Hemostais

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Learning objectives

1. Primary hemostasis & thrombocytes
2. Secondary hemostasis – Hemocoagulation (protein vs cell model)
3. Regulation of hemostasis
4. Basic Coagulation tests
5. Circulation and hemostasis

Hemostasis

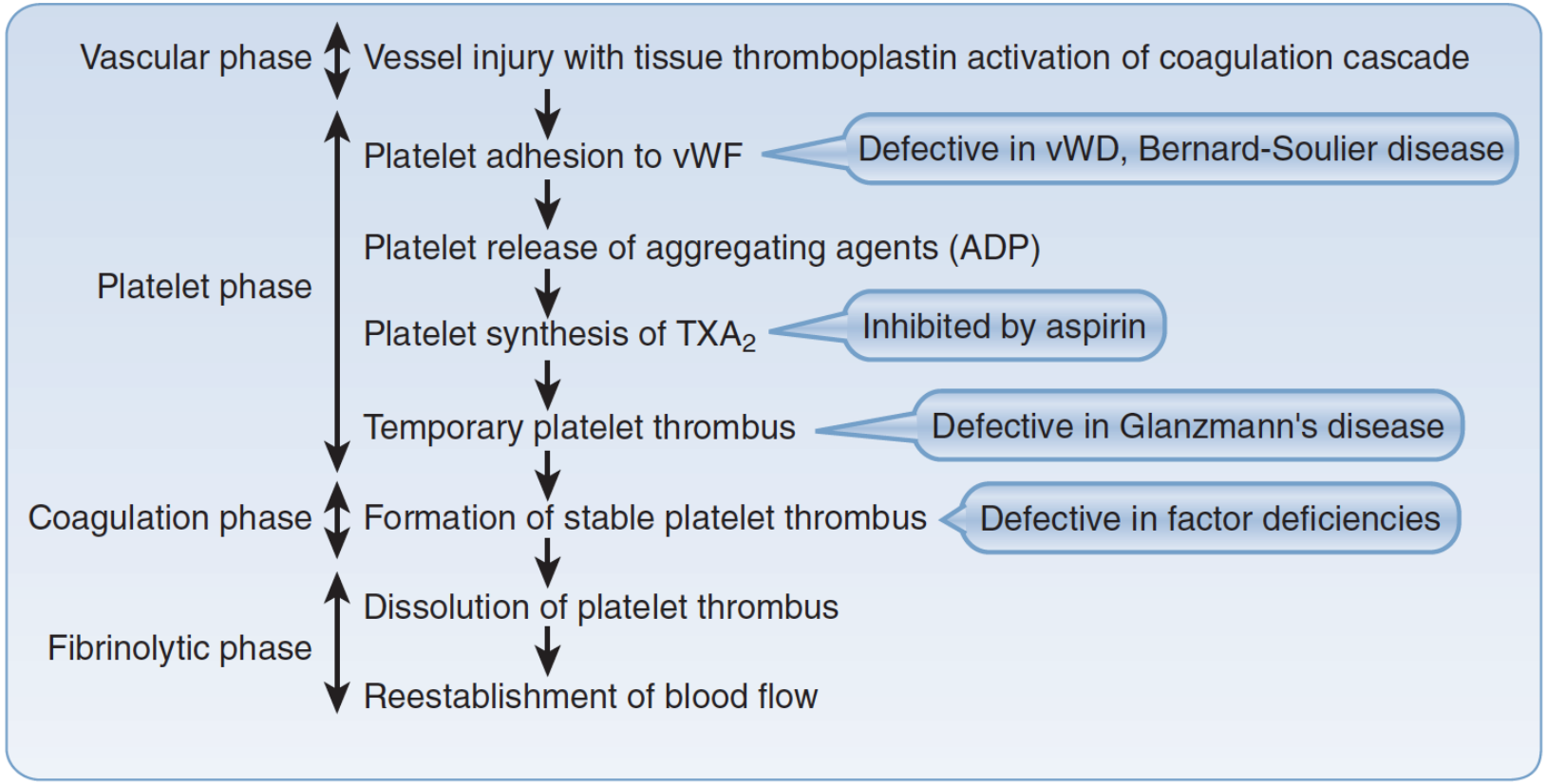
- Integrity of the blood vessel is necessary to carry blood to tissue.
- Damage to wall is repaired by **hemostasis** (by formation of thrombus (clot) at injury site)
- Prevention of blood loss require the interaction of **blood vessels, platelets , coagulation factors , fibrinolytic agents**

4 steps of Hemostasis

- Hemostasis occurs in 4 steps :

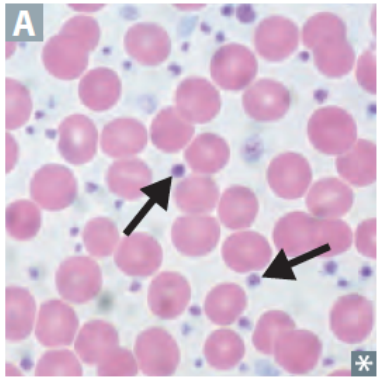
1. **Vascular phase (transiant vasoconstriction)**
2. **Platelet phase (Primary hemostasis)**
3. **Coagulation phase (Secondary hemostasis)**
4. **Fibrinolytic phase**

Hemostasis following injury to the vessel



Platelets

Thrombocytes (platelets)



Involved in 1° hemostasis. Small cytoplasmic fragments A derived from megakaryocytes. Life span of 8–10 days. When activated by endothelial injury, aggregate with other platelets and interact with fibrinogen to form platelet plug. Contain dense granules (ADP, Ca^{2+}) and α granules (vWF, fibrinogen, fibronectin, platelet factor 4). Approximately ⅓ of platelet pool is stored in the spleen.

Thrombocytopenia or ↓ platelet function results in petechiae.

vWF receptor: GpIb.

Fibrinogen receptor: GpIIb/IIIa.

Thrombopoietin stimulates megakaryocyte proliferation.

Alfa granules contain vWF, fibrinogen, fibronectin, platelet factor 4.

Platelet structure

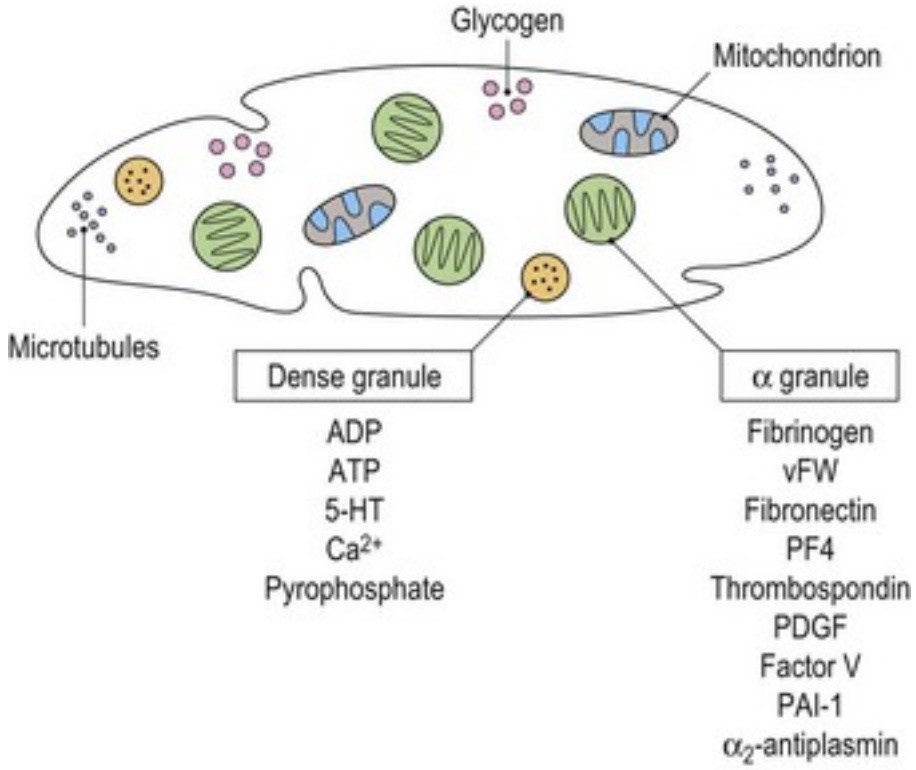
Contractile element called **thrombosthenin** helps in clot retraction.

Dense bodies contain:

- **ADP**, an aggregating agent
- **Calcium**, a binding agent for vitamin K–dependent factors

α-Granules contain:

- **vWF**
- **Fibrinogen**
- **Platelet-derived growth factor (PDGF),**
- **Platelet factor 4 (PF4),** (a heparin-neutralizing factor)



Primary hemostasis – 4 steps (results in formation of weak platelet plug)

Transient vasoconstriction of damaged vessel

i. Mediated by **reflex neural stimulation** and **endothelin** release from endothelial cells

Platelet adhesion to the surface of disrupted vessel

i. **Von willbrand factor (vWF)** binds exposed **subendothelial collagen (SEC)**

ii. **Platelets** bind vWF using **GP1b**

iii. Note : vWF is drived from Weibel-Palade bodies of endothelial cells and a-granules of plateles

Platelet degranulation

- Adhesion induces shape change in platelets and degranulation with release of multiple mediators ;

i. **ADP** is released from platelet dense granules ; promotes exposure of **GPIIb/IIIa** receptors on platelets

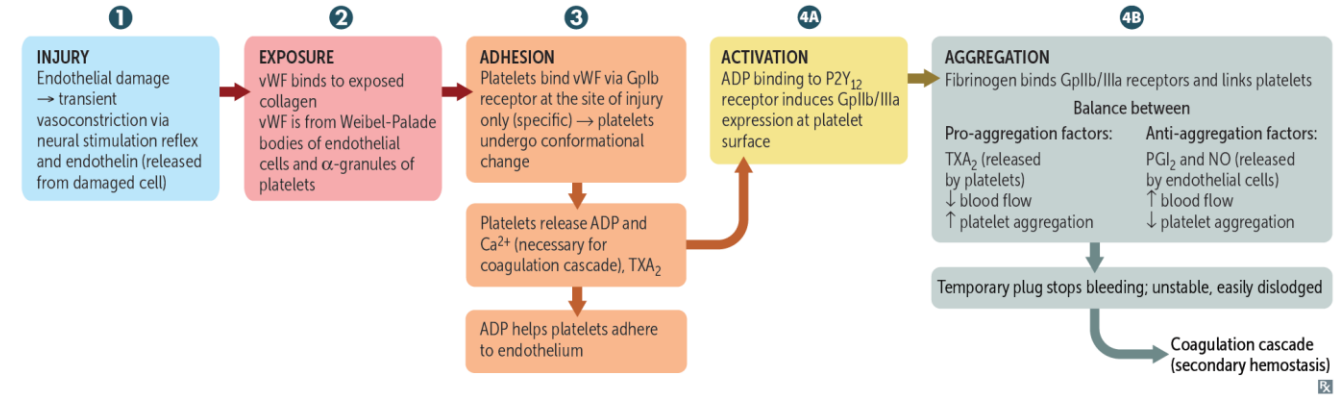
ii. **TXA2** is synthesized by platelet **cyclooxygenase (COX**) and released ; promotes platelet aggregation

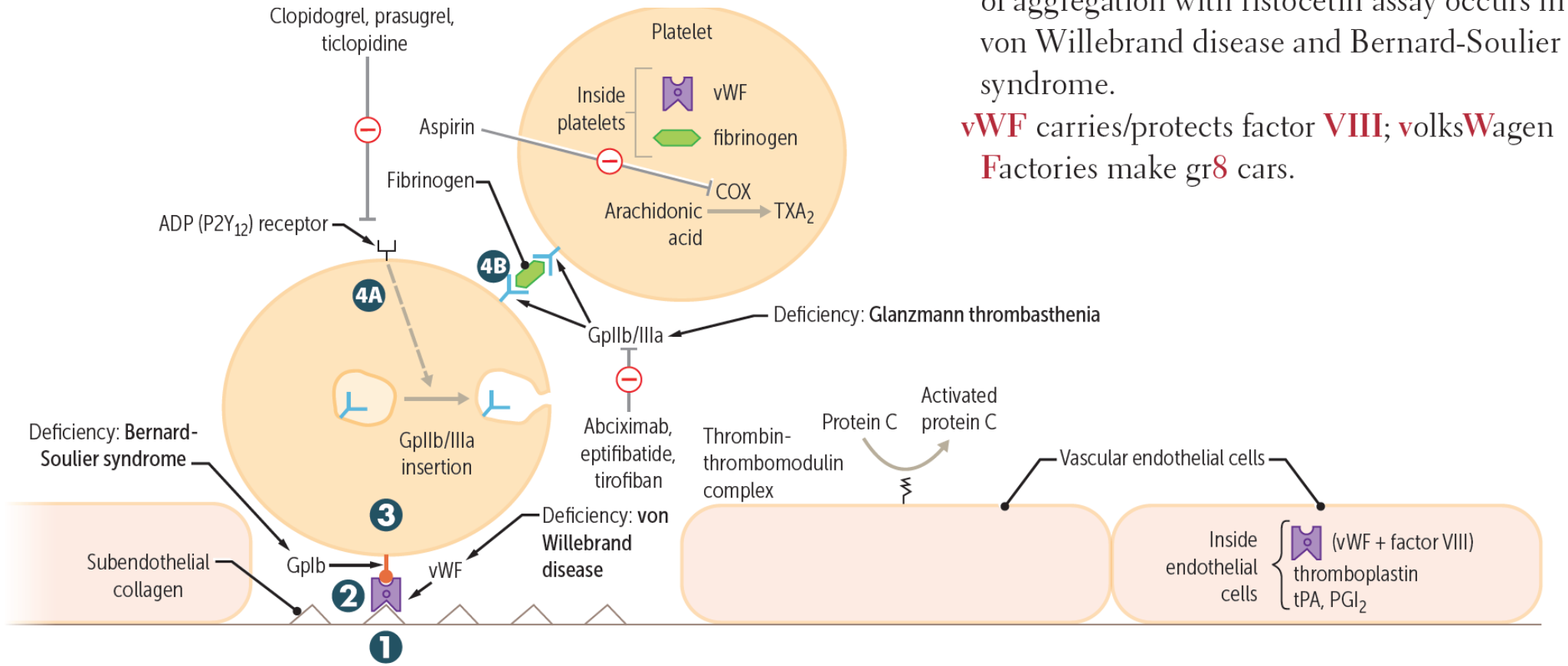
Platelet aggregation

i. Platelets aggregate at the site of injury via GPIIb/IIIa using **fibrinogen** (from plasma) as a linking molecule, results in formation of platelet plug

ii. **Platelet plug is weak** ; coagulation cascade (secondary hemostasis) stabilizes it

Thrombogenesis





Formation of insoluble fibrin mesh.

Aspirin irreversibly inhibits cyclooxygenase, thereby inhibiting TXA_2 synthesis.

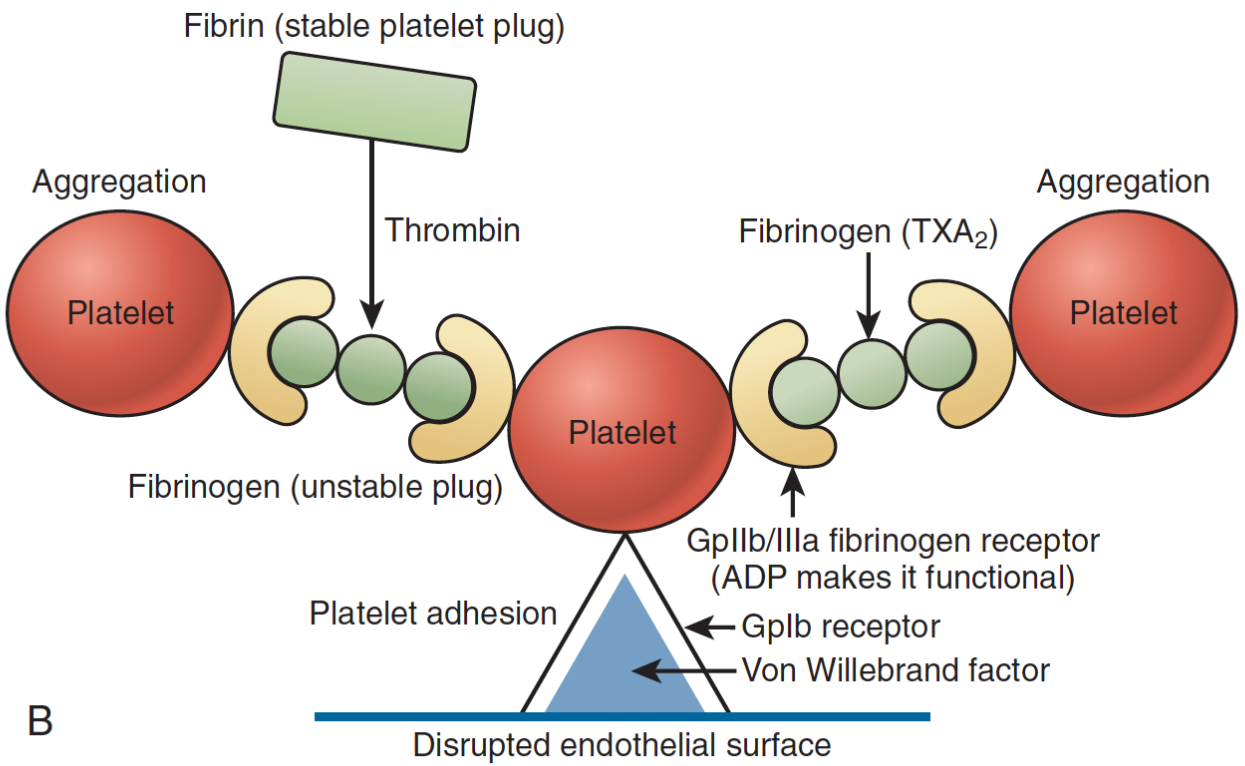
Clopidogrel, prasugrel, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa by irreversibly blocking $P2Y_{12}$ receptor.

Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.

Ristocetin activates vWF to bind GpIb. Failure of aggregation with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome.

vWF carries/protects factor **VIII**; **v**olks**W**agen **F**actories make gr**8** cars.

Platelet Adhesion, Activation & Agreggation (3A)



Secondary hemostasis

Secondary hemostasis : **stabilizes the platelet plug** and is mediated by **the coagulation cascade**

- coagulation cascade generates thrombin (FIIa) which converts Fibrinogen in the platelet plug to fibrin
- Fibrin is then cross-linked, yielding a stable platelet-fibrin thrombus.

➢ Factors of the coagulation cascade are produced in the liver in an inactive state

Activation requires :

1. **Exposure to an activating substance**

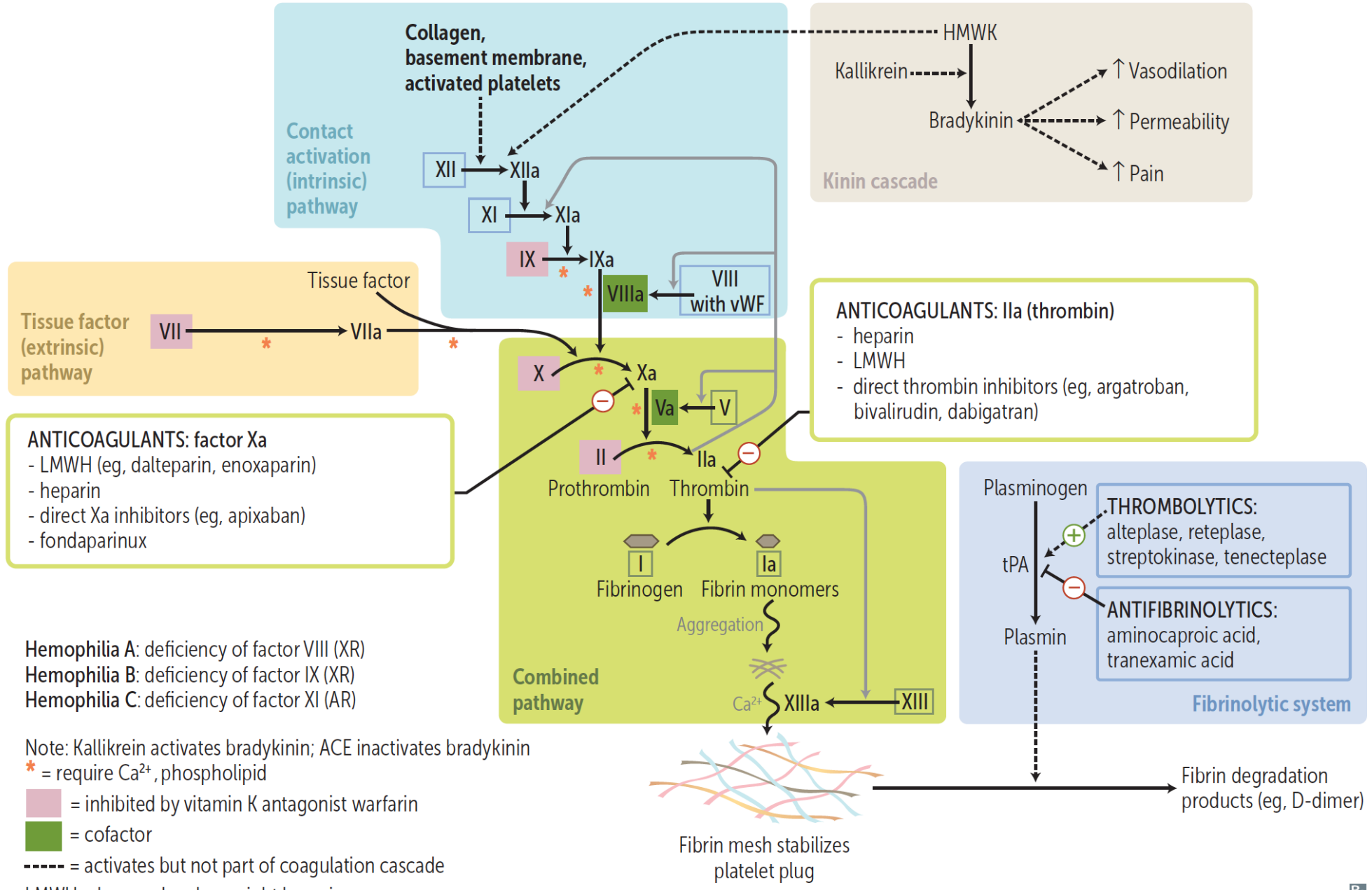
Tissue Factor (TF) → F VII (extrinsic pathway)

Subendothelial collagen (SEC) → F XII (intrinsic Pathway)

2. Phospholipid surface of the platelets

3. **Calcium** (derived from platelet dense granules)

Coagulation and kinin pathways



Hemophilia A: deficiency of factor VIII (XR)
Hemophilia B: deficiency of factor IX (XR)
Hemophilia C: deficiency of factor XI (AR)

Note: Kallikrein activates bradykinin; ACE inactivates bradykinin

* = require Ca^{2+}, phospholipid

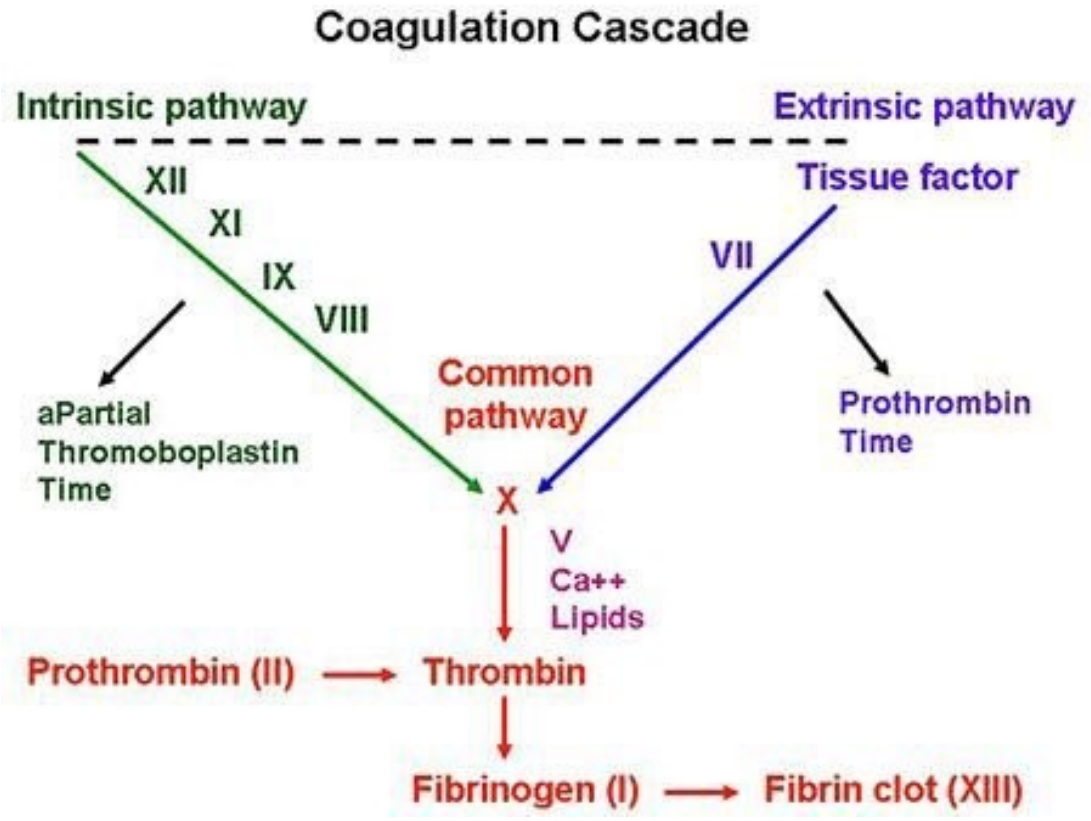
= inhibited by vitamin K antagonist warfarin

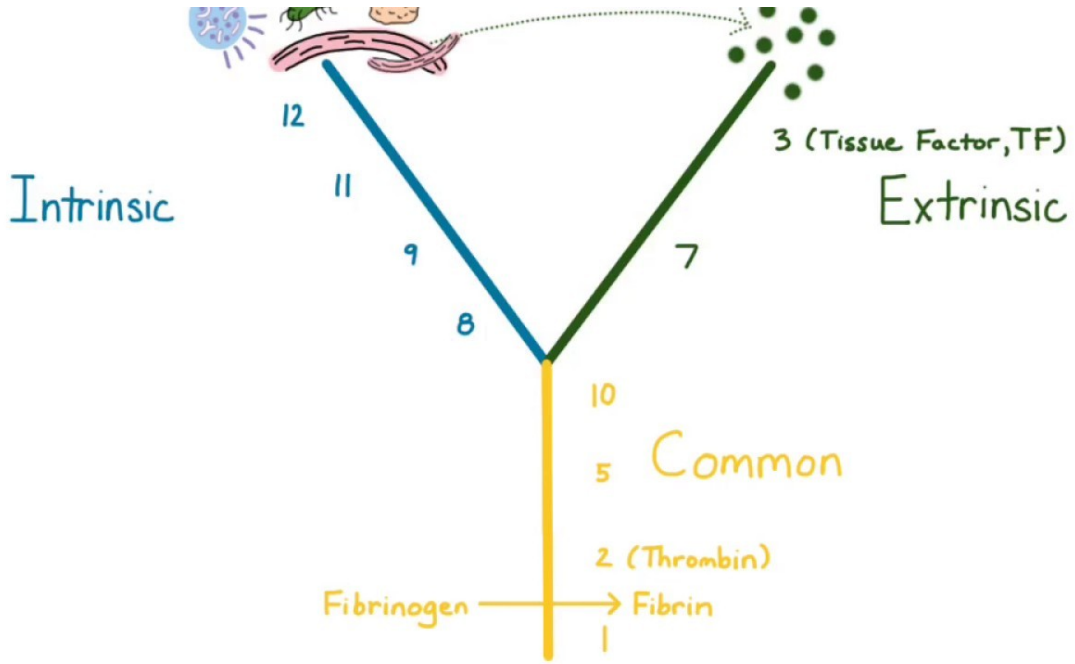
= cofactor

----- = activates but not part of coagulation cascade

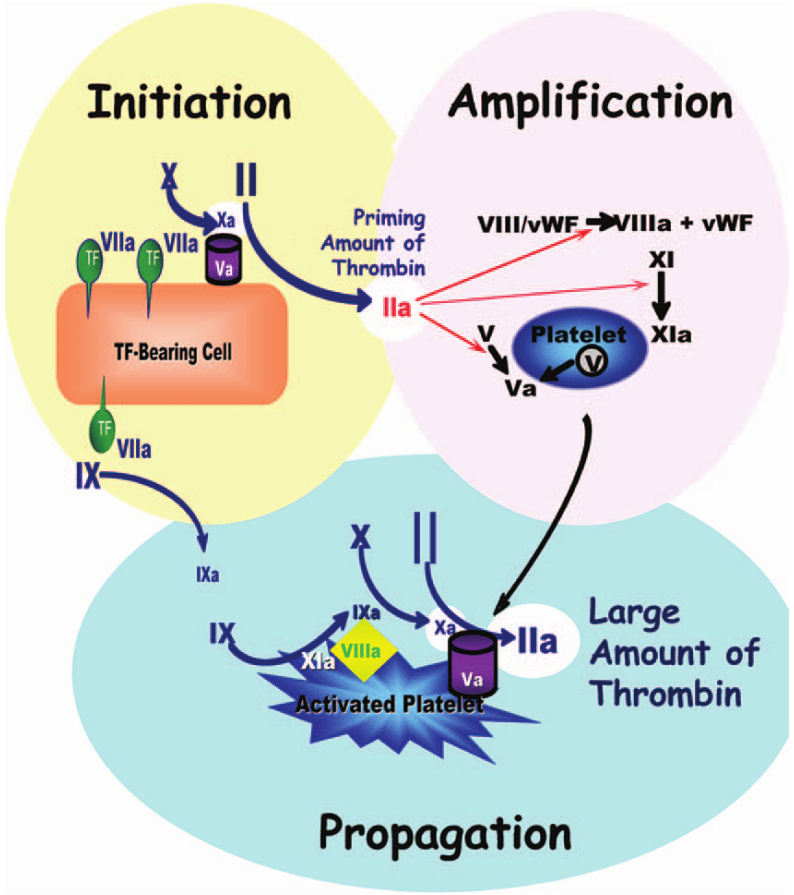
LMWH = low-molecular-weight heparin

Coagulation cascade made easy (protein based model)





Cell-model theory of coagulation



https://www.youtube.com/watch?v=T4MG7bzQ2NI&t=58s&ab_channel=ThePhysiologyChannel

Table 18-4 Procoagulant and Anticoagulant Factors

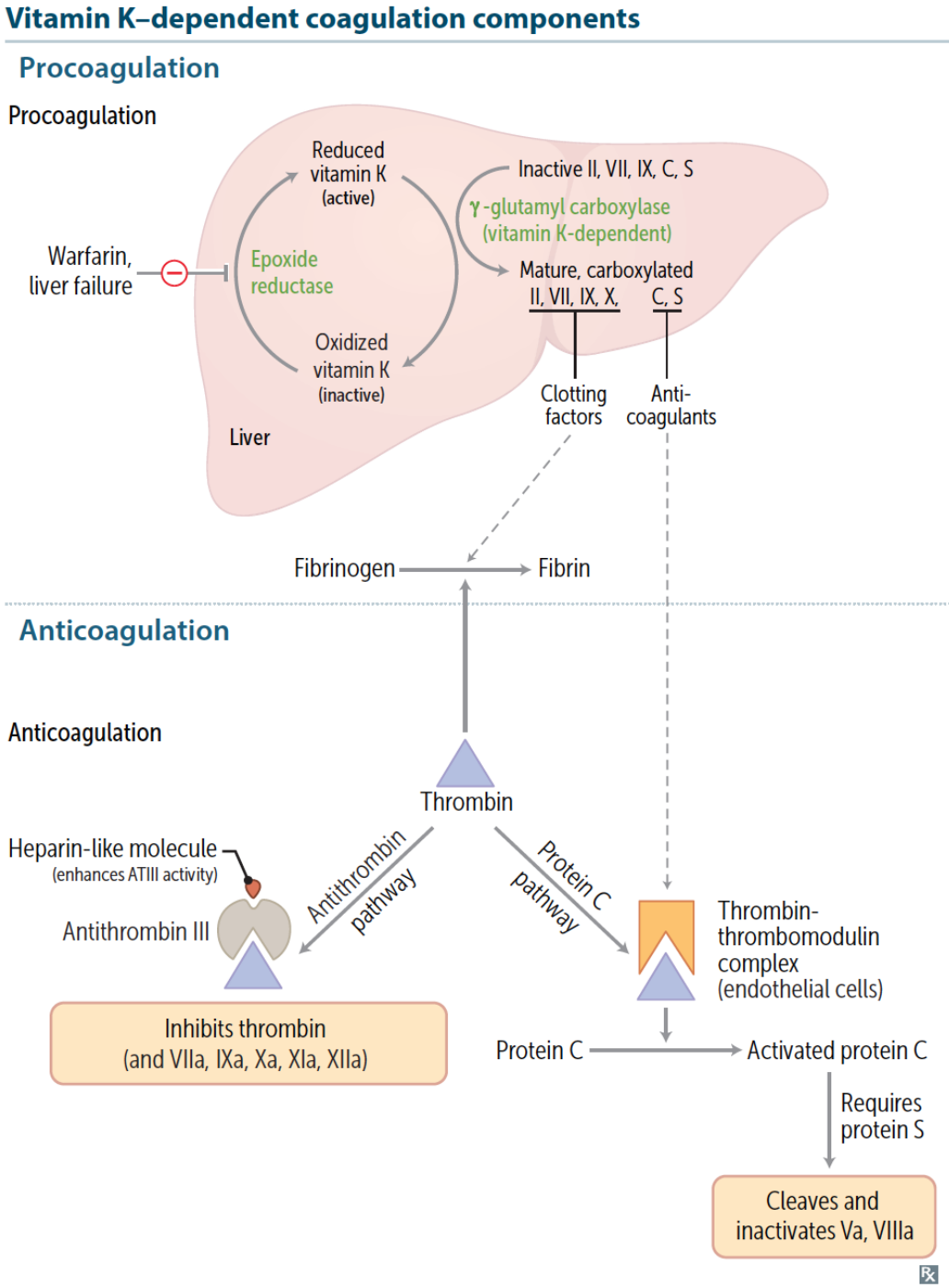
Name	Alternate Names	Properties
Procoagulant Factors		
Factor I	Fibrinogen	A plasma globulin
Factor Ia	Fibrin	
Factor II	Prothrombin	A plasma α_2-globulin Synthesis in liver requires vitamin K*
Factor IIa	Thrombin	A serine protease
Factor III (cofactor)	Tissue factor Tissue thromboplastin	An integral membrane glycoprotein; member of type II cytokine receptor family Receptor for factor VIIa Must be present in a phospholipid membrane for procoagulant activity
Factor IV	Ca^{2+}	
Factor V	Labile factor Proaccelerin Accelerator globulin	A plasma protein synthesized by liver and stored in platelets Single-chain protein
Factor Va (cofactor)		Heterodimer held together by a single Ca^{2+} ion Highly homologous to factor VIIIa
Factor VII	Stable factor Serum prothrombin conversion accelerator (SPCA) Proconvertin	A plasma protein Synthesis in liver requires vitamin K*
Factor VIIa		A serine protease
Factor VIII	Antihemophilic factor (AHF) Factor VIII procoagulant component (FVIII:C)	A plasma protein with phospholipid binding domain
Factor VIIIa (cofactor)		Highly homologous to factor Va
Factor IX	Christmas factor Plasma thromboplastin component (PTC)	A plasma protein Synthesis in liver requires vitamin K*
Factor IXa		A protease Disulfide-linked heterodimer
Factor X	Stuart factor	A plasma glycoprotein Synthesis in liver requires vitamin K*
Factor Xa		A protease
Factor XI	Plasma thromboplastin antecedent (PTA)	A plasma protein produced by megakaryocytes and stored in platelets
Factor XIa		A protease Disulfide-linked homodimer
Factor XII	Hageman factor (HAF)	A plasma glycoprotein
Factor XIIa		A protease
Factor XIII	Fibrin stabilizing factor (FSF)	A plasma protein stored in platelets

Table 18-4 Procoagulant and Anticoagulant Factors—cont'd

Name	Alternate Names	Properties
Factor XIIIa		A transglutaminase A tetramer of two A chains and two B chains
HMWK	High-molecular-weight kininogen Fitzgerald factor	A plasma protein stored in platelets Kallikrein clips bradykinin from HMWK
Plasma prekallikrein	Fletcher factor Plasma kallikrein precursor	A plasma protein
Plasma kallikrein		A serine protease Kallikrein clips bradykinin from HMWK
von Willebrand factor	vWf	A plasma glycoprotein made by endothelial cells and megakaryocytes Stabilizes factor VIIIa Promotes platelet adhesion and aggregation
Anticoagulant Factors		
TFPI	Tissue factor pathway inhibitor	Protease inhibitor produced by endothelial cells GPI linked to the cell membrane
Antithrombin III	AT III	A plasma protein Serine protease inhibitor, member of serpin family Inhibits factor Xa and thrombin, and probably also factors XIIa, XIa, and IXa Heparan and heparin enhance the inhibitory action
Thrombomodulin (cofactor)		Glycosaminoglycan on surface of endothelial cell Binds thrombin and promotes activation of protein C
Protein C	Anticoagulant protein C Autoprothrombin IIA	A plasma protein Synthesis in liver requires vitamin K*
Protein Ca		A serine protease Disulfide-linked heterodimer
Protein S (cofactor)		A plasma protein Synthesis in liver requires vitamin K* Cofactor for protein C

*See Chapter 58 for a discussion of vitamin K.

Vitamin K dependent Coagulation factors



Vitamin K deficiency: ↓ synthesis of factors II, VII, IX, X, protein C, protein S.

Warfarin inhibits vitamin K epoxide reductase. Vitamin K administration can potentially reverse inhibitory effect of warfarin on clotting factor synthesis (delayed). FFP or PCC administration reverses action of warfarin immediately and can be given with vitamin K in cases of severe bleeding.

Neonates lack enteric bacteria, which produce vitamin K. Early administration of vitamin K overcomes neonatal deficiency/coagulopathy.

Factor VII (Seven)—Shortest half life.

Factor II (Two)—Longest (Tallest) half life.

Antithrombin inhibits thrombin (factor IIa) and factors VIIa, IXa, Xa, XIa, XIIa.

Heparin enhances the activity of antithrombin.

Principal targets of antithrombin: thrombin and factor Xa.

Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C.

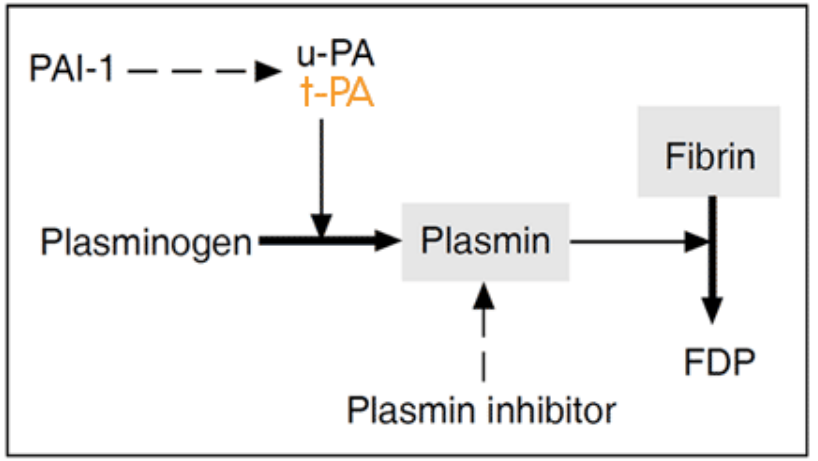
tPA is used clinically as a thrombolytic.

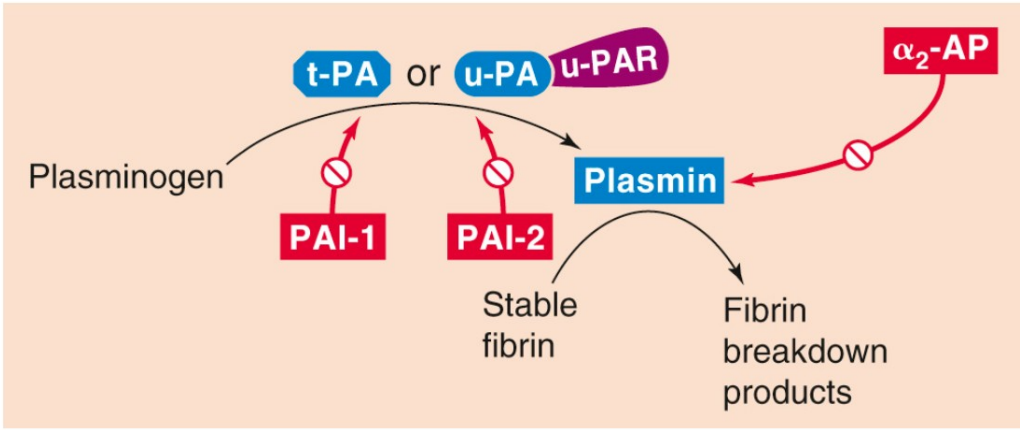
Fibrinolytic phase

a. **Tissue plasminogen activator (tPA)** activates plasminogen to release the enzyme plasmin**.**

Plasmin →

1. Cleaves insoluble fibrin monomers and fibrinogen into **fibrinogen degradation products (FDPs)** (note : Fragments of cross-linked insoluble fibrin monomers are called **d-dimers**.)
2. Degrades factors V and VIII, and fibrinogen
3. 3. **α2-Antiplasmin**, which is synthesized in the liver, inactivates plasmin.





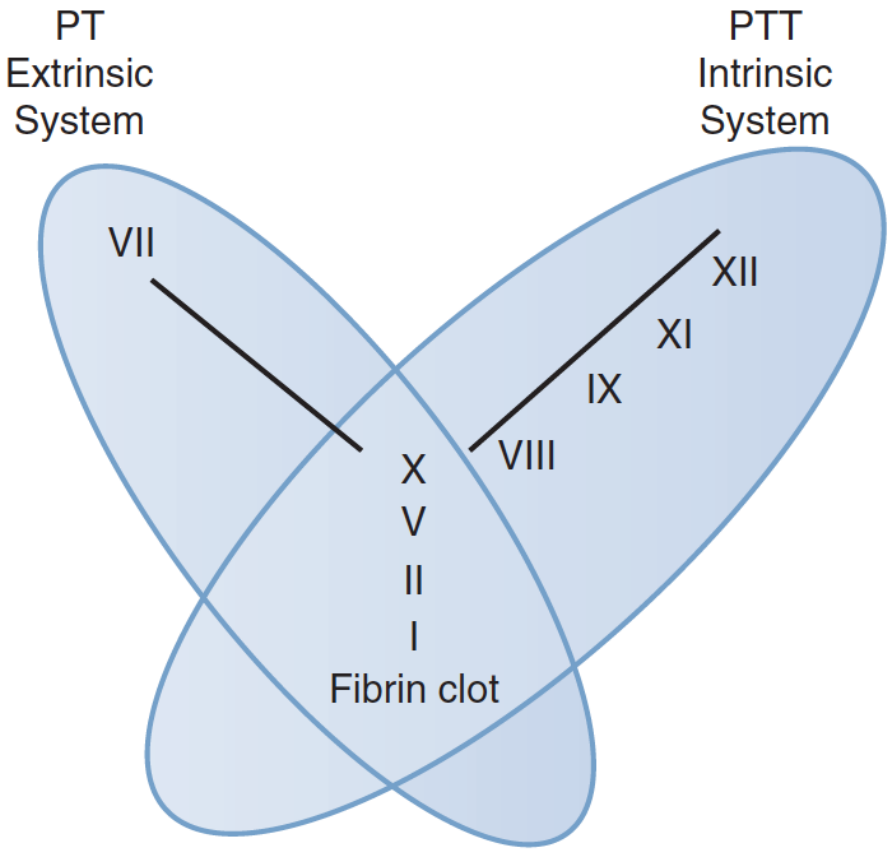
Fibrinolytics

NAME	ALTERNATE NAME	PROPERTIES
Tissue-type plasminogen activator	t-PA	Serine protease that catalyzes hydrolysis of plasminogen at the junction between the N-terminal heavy chain and C-terminal light chain N terminus contains two loop structures called kringles
Urokinase-type plasminogen activator	u-PA	Serine protease
Urokinase-type plasminogen activator receptor	u-PAR	Binds to and required for the activity of u-PA
Plasminogen		Single-chain plasma glycoprotein with large N-terminal and small C-terminal domain. N terminus contains five kringles
Plasmin	Fibrinolysin	Serine protease
Plasminogen activator inhibitor 1	PAI-1	Serpin (serine protease inhibitor) In plasma and platelets Forms 1 : 1 complex with t-PA in blood
Plasminogen activator inhibitor 2	PAI-2	Serpin (serine protease inhibitor) Detected only in pregnancy
α_2-antiplasmin	α_2-AP	Serpin (serine protease inhibitor) Forms 1 : 1 complex with plasmin in blood

Coagulation tests (PT,INR,PTT)

I. Coagulation tests (Fig. 15-4)

1. Prothrombin time (PT)
   a. Evaluates the extrinsic coagulation system down to the formation of the fibrin clot
      - Factors that are evaluated include VII, X, V, II, I (separate test).
   b. Normal reference is 11 to 15 seconds; however, this varies in different laboratories.
      - The time is only prolonged when a factor level is 30% to 40% of normal; hence it is not a very sensitive test.
   c. International normalized ratio (INR)
      (1) INR standardizes the PT for use in monitoring warfarin anticoagulation therapy.
      (2) Results are the same regardless of the reagents used to perform the test.
      (3) Usual range for the international normalized ratio is 2 to 3.
   d. Uses of the PT
      (1) Monitoring persons who are taking warfarin for anticoagulation
      (2) Evaluates liver synthetic function
         - Increased PT indicates severe liver dysfunction (e.g., cirrhosis of the liver, chronic hepatitis).
      (3) Used to detect factor VII deficiency if the PTT is normal
2. Partial thromboplastin time (PTT)
   a. Evaluates the intrinsic coagulation system down to formation of a fibrin clot
      - Factors that are evaluated include XII, XI, IX, VII, X, V, II, I (separate test).
   b. Normal reference interval is 25 to 40 seconds; however, this varies in different laboratories.
      - Time is only prolonged when a factor level is 30% to 40% of normal.
   c. Uses of the PTT
      (1) Most commonly used to monitor heparin anticoagulation therapy
         (a) Heparin enhances antithrombin III activity.
         (b) PTT is *not* required to follow low-molecular-weight heparin therapy.
      (2) Used to detect factor deficiencies in the intrinsic coagulation system if the PT is normal

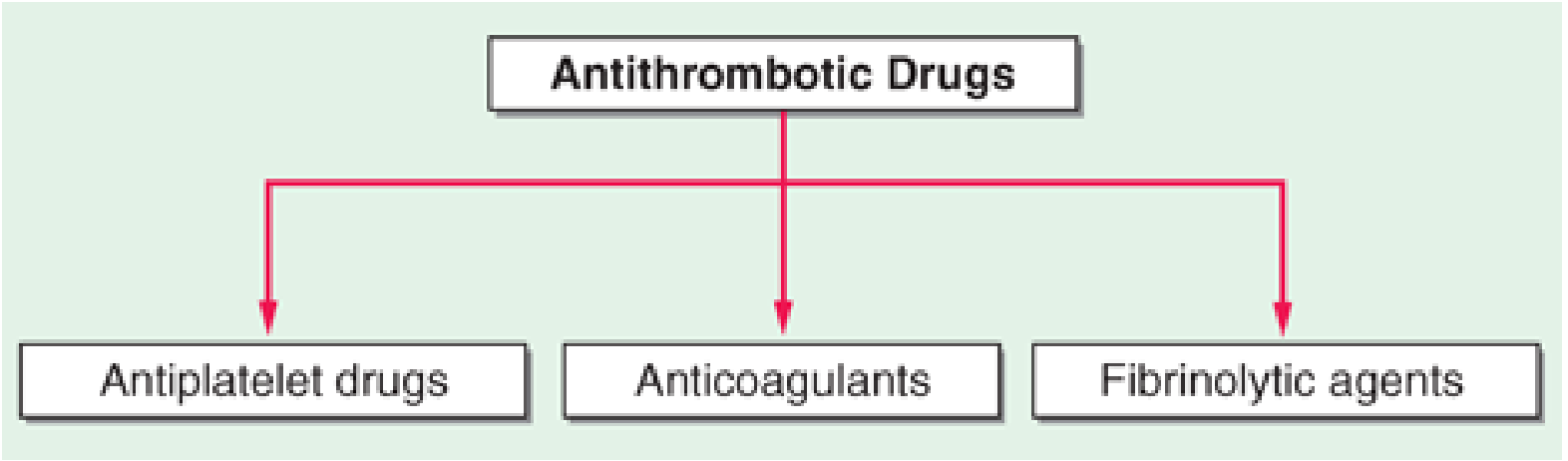


Platelet test

H. Platelet tests

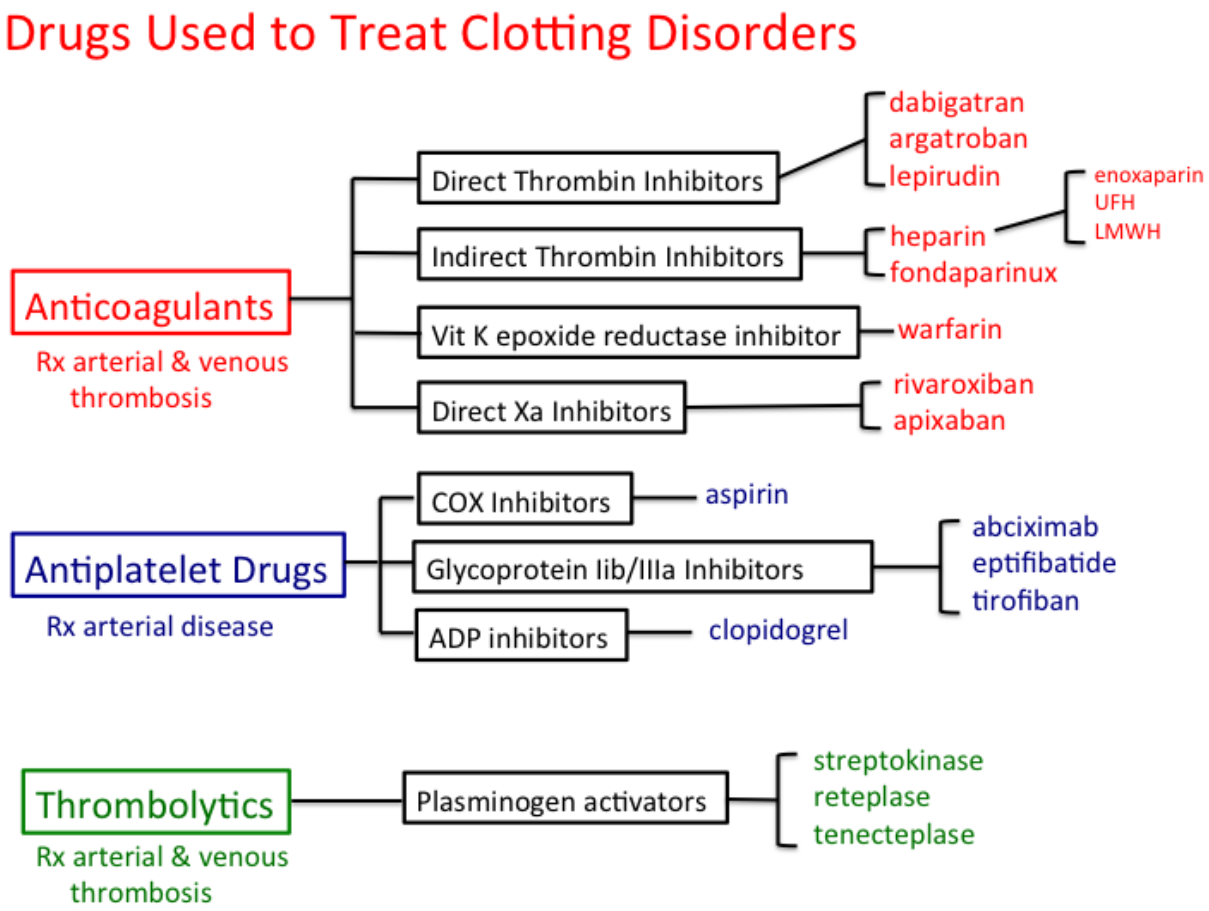
1. Platelet count
   a. Normal platelet count is 150,000 to 400,000 cells/mm^3.
   b. Normal count does *not* guarantee normal platelet function.
2. Bleeding time (BT)
   a. Evaluates platelet function up to the formation of the temporary platelet thrombus
      (1) Normal reference interval is 2 to 7 minutes
      (2) Many laboratories have discontinued using the BT, because it is time intensive.
   b. Disorders causing a prolonged BT are listed in Table 15-1
3. Platelet aggregation test
   a. The test evaluates platelet aggregation in response to aggregating reagents added to a test tube.
   b. Aggregating agents that are used include ADP, epinephrine, collagen, and ristocetin.
4. Tests for vWF
   a. Ristocetin cofactor activity
      (1) Evaluates von Willebrand factor function
      (2) Abnormal functional assay occurs in:
         (a) Classic von Willebrand disease (vWD; deficiency of vWF)
         (b) Bernard-Soulier disease (absent GpIb vWF receptor)

Figure 118-1



Classification of antithrombotic drugs.

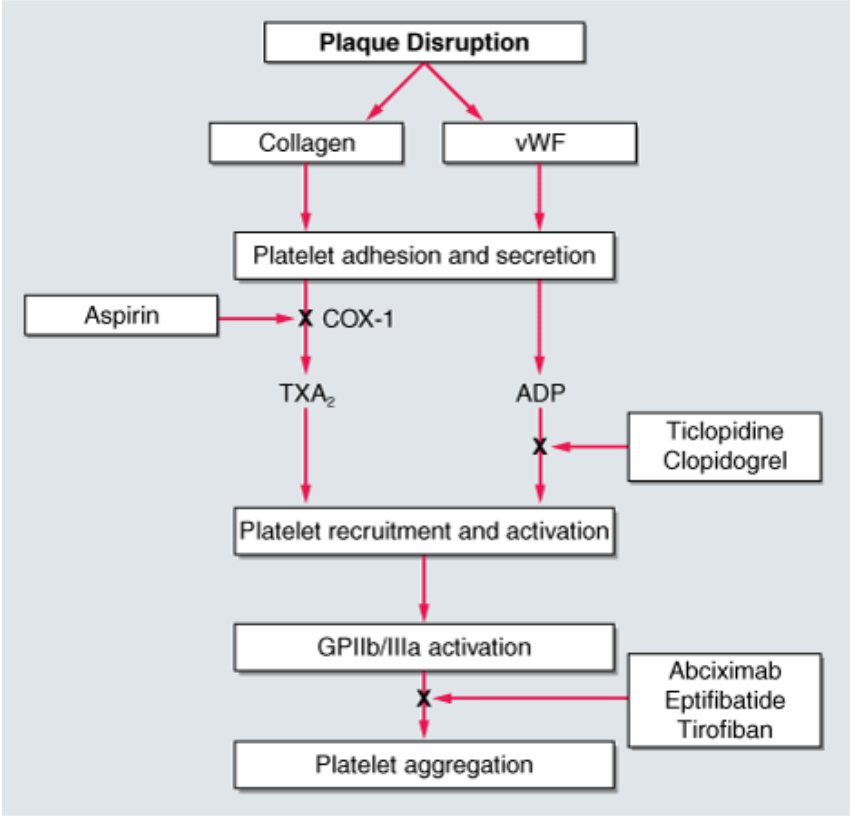
antithrombotics



Antiplatelets

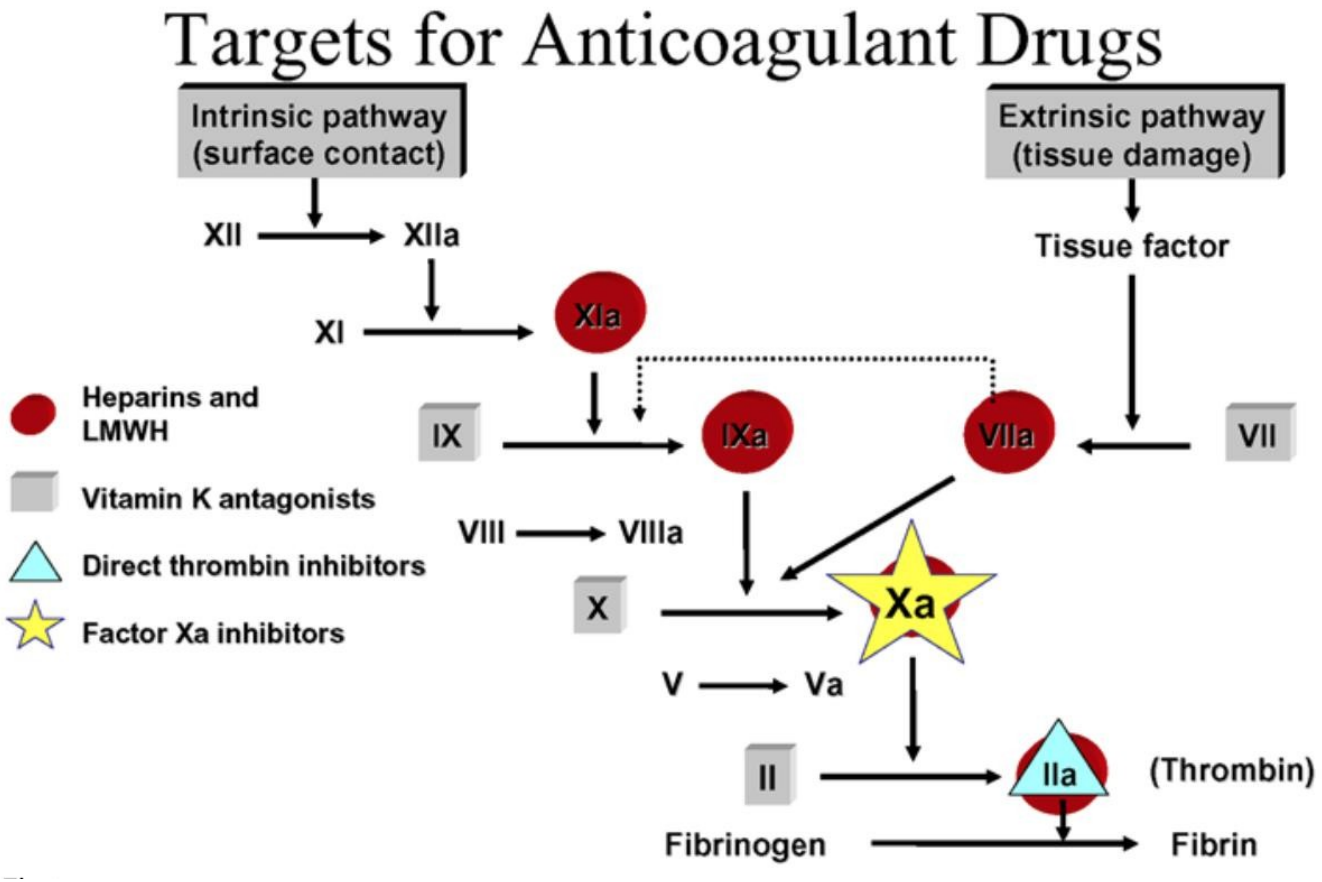
We influence function of thrombocytes, not number of throbocytes!

1. Inhibitors of cyklooxygenase/inhibitors of thromboxane A_2 synthesis or antagonists of the receptors
2. Inhibitors of ADP receptors ($P2Y_{12}$)
3. Antagonists of protease-activated receptors (PAR-1)
4. Antagonists of surface glycoproteins (GP IIb/IIa)
5. Blockage of serotonin pathway
6. Other mechanisms



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Anticoagulant



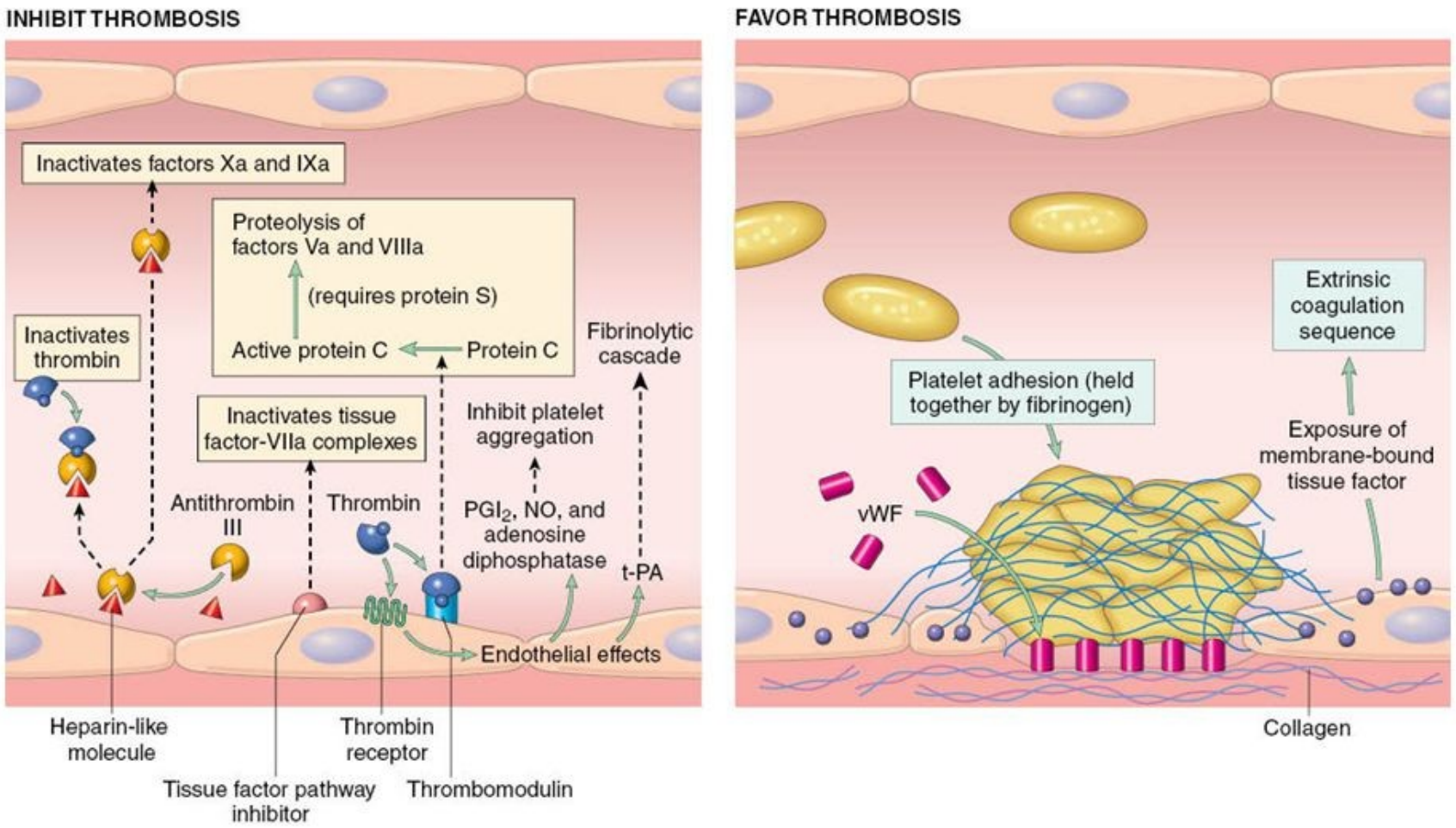


FIGURE 4–6 Anti- and procoagulant activities of endothelium. NO, nitric oxide; PGI_2, prostacyclin; t-PA, tissue plasminogen activator; vWF, von Willebrand factor. The thrombin receptor is also called a protease-activated receptor (PAR).

Role of Endothelial cells in hemostasis

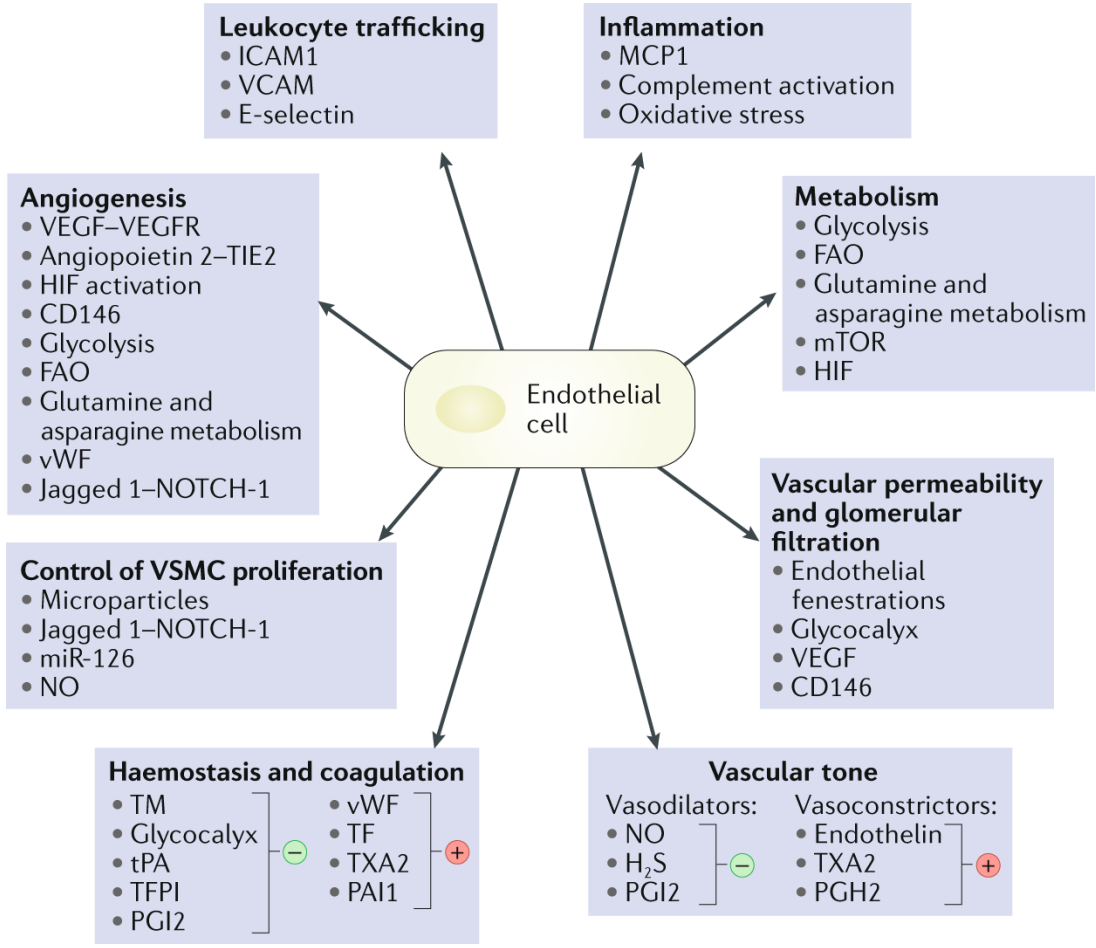
Endothelial cells **prevent thrombosis by several mechanism** ;

1. Block **exposure of to Subendothelial collagen (SEC)** and Tissue Factor (TF)
2. Produce **Prostacyclin (PGI2**) and **NO** → Vasodilation and inhibition of platelet aggregation
3. Expresses **heparin-like molecules** → **augment antithrombin III** → ATIII inactivates **thrombin (FII)** and other factors (XII,XI,IX,VIII,**X**)
4. Expresses **Tissue Plasminogen aktivator (t-PA)** → converts **plasminogen to plasmin** → cleaves **fibrin and fibrinogen/**destroys **clotting factors &** inhibit **platelet aggregation**
5. Expresses **thrombomodulin** → **thrombin-thrombomodulin complex** → **activates Protein C (together with Protein S)** → inactivates **factor V and VIII**
6. **Plasminogen aktivator inhibitor (PAI) → inhibits activation of plasminogen to plasmin**

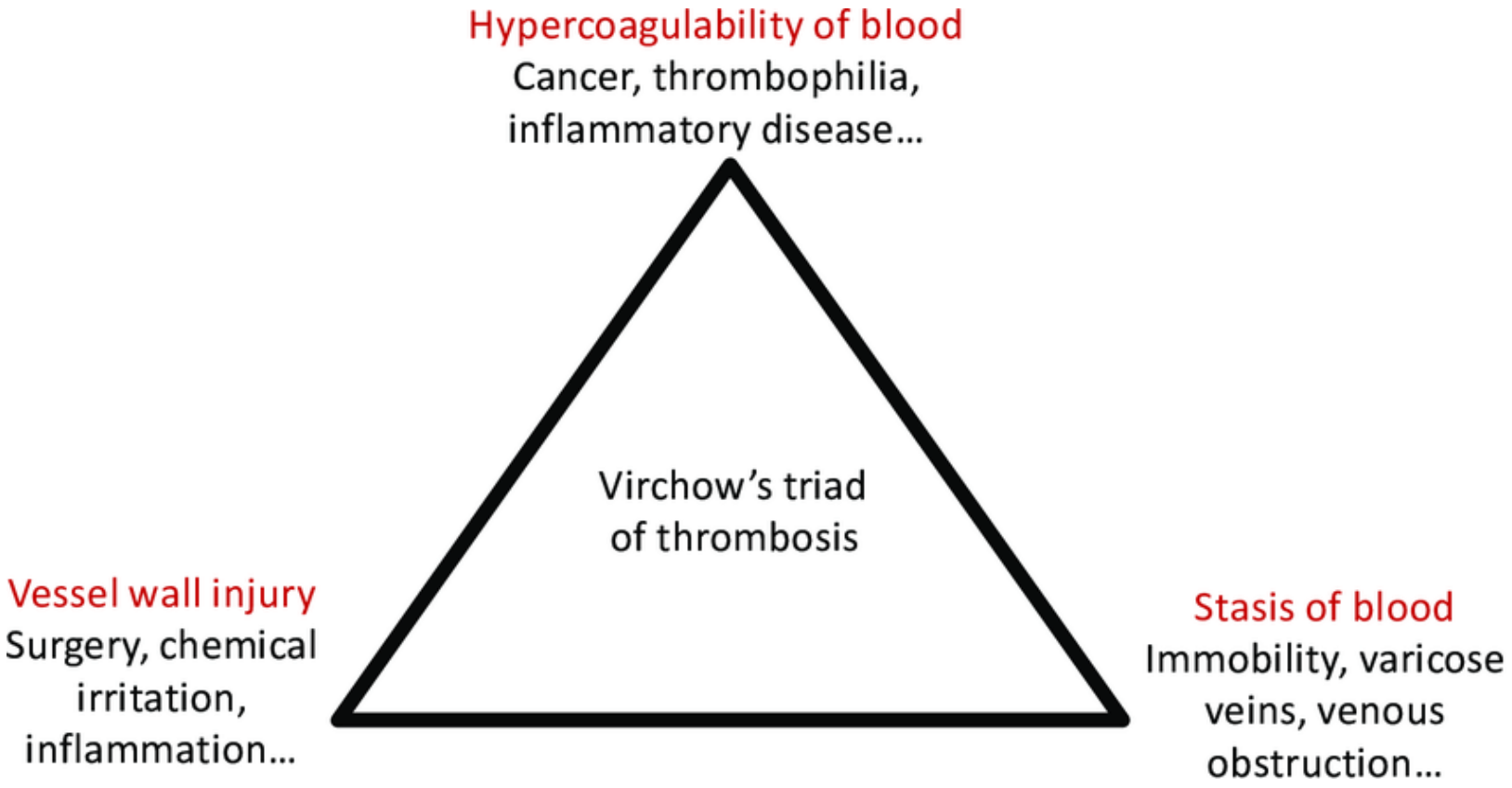
Factors enhancing thrombus formation

1. **Thromboxan A2** → Vasoconstrictor and enhances platelet aggregation
2. **Von willbrand factor (vWF)** → Platelet adhesion molecule
3. **Tissue thromboplastin (Factor III)** → activates factor VII (exterinsic pathway)

Endothelial function



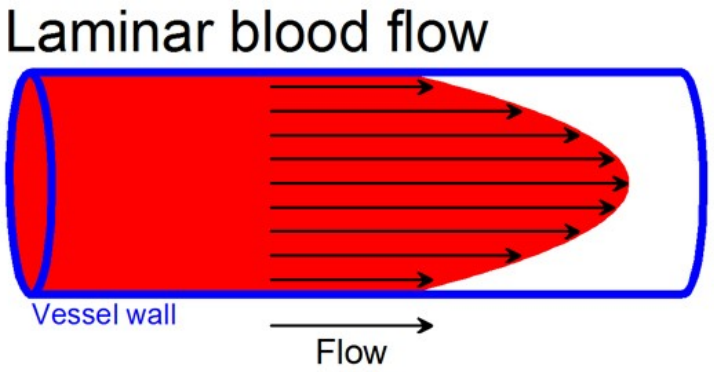
Thrombosis - Virchows triad

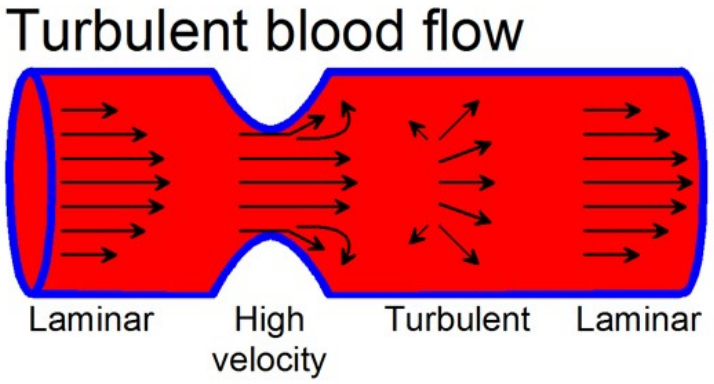


Blood flow in the vessels

- Blood flows in the vessels in continues and streameline (straight line) fashion → **laminar flow**
- laminar flow **keeps platelets and clotting factors dispersed and inactivated (anti-thrombotic)**

Stasis or Turbulance blood flow → increase risk of Clot formation **(thrombosis)**





BLOOD FLOW

Key Principles

- *Blood flow* —
  - Amount of blood that passes by a given point in a given amount of time.
- *Blood flow velocity* —
  - Distance blood travels in a given amount of time.

Atherosclerosis

- *Plaques* —
  - Fat and cholesterol build up and restrict blood flow.
  - Can detach and completely obstruct blood flow in smaller vessels.

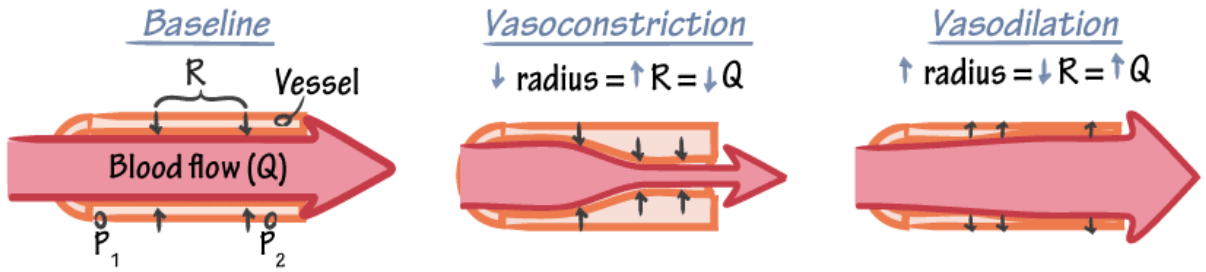
Murmurs

- Blood flow turbulence produces sounds that can be auscultated.
- Bruits are arterial murmurs;
- Can indicate vessel shunts or stenoses.
- Cardiac murmurs often occur from structural valvular disease.

Blood Flow (Q) & Ohm's Law

$$Q = \frac{\Delta P}{R}$$

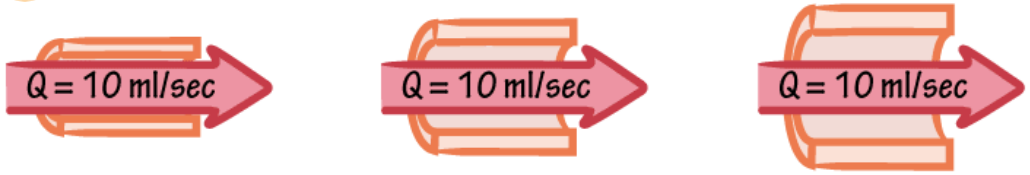
- ΔP = Change in pressure (P_1 - P_2)
- R = Resistance of vessel
- Total blood flow ~ 5 L/min
  - Total blood flow = Cardiac output



Velocity (v)

$$v = \frac{Q}{A}$$

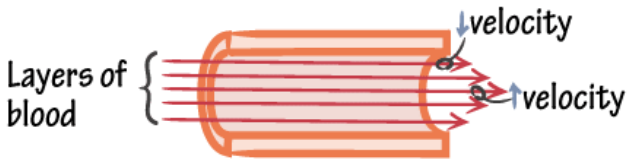
- Q = Blood flow
- A = Cross-sectional area(πr^2)
- As vessel radius increases, velocity decreases.



	A = 1 cm^2	A = 10 cm^2	A = 100 cm^2
$\frac{Q}{A}$	$\frac{10\ ml/sec}{1\ cm^2}$	$\frac{10\ ml/sec}{10\ cm^2}$	$\frac{10\ ml/sec}{100\ cm^2}$
v =	10 cm/sec	1 cm/sec	0.1 cm/sec

Types of Flow

- *Laminar flow* —
  - Normal, linear blood flow with parabolic profile:
  - Velocity is highest in the center, lowest near vessel wall.



- *Turbulent flow* —
  - Blood layers mix and run radially and axially.
  - Result of vessel irregularity, changes in blood velocity or viscosity.
  - Can result in reduced tissue perfusion.

LAMINAR VS. TURBULENT FLOW

Laminar flow is streamlined (in a straight line), turbulent flow is not.

Reynolds' number predicts whether blood flow will be laminar or turbulent.

$$\text{Reynold's number} = \frac{\text{(diameter) (velocity) (density)}}{\text{viscosity}}$$

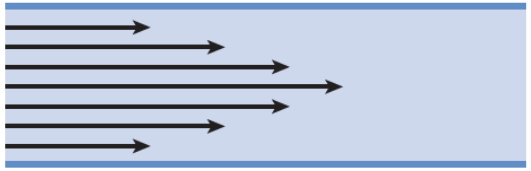


Figure V-1-6. Laminar Flow

When Reynolds' number is increased, there is a greater tendency for **turbulence,** which causes audible vibrations called **bruits.**

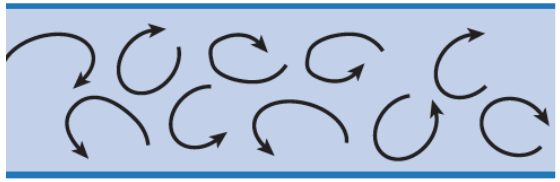


Figure V-1-7. Turbulent Flow

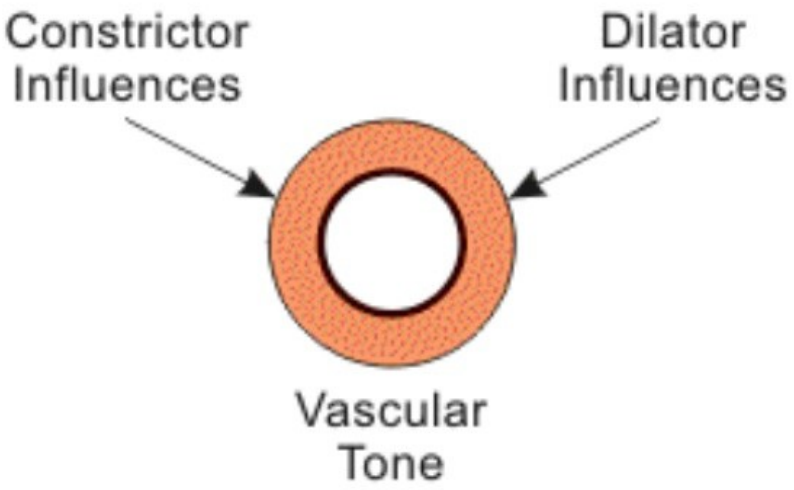
The following promote the development of turbulent flow (i.e., increase Reynolds' number):

- Increasing tube diameter
- Increasing velocity
- Decreasing blood viscosity, e.g., anemia (cardiac flow murmer)

›2,000: turbulent fl w

‹2,000: laminar fl w

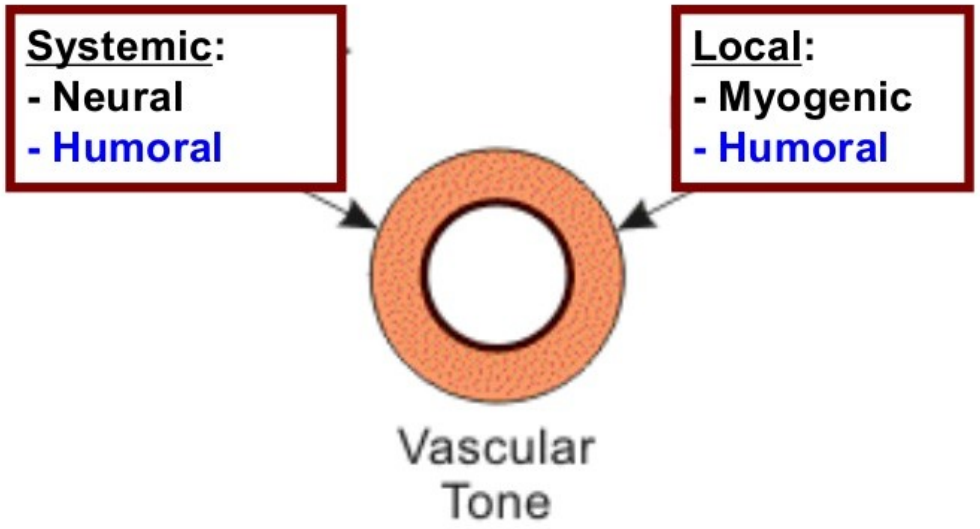
Regulation of vascular tone



Vasoconstrictor and vasodilator influences acting on arteries and veins determine their state of vascular tone, which is the balance between constrictor and dilator influences.

Courtesy of Prof.Babula

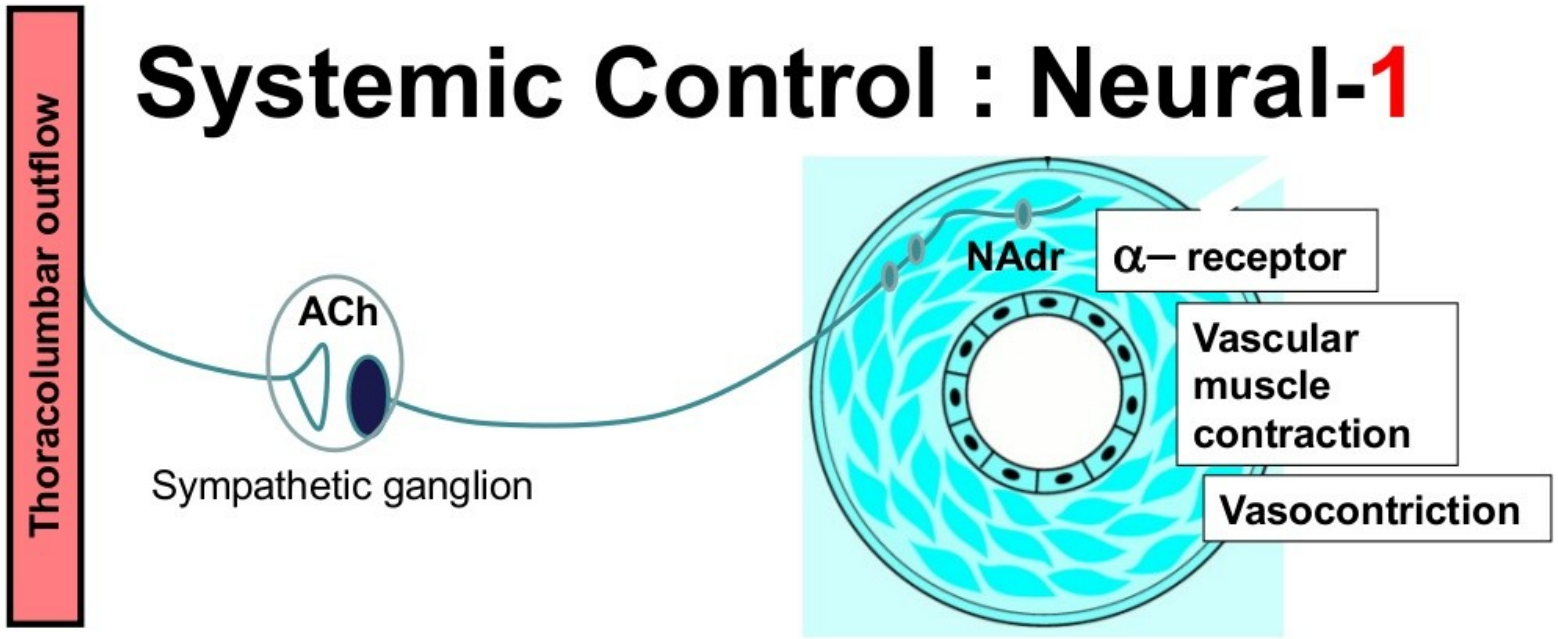
Regulation of vascular tone



Humoral = chemical substances (e.g. hormones, ions, metabolites, dissolved gases, drugs) in blood or other body fluids

Courtesy of Prof.Babula

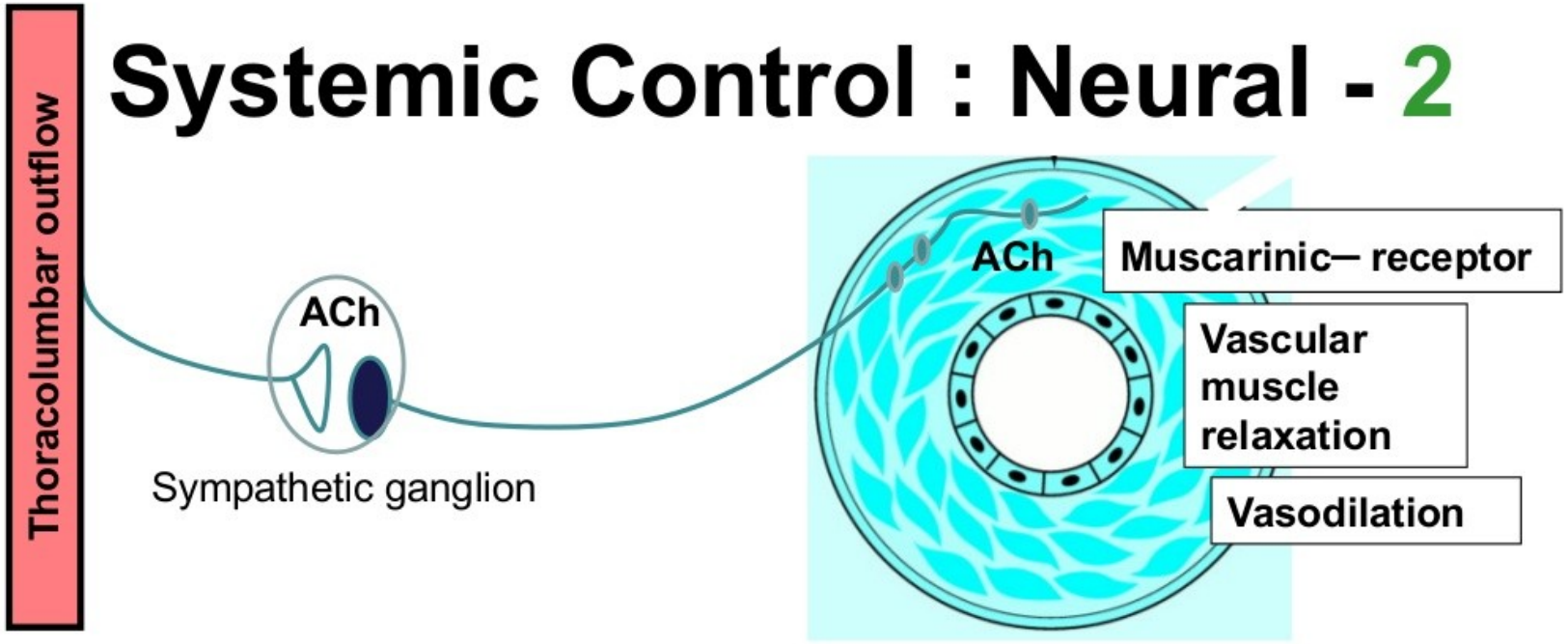
Systemic Control : Neural-1



- Continuous Sympathetic noradrenergic discharge (Sympathetic tone) maintains vascular tone
- Most important control
- moment to moment variation in vascular tone is effected by variation in sympathetic tone

Courtesy of Prof.Babula

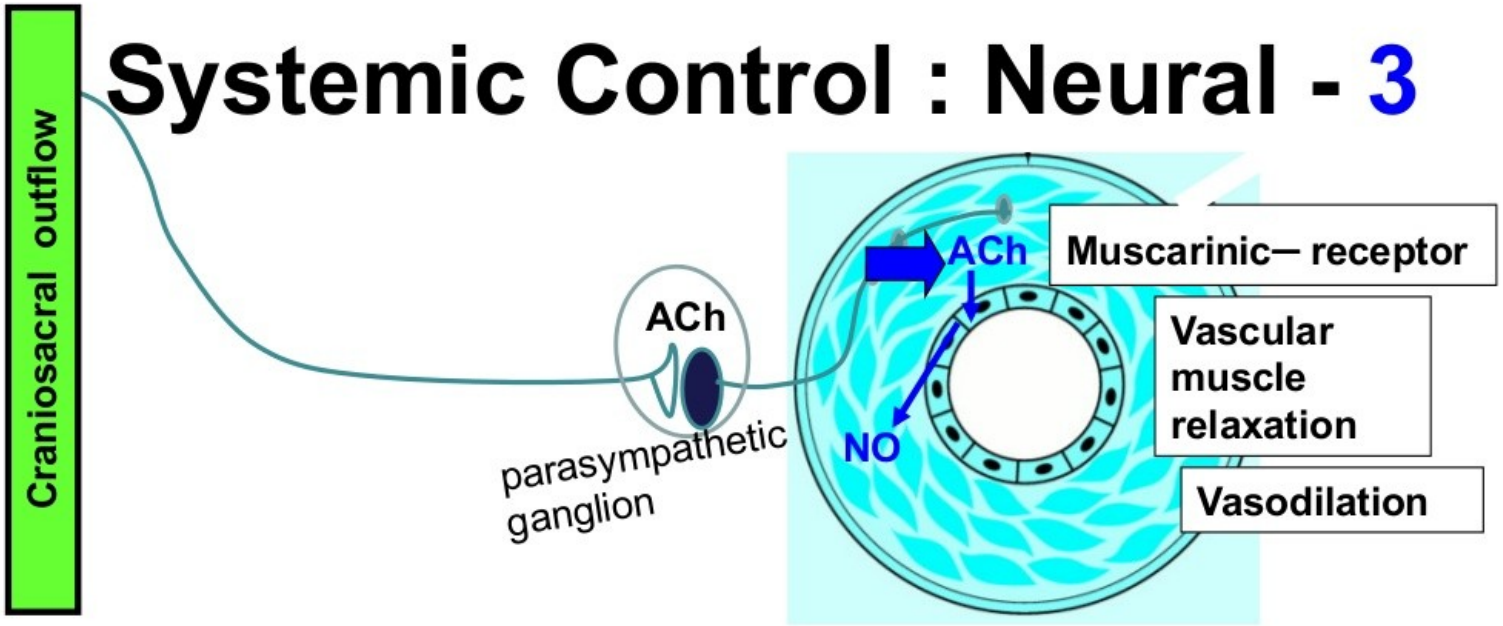
Systemic Control : Neural - 2



- Sympathetic cholinergic vasodilator system supplies the vessels of the skeletal muscles
- Not important for normal control
- Sudden emotional shock ➔ activation of this system ➔ pooling of blood in skeletal muscles of lower limbs ➔ fainting

Courtesy of Prof.Babula

Systemic Control : Neural - 3



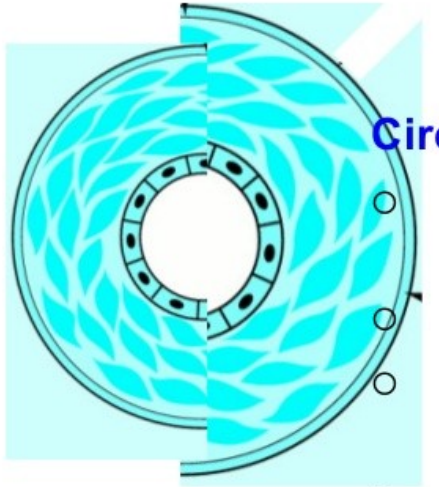
- Parasympathetic nervous system
- Not important for systemic control of vascular tone
- Causes vasodilation in
  - actively secreting glands
  - erectile reproductive tissue
- Mediated by Nitric Oxide (NO) from endothelial cells

Courtesy of Prof.Babula

Systemic Control : Humoral

Circulating Vasoconstrictors

- **Noradrenaline**
- **Angiotensin II**
- **Vasopressin**
- **Adrenaline (skin, splanchnic)**
- **Dopamine**
- **Neuropeptide Y**
- **Calcium ions**



Circulating Vasodilators

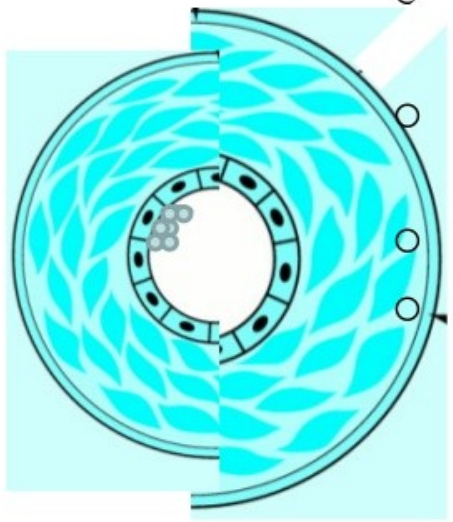
- **Adrenaline (liver, skeletal muscle)**
- **Dopamine (kidney)**
- **Atrial Natriuretic peptide (ANP)**
- **VIP (Vasoactive Intestinal Peptde)**
- **Kinins**
- **Substance P**

Courtesy of Prof.Babula

Local Control : Humoral

Vasoconstrictors

- **Serotonin (5-HT) (from platelets)**
- **Thromboxane A2 (from platelets)**
- **Endothelin (from endothelial cells)**



Vasodilators

- **Nitric oxide (from endothelial cells)**
- **Prostacyclin (from endothelial cells)**
- **Histamine**
- **Vasodilator metabolites (VDMs) from tissue metabolism**

Courtesy of Prof.Babula

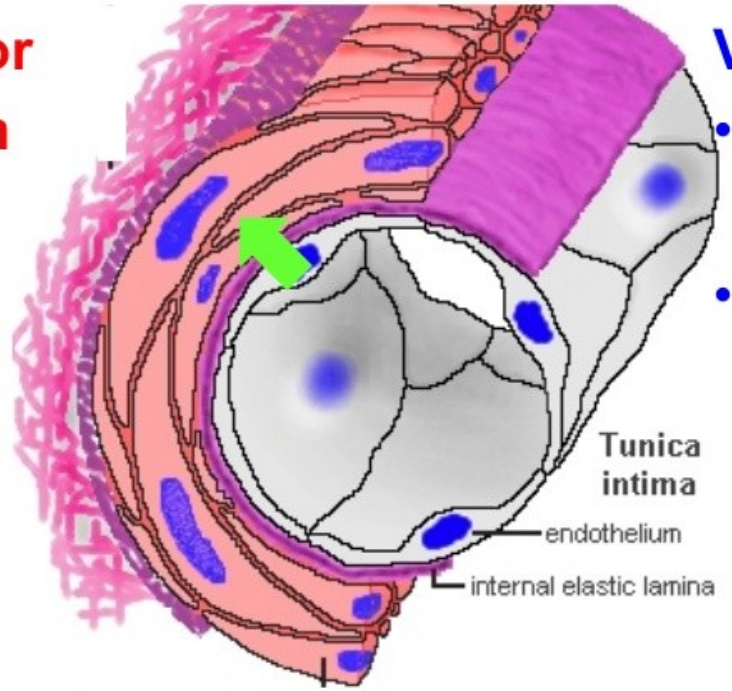
Endothelial control of vascular tone:

Endothelial cells secrete

Vasoactive substances:

Vasoconstrictor

- **Endothelin** (peptide)



Vasodilators

- **NO** (gas)
- **Prostacyclin** (prostaglandin)

Courtesy of Prof.Babula

Thrombophilia = Hypercoagulability

- Factor V Leiden
- Prothrombin 20210A variant
- Antiphospholipid Ab syndrome
  - lupus anticoagulant
  - anticardiolipin antibody

- Deficiencies of:
  - Antithrombin
  - Protein C
  - Protein S
  - Heparin cofactor II
  - ↑ Factor VIII, IX, XI, II

- Hyperhomocysteinemia
- Fibrinolytic dysfunction
- Myeloprolif. disorders:
  - PRV, ET
- Dysfibrinogenemia
- DIC

DIC = disseminated intravscular coagulation;
ET = essential thrombocytosis; PRV = polycythemia rubra vera

A 24-year-old woman comes to the physician because of pain and swelling of her left leg over the past 24 hours. The pain is worse while walking and improves when resting. Seven months ago, she was diagnosed with a pulmonary embolism and was started on warfarin. Anticoagulant therapy was discontinued 1 month ago. Her sister has systemic lupus erythematosus. The patient does not smoke. She currently takes no medications. Her temperature is 37.8°C (100°F), pulse is 78/min, and blood pressure is 123/72 mm Hg. On physical examination, the left calf is diffusely erythematous, swollen, and tender. Dorsal flexion of the left foot elicits pain. Cardiopulmonary examination shows no abnormalities. On duplex ultrasonography, the left popliteal vein is not compressible. Laboratory studies show an elevated serum concentration of D-dimer and insensitivity to activated protein C. Further examination is most likely to show which of the following?

A. Deficiency of antithrombin III
B. Elevated coagulation factor VIII levels
C. Deficiency of protein S
D. Antiphospholipid antibodies
E. Mutation of coagulation factor V
F. Mutation of prothrombin
G. Elevated levels of homocysteine
H. Deficiency of protein C

A 24-year-old woman comes to the physician because of pain and swelling of her left leg over the past 24 hours. The pain is worse while walking and improves when resting. Seven months ago, she was diagnosed with a pulmonary embolism and was started on warfarin. Anticoagulant therapy was discontinued 1 month ago. Her sister has systemic lupus erythematosus. The patient does not smoke. She currently takes no medications. Her temperature is 37.8°C (100°F), pulse is 78/min, and blood pressure is 123/72 mm Hg. On physical examination, the left calf is diffusely erythematous, swollen, and tender. Dorsal flexion of the left foot elicits pain. Cardiopulmonary examination shows no abnormalities. On duplex ultrasonography, the left popliteal vein is not compressible. Laboratory studies show an elevated serum concentration of D-dimer and insensitivity to activated protein C. Further examination is most likely to show which of the following?

A	Deficiency of antithrombin III	6%	—
B	Elevated coagulation factor VIII levels	3%	—
C	Deficiency of protein S	8%	—
D	Antiphospholipid antibodies	15%	—
E	Mutation of coagulation factor V	61%	✓
F	Mutation of prothrombin	3%	—
G	Elevated levels of homocysteine	1%	—
H	Deficiency of protein C	4%	—

References :

1. Le T, Bhushan V, Sochat M, et al., eds. *First Aid for the USMLE Step 1 2021*. McGraw Hill; 2021.

2. Sattar HA. *Fundamentals of Pathology: Medical Course and Step 1 Review*. Pathoma.com; 2011. Accessed December 26, 2021.

3. Boron WF, Boulpaep EL, eds. *Medical Physiology*. Third edition. Elsevier; 2017.

4. Wilson LB. *USMLE Step 1 Lecture Notes 2017: Physiology*.; 2017.

Remember , at the end of the day, patient can present with either bleeding disorder or sign & symptoms of formation of pathological clot.

The fundamental knowladge of hemostasis and pharmacological approach helps you save them !

THANK YOU ☺