THROMBOSIS

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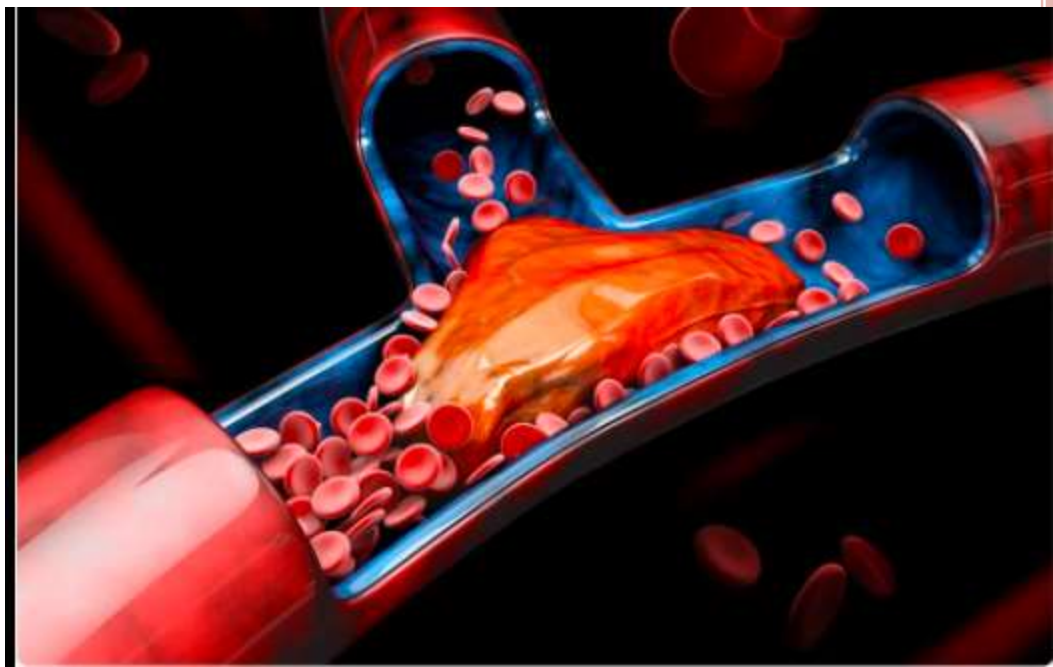
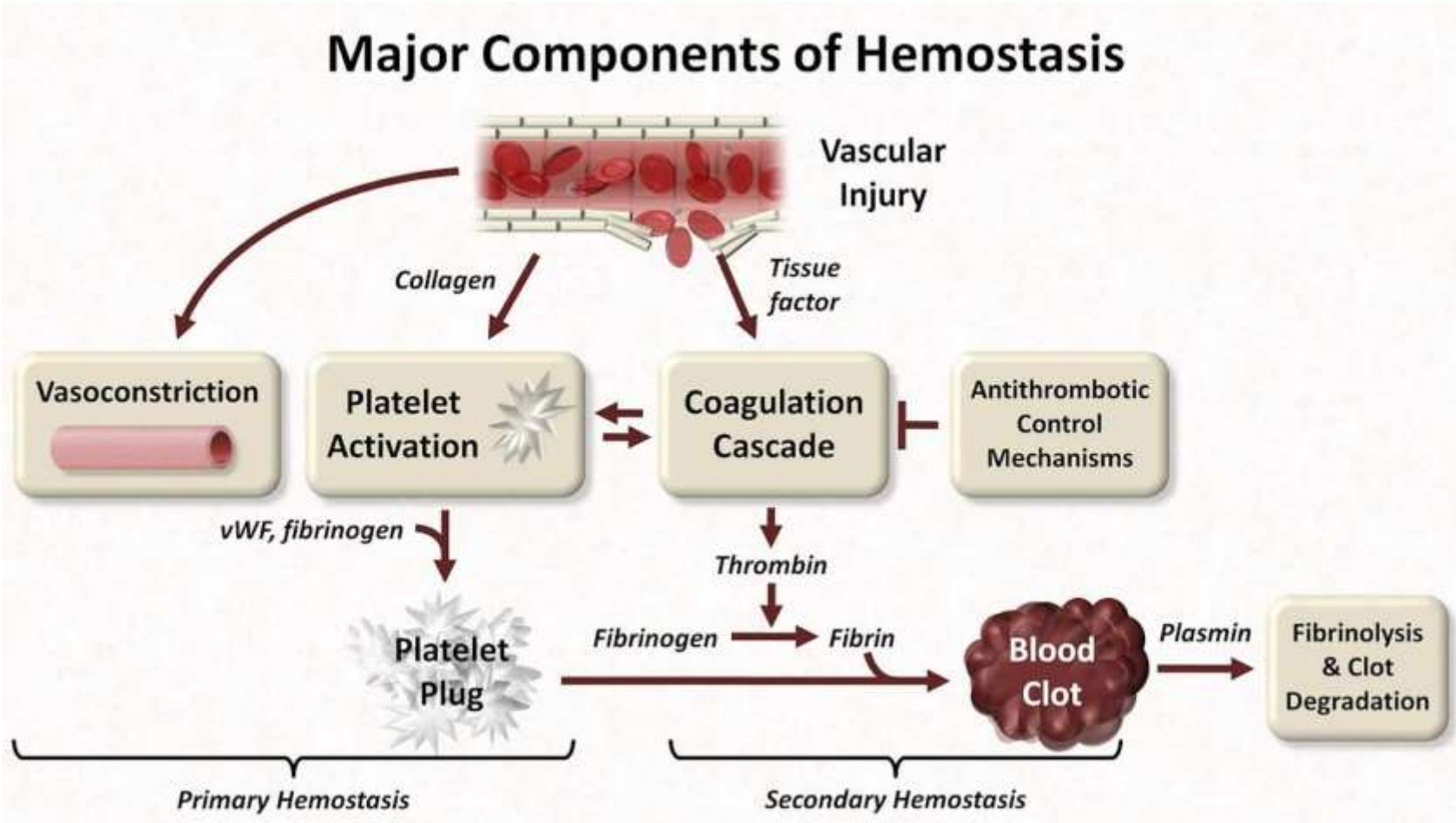


Major Components of Hemostasis

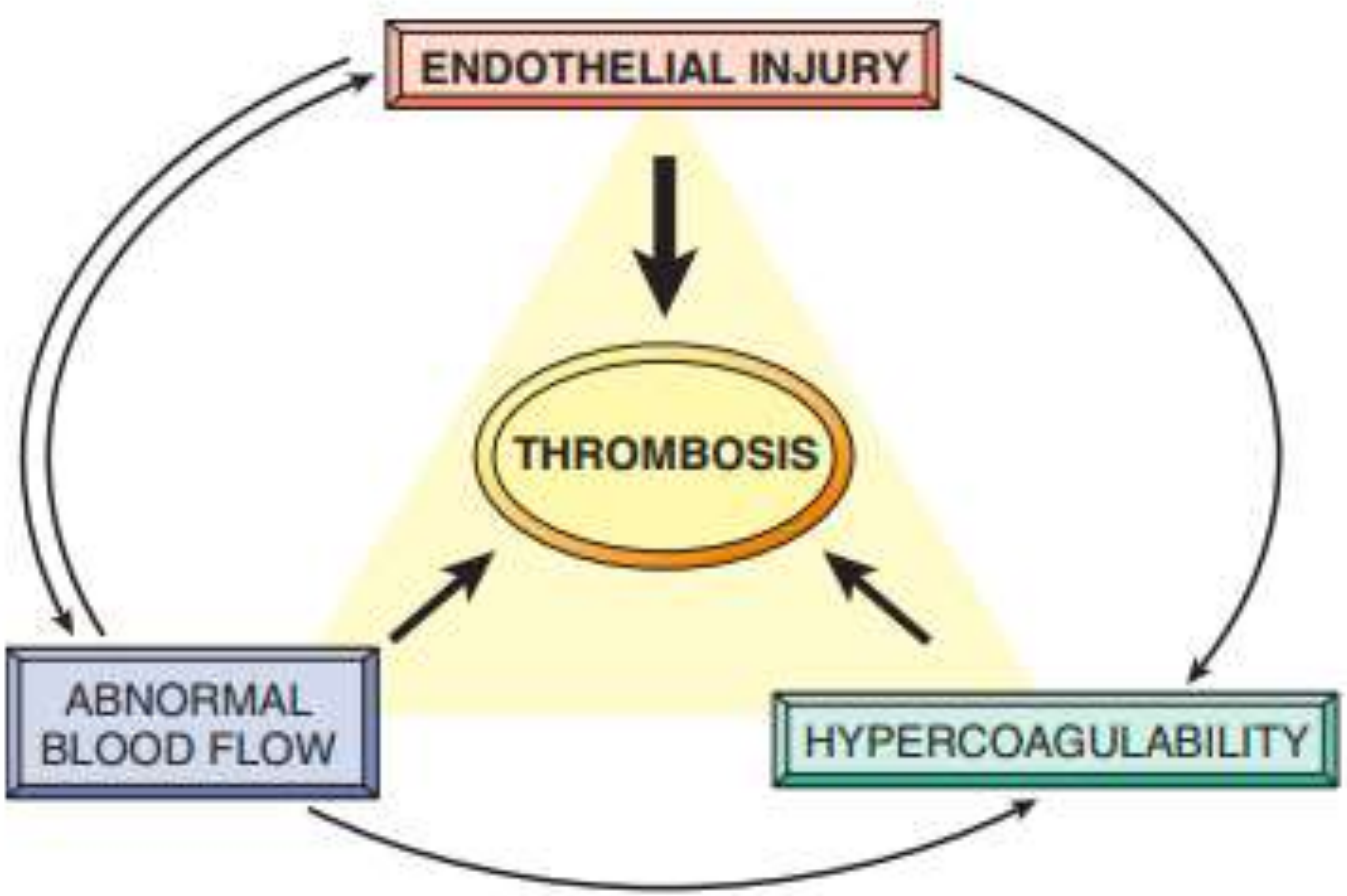


Thrombosis

- **Thrombosis** is the formation of a blood clot, known as a thrombus, within a blood vessel.

- The primary abnormalities that lead to intravascular thrombosis are:
  - (1) endothelial injury.
  - (2) stasis or turbulent blood flow.
  - (3) hypercoagulability of the blood

➢(the so-called “Virchow triad”)



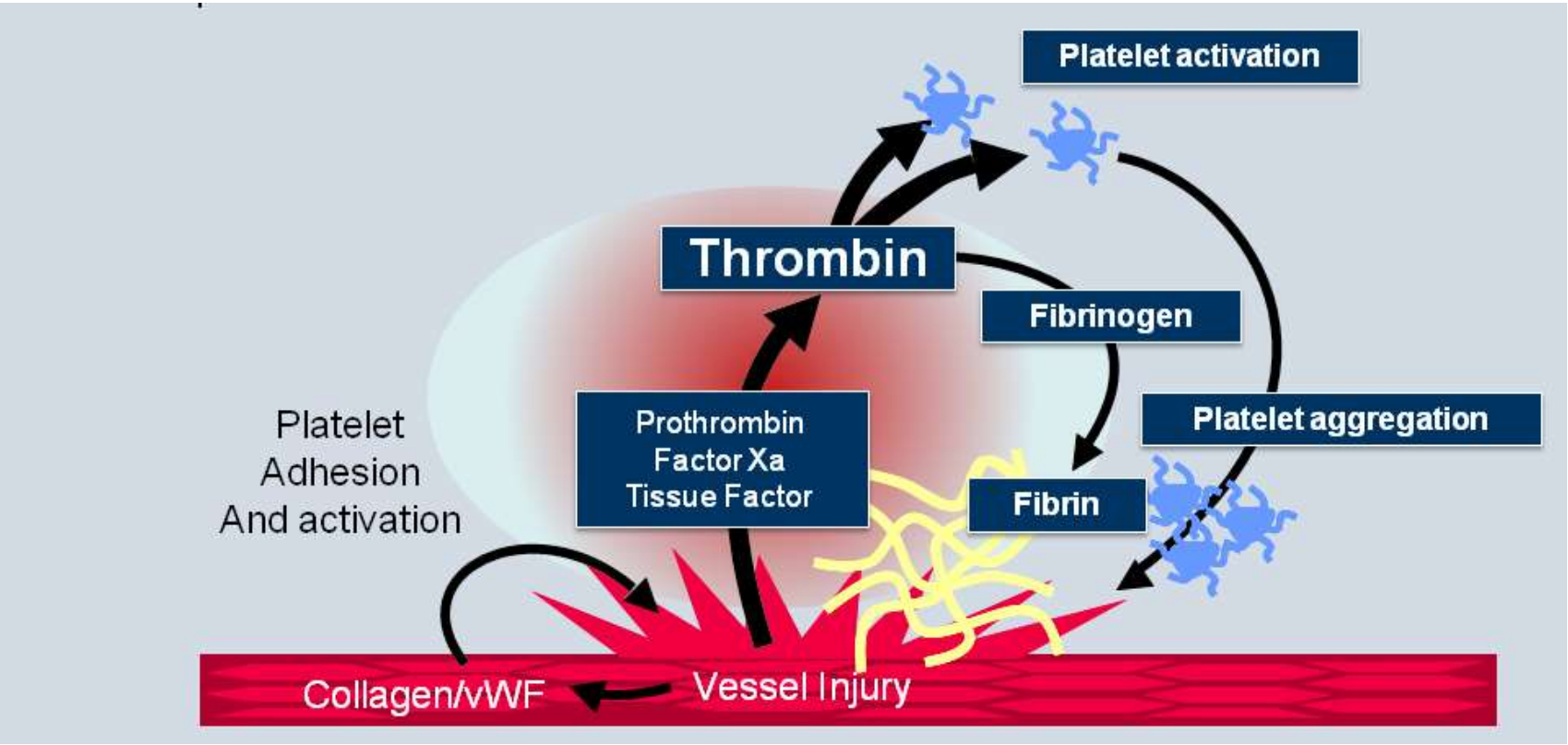
1. Endothelial Injury

- Endothelial injury leading to platelet activation.

- cardiac and arterial clots are typically rich in platelets.

- Endothelial injury may be caused by:
  - physical injury.
  - infectious agents.
  - inflammatory mediators.
  - metabolic abnormalities, such as hypercholesterolemia or homocystinemia,
  - toxins absorbed from cigarette smoking.

severe endothelial injury may trigger thrombosis by exposing VWF and tissue factor

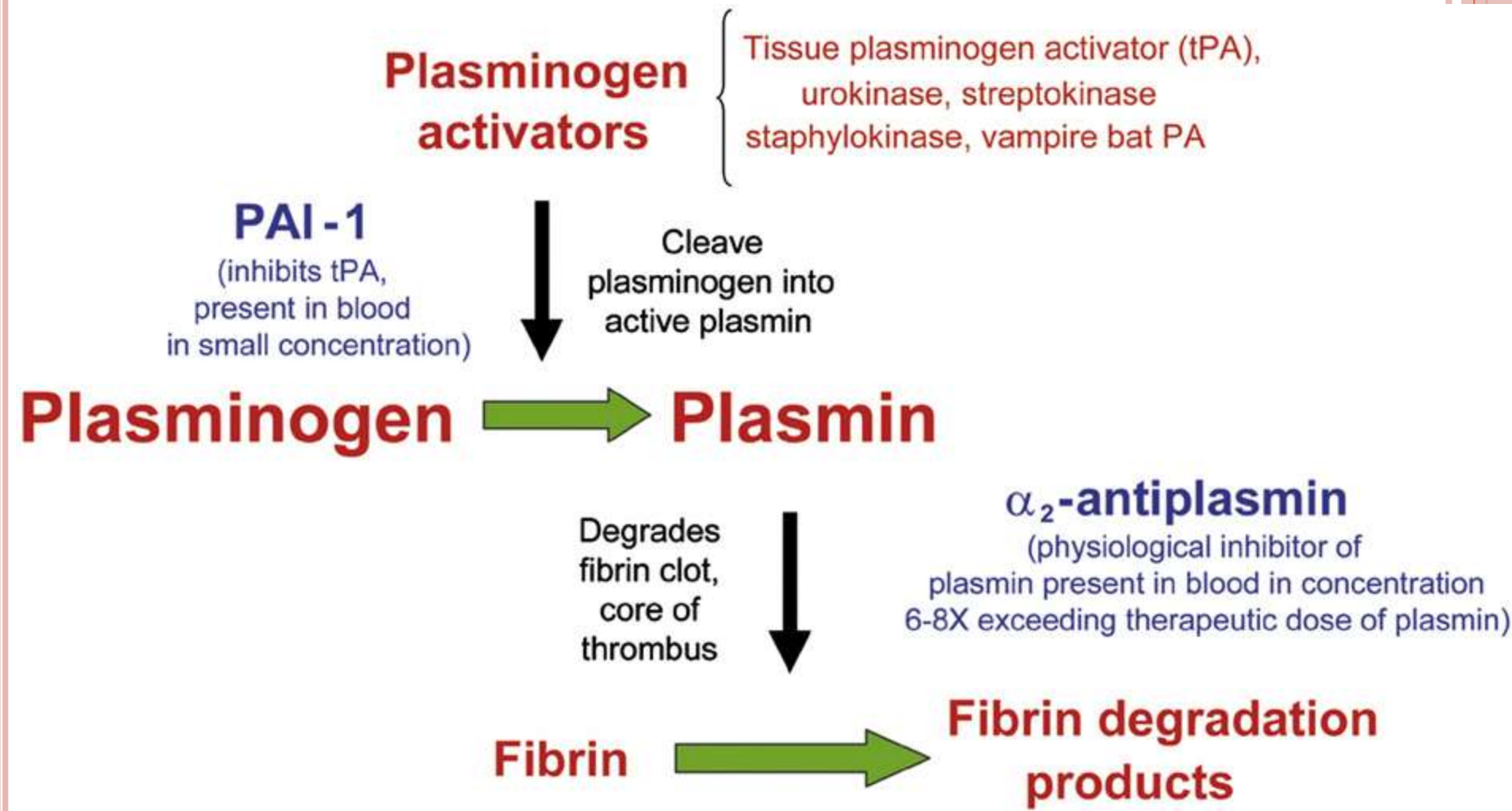


- Endothelial injury …..that's mean:

- platelet activation: exposed VWF, TF.
- Endothelial dysfunction : <u>prothrombotic endothelium</u>.

- Procoagulant changes:
- ↓thrombomodulin, ↑thrombin

- Anti-fibrinolytic effects:
- ↑ Plasminogen activator inhibitors (PAI).
- ↓t-PA.


Plasminogen activators
Tissue plasminogen activator (tPA), urokinase, streptokinase staphylokinase, vampire bat PA
PAI-1
(inhibits tPA, present in blood in small concentration)
Cleave plasminogen into active plasmin
Plasminogen
Plasmin
Degrades fibrin clot, core of thrombus
α2-antiplasmin
(physiological inhibitor of plasmin present in blood in concentration 6-8X exceeding therapeutic dose of plasmin)
Fibrin
Fibrin degradation products

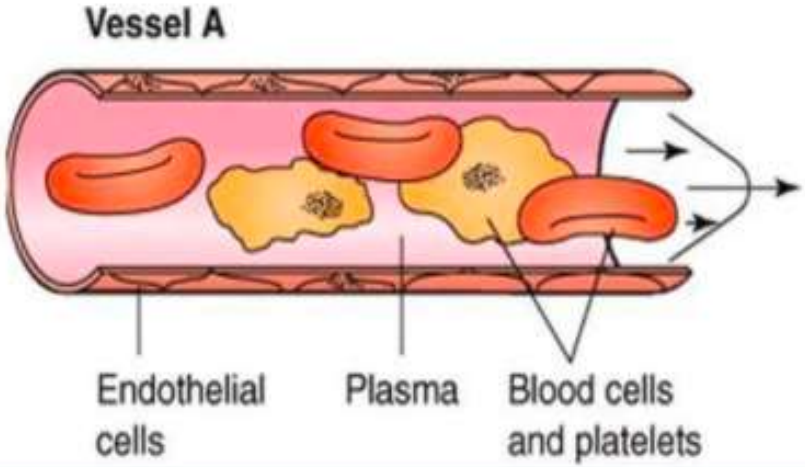
2. Abnormal Blood Flow

- Stasis is a major factor in the development of venous thrombus.

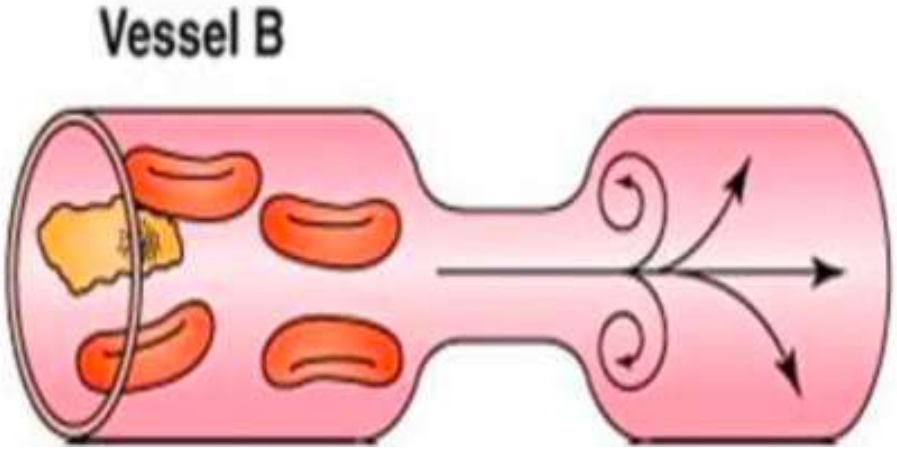
- stasis and turbulence have the following effects:

- Stasis allows platelets and leukocytes to come into contact with the endothelium when the flow is sluggish.
- Stasis also slows the washout of activated clotting factors and impedes the inflow of clotting factor inhibitors.

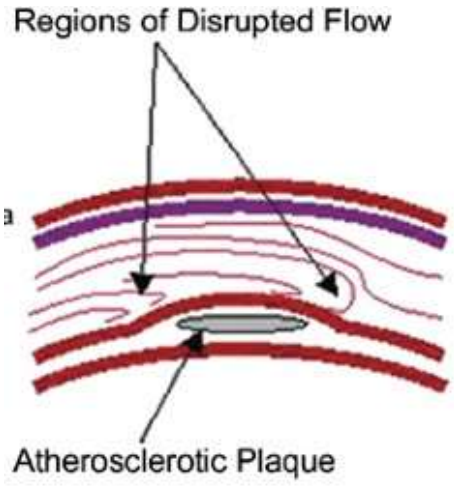
- Normally laminar, with the blood components arranged in layers
- The plasma forms the outer layer & slides smoothly along the endothelium
- Blood cells form the 'axial' layer in the centre of the blood stream
- This allows the blood to flow smoothly, layers slide over each other, axial part moves fastest.

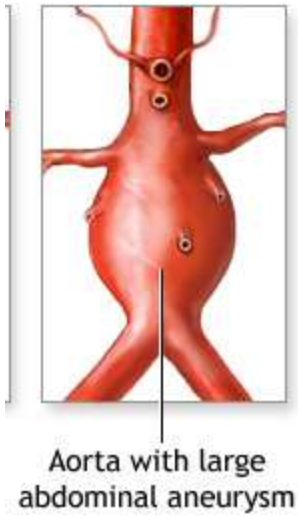


- When we take a blood pressure the sounds we here are caused by turbulent flow of blood
- Turbulent flow -caused by change in vessel diameter, increase in velocity, & low blood viscosity



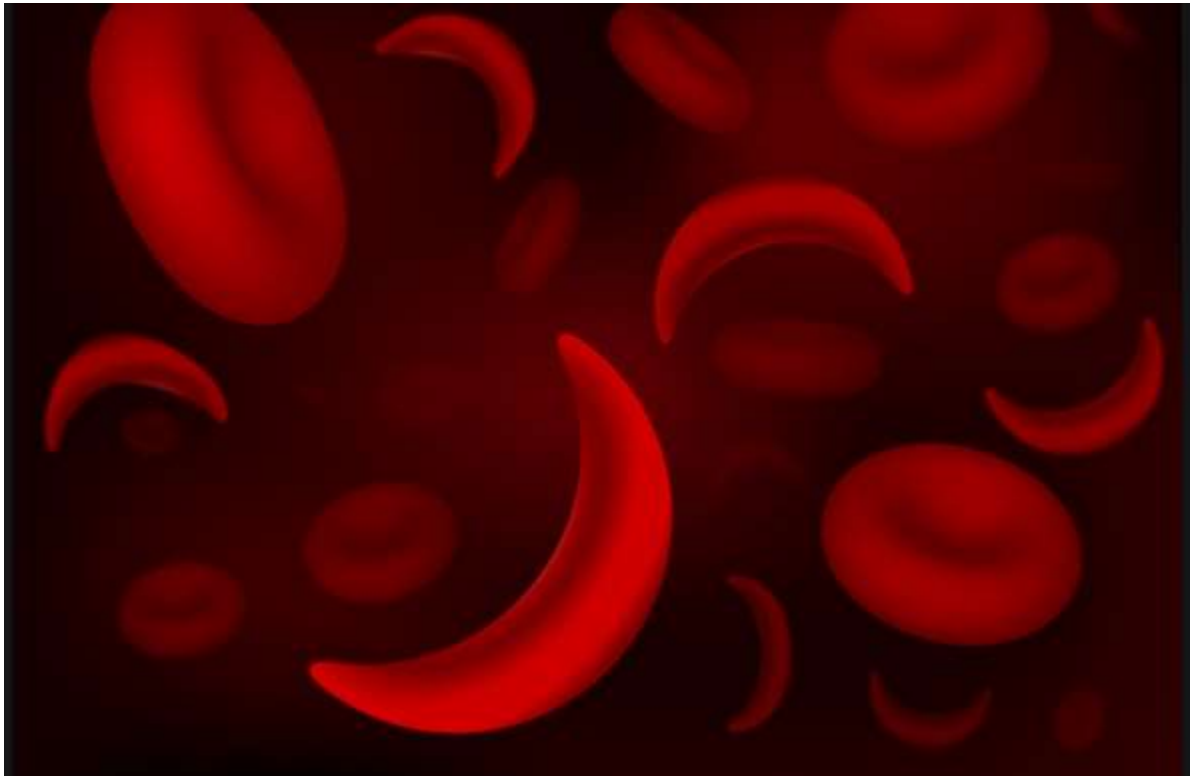
- Turbulent and static blood flow contributes to thrombosis in a number of clinical setting:
- 1. Ulcerated atherosclerotic plaques.
- 2. aortic aneurysms create local stasis and consequently are fertile sites for thrombosis





- 3. Hyperviscosity syndromes (such as polycythemia vera)increase resistance to flow and cause small vessel stasis.

- 4. sickle cell anemia:
- The deformed red cells in cause vascular occlusions.



3. Hypercoagulability

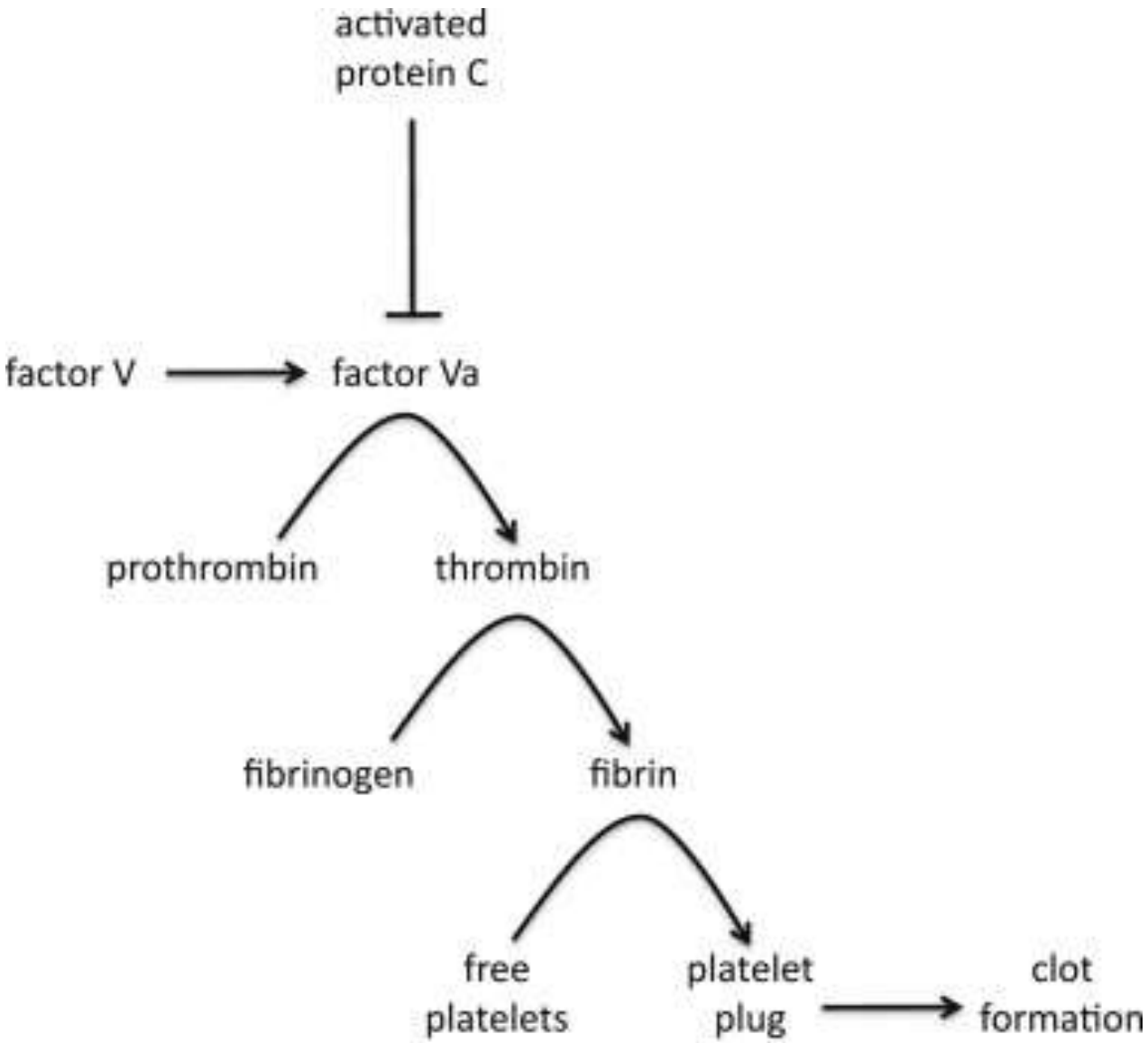
- Hypercoagulability refers to an abnormally high tendency of the blood to clot, and is typically caused by alterations in coagulation factors.

- Is an important underlying risk factor for venous thrombosis

- The alterations of the coagulation pathways that predispose affected persons to thrombosis can be divided into:

- Primary (genetic):
- mutations in the factor V .
- elevated levels of homocysteine *

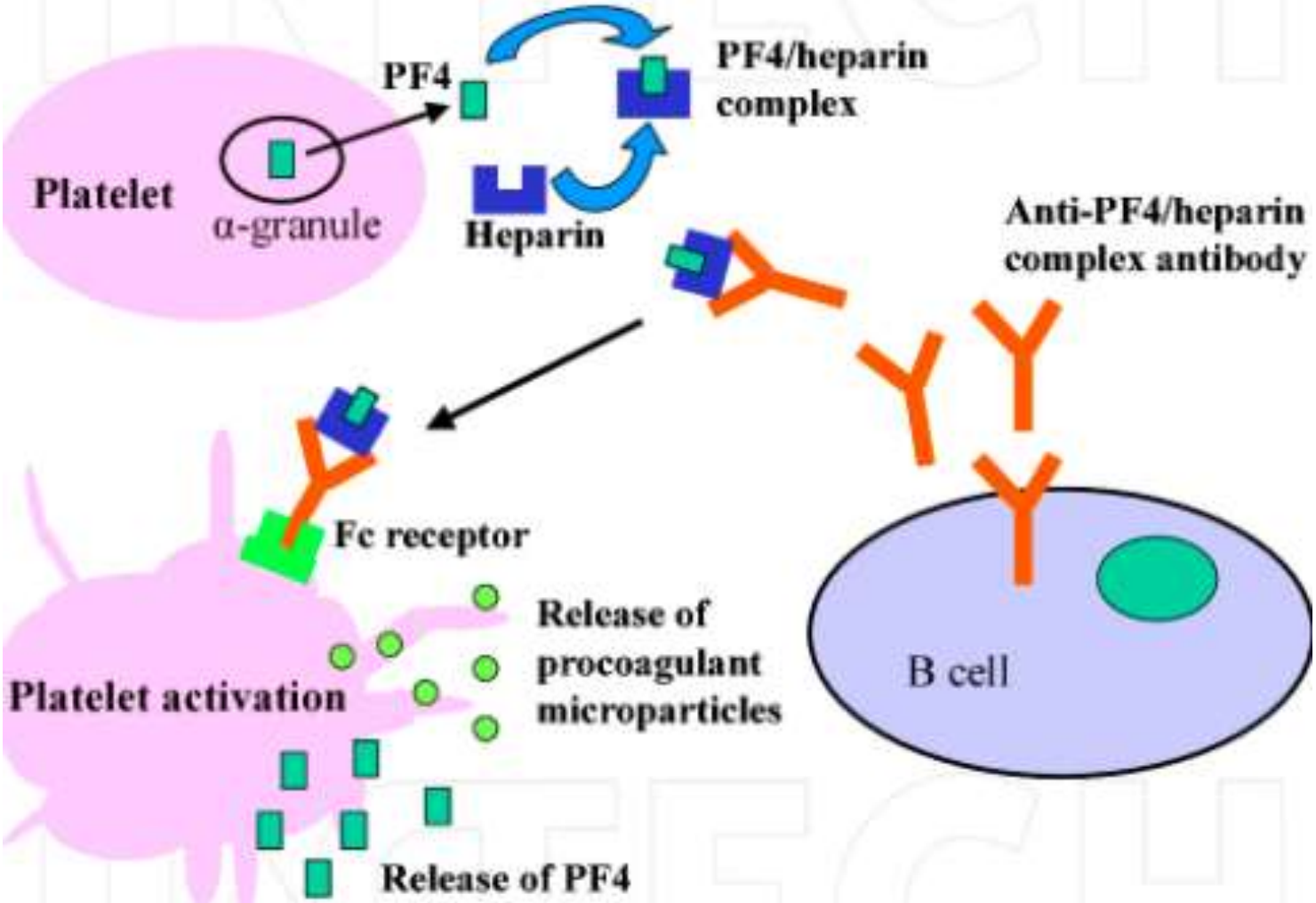
- secondary (acquired) disorders:
- oral contraceptive.
- Pregnancy**.
- Cancers***.


activated
protein C
factor V
factor Va
prothrombin
thrombin
fibrinogen
fibrin
free
platelets
platelet
plug
clot
formation

- Among the acquired thrombophilic states, two are particularly important clinical problems and deserve special mention:

- 1. Heparin-induced thrombocytopenia (HIT) syndrome:

- occurs in patients treated with unfractionated heparin.
- It is marked by the development of autoantibodies that bind complexes of heparin and platelet membrane protein (platelet factor-4).
- Its resulting in platelet activation, aggregation, and consumption (hence thrombocytopenia), as well as causing endothelial cell injury.


PF4
PF4/heparin complex
Platelet
α-granule
Heparin
Anti-PF4/heparin complex antibody
Fc receptor
Release of procoagulant microparticles
Platelet activation
B cell
Release of PF4

- 2. Anti-phospholipid antibody syndrome:

- Acquired antibodies against phospholipid - protein complexes.
- Suspected antibody targets include β2-glycoprotein I, a plasma protein that associates with the surfaces of endothelial cells, trophoblasts, and prothrombin

- clinical manifestations, including :
  - recurrent thromboses.
  - repeated miscarriages.
  - cardiac valve vegetations.
  - thrombocytopenia

- Depending on the vascular bed involved, the clinical presentations can include:

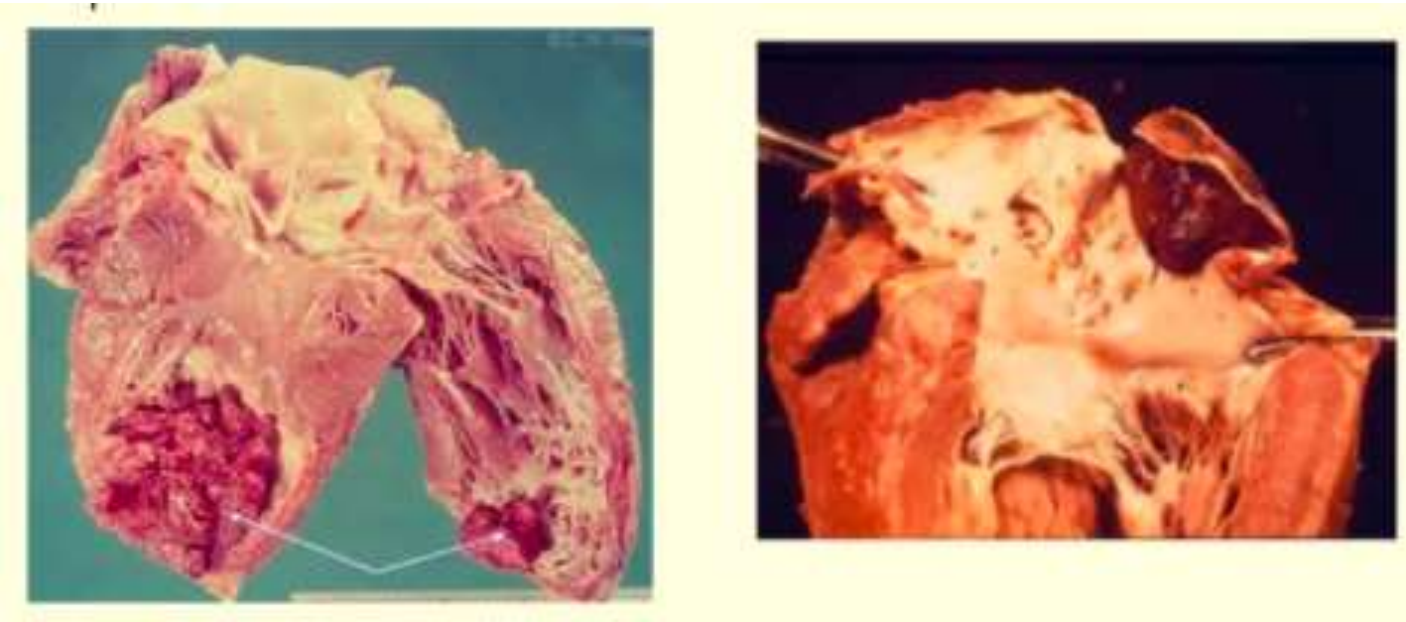
- pulmonary embolism (following lower extremity venous thrombosis).
- pulmonary hypertension (from recurrent subclinical pulmonary emboli)
- Stroke.
- bowel infarction.
- renovascular hypertension.

MORPHOLOGY

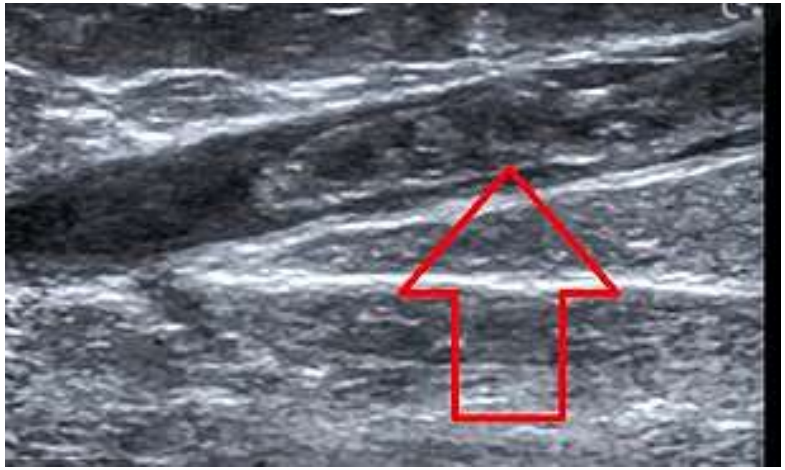
- Thrombi can develop anywhere in the cardiovascular system.

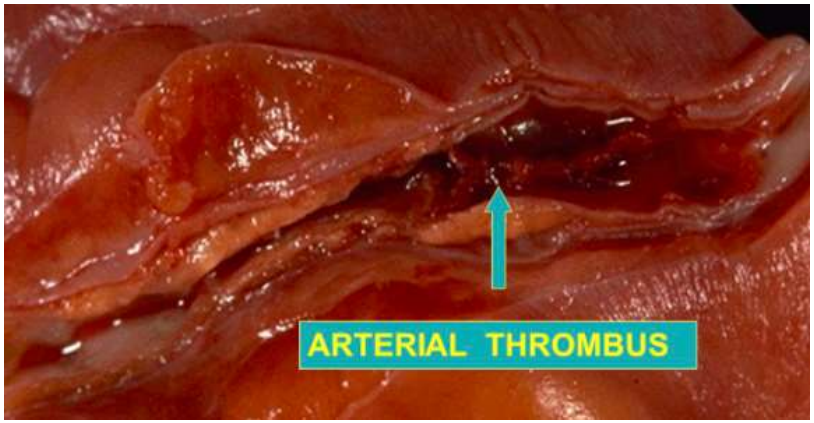
- Arterial or cardiac thrombi typically arise at sites of endothelial injury or turbulence.
- venous thrombi characteristically occur at sites of stasis.

- Mural thrombi:
- Thrombi occurring in heart chambers or in the aortic lumen



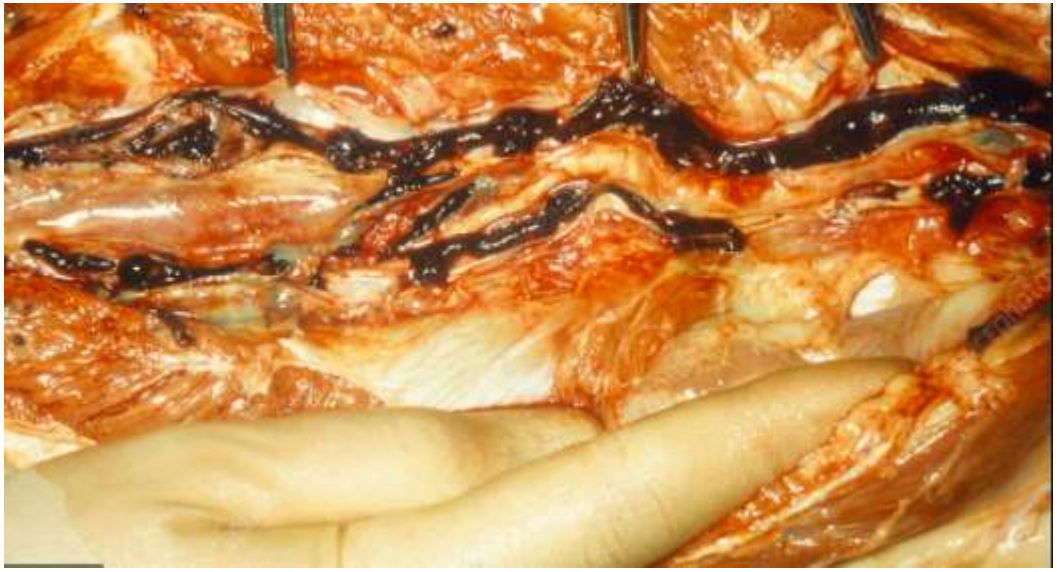
*Arterial thrombi are frequently occlusive. They are typically rich in platelets





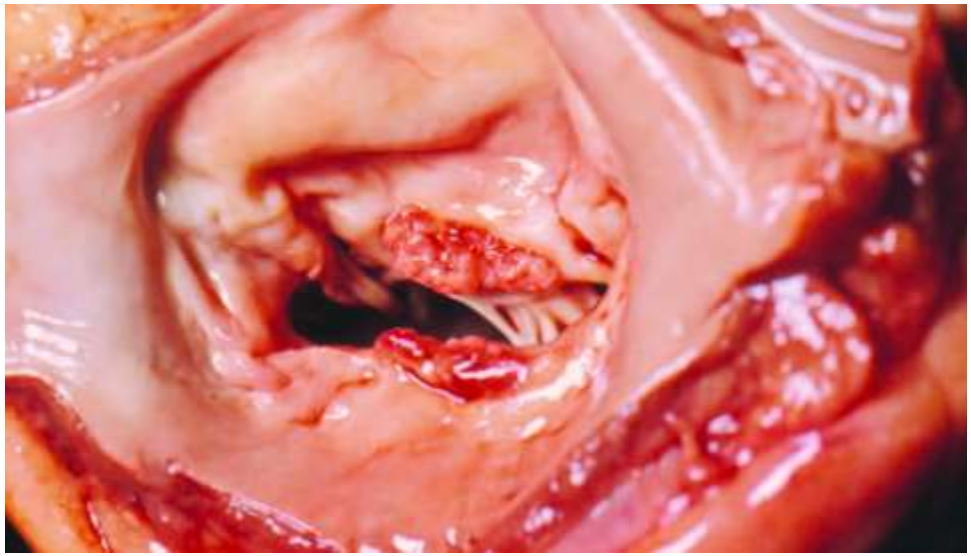
Venous thrombi (phlebothrombosis):

- they frequently propagate some distance toward the heart, forming a long cast within the vessel lumen that is prone to give rise to emboli.
- they tend to contain more red cells.

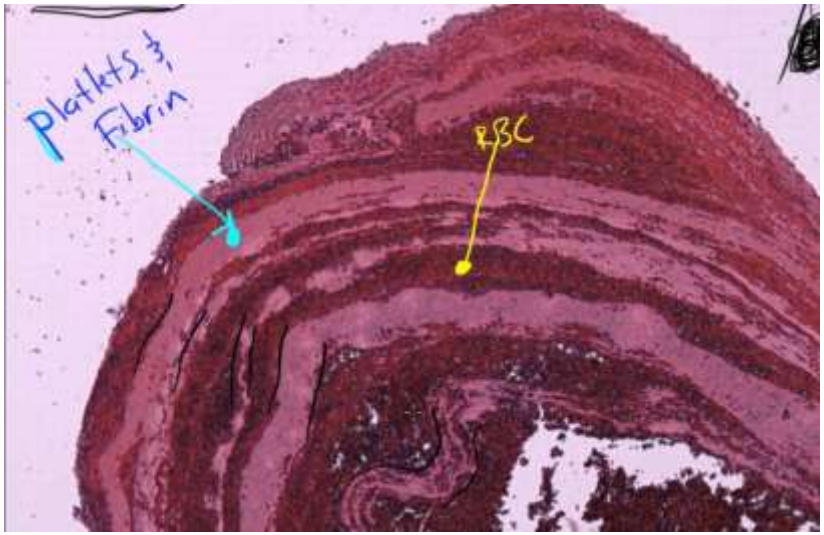


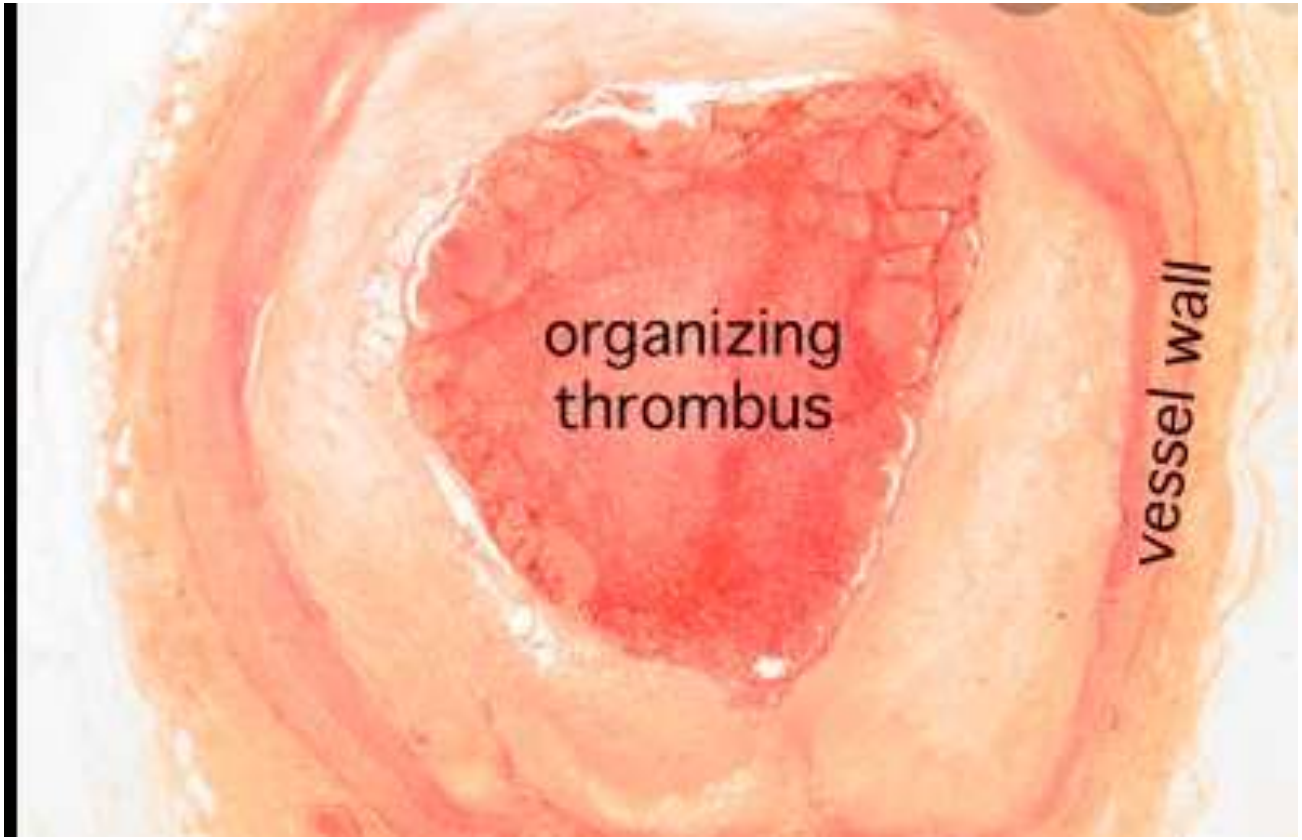
- Vegetations: Thrombi on heart valves , divided into :

- infective endocarditis: Infective thrombotic masses
- nonbacterial thrombotic endocarditis: Sterile vegetations.
- LibmanSacks endocarditis:
- Sterile, occur in the systemic lupus erythematosus.



- Thrombi can have grossly (and microscopically) apparent laminations called lines of Zahn; these represent
- pale platelet and fibrin layers alternating with darker red cell–rich layers.



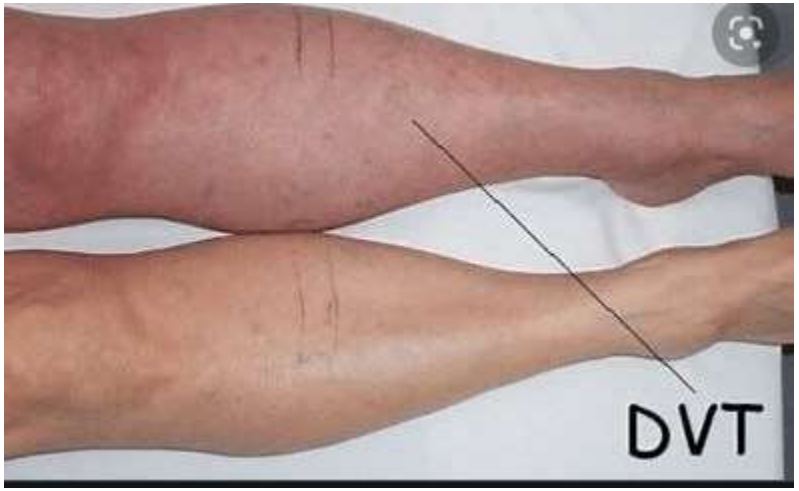

organizing
thrombus
vessel wall

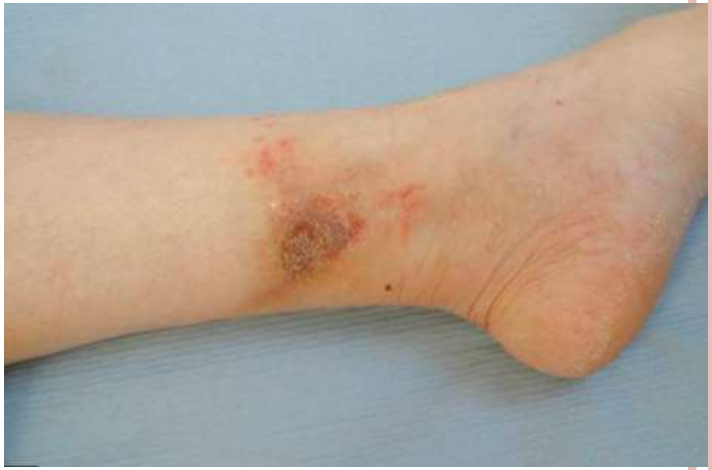
Fate of the Thrombus

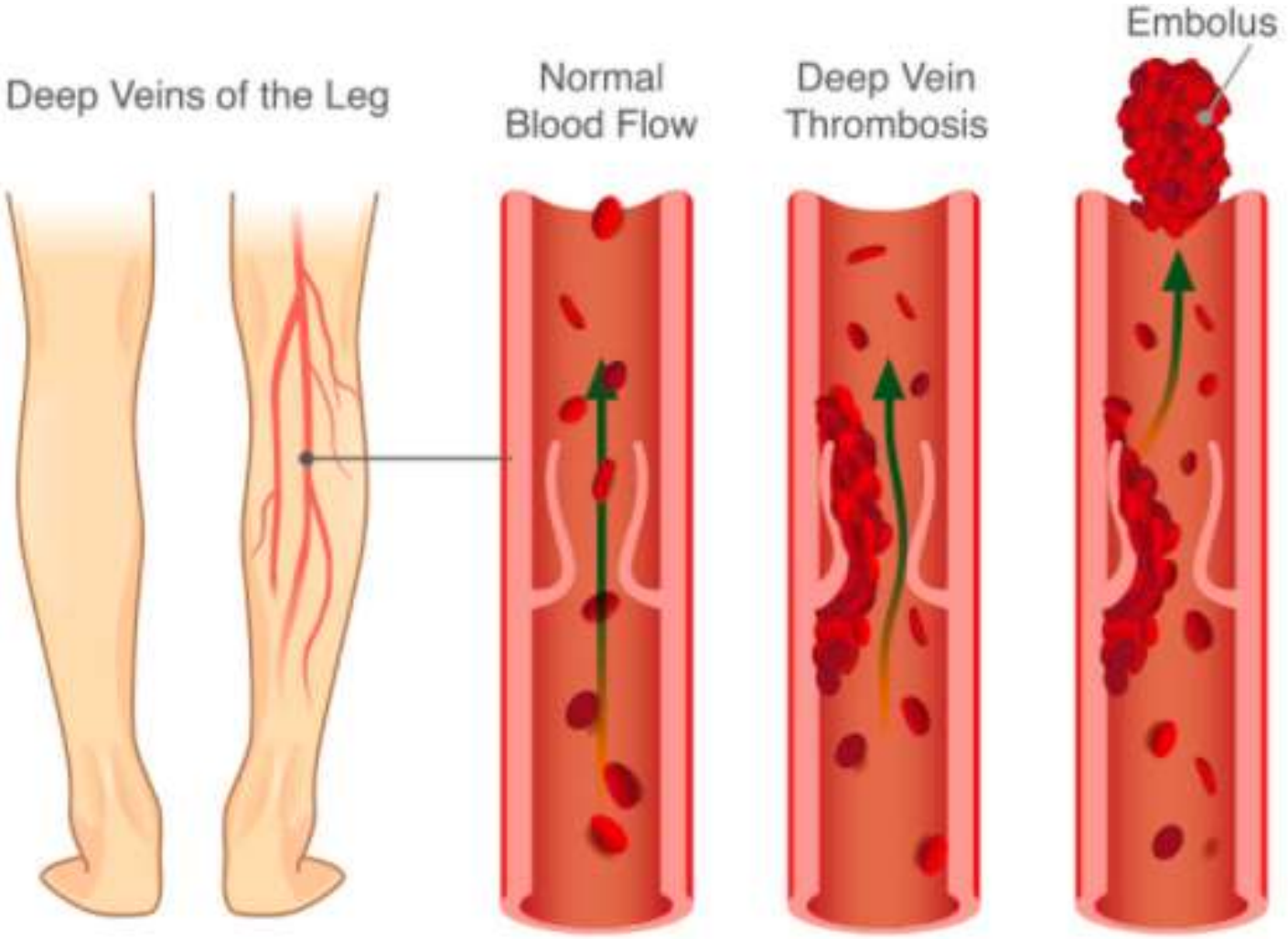
- 1. Propagation: The thrombus enlargment.
- 2. Embolization: transported in the vasculature.
- 3. Dissolution: shrinkage and complete dissolution.
- 4. Organization
- ingrowth of endothelial cells, smooth muscle cells, and fibroblasts.
- 5. Recanalization: capillary channels are formed create canal along the length of the thrombus, thereby reestablishing the continuity of the original lumen.

Clinical Features

- 1. Venous Thrombosis (Phlebothrombosis)
- Pain.
- local congestion and swelling from impaired venous outflow.
- varicose ulcers.
- rarely embolize.



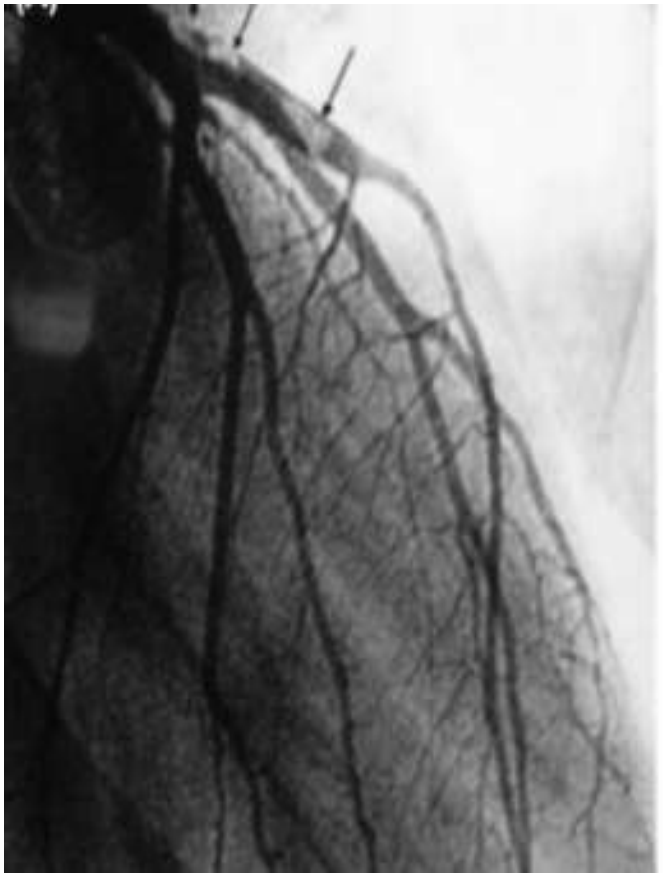


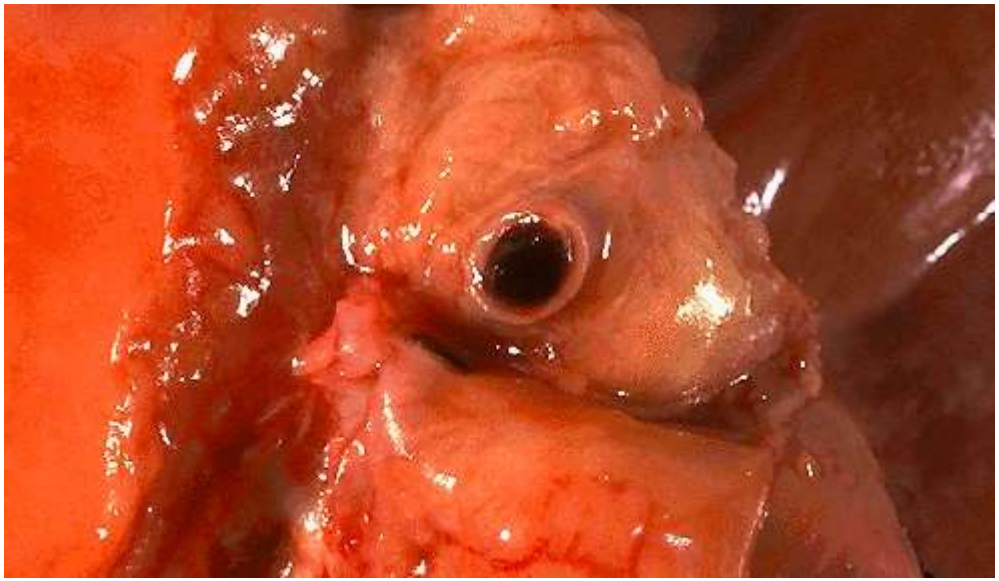

Deep Veins of the Leg
Normal Blood Flow
Deep Vein Thrombosis
Embolus

- 2. Arterial and Cardiac Thrombosis;

- Atherosclerosis is a major cause of arterial thromboses because it is associated with the loss of endothelial integrity and with abnormal blood flow.

- Both cardiac and aortic mural thrombi are prone to embolization. . The brain, kidneys, and spleen are particularly likely targets because of their rich blood supply.



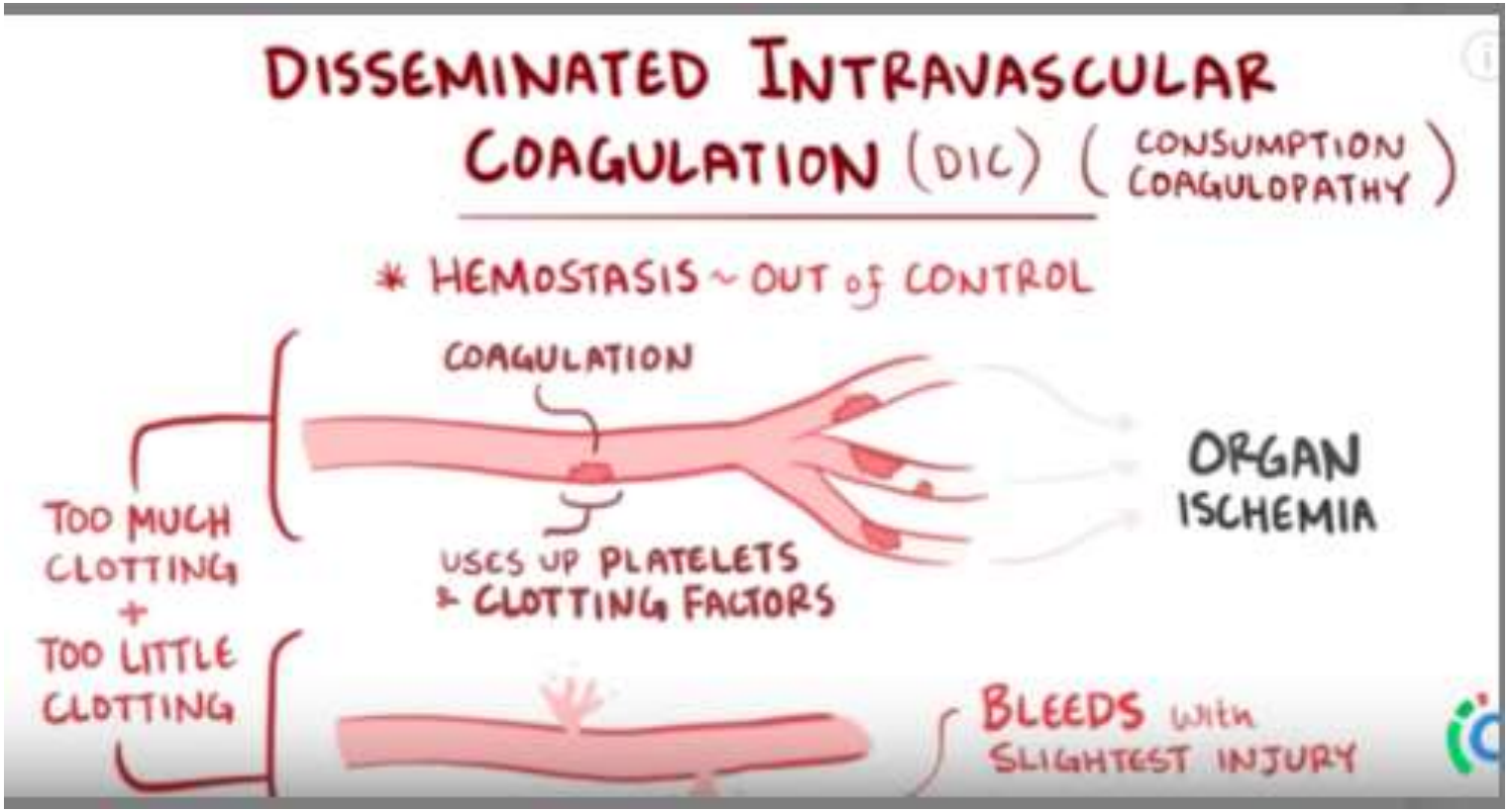


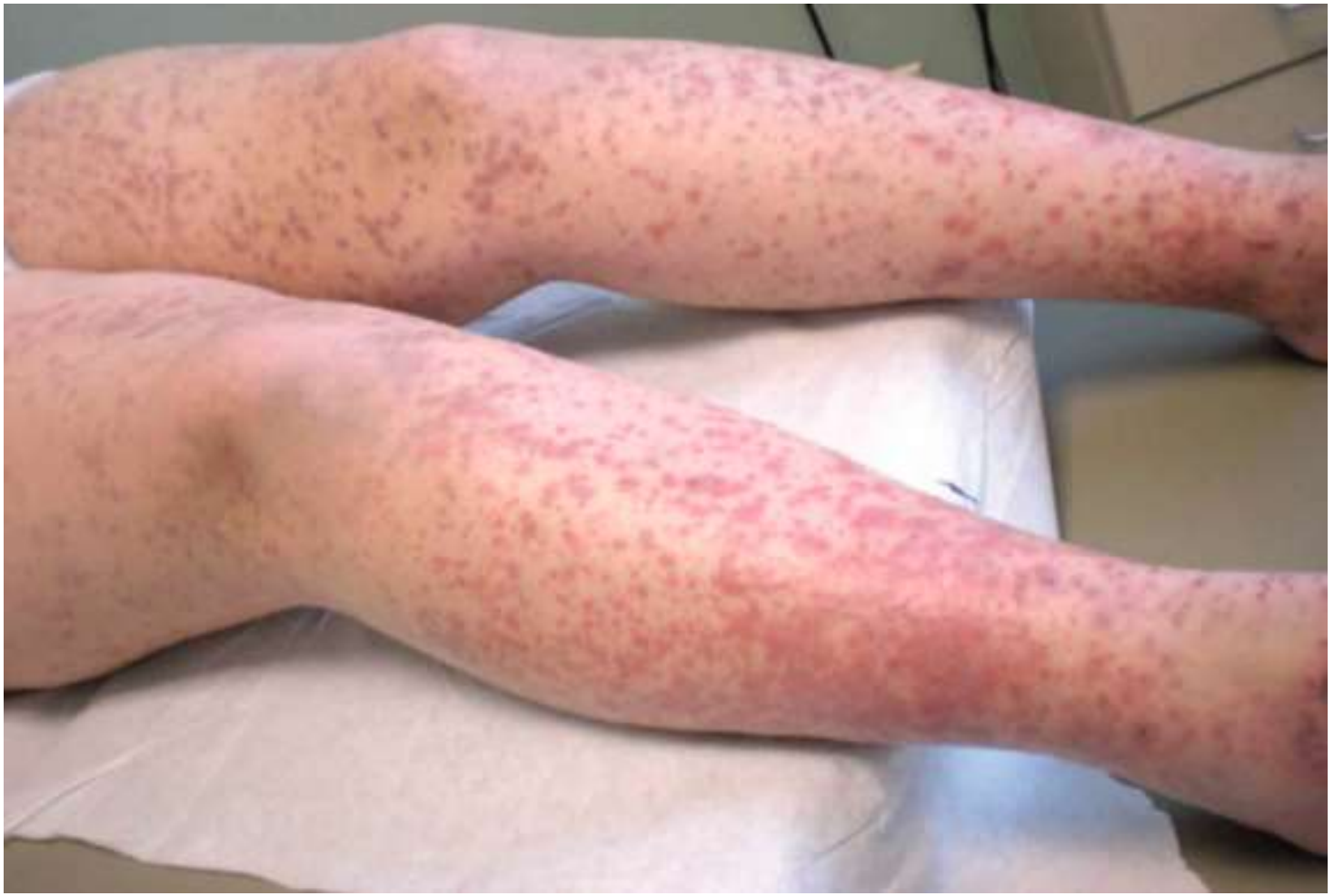
thrombosis of a coronary artery

Massive thrombosis (*arrows*) from distal portion of left main coronary artery

Disseminated Intravascular Coagulation (DIC)

- DIC is widespread thrombosis within the microcirculation that may be of sudden or insidious onset.
- DVT = widespread microvascular thrombosis + fibrinolytic mechanisms activation.
- DVT consumes platelets and coagulation proteins (hence the synonym consumptive coagulopathy).


DISSEMINATED INTRAVASCULAR COAGULATION (DIC) (CONSUMPTION COAGULOPATHY)
* HEMOSTASIS ~ OUT of CONTROL
COAGULATION
TOO MUCH CLOTTING
+
TOO LITTLE CLOTTING
USES UP PLATELETS & CLOTTING FACTORS
ORGAN ISCHEMIA
BLEEDS with SLIGHTEST INJURY



Excessive hemorrhage (Bruising, petechiae).