

# The module: Mechanism of Disease

## Haemostasis and Thrombosis (II)

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# Haemostasis and Thrombosis (II)



## • Learning objectives:

### 3. Embolism;

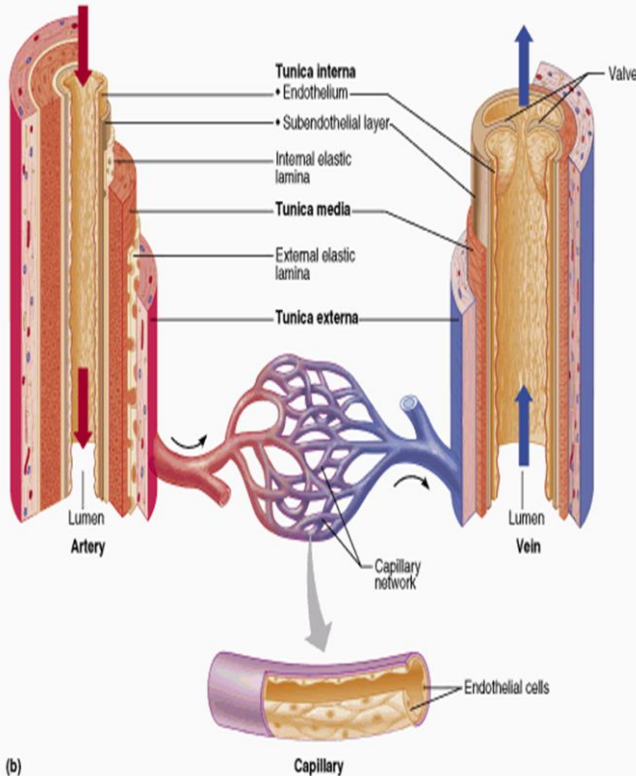
- Definition
- Thromboembolism particularly DVT and pulmonary embolism
- Other types of embolism

### 4. Anti-coagulant therapy;

- Heparin
- Warfarin
- Prophylaxis in general

### 5. Other disorders of coagulation;

- Haemophilia
- Disseminated intravascular coagulation
- Thrombocytopenia
- Thrombophilia



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### 3- EMBOLISM

- ▶ An *embolus* is a *detached* intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.
- ▶ Virtually **99%** of all emboli represent some part of a dislodged thrombus, hence the term *thromboembolism*.
- ▶ **Less common** types of emboli include fat droplets, bubbles of air or nitrogen, atherosclerotic debris (*cholesterol emboli*), tumor fragments, bits of bone marrow, and amniotic fluid.



## Clinical Correlations:

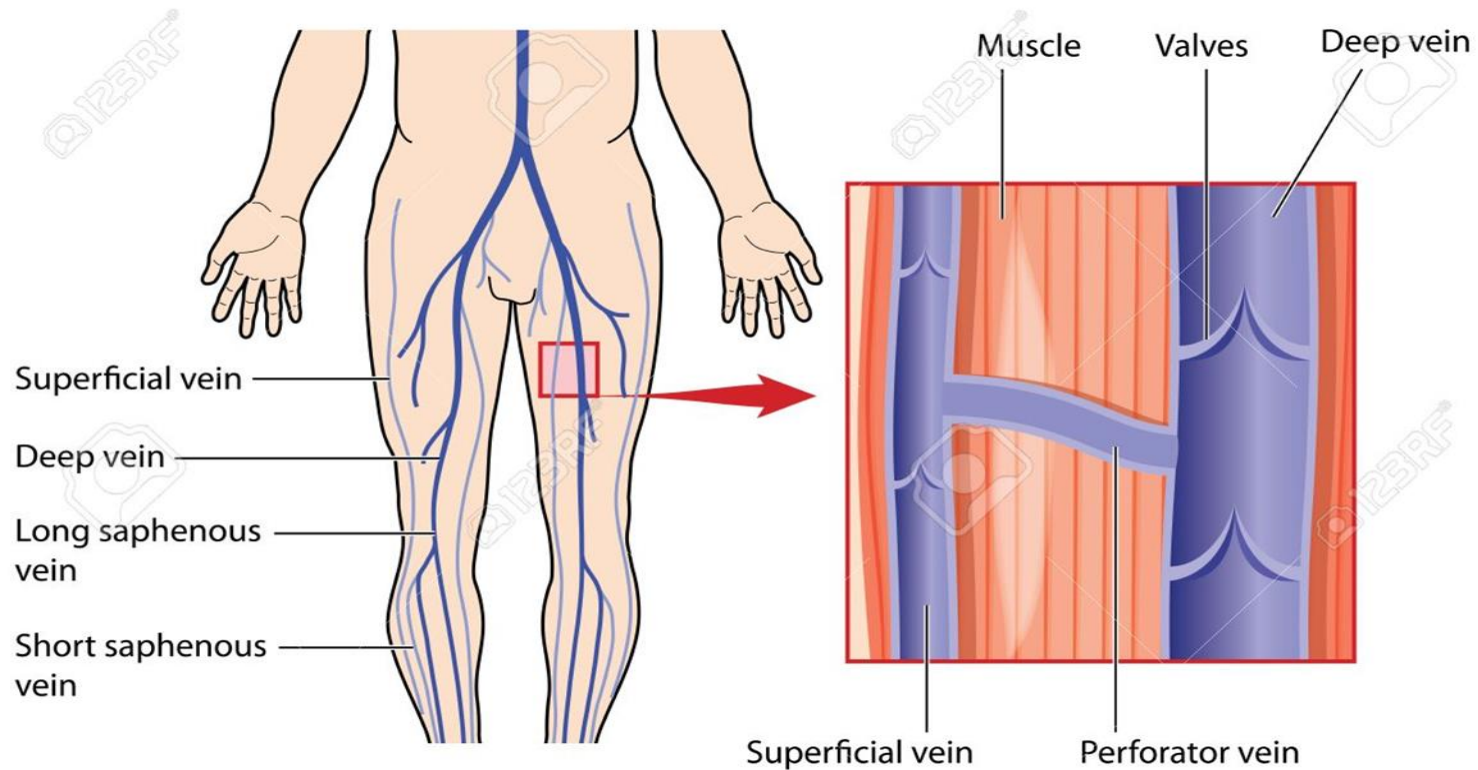
# Venous versus Arterial Thrombosis

- ▶ Thrombi are **significant** because *they cause **obstruction of arteries and veins and are potential **sources of emboli.*****
- ▶ **Venous** thrombi can cause **congestion and oedema** in vascular beds **distal** to an obstruction, but they are most worrisome for their **capacity to embolize** to the lungs and cause death.
- ▶ Conversely, while **arterial** thrombi can embolize and even cause **downstream tissue infarction**, their role in vascular obstruction at critical sites (e.g., coronary and cerebral vessels) is much more significant clinically.



# Venous Thrombosis (Phlebothrombosis)

- ▶ Most venous thrombi occur in either the **superficial** or the **deep** veins of the leg.

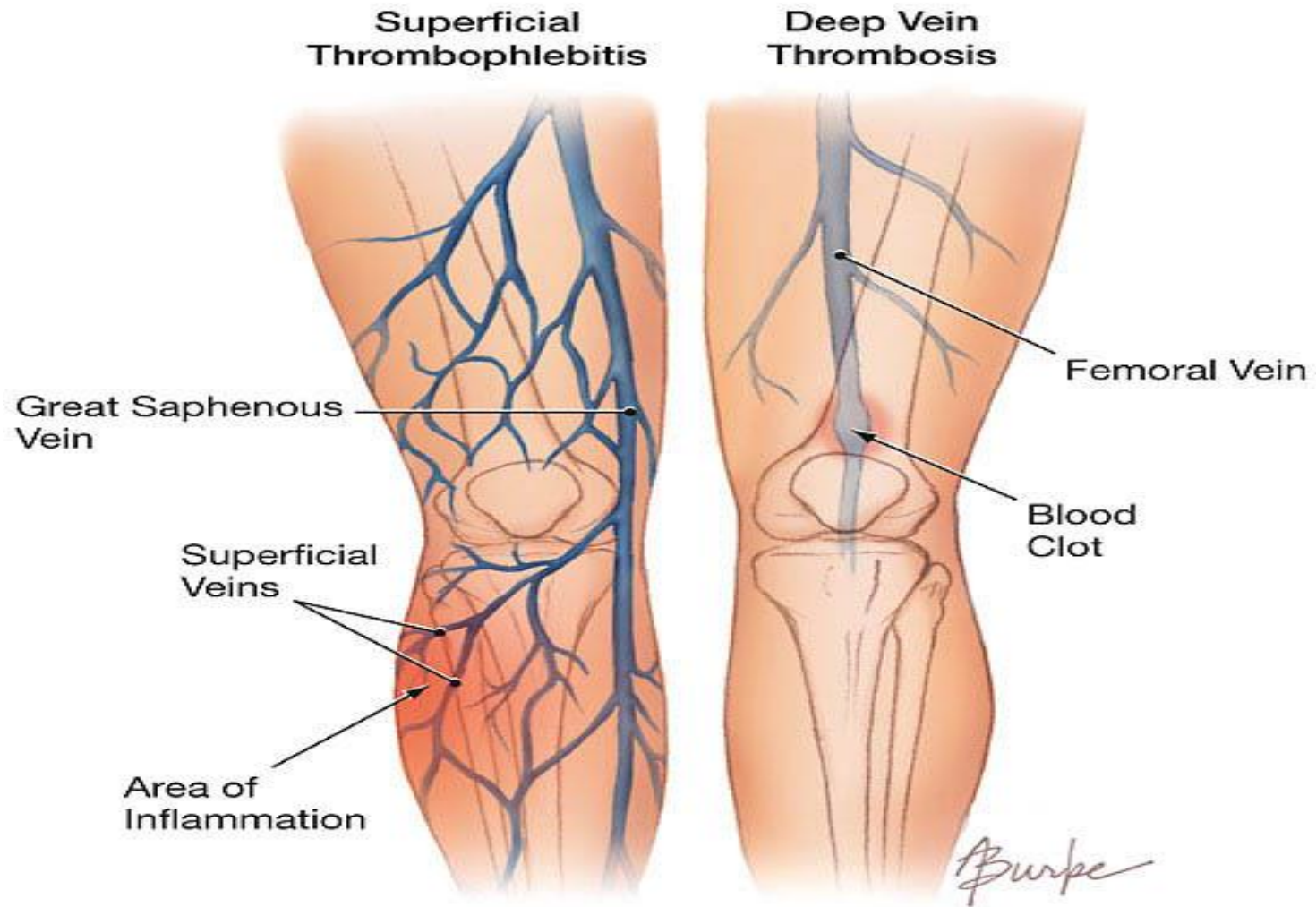


# Venous Thrombosis (Phlebothrombosis)

- ▶ **Superficial** venous thrombi usually arise in the saphenous system (varicosities); these **rarely embolize** but can be painful and can cause local congestion and swelling from impaired venous outflow.
- ▶ **Deep** venous thromboses (DVTs) in the larger leg veins at or above the knee joint (e.g., popliteal, femoral, and iliac veins) are more serious because they are **prone to embolize**.



# Venous Thrombosis (Phlebothrombosis)



# Venous Thrombosis (Phlebothrombosis)

- ▶ Consequently, DVTs are entirely **asymptomatic** in approximately **50%** of patients and are recognized only after they have embolized.
- ▶ Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), has an incidence of about 1 per 1000 per annum, with two-thirds presenting as DVT and one-third as PE.





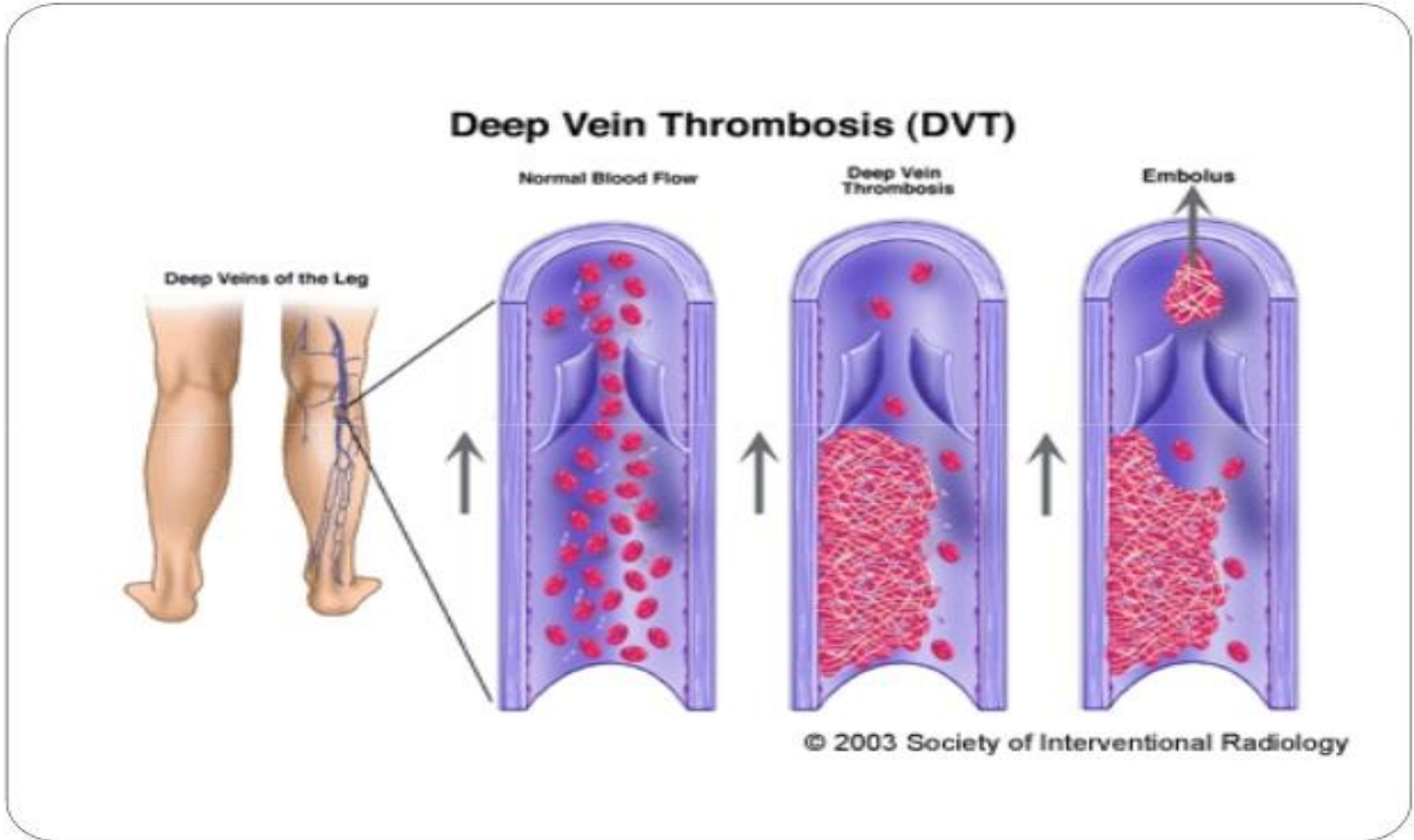
# Deep veins thrombosis

## ▶ Predisposing factors:

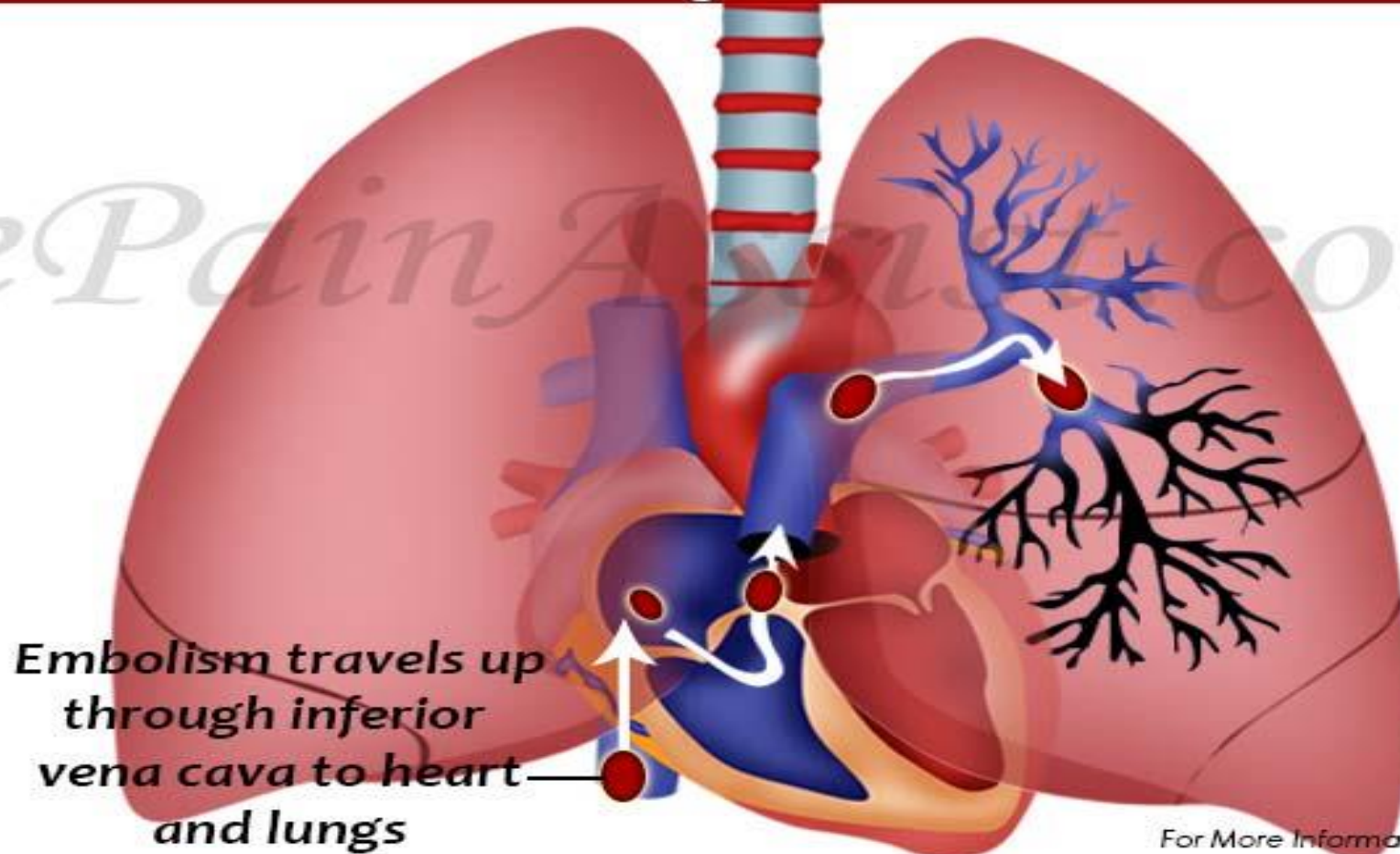
1. Immobility and bed rest.
2. Pregnancy and post-partum state.
3. Post-operative.
4. Sever burns.
5. Heart failure.
6. Disseminated cancer.



# Pulmonary Thromboembolism



# Risk Factors for Pulmonary Embolism



For More Information:  
Visit: [www.epainassist.com](http://www.epainassist.com)

**The blockage in the pulmonary artery of the lung caused by a blood clot or a foreign material is called as pulmonary embolism or PE.**

- ▶ In greater than **95%** of cases, venous emboli originate from thrombi within **deep leg veins** proximal to the popliteal fossa; embolization from lower leg thrombi is uncommon.
- ▶ The patient who has had one pulmonary embolus is at high risk of having more.
- ▶ Most pulmonary emboli (**60% to 80%**) are clinically **silent** because they are small.



- ▶ **Clinical presentation of PE** depends on the *size, location and number of emboli*, and the *patient's underlying cardiorespiratory reserve*.
- ▶ The **classic triad** of *chest pain, haemoptysis* and *dyspnoea* is present in less than 20% of patients, but nearly all will have at least one of pleuritic chest pain, dyspnoea or tachypnoea.
- ▶ Sudden death, right ventricular failure (*cor-pulmonale*), or cardiovascular collapse occurs when **60% or more** of the pulmonary circulation is obstructed with emboli.



# Systemic Thromboembolism

- ▶ *Systemic thromboembolism refers to emboli in the arterial circulation.*
- ▶ Most (80%) arise from intracardiac mural thrombi, two-thirds of which are associated with left ventricular wall infarcts and another third with dilated left atria (e.g., secondary to mitral valve disease).
- ▶ By contrast with venous emboli, which lodge primarily in the lung, arterial emboli can travel virtually anywhere.



# Systemic Thromboembolism

- ▶ Common arteriolar embolization sites include the *lower extremities* (75%) and *central nervous system* (10%); intestines, kidneys, and spleen are less common targets.
- ▶ The consequences of embolization depend on the *caliber of the occluded vessel*, the *collateral supply*, and the *affected tissue's vulnerability to anoxia*.
- ▶ Arterial emboli often lodge in end arteries and cause infarction.



# Fat Embolism

- ▶ Microscopic fat globules can be found in the circulation after fractures of long bones (which contain fatty marrow) or after soft-tissue trauma. Fat enters the circulation by rupture of the marrow vascular sinusoids or rupture of venules in injured tissues.
  
- ▶ *fat embolism syndrome* characterized by pulmonary insufficiency, neurologic symptoms, anaemia, thrombocytopenia, and a diffuse petechial rash, which is fatal in 10% of cases.





# Amniotic Fluid Embolism

- ▶ Amniotic fluid embolism is an uncommon, grave complication of labor and the immediate postpartum period (1 in 40,000 deliveries).
- ▶ The mortality rate approaches 80%, making it the most common cause of maternal death in the developed world.
- ▶ The underlying cause is entry of amniotic fluid (and its contents) into the maternal circulation via *tears in the placental membranes* and/or *uterine vein rupture*.

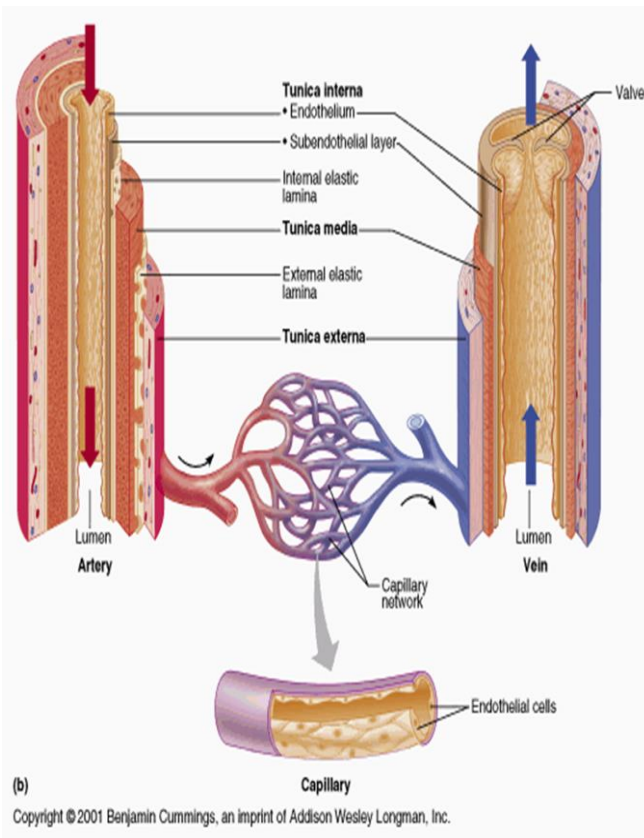


# Air Embolism

- ▶ Gas bubbles within the circulation can obstruct vascular flow (and cause distal ischemic injury) almost as readily as thrombotic masses can.
- ▶ Air may enter the circulation during *obstetric procedures* or as a consequence of *chest wall injury*. Generally, more than 100 mL of air are required to produce a clinical effect; bubbles can coalesce to form frothy masses sufficiently large to occlude major vessels.
- ▶ *Decompression sickness* is caused by sudden changes in atmospheric pressure. *caisson disease* in which recurrent or persistent gas emboli in the bones lead to multifocal ischemic necrosis.



# Haemostasis and Thrombosis (II)



## • Learning objectives:



3. Embolism;
  - Definition
  - Thromboembolism particularly DVT and pulmonary embolism
  - Other types of embolism

## 4. Anti-coagulant therapy;

- Heparin
- Warfarin
- Prophylaxis in general

## 5. Other disorders of coagulation;

- Haemophilia
- Disseminated intravascular coagulation
- Thrombocytopenia
- Thrombophilia

# 4- ANTI-COAGULANT THERAPY

## Heparin:

- ▶ Unfractionated heparin (**UFH**) is a naturally occurring glycosaminoglycan produced by mast cells.
- ▶ For most clinical indications there has been a move from UFH to low-molecular-weight heparin (**LMWH**).
- ▶ Heparins are only active when administered **parenterally**.
- ▶ The **APTT** is used for routine monitoring of therapeutic doses of **UFH**
- ▶ Falls in platelet count (>50% compared with baseline) after 5 days of treatment should raise the possibility of *heparin-induced thrombocytopenia (HIT)*



# 4- ANTI-COAGULANT THERAPY

## Heparin:

- ▶ The anticoagulant action of heparin is primarily a result of its ability to **bind to antithrombin (AT)**, thereby accelerating and enhancing the latter's rate of inhibition of the major coagulation enzymes (i.e., factors IIa and Xa and to lesser extents IXa, XIa and XIIa).
- ▶ The two main effects of heparin, the antithrombin and the anti-Xa effects, are differentially dependent on the size of the heparin molecule.
- ▶ Heparin also produces some anticoagulant effect by promoting the release of tissue factor pathway inhibitor (TFPI) from the endothelium.



# ANTI-COAGULANT THERAPY

## Warfarin:

- ▶ Warfarin is vitamin K antagonist, that inhibit synthesis of normal FII, FVII, FIX and FX and so result in anticoagulation.
- ▶ Vitamin K is needed for the post-translational modification of the vitamin-K- dependent factors (II, VII, IX, X, protein C and protein S).
- ▶ The anticoagulant effect varies between individuals and over time and needs to be monitored by the *International Normalized Ratio (INR)*.



# ANTI-COAGULANT THERAPY

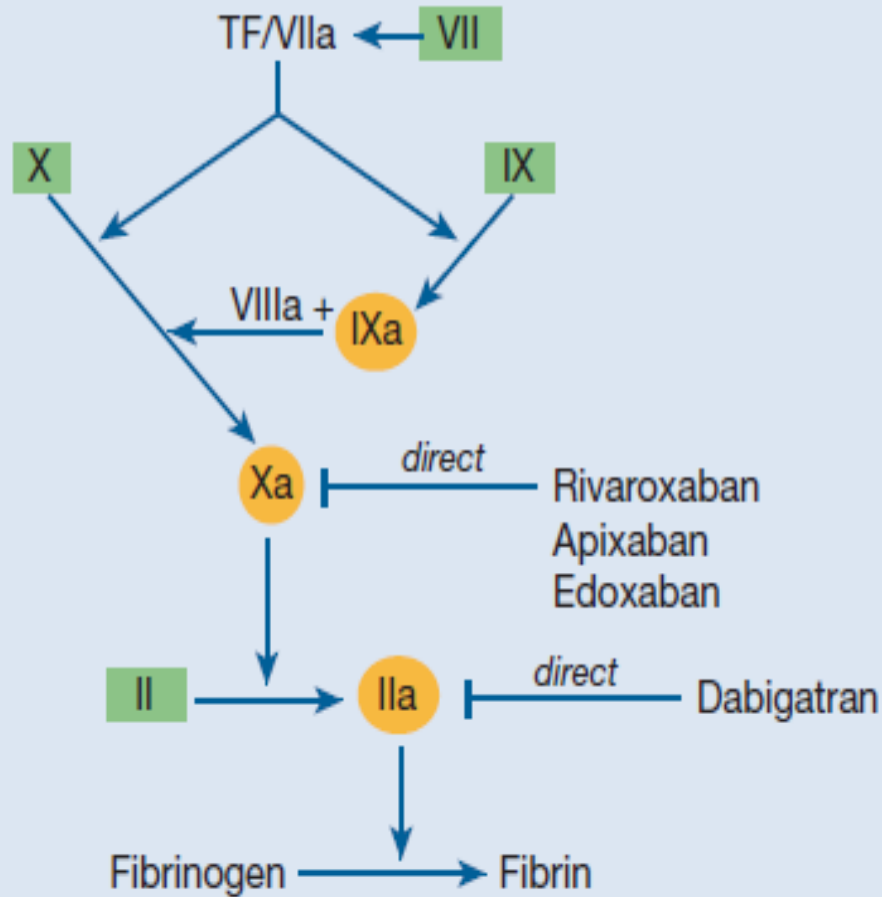
## Warfarin:

- ▶ After warfarin is given, factor VII levels fall considerably within 24 hours but prothrombin has a longer plasma half-life and only falls to 50% of normal at 3 days; *so if immediate anticoagulation is needed, heparin is given initially.*



INITIATION

AMPLIFICATION  
PROPAGATION



- Targets of VKAs (e.g. warfarin) which inhibit their activation by  $\gamma$ -carboxylation
- Targets of heparin (UFH, LMWH) (which activates the natural anticoagulant-antithrombin (AT))

VKA, vitamin K antagonist

UFH also inhibits native XIa and VIIa

LMWH inhibits Xa more than IIa

VKAs (warfarin) also inhibit activation of the natural anticoagulant proteins C and S



# ANTI-COAGULANT THERAPY

## Prophylaxis in general:

- ▶ The decision as to whether to continue anticoagulant treatment indefinitely after a first proximal DVT or PE is dependent on the ***risk of recurrence without continued treatment and the perceived risk of bleeding on anticoagulation.***
- ▶ Long-term anticoagulation is usually given after recurrent unprovoked VTE.
- ▶ For patients who receive long-term anticoagulation the ***risk–benefit ratio*** of continued treatment should be reassessed at regular intervals.



# ANTI-COAGULANT THERAPY

## Prophylaxis in general:

- ▶ Following an episode of venous thrombosis, patients are **40 times** more likely to suffer an event in the future than patients who have not previously suffered from venous thrombosis.
- ▶ Patients with VTE provoked by **surgery** have an annualized recurrence rate of **<1%**. Patients with VTE provoked by a **non-surgical** factor have an annualized risk of **4%** and patients with **unprovoked** VTE have an annualized event rate of **7%**.



# *Suggested duration of anticoagulation*

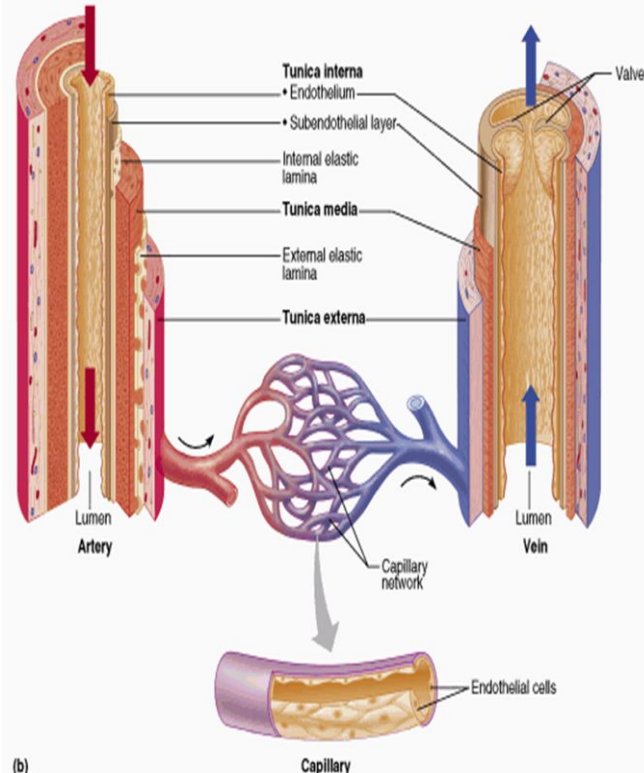
3 months	3 months then consider for long-term	Usually long-term
<ul style="list-style-type: none"><li>• First proximal DVT or PE associated with a transient risk factor*</li><li>• First unprovoked isolated calf DVT (consider 6 weeks if post surgery)</li></ul>	<ul style="list-style-type: none"><li>• First unprovoked proximal DVT or PE**</li></ul>	<ul style="list-style-type: none"><li>• Recurrent unprovoked DVT or PE</li><li>• Proximal DVT or PE with a significant continuing risk factor (e.g. active cancer, antiphospholipid antibodies) and no other cause</li></ul>

\*Transient risk factors: surgery, significant trauma e.g. fracture, plaster cast; combined pill/hormone replacement therapy; pregnancy/puerperium

\*\* A stronger case for continuing in: males; those with raised D-dimers after completing anticoagulation; those with PE



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5. **Other disorders of coagulation;**
  - **Haemophilia**
  - **Disseminated intravascular coagulation**
  - **Thrombocytopenia**
  - **Thrombophilia**



## 5- Other disorders of coagulation

### Haemophilia:

- ▶ *Haemophilia A (factor VIII deficiency)*: It is the most common of the hereditary clotting factor deficiencies.
- ▶ *Haemophilia B (Christmas disease, factor IX deficiency)*: The incidence is one-fifth that of haemophilia A.
- ▶ The inheritance is sex-linked but up to one-third of patients have no family history and these cases result from recent mutation.



## Haemophilia A: clinical severity

<b>FVIII (units/dL)</b>	<b>Bleeding tendency</b>	<b>Relative incidence (%)</b>
<1	Severe: frequent spontaneous <sup>†</sup> bleeding into joints, muscles and internal organs	50
1–5	Moderate: some 'spontaneous' bleeds, bleeding after minor trauma	30
>5–45	Mild: bleeding only after significant trauma, surgery	20

<sup>†</sup> 'Spontaneous' bleeding refers to those episodes in which no obvious precipitating event preceded the bleed. No doubt, minor tissue damage consequent on everyday activities actually initiates bleeding.



# Haemophilia:

- ▶ The characteristic bleeding pattern of haemophilia, which is both delayed after trauma and much prolonged.
- ▶ Replacement by intravenous infusion of the deficient factor can normalize the haemostatic mechanism.
- ▶ Recurrent painful haemarthroses and muscle haematomas dominate the clinical course of severely affected patients and, if inadequately treated, lead to progressive joint deformity and disability





Haemophilia A showing severe disability of the left Knee



## 5- Other disorders of coagulation

### Disseminated intravascular coagulation:

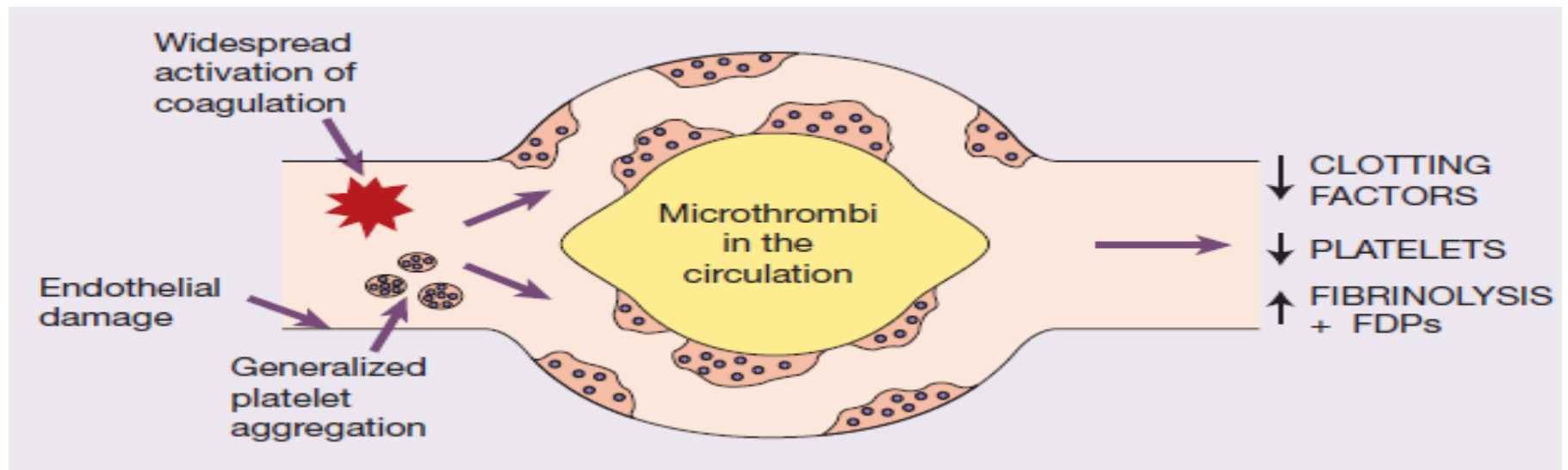
- ▶ Widespread inappropriate intravascular deposition of fibrin with consumption of coagulation factors and platelets, occurs as a consequence of many disorders that release procoagulant material into the circulation or cause widespread endothelial damage or platelet aggregation.
- ▶ It may be associated with a *fulminant haemorrhagic or thrombotic syndrome* with organ dysfunction **or** run a *less severe* and more chronic course. The main clinical presentation is with bleeding but 5–10% of patients manifest thrombotic lesions.



# Other disorders of coagulation

## Disseminated intravascular coagulation:

- ▶ The key event underlying DIC is increased activity of thrombin in the circulation that overwhelms its normal rate of removal by natural anticoagulants.



The pathogenesis of disseminated intravascular coagulation and the changes in clotting factors, platelets and fibrin degradation products (FDPs) that occur in this syndrome

# Other disorders of coagulation

## Thrombocytopenia:

- ▶ Thrombocytopenia defines a subnormal number of platelets in the circulating blood, usually below  $100 \times 10^9/L$ . Thrombocytopenia, if severe, also causes skin and mucous membrane bleeding.
- ▶ It has a wide range of causes including:
  - (i) failure of platelet production from a congenital cause, drugs or viral infection or a general bone marrow failure;
  - (ii) increased consumption of platelets. This may be acute or chronic autoimmune, drug-induced, caused by disseminated intravascular coagulation or thrombotic thrombocytopenic purpura.



# Other disorders of coagulation

## Thrombophilia:

- ▶ There is no internationally accepted definition of thrombophilia. The term is sometimes used to describe disorders of haemostasis detected in the laboratory that appear to predispose to venous thrombosis.
- ▶ A clinical definition of heritable thrombophilia describes an inherited tendency for venous thrombosis, i.e. deep vein thrombosis (DVT) with or without associated pulmonary embolus (PE).



# Other disorders of coagulation

## Thrombophilia:

Prevalence of heritable thrombophilias shown to be associated with at least a two fold increased risk of venous thrombosis in patients and controls

	General population
Antithrombin	0.03%
Protein C deficiency	0.3%
Protein S deficiency	0.3%
FVR506Q (FV Leiden)*	4%
<i>F2G20210A*</i>	2%



# Risk factor for venous thromboembolism

## *Inevitable/environmental*

- Increasing age
- Pregnancy and puerperium
- Prolonged immobility, e.g. long-haul travel
- Obesity
- Trauma

## *Iatrogenic*

- Surgery
- Indwelling venous devices
- Pharmacological
- Oestrogen related: combined oral contraceptive, hormone-replacement therapy, tamoxifen
- Ovarian stimulation regimens
- Chemotherapy and radiotherapy
- Heparins

## *Disease-related*

- Antiphospholipid syndrome
- Cancer
- Myeloproliferative diseases
- Acute promyelocytic leukaemia
- Inflammatory states e.g. nephrotic syndrome, inflammatory bowel disease, connective tissue disorders
- Stroke
- Paroxysmal nocturnal haemoglobinuria
- Thrombotic thrombocytopenic purpura
- Sickle cell disease and other sickling syndromes
- Congestive cardiac failure



THANK YOU