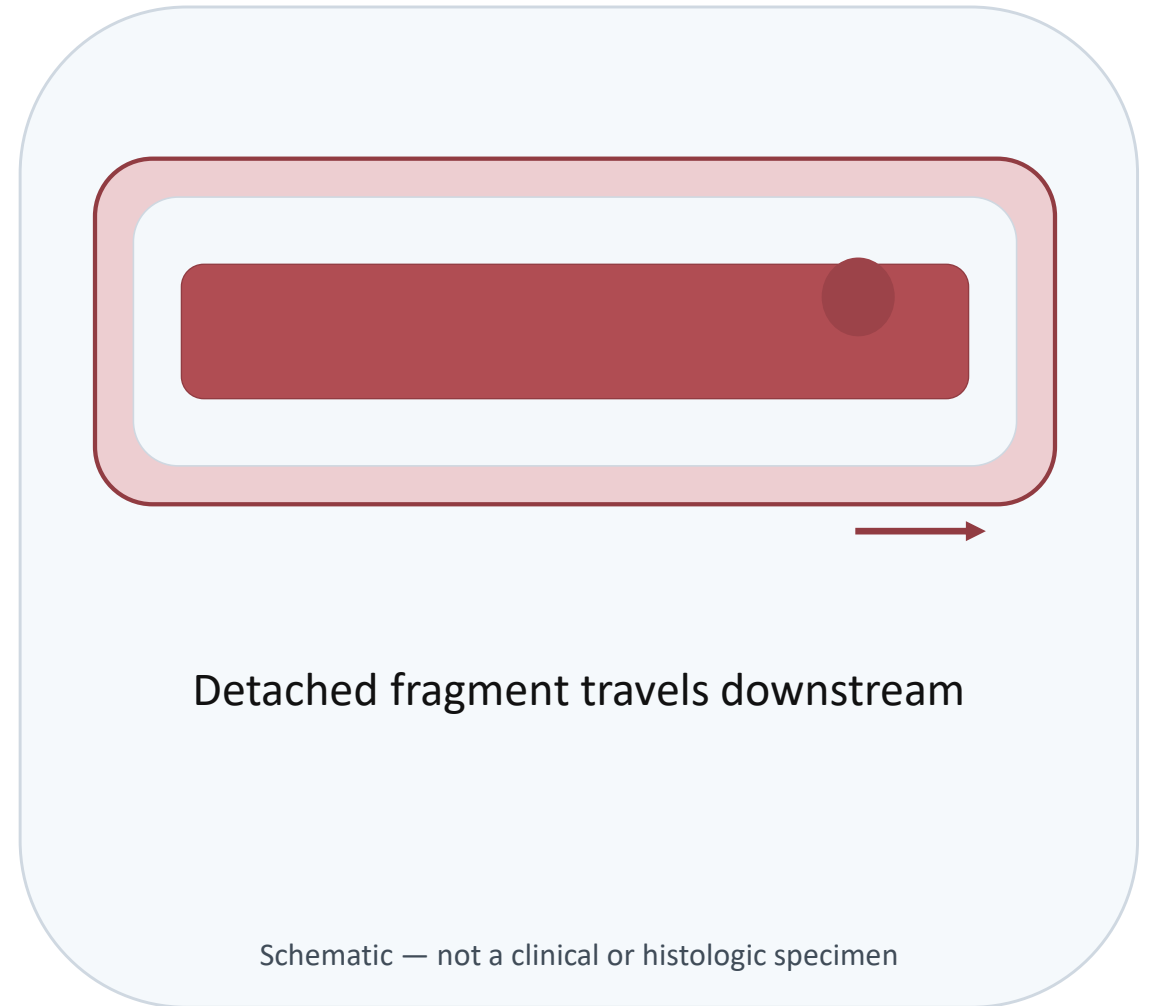
Propagation increases mass and risk of obstruction

- Additional platelets and fibrin accumulate on the initial thrombus.
- The extension may have a weak attachment to the original site.
- Larger clot burden raises the risk of occlusion or fragmentation.



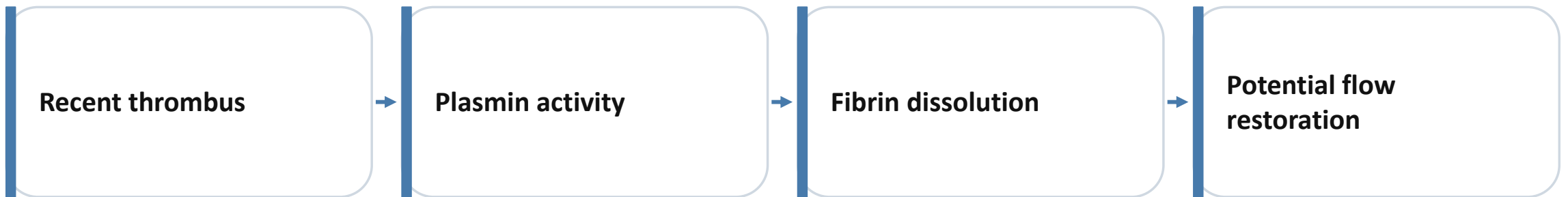
Embolization converts a local lesion into a distant one

- A thrombus fragment breaks loose from its site of formation.
- It travels with the bloodstream until obstructed by a smaller vessel.
- Resulting dysfunction depends on embolus size and destination.



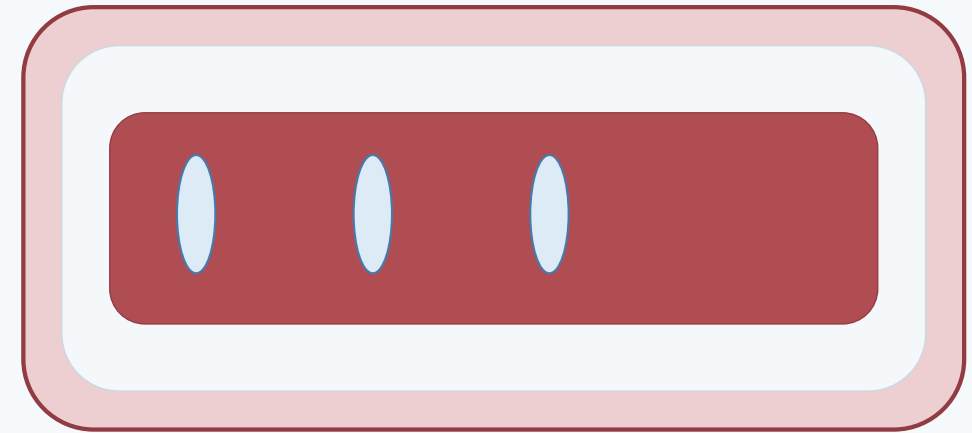
Recent thrombi are more susceptible to dissolution

- The fibrinolytic system can remove new fibrin-rich material.
- Older thrombi become more cross-linked and resistant to lysis.
- This temporal difference is relevant to thrombolytic treatment rationale.



Organization replaces thrombus with fibrovascular tissue

- Endothelium, smooth muscle cells, and fibroblasts grow into thrombus.
- Connective tissue gradually incorporates the mass into the vascular wall.
- The original clot may become a residual fibrous lesion.

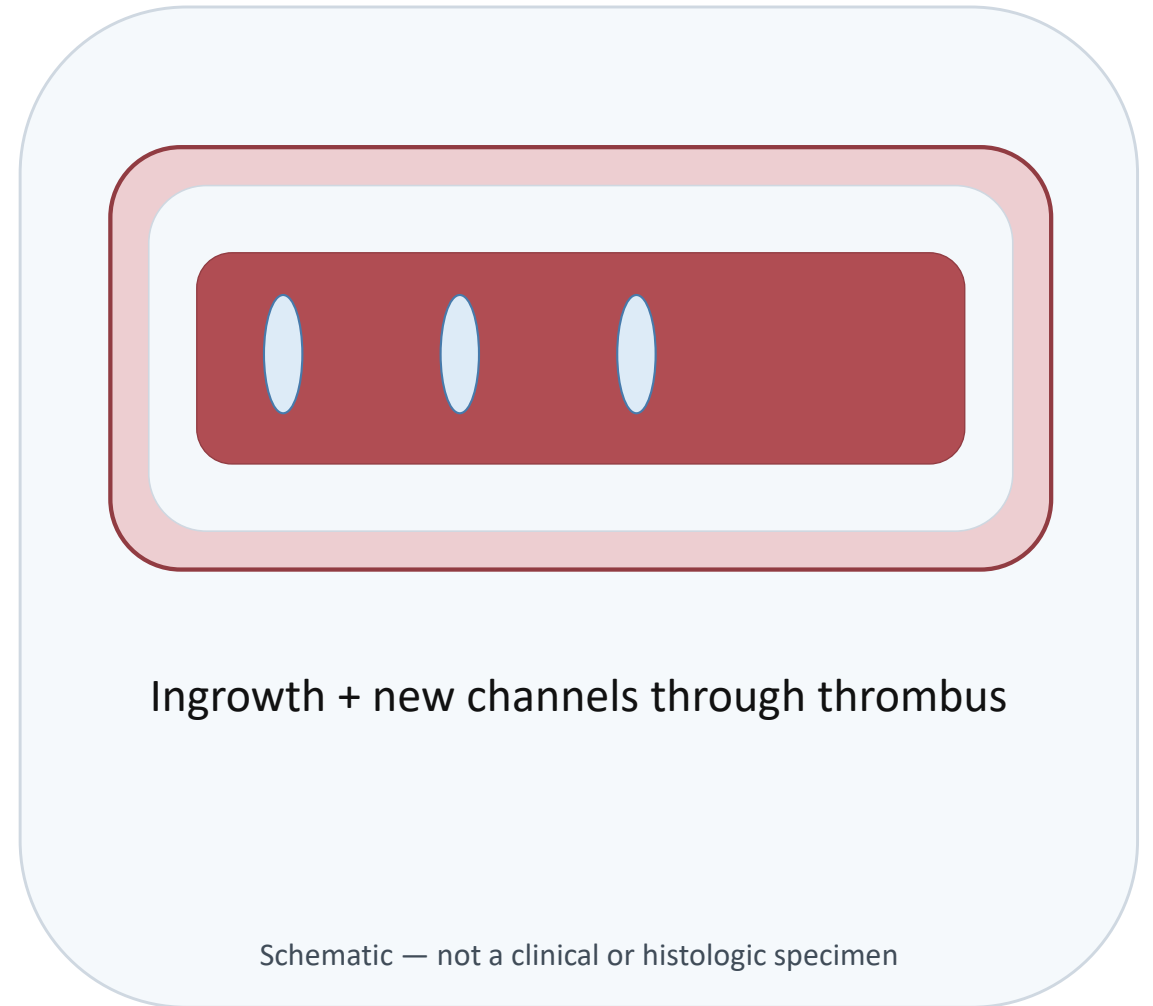


Fibrovascular ingrowth forms organized tissue

Schematic — not a clinical or histologic specimen

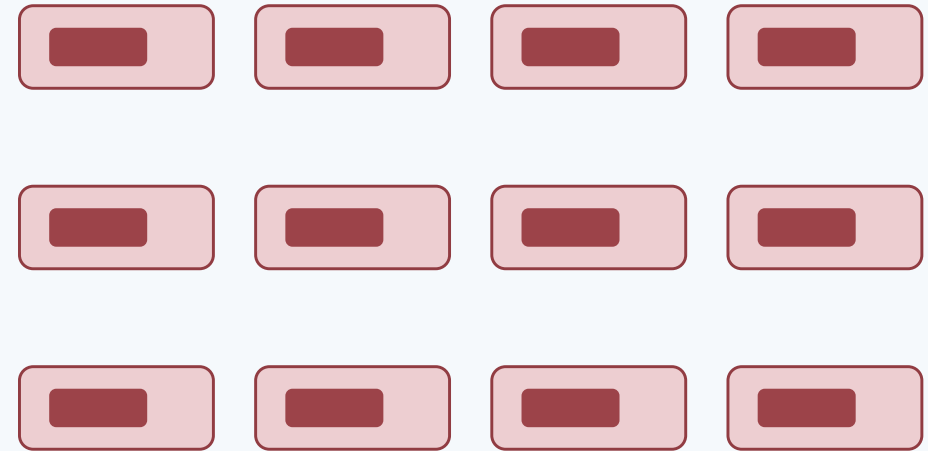
Recanalization creates new channels through an organized clot

- Small capillary channels form through organized thrombotic tissue.
- These channels restore luminal continuity to a variable degree.
- Recanalization does not necessarily restore a normal vascular caliber.



DIC combines diffuse microvascular thrombosis and bleeding

- Systemic thrombin activation forms numerous microvascular thrombi.
- Diffuse occlusion produces tissue hypoperfusion and organ injury.
- Platelet and coagulation-factor consumption can cause severe hemorrhage.

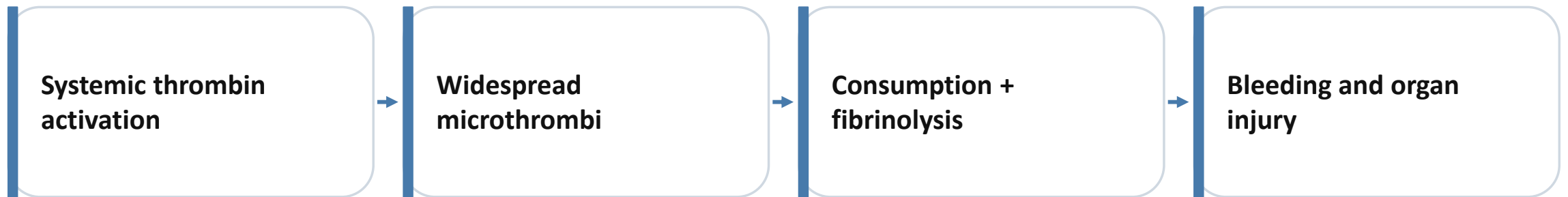


Diffuse microvascular clotting

Schematic — not a clinical or histologic specimen

DIC demonstrates that coagulation and bleeding can coexist

- Pathologic systemic coagulation is not effective localized hemostasis.
- Consumption depletes platelets and coagulation factors.
- Fibrinolysis and organ dysfunction complicate the clinical course.



Case: Postoperative leg swelling and immobilization

A patient has prolonged bed rest after major surgery and develops unilateral leg swelling.

- Which components of Virchow triad are activated, and why?
- What important complication should be anticipated?

Case analysis: Venous thrombosis is multifactorial

- Reduced calf-muscle pumping favors venous stasis.
- Operative tissue/vascular injury adds a procoagulant stimulus.
- A proximal deep vein thrombus is a potential source of pulmonary emboli.

Case: Arterial thrombosis over a disrupted plaque

A patient develops abrupt myocardial ischemia in the setting of advanced coronary atherosclerosis.

- Why do platelet adhesion and endothelial injury dominate?
- How does disturbed arterial flow augment the event?

Case analysis: Plaque injury plus high-shear platelet activation

- Plaque disruption exposes collagen, vWF, and tissue factor.
- High shear favors platelet-dependent thrombus initiation.
- Turbulence and coagulation generate an increasingly occlusive lesion.

Case: Low platelets and new thrombosis after heparin

A hospitalized patient exposed to heparin develops falling platelets and a new thrombosis.

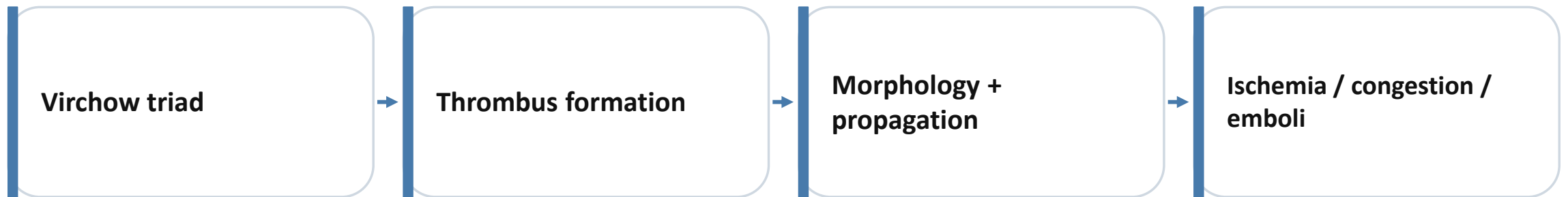
- Why does thrombocytopenia not imply reduced thrombotic risk?
- What immune target is characteristic?

Case analysis: Immune platelet activation in HIT

- Anti-PF4/heparin antibodies activate platelets through Fc receptors.
- Activated platelets promote coagulation and are also cleared from blood.
- HIT therefore produces the dangerous combination of thrombocytopenia and thrombosis.

Integrated mechanism–morphology–consequence map

- Injury, abnormal flow, and hypercoagulability initiate a thrombus.
- Hemodynamics shape platelet-rich arterial versus red-cell-rich venous morphology.
- Obstruction, embolization, and organization govern clinical outcomes.



Thrombosis: High-yield synthesis

- Virchow triad is a causal framework, not three mutually exclusive diagnoses.
- Arterial disease emphasizes endothelial injury, disturbed flow, and platelets.
- Venous disease emphasizes stasis and hypercoagulability.
- Attachment, lamination, location, and fate explain clinical behavior.

References

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 4, pp. 102–114.
- For extended clinicopathologic context: cardiovascular chapters addressing blood vessels and the heart.