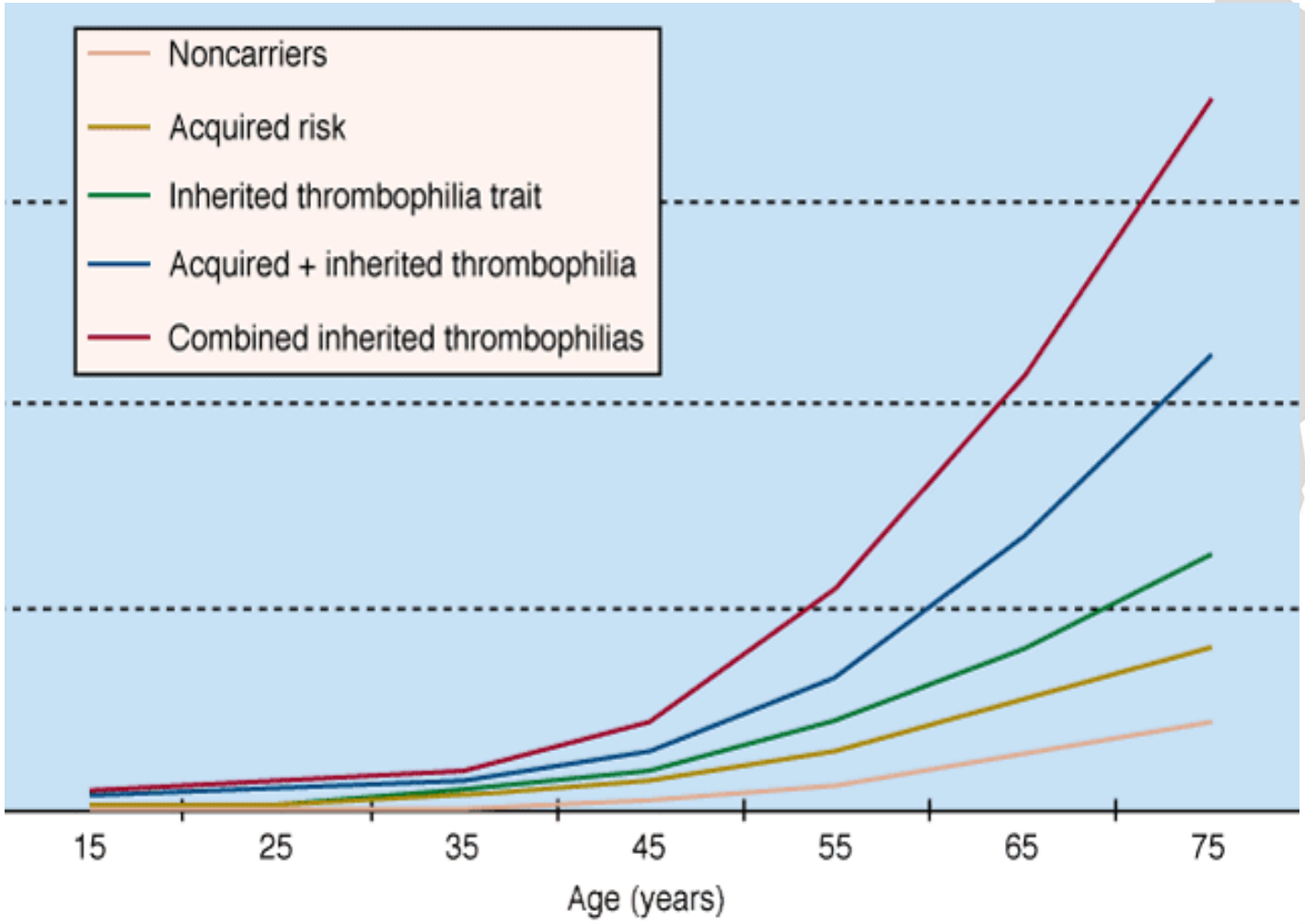
Thrombosis

By Dr. Sara Mohamed Abuelgasim

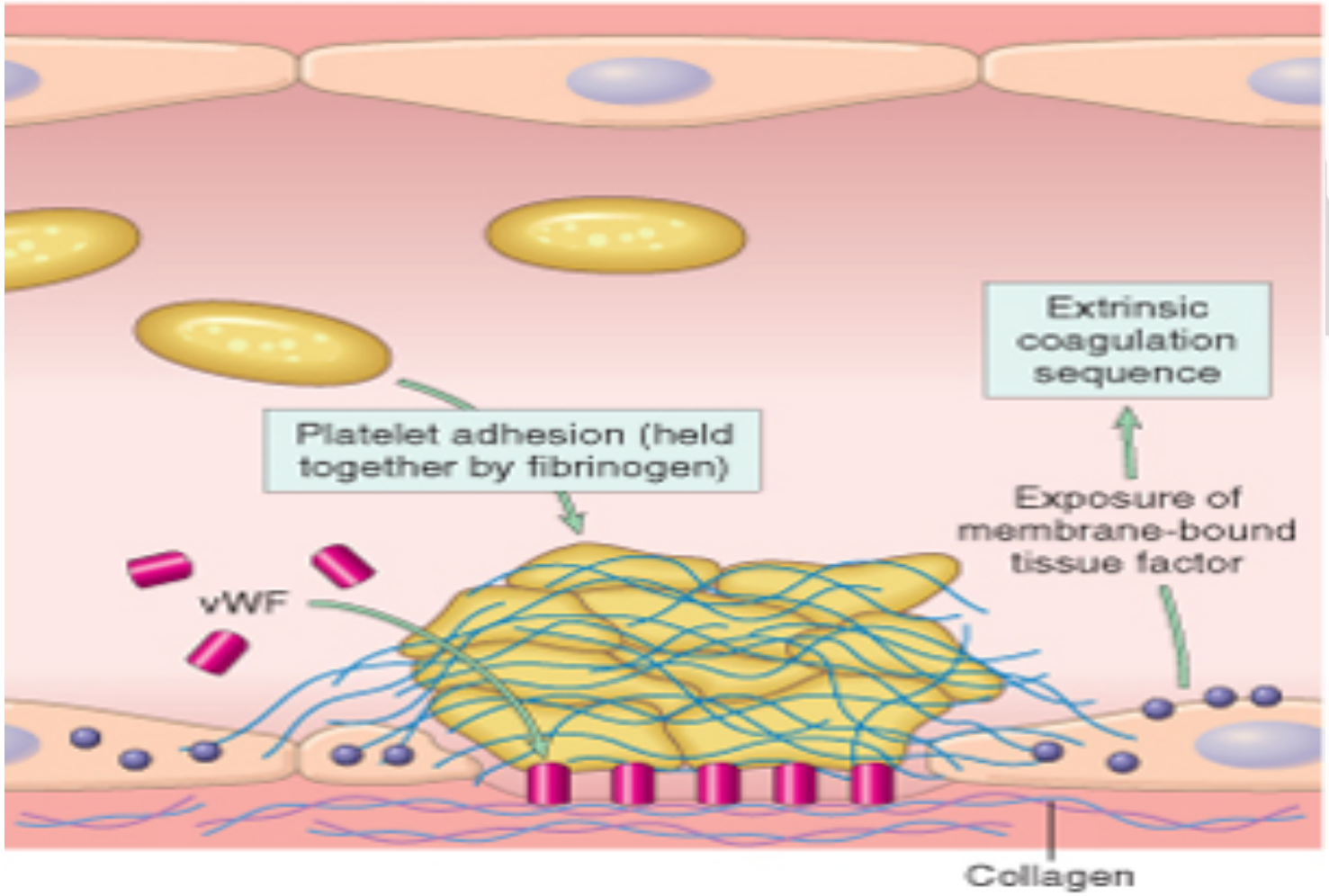
Thrombosis

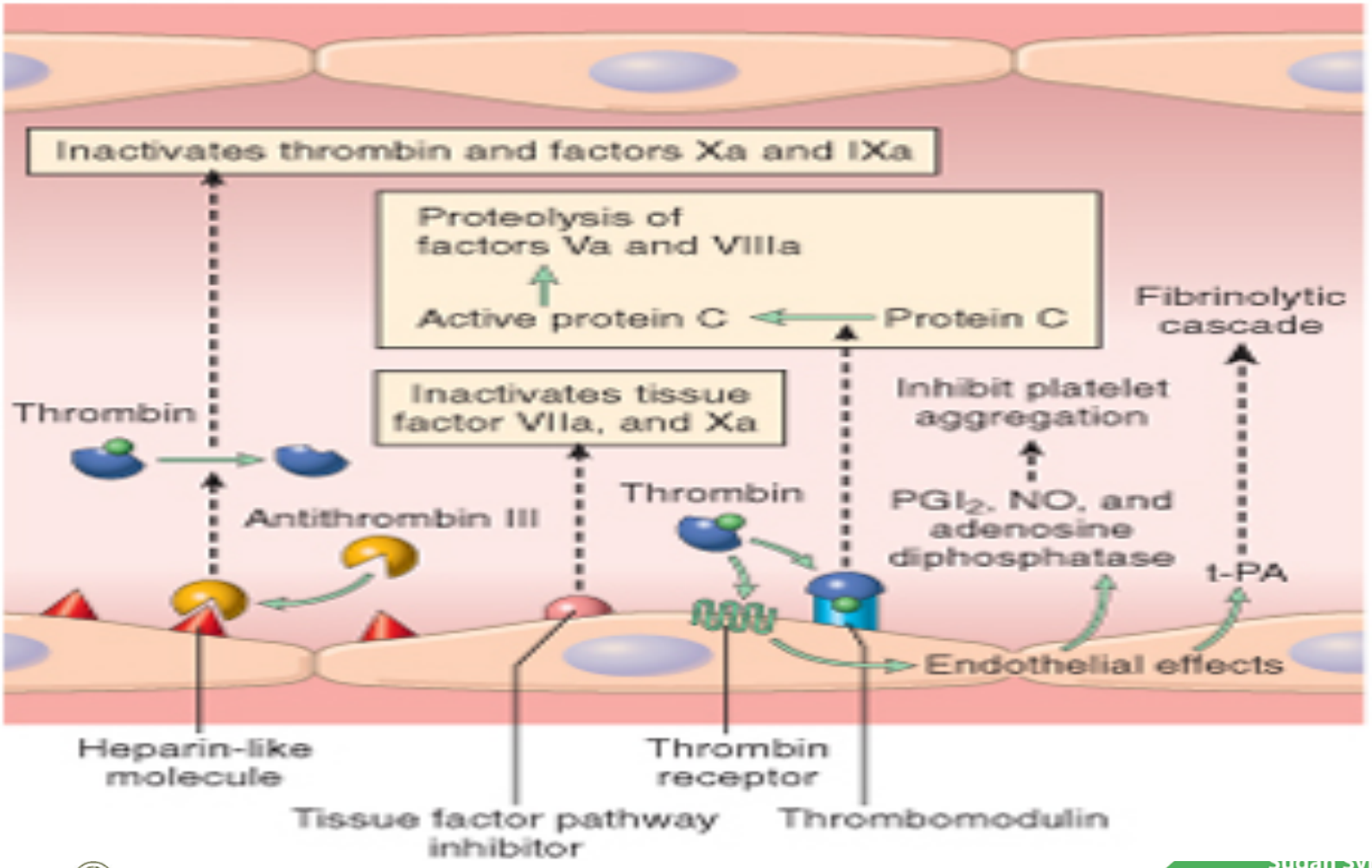
- Unchecked, blood coagulation would lead to dangerous occlusion of blood vessels if the protective mechanisms of coagulation factor inhibitors, blood flow and fibrinolysis were not in harmony.
- Thrombi are solid masses or plugs formed in the circulation from blood constituents. Platelets and fibrin and trapped cells form the basic structure.

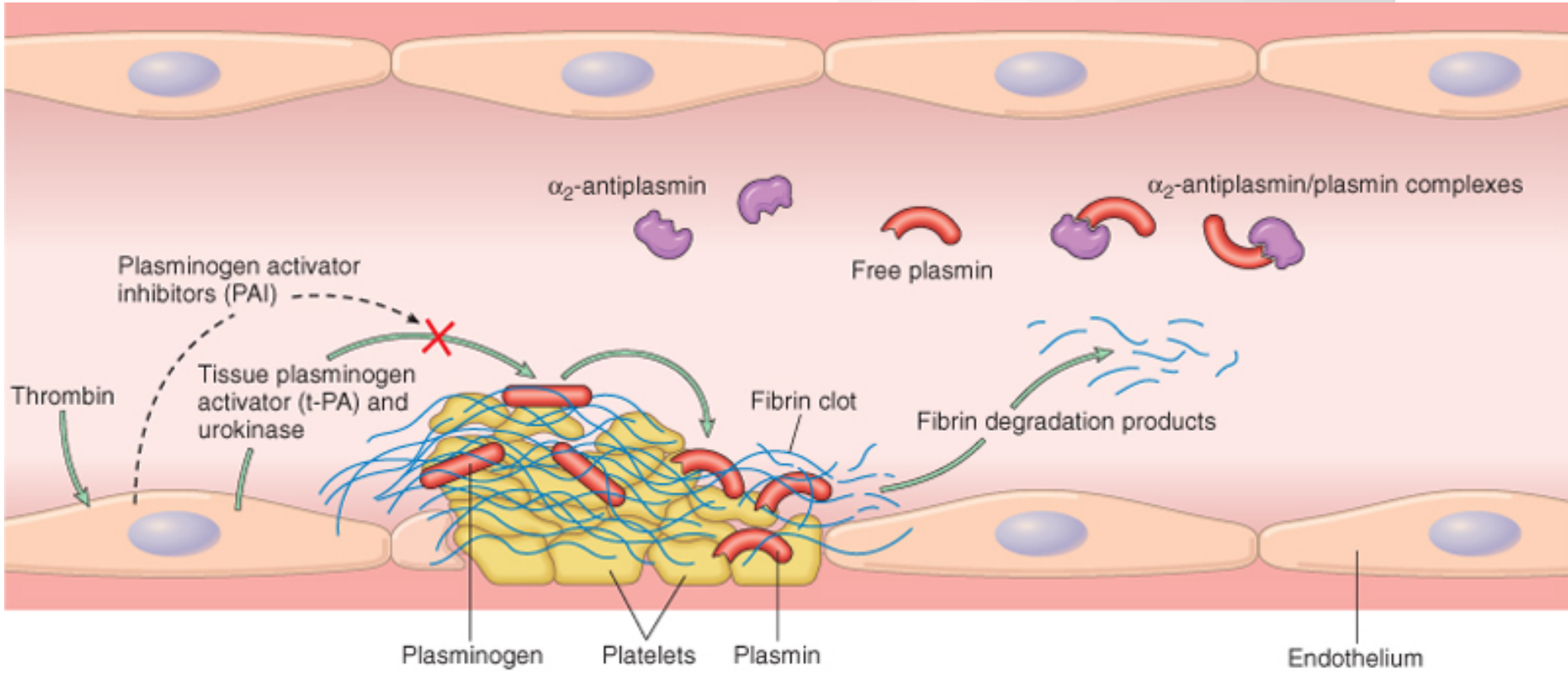
- Venous thrombosis is a multicausal disease.
- Venous thrombosis is a disease in which genetic and acquired risk factors interact dynamically.
- Interaction occurs when two risk factors in combination produce an effect that exceeds the sum of their separate effects.


Noncarriers
Acquired risk
Inherited thrombophilia trait
Acquired + inherited thrombophilia
Combined inherited thrombophilias
15
25
35
45
55
65
75
Age (years)

Thrombus Formation




Inactivates thrombin and factors Xa and IXa
Proteolysis of factors Va and VIIIa
Active protein C
Protein C
Fibrinolytic cascade
Thrombin
Inactivates tissue factor VIIa, and Xa
Inhibit platelet aggregation
Thrombin
PGI2, NO, and adenosine diphosphatase
Antithrombin III
t-PA
Endothelial effects
Heparin-like molecule
Thrombin receptor
Tissue factor pathway inhibitor
Thrombomodulin



- All these systems are carefully regulated
- Bleeding is minimal, the blood flow is maintained and the BV is restored to normal.
- In deregulation either bleeding or thrombosis occurs.

Types Of Thrombus

Arterial → White thrombi.

Venous→ Red thrombi.

Arterial Thrombus Formation

- White thrombi composed of platelets, fibrin and a few WBC's and RBC's.
- Form at areas where the flow has been disturbed via damage to endothelium, especially atherosclerotic plaques.

Risk Factors of Arterial Thrombus

- Hypercholesterolemia
- Hypertension
- Smoking
- Physical inactivity
- Obesity
- Diabetes
- Inflammatory processes related to atherosclerosis

Venous Thrombi

- Red thrombi
  - Composed of RBC's trapped in fibrin mesh with few platelets and WBC's.
- For venous thrombosis, increased systemic coagulability and stasis are most important, vessel wall damage being less important than in arterial thrombosis, although it may be important in patients with sepsis and inserted catheters.

Pathophysiology of thrombosis:

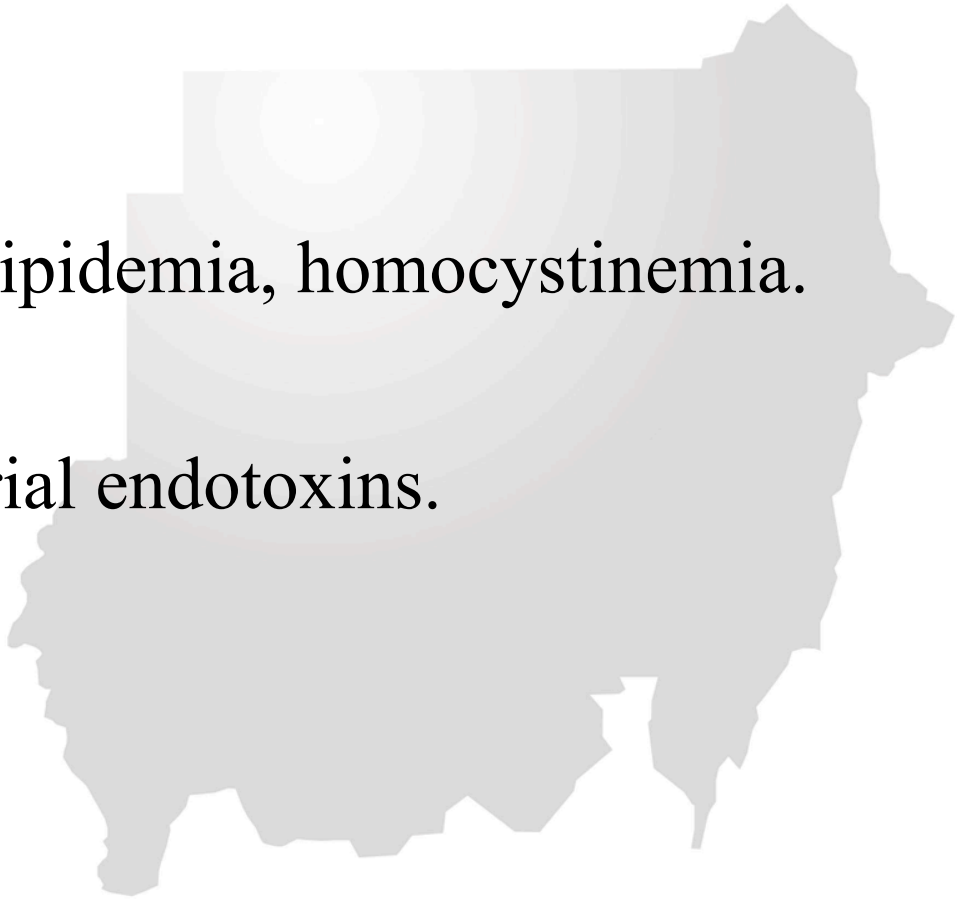
- Pathogenesis of venous and arterial thrombosis is complex and multifactorial. The classic Virchow's triad includes:
  I. Endothelial injury
  II. Stasis or turbulent blood flow
  III. Hyper-coagulability of the blood

Endothelial injury

Causes of endothelial injury:

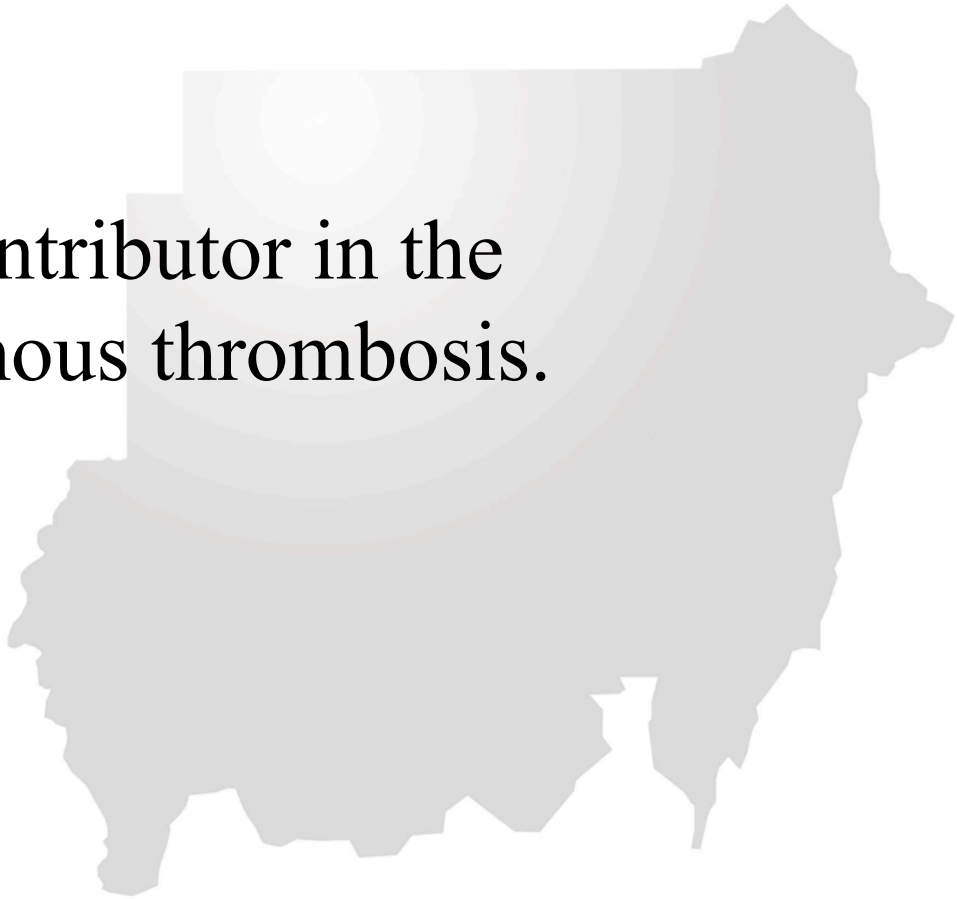
1. Endocardial injury after myocardial infarction.
2. Hemodynaminc injury e.g. hypertension.
3. Atherosclerosis.
4. Inflammation (thrombophlebitis)
5. Autoimmune diseases e.g. Polyarteritis nodosa (PAN).

6. Metabolic: hyperlipidemia, homocystinemia.
7. Trauma.
8. Infections , bacterial endotoxins.
9. Radiation injury.



Alteration in normal blood flow :

- Stasis is a major contributor in the development of venous thrombosis.



III.Hypercoagulability (thrombophilia):

The hypercoagulable states are clinical conditions of patients who are unusually predisposed to venous or arterial thromboembolism; they are also referred to as thrombophilias or prothrombotic disorders.

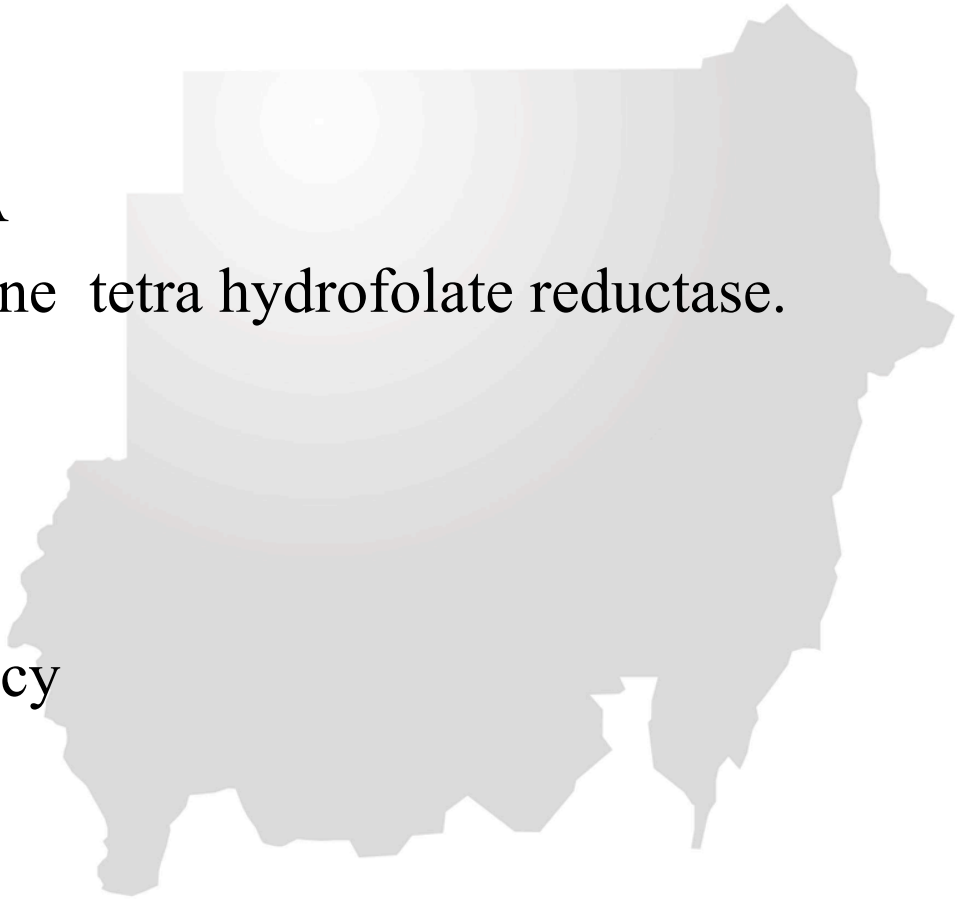
It can be divided into:

1. Primary or genetic disorders.
2. Secondary or acquired disorders.

Primary or genetic disorders:

- Is due to defects in the proteins of the coagulation or fibrinolytic system, rather than platelet abnormalities.
- Typical clinical presentations of congenital hypercoagulable states are:
  - idiopathic.
  - thrombosis in patients of relatively young age (<50 years) .
  - thrombosis at unusual sites mesenteric, portal vein thrombosis.
  - positive family history of thrombosis.

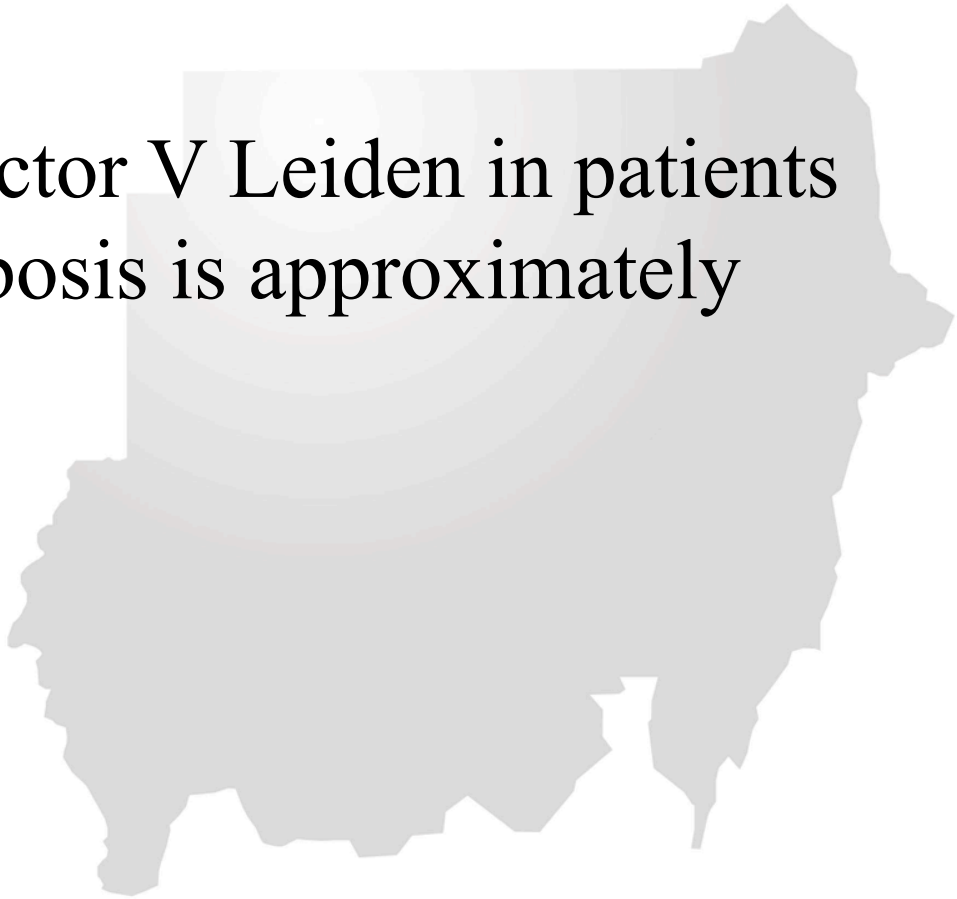
- Common
  - Factor V Leiden
  - Prothrombin G20210A
  - Homozygous methylene tetra hydrofolate reductase.
- Rare
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin deficiency
- Very rare
  - Dysfibrinogenemia
  - ABO blood group



Factor V Leiden gene mutation
(Activated Protein C Resistance)

- Autosomal dominant.
- This is the most common inherited cause of an increased risk of venous thrombosis.
- It occurs in approximately 4% of Caucasian factor V alleles.
- Factor V Leiden (FVL) is a single point mutation in the factor V (FV) molecule in which glutamine is substituted for arginine at position 506 (Arg506Gln), which makes factor V less susceptible to cleavage by activated protein C.

- The incidence of factor V Leiden in patients with venous thrombosis is approximately 20-40%.



- Patients who are heterozygous for factor V Leiden are at an approximately 5-8-fold increased risk of thrombosis compared to the general population.
- Individuals who are homozygous have a 30-140 fold risk.
- Following venous thrombosis they have a higher risk of re-thrombosis compared to individuals with deep vein thrombosis (DVT) but normal factor V.

- A small minority of patients with activated protein C resistance do not have factor V Leiden and have other mutations of factor V.

- Polymerase chain reaction (PCR) screening for the mutation is relatively simple and the test is widely performed.

Antithrombin Deficiency

- Antithrombin is a serpin (*serine protease inhibitor).*
- Inheritance: Autosomal dominant
- Women and men are equally affected.
- Homozygotes (with no plasma antithrombin) unknown (embryonic lethal?)
- Its concentration in the circulation is higher than that of prothrombin.

- Antithrombin is activated by binding to heparin-like molecules on endothelial cells- hence the usefulness of administering heparin in clinical situations to reduce thrombotic activity .
- Antithrombin is a plasma protease inhibitor (serpin) that inhibits thrombin and IXa, Xa, XIa, and Xlla.

- The prevalence of AT deficiency is 0.02% in the general population, whereas it is more than 50 times higher in patients with VTE .
- The risk of thrombosis increases as the functional AT activity decreases, with the highest risk occurring when AT levels are <60% of normal.

Causes of Acquired Antithrombin deficiency

- Chronic liver disease.
- Protein wasting disorders.
- Heparin therapy.
- 3rd trimester of pregnancy.
- Acute leukaemia.
- Burns.
- Renal disease.
- Gram –ve sepsis.

- Management for patients who develop acute thrombotic complications due to AT deficiency is heparin administration in conjunction with exogenous AT administration.
- This is achieved by administering fresh frozen plasma.
- Long-term warfarin therapy is recommended for affected patients who have suffered a thrombotic event.

Protein C or Protein S Deficiency

- Proteins C and protein S are vitamin K-dependent natural anticoagulants synthesized by the liver.
- PC, a zymogen of serine protease, is activated after thrombin binds to its endothelial receptor (thrombomodulin). Activated PC (APC) cleaves and inactivates cofactors Va and VIIIa rapidly, thereby inhibiting clot formation.

Protein C

- Inheritance is autosomal dominant .
- Protein C levels in heterozygotes are approximately 50% of normal.
- Prevalence of approximately 1/300.
- Protein C deficiency also occurs with surgery, trauma, pregnancy, liver or renal failure, DIC and warfarin usage .

Protein S

- PS deficiency is autosomal dominant.
- Protein S is a vitamin K-dependent glycoprotein produced by the liver, endothelial cells and megakaryocytes.
- Protein S is a non-enzymatic cofactor for APC, which inactivates Va, VIIIa.

Causes of Acquired Protein S Deficiency

- Decreased PS synthesis
- Increased PS consumption: occurs in acute thrombosis, DIC and sickle cell disease
- Decreased Functional PS activity in vitamin K deficiency, warfarin, liver disease
- Elevated C4bBP
  - C4bBP is an acute phase reactant and may be elevated in inflammation, pregnancy, SLE, causing a drop in free PS

Prothrombin Gene Variant (G20210A)

- Prothrombin, a vitamin K-dependent Zymogen, plays a key role in its activated form (thrombin) in the conversion of fibrinogen to fibrin.
- In 1996, a novel genetic factor involved in the etiology of VTE was described: a G-^A transition at nucleotide position 20210 (G20210A) in the 3'-untranslated region of the coagulation prothrombin gene.

- This process results in increased synthesis and secretion of prothrombin by the liver, elevated concentrations of plasma prothrombin and a tendency to hypercoagulability due to the greater availability of prothrombin for conversion to thrombin.
- Diagnosed only by gene analysis.

Hyperhomocystinaemia

- Higher levels of plasma homocysteine may be genetic or acquired and are associated with increased risk for both venous and arterial thrombosis.
- Homocysteine is derived from dietary methionine and is removed by either remethylation to methionine or conversion to cysteine via a transsulphuration pathway.

- Inherited severe hyperhomocysteinemia, as seen in classic homocystinuria, may result from:
  - homozygous methylene tetrahydrofolate reductase (MTHFR) deficiency .
  - cystathionine β-synthase (CBS) deficiency .
  - vit deficiency (B12, B6 or folate)

The pathogenesis of thrombosis in hyperhomocysteinemia is unclear.

- Direct endothelial injury.
- Increased TF activity.
- Inhibition of PC activation.
- Increased platelet activation and aggregation.
- Suppression of thrombomodulin expression.
- Impaired fibrinolysis by inhibition of tissue plasminogen activator (t-PA) binding to its endothelial cell receptor.

Defects of Fibrinogen

- Defects of fibrinogen are usually clinically silent or cause excess bleeding. Thrombosis is a rare association.
- ABO blood group:
  - Non - O blood group carries have a higher risk of venous thrombosis than O carries.
  - This related to their higher plasma level of von Willebrand and F VIII.

Acquired Hypercoagulable States

- The acquired or secondary hypercoagulable states include a variety of clinical conditions that are known to have an increased risk for developing thrombotic complications.
  - Pregnancy
  - use of oral contraceptives
  - hormone replacement therapy
  - Immobilization
  - trauma or major surgery
  - prolonged travel.

- Malignancy
- myeloproliferative disorders
- nephrotic syndrome
- antiphospholipid syndrome
- paroxysmal nocturnal hemoglobinuria.

Clinical presentation

- Pts present with previous DVT, prolong immobility, postpartum, postoperative or malignancy.
- O/E there is unilateral leg and thigh swelling, pain and tenderness, pitting oedema and superficial collateral veins.
- 50% are asymptomatic and present only when there is PE.

Which patients should be screened for possible thrombophilia ?

- Arterial thrombosis, e.g. patients <30 years, without obvious arterial disease.
- Venous thrombosis:
- Patients <40 years with no obvious risk factors.
- Unexplained recurrent thrombosis.
- VTE and family history of thrombosis in first degree relatives.
- Unusual site, e.g. mesenteric, portal vein thrombosis.
- Unexplained neonatal thrombosis.
- Recurrent miscarriage (≥3).

Investigation of thrombophilia

- Blood count and (ESR).
- Blood film examination.
- Prothrombin time (PT) and APTT.
- Anticardiolipin and anti-~2-GPIantibodies.
- Thrombin time .
- Fibrinogen assay.
- Activated protein C (APC) resistance test and
- DNA analysis for factor V Leiden.

- Antithrombin-immunological and functional assays.
- Protein C and protein S-immunological and functional assays.
- Prothrombin gene analysis for the G20210A variant.
- Plasma homocysteine estimation.
- Test for CD59 and CD55 expression (paroxysmal nocturnal haemoglobinuria).
- Test for JAK2 mutation.
- Protein electrophoresis .

- Plasma D dimer concentration
- Serial compression ultrasound
- Contrast venography
- C T angiography
- Magnetic resonance imaging (MRI)

Thanks