

Hypercoagulability

Inherited and acquired prothrombotic states

Mechanisms • Clinical consequences • Pathologic reasoning

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Learning objectives

- Locate hypercoagulability within Virchow's triad and explain its importance in venous thrombosis.
- Compare common inherited variants with deficiencies of natural anticoagulants.
- Classify major acquired prothrombotic states and explain why risk factors interact.
- Trace antibody-mediated thrombosis in HIT, VITT and antiphospholipid syndrome.
- Apply mechanistic reasoning to illustrative clinical presentations.

An increased tendency to form clots

Core definition

Blood has an abnormally high propensity to clot.

Typical substrate

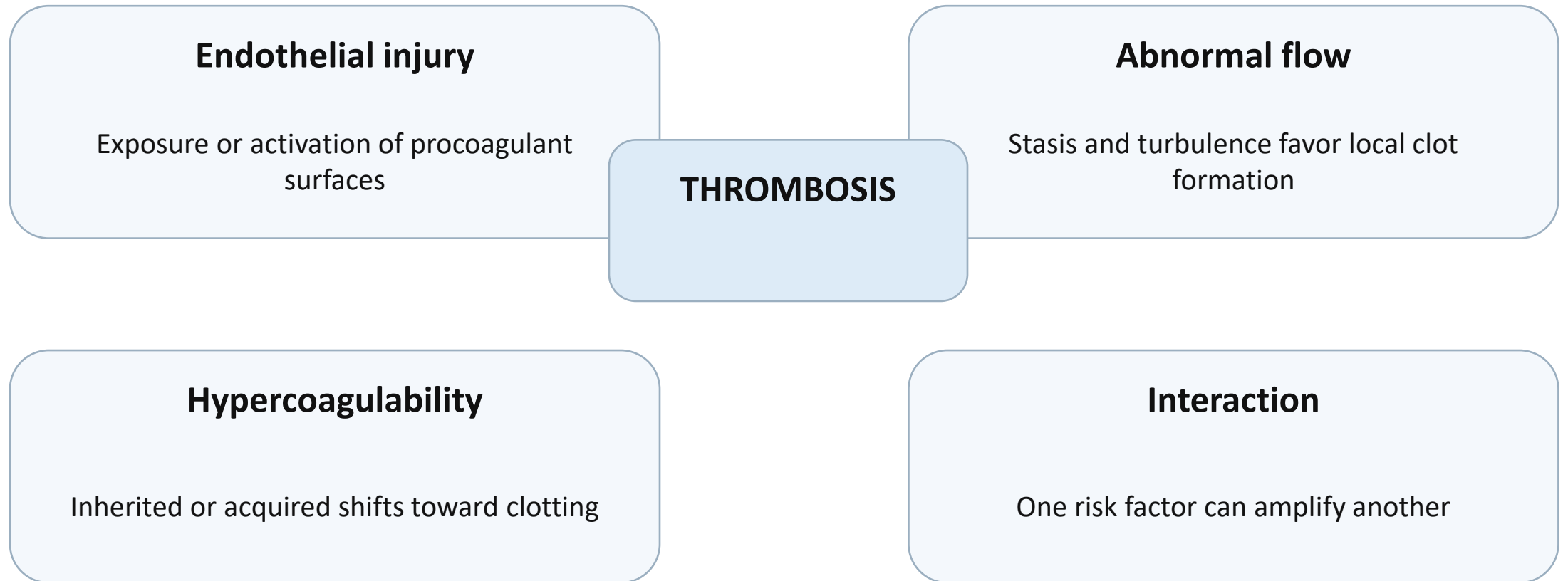
Altered coagulation factors or loss of anticoagulant control.

Clinical expression

Venous thrombosis is especially important.

Hypercoagulability is a predisposition; Thrombosis is its possible event.

Virchow's triad: Interacting contributors



Why hypercoagulability matters in venous disease

Venous circulation

- Stasis facilitates persistence of activated factors.
- Many inherited thrombophilias present with deep venous thrombosis.
- Venous thrombi may embolize to pulmonary arteries.

Arterial / cardiac circulation

- Endothelial damage and altered flow often dominate.
- Platelet activation is prominent at high shear.
- Selected disorders, including APS and HIT, affect arteries too.

Normal anticoagulant restraint

Activated coagulation

Clotting factors generate thrombin.



Natural inhibitors

Protein C, protein S and antithrombin restrain the cascade.



Hemostatic balance

Clot formation remains localized and regulated.

Hypercoagulability results when procoagulant drive increases or restraint is weakened.

Two broad etiologic categories

Primary (genetic)

- Variants in coagulation-factor genes.
- Deficiencies of natural anticoagulants.
- Rare defects of fibrinolysis or homocysteine metabolism.

Secondary (acquired)

- Immobilization, injury or abnormal flow.
- Estrogen exposure and disseminated cancer.
- Immune-mediated states: HIT and APS.

Genotype is not identical to thrombosis

- Carriage of a thrombophilic variant confers susceptibility, not inevitable disease.
- A common heterozygous variant may remain clinically silent throughout life.
- Homozygosity or combined variants can impart greater thrombotic risk.
- Acquired exposures may convert predisposition into a clinical event.

Risk is conditional on genotype, coexisting disorders and exposure.

Inherited hypercoagulability: Mechanism map

More procoagulant activity

Factor V Leiden; Prothrombin G20210A; Increased clotting factors

Less inhibition

Antithrombin, protein C or protein S deficiencies

Less effective clearance

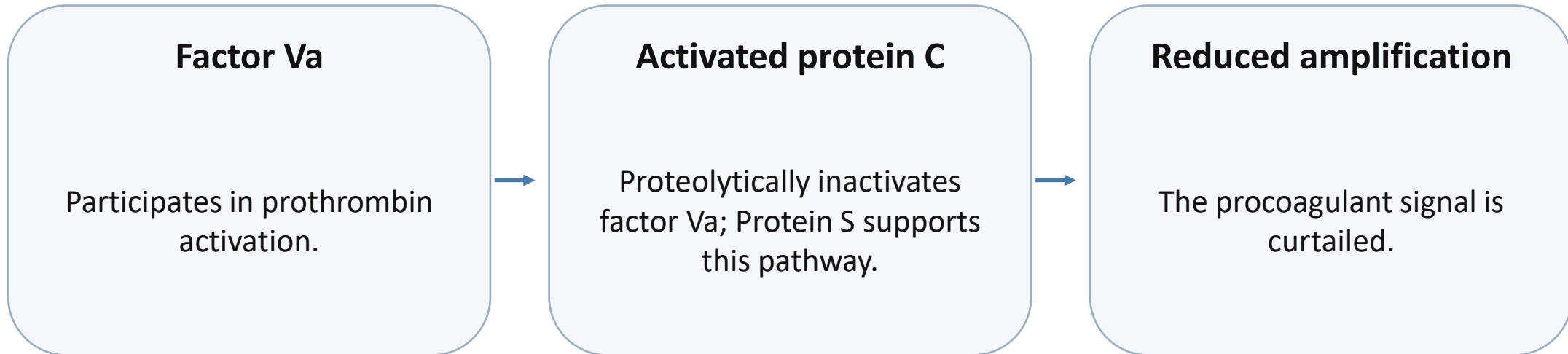
Rare fibrinolytic abnormalities

Different molecular defects converge on excessive thrombus formation.

Genetic causes: Classification in the source

Source category	Representative abnormalities
Common	Factor V Leiden; Prothrombin G20210A
Common	Increased factors VIII, IX, XI or fibrinogen (genetic basis uncertain)
Rare	Antithrombin, protein C or protein S deficiency
Very rare	Fibrinolysis defects; Homozygous homocystinuria

Activated protein C normally limits factor V



This inhibitory checkpoint is central to understanding factor V Leiden.

Factor V Leiden: Resistance to inactivation

F5 variant

Arg506Gln substitution in factor V.



Protein C resistance

Factor V is less susceptible to cleavage and inactivation.



Persistent procoagulant effect

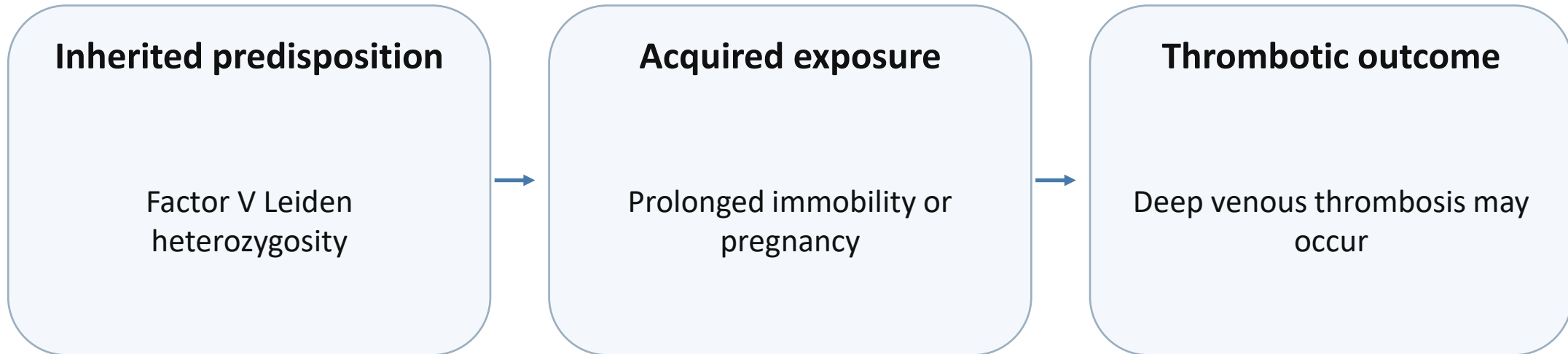
Natural antithrombotic regulation is reduced.

The source identifies this as a common inherited cause of venous thrombosis.

Factor V Leiden: Risk is genotype dependent

- Heterozygosity increases the relative risk of venous thrombosis.
- Homozygous carriers have a greater susceptibility than heterozygotes.
- Most otherwise healthy carriers do not develop a thrombotic event.
- Interpret family or genetic findings alongside provoking circumstances.

Factor V Leiden and a provoking exposure

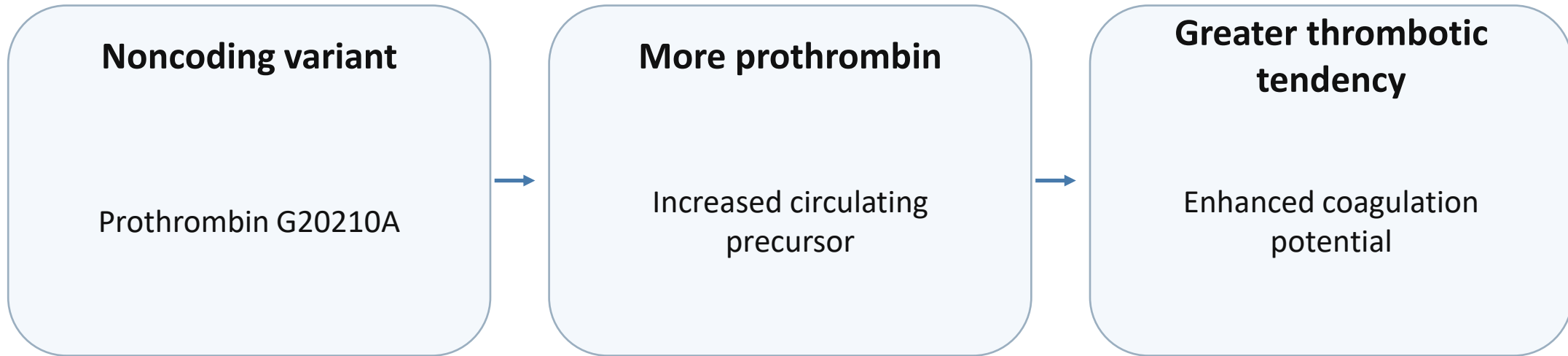


The inherited variant and acquired environment can cooperate rather than act separately.

Prothrombin G20210A: The gene alteration

- A single-nucleotide variant lies in the 3' untranslated region of the prothrombin gene.
- The alteration is associated with increased circulating prothrombin.
- Elevated substrate availability favors thrombin generation.
- It is another common inherited cause of venous thrombophilia.

Prothrombin variant: Mechanistic sequence



The prothrombin variant differs mechanistically from factor V Leiden.

Two common inherited variants

Factor V Leiden

- Affects the factor V protein.
- Conveys resistance to activated protein C.
- Reduces normal inactivation of a coagulation cofactor.

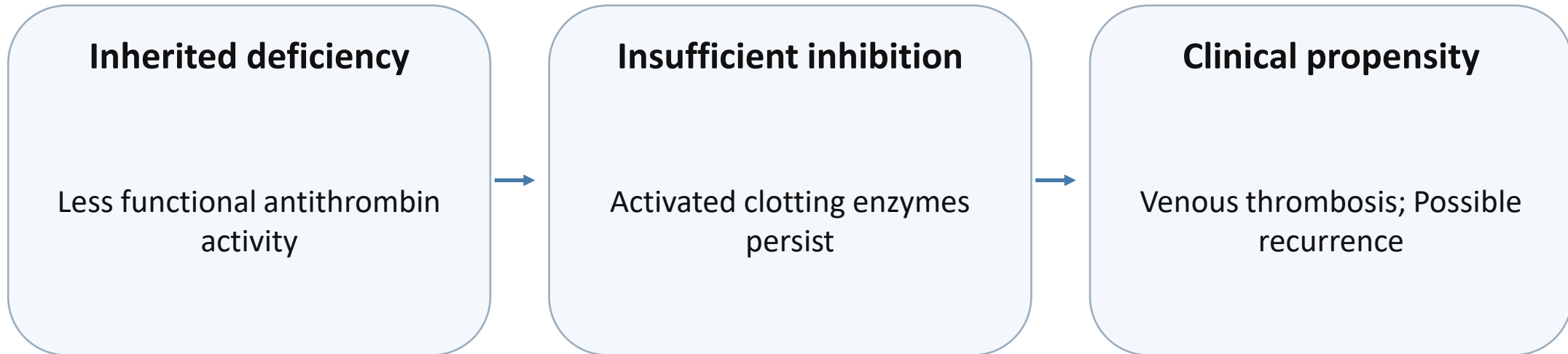
Prothrombin G20210A

- Variant occurs in a noncoding region.
- Associated with higher prothrombin levels.
- Increases substrate supporting coagulation.

Antithrombin: A key plasma inhibitor

- Antithrombin belongs to the normal anticoagulant defense system.
- It limits activated coagulation enzymes, notably thrombin.
- Deficiency decreases an important brake on the coagulation cascade.
- The source classifies antithrombin deficiency as a rare inherited cause.

Antithrombin deficiency: Loss of inhibition



The source associates rare natural anticoagulant deficiencies with early and recurrent thromboembolism.

Protein C deficiency: The regulatory defect

- Protein C is part of a normal thrombin-regulated anticoagulant pathway.
- When activated, it helps inactivate procoagulant factors.
- Deficiency weakens feedback inhibition and favors clot propagation.
- Inherited deficiency may present with venous thrombosis relatively early in life.

Protein S deficiency: Reduced cofactor support

- Protein S supports the anticoagulant effects of activated protein C.
- Its deficiency impairs the efficiency of the protein C pathway.
- The resulting tendency is toward venous thrombosis.
- Protein S deficiency is listed among rare inherited thrombophilias.

Inherited inhibitor deficiencies: Functional comparison

Deficient factor	Main conceptual defect	Expected consequence
Antithrombin	Less inhibition of activated enzymes	Persisting clotting activity
Protein C	Less proteolytic anticoagulant action	Reduced feedback control
Protein S	Less support for activated protein C	Impaired anticoagulant pathway

Increased coagulation-factor levels

- The textbook table includes increased factors VIII, IX and XI.
- Increased fibrinogen is also categorized with common genetic predispositions.
- The genetic explanations for these elevations are described as uncertain.
- A high procoagulant-factor burden can tip balance toward clot formation.

Rare disturbances of fibrinolysis

- Fibrinolysis is the physiological pathway for removing fibrin-containing clots.
- A defect in this system can impede thrombus clearance.
- The textbook groups inherited fibrinolysis defects as very rare causes.
- This is a mechanistic category rather than a single specified gene defect.

Homocysteine: Inherited and acquired elevation

Inherited

- Marked elevations may result from cystathionine β -synthase deficiency.
- Homozygous homocystinuria is listed as very rare.
- Biochemical elevation is not itself proof of thrombosis.

Acquired

- Vitamin B₆, B₁₂ or folate deficiency may elevate homocysteine.
- Some studies report prothrombotic effects; Others do not.
- The source explicitly acknowledges uncertain causality.

When should inherited causes enter the differential?

Age and presentation

Consider hereditary risk in thrombosis before age 50.

Phenotype

Recurrent venous thromboembolism increases concern.

Provoking factors

A triggering exposure does not exclude inherited susceptibility.

A provoking event and hereditary susceptibility can coexist.

Case: Thrombosis during prolonged travel

HYPOTHETICAL TEACHING VIGNETTE

A 34-year-old develops a first lower-extremity DVT following prolonged immobility during travel. A relative had venous thrombosis at a young age.

- Is the provoking exposure sufficient to exclude inherited susceptibility?
- Which common inherited variants are relevant to the mechanism?

Case discussion: Inherited plus acquired risk

HYPOTHETICAL TEACHING VIGNETTE

The vignette combines an environmental trigger with a possible hereditary susceptibility.

Reasoning

Immobility promotes stasis, while factor V Leiden or prothrombin G20210A can increase baseline coagulation tendency. The coexistence of both mechanisms is the intended inference; The vignette does not establish a genotype.

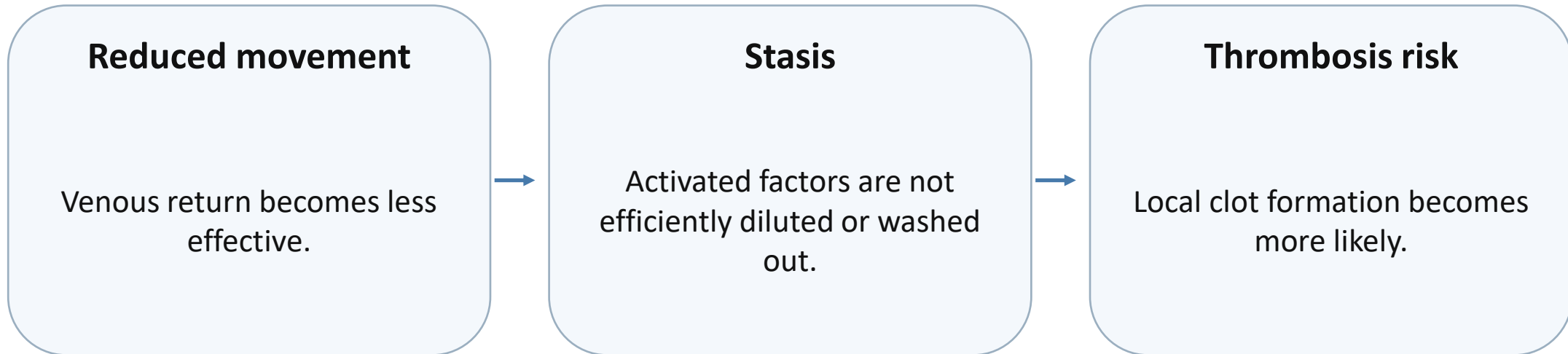
Acquired states: Strong risk factors

Circulatory / injury	Systemic / immune
Prolonged bed rest or immobilization	Cancer
Myocardial infarction	Disseminated intravascular coagulation
Atrial fibrillation	Heparin-induced thrombocytopenia
Surgery, fracture or burn	Antiphospholipid syndrome
Prosthetic cardiac valves	—

Other acquired thrombosis risk factors

Physiologic / hormonal	Medical / environmental
Pregnancy and postpartum	Nephrotic syndrome
Oral contraceptive use	Cardiomyopathy
—	Sickle cell anemia
—	Smoking

Immobilty: Abnormal flow meets coagulation



Prolonged bed rest is a strong acquired thrombosis risk factor in the source.

Cardiac conditions: Flow disturbance as a driver

Myocardial infarction

- Noncontractile myocardium may promote local stasis.
- Mural thrombus can form in regions of disturbed flow.
- Injury and stasis may contribute more than a systemic coagulation defect.

Atrial fibrillation

- Abnormal atrial contraction favors blood stasis.
- Left atrial dilation can deepen flow disturbance.
- Thrombosis reflects Virchow's triad, not an isolated factor mutation.

Tissue injury provides multiple prothrombotic signals

Operative injury

Vascular/tissue trauma and
postoperative immobility

Fracture or burn

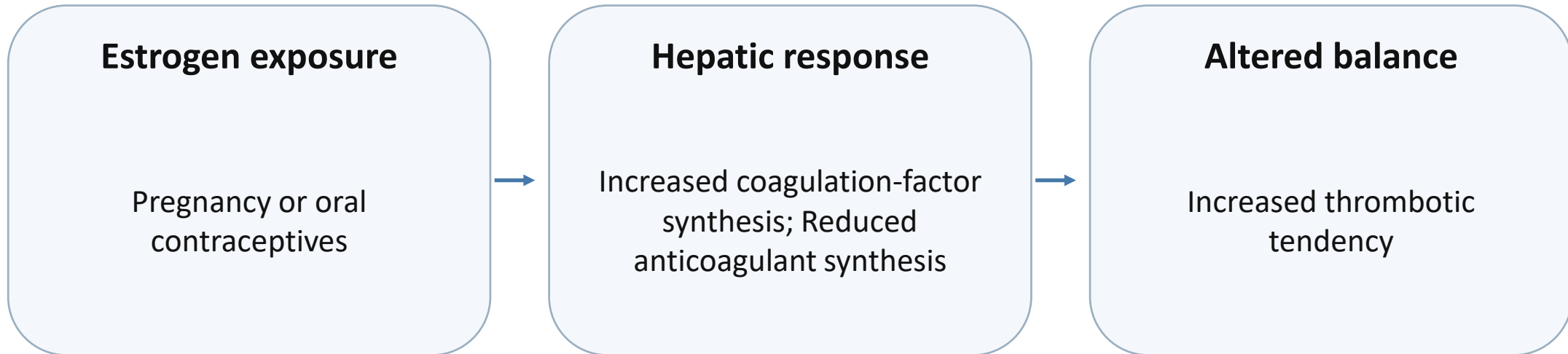
Tissue damage with local and
systemic response

Trauma

Vascular injury and stasis may
dominate mechanism

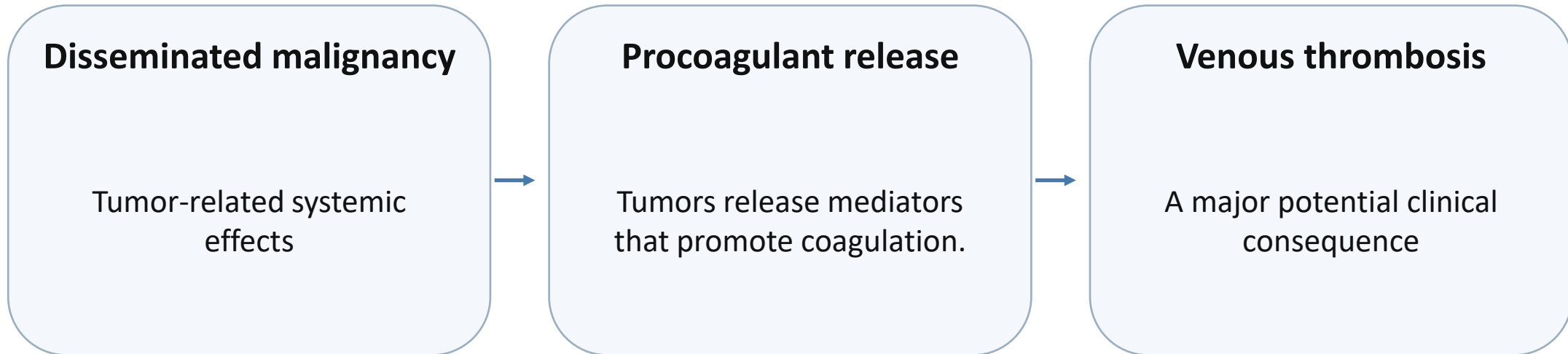
Acquired thrombophilia is frequently multifactorial.

Hyperestrogenic states and thrombosis



The textbook characterizes this proposed pathway as probable, not uniquely proven.

Cancer-associated hypercoagulability



In cancer, tumor procoagulants as a mechanism for thrombosis.

Additional conditions in acquired thrombophilia

- Nephrotic syndrome and cardiomyopathy appear's acquired risk-factor table.
- Sickle cell anemia may impede microvascular flow through deformed erythrocytes.
- Hyperviscosity in polycythemia vera can promote small-vessel stasis.
- The mechanisms differ; Their shared endpoint is increased thrombotic risk.

Smoking, obesity and aging

- Smoking and obesity are identified as acquired contributors to hypercoagulability.
- The source notes that their precise prothrombotic mechanisms are not fully defined.
- Advancing age may reduce endothelial prostacyclin (PGI₂) production.
- Avoid assigning a single established pathway to a multifactorial exposure.

Acquired thrombophilia is mechanistically heterogeneous

Stasis

Bed rest, atrial fibrillation,
cardiac dysfunction

Vascular / tissue injury

Trauma, surgery, myocardial
infarction

Coagulation activation

Cancer, pregnancy, immune-
mediated conditions

Clinical risk factors may affect more than one arm of Virchow's triad.

Heparin-induced thrombocytopenia: Central paradox

- HIT is an immune-mediated complication following heparin exposure.
- Antibodies against platelet factor 4 (PF4)–heparin complexes activate platelets.
- Platelet consumption produces thrombocytopenia.
- At the same time, platelet activation promotes serious venous or arterial thrombosis.

Falling platelet counts do not imply protection against thrombosis.

HIT starts with PF4–heparin immune complexes

PF4 release

Platelets release PF4 from α -granules.



Heparin binding

PF4 binds heparin and undergoes antigenic change.

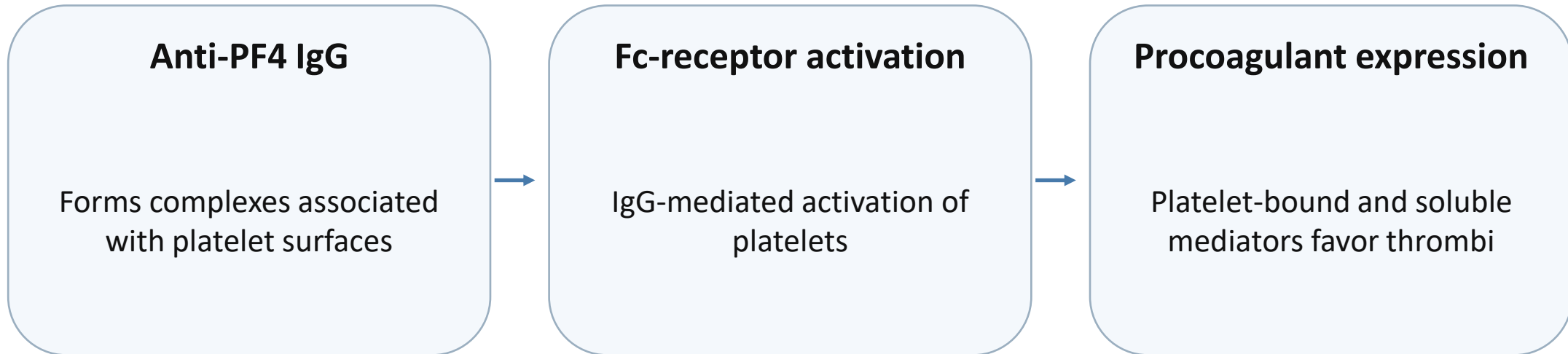


IgG response

Antibodies recognize the altered PF4 complex.

The immunogenic PF4 complex is the trigger.

HIT: Immune complex to platelet activation



Some intermediate molecular details remain incompletely defined.

HIT: The two consequences of antibody binding

Thrombocytopenia

- Antibody-coated platelets are removed by macrophages.
- Platelet counts fall.
- This laboratory finding gives the syndrome its name.

Thrombosis

- Immune-mediated platelet activation promotes coagulation.
- Veins and arteries may both be affected.
- Thrombosis is the more dangerous manifestation.

HIT: Clinically serious complications

- Venous thrombosis can develop during the immune response.
- Arterial thrombosis may cause limb ischemia, stroke or myocardial infarction.
- Skin necrosis and gangrene are described consequences.
- Recognition matters because the complication can be life-threatening.

HIT: Pathologic evidence and diagnostic framing

Exposure

History of heparin
administration

Platelet phenotype

Thrombocytopenia with
possible new thrombosis

Immune mechanism

Demonstration of anti-PF4-
heparin antibodies

The source discusses antibody demonstration; It does not supply a complete testing algorithm.

Heparin preparations and HIT risk

Unfractionated heparin

- HIT after exposure to unfractionated heparin.
- PF4–heparin complexes form the relevant antigenic substrate.

Other anticoagulants

- Low-molecular-weight heparin causes HIT less frequently.
- Direct factor Xa or thrombin inhibitors avoid heparin-associated PF4 complex formation.

Vaccine-induced thrombotic thrombocytopenia (VITT)

- An extremely rare syndrome described after certain adenoviral-vector COVID-19 vaccines.
- Like HIT, VITT is characterized by antibodies to platelet factor 4.
- The source attributes PF4 immunogenicity to interactions with some adenoviral proteins.
- VITT may be life-threatening and requires prompt recognition.

VITT: Anatomic distribution of thrombosis

Site	Potential clinical consequence
Cerebral venous sinuses	Venous obstruction, sometimes with hemorrhage
Deep leg veins	Deep venous thrombosis
Pulmonary arteries	Pulmonary thromboembolism
Splanchnic veins	Abdominal venous thrombosis

HIT and VITT: Similarity is not identity

HIT

- Typically follows heparin exposure.
- Anti-PF4–heparin immune complexes are central.
- Immune platelet activation causes thrombosis with thrombocytopenia.

VITT

- Reported after certain adenoviral-vector vaccines.
- Anti-PF4 antibodies arise without administered heparin.
- Characteristic thromboses may occur in unusual venous beds.

Antiphospholipid syndrome: Diagnostic concept

- APS is an autoimmune prothrombotic condition associated with antiphospholipid antibodies.
- Clinical expression includes venous or arterial thrombosis.
- Pregnancy morbidity is another major manifestation.
- An antibody result alone is not equivalent to the complete clinical syndrome.

Primary and secondary APS

Primary APS

- Characteristic thrombotic or obstetric features.
- No established associated systemic autoimmune disorder.
- Can present with varied vascular complications.

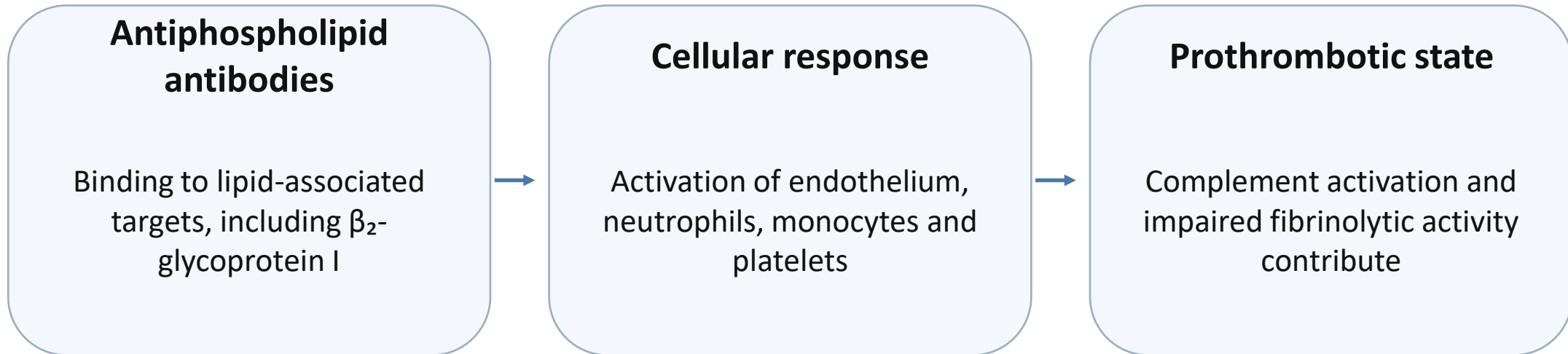
Secondary APS

- Associated with a defined autoimmune disease.
- Systemic lupus erythematosus is an important example.
- Thrombotic and obstetric effects can overlap with primary APS.

Antiphospholipid antibodies: Targets

- These antibodies recognize phospholipids or associated proteins.
- Cardiolipin is among the targets discussed in the source.
- β_2 -glycoprotein I binds avidly to phospholipid-containing cell surfaces.
- Anti- β_2 -glycoprotein I antibodies are implicated in the pathogenesis of APS.

APS: Immune activation promotes thrombosis



The source describes the mechanisms as complex and incompletely understood.

APS: Venous and arterial manifestations

- Recurrent venous thrombosis may lead to pulmonary embolism.
- Recurrent subclinical emboli can contribute to pulmonary hypertension.
- Arterial events include stroke, bowel infarction and renovascular manifestations.
- Cardiac valve vegetations and thrombocytopenia may accompany vascular disease.

APS-associated pregnancy morbidity

Early fetal loss

- The source emphasizes interference with trophoblast growth and differentiation.
- Impaired placentation may occur without primary thrombotic causation.
- Do not reduce all obstetric APS effects to placental clots.

Later pregnancy complications

- Preeclampsia and preterm birth may develop.
- Trophoblast dysfunction and inflammation contribute.
- Antiphospholipid antibodies and complement have implicated roles.

The lupus anticoagulant paradox

In vivo

Associated with an increased risk of thrombosis

In vitro

Phospholipid-dependent clotting assays can be prolonged

Clinical interpretation

Prolonged PTT is not proof of a bleeding disorder

Anticoagulant in the assay; Prothrombotic in the patient.

APS: Why a positive antibody may be insufficient

- Antiphospholipid antibodies may occur in apparently healthy individuals.
- The source proposes that an additional prothrombotic stimulus may be required.
- Infection, smoking and pregnancy are described as potential “second hits.”
- Clinical manifestations and antibody findings must be interpreted together.

APS: Serologic and clinicopathologic clues

- The textbook bases diagnosis on clinical findings plus serum antibodies.
- The lupus anticoagulant may prolong an in-vitro PTT.
- Anticardiolipin reactivity can yield a false-positive syphilis serologic result.
- Neither finding alone establishes a thrombotic event or a full clinical syndrome.

HIT versus APS: Immune mechanisms differ

Feature	HIT	APS
Typical context	Heparin exposure	Autoimmune / idiopathic context
Antibody target	PF4–heparin complexes	Phospholipid-associated antigens
Cellular effect	Platelet activation	Multiple cell and complement pathways
Typical manifestations	Thrombocytopenia and thrombosis	Thrombosis and pregnancy morbidity

Case: Thrombocytopenia with new thrombosis

HYPOTHETICAL TEACHING VIGNETTE

A hospitalized patient receives unfractionated heparin. A subsequent fall in platelets is accompanied by acute venous thrombosis.

- How can thrombocytopenia coexist with a prothrombotic state?
- Which immune complex provides the mechanistic explanation?

Case discussion: Immune platelet activation

HYPOTHETICAL TEACHING VIGNETTE

The clinical pattern is compatible with the mechanism described for heparin-induced thrombocytopenia.

Reasoning

Anti-PF4–heparin IgG complexes can activate platelets while antibody-coated platelets are also removed by macrophages. Platelet count decline and thrombosis are parallel consequences, not contradictory findings.

Case: Recurrent losses and venous thrombosis

HYPOTHETICAL TEACHING VIGNETTE

A woman has a history of recurrent pregnancy losses and an objectively confirmed lower-extremity venous thrombosis. Laboratory evaluation raises concern for antiphospholipid antibodies.

- Which clinical domains define the APS phenotype in the source?
- Why might an in-vitro PTT be prolonged?

Case discussion: Antiphospholipid syndrome

HYPOTHETICAL TEACHING VIGNETTE

The vignette combines obstetric morbidity with a thrombotic phenotype.

Reasoning

APS involves antibodies against phospholipid-associated targets, with cell activation, complement engagement and effects on placentation. Lupus anticoagulant activity may prolong phospholipid-dependent assays despite prothrombotic clinical behavior.

Mechanistic pattern recognition

Clue	Mechanism to consider
Young patient + VTE + provoking exposure	Inherited predisposition plus acquired risk
Heparin + falling platelets + thrombosis	Anti-PF4 immune platelet activation
Thrombosis + obstetric complications	Antiphospholipid-associated mechanisms
Cancer + new venous thrombosis	Tumor-related procoagulant activity
Immobilization + DVT	Venous stasis with additional risk factors

Reasoning traps in hypercoagulability

- Do not equate a thrombophilic genotype with certain future thrombosis.
- Do not dismiss hereditary risk merely because immobilization or pregnancy is present.
- Do not interpret HIT thrombocytopenia as a low-risk or bleeding-only state.
- Do not interpret a prolonged lupus anticoagulant–related PTT as protection from clotting.
- Do not assume APS pregnancy complications all result from placental thrombosis.

Integrated take-home framework

Identify the milieu

Inherited predisposition,
acquired exposures or both

Find the pathway

Excess procoagulants; Impaired
inhibition; Immune activation

Predict the phenotype

Venous, arterial or obstetric
manifestations

A mechanistic classification is more informative than a flat list of risk factors.

Source and interpretation

- Core source: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th edition (2026), Chapter 4.
- Primary topic: Hypercoagulability, printed pages 110–112; contextual hemostasis and altered-flow sections immediately preceding.
- The lecture paraphrases the supplied source and uses original editable teaching schematics.
- Illustrative vignettes are hypothetical. No clinical specimens or externally verified updates are represented.