Thrombosis

TUCOM
Dep. of Medicine
5th year
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Thrombosis

1. Define venous thromboembolism
2. List the factors predisposing to venous thrombosis
3. Discuss the deep venous thrombosis (DVT)
4. Explain pulmonary embolism
5. Outline the investigations of venous thromboembolism
6. Review the treatment of venous thromboembolism
7. Review antiphospholipid syndrome (APS)

Venous thromboembolism (VTE)

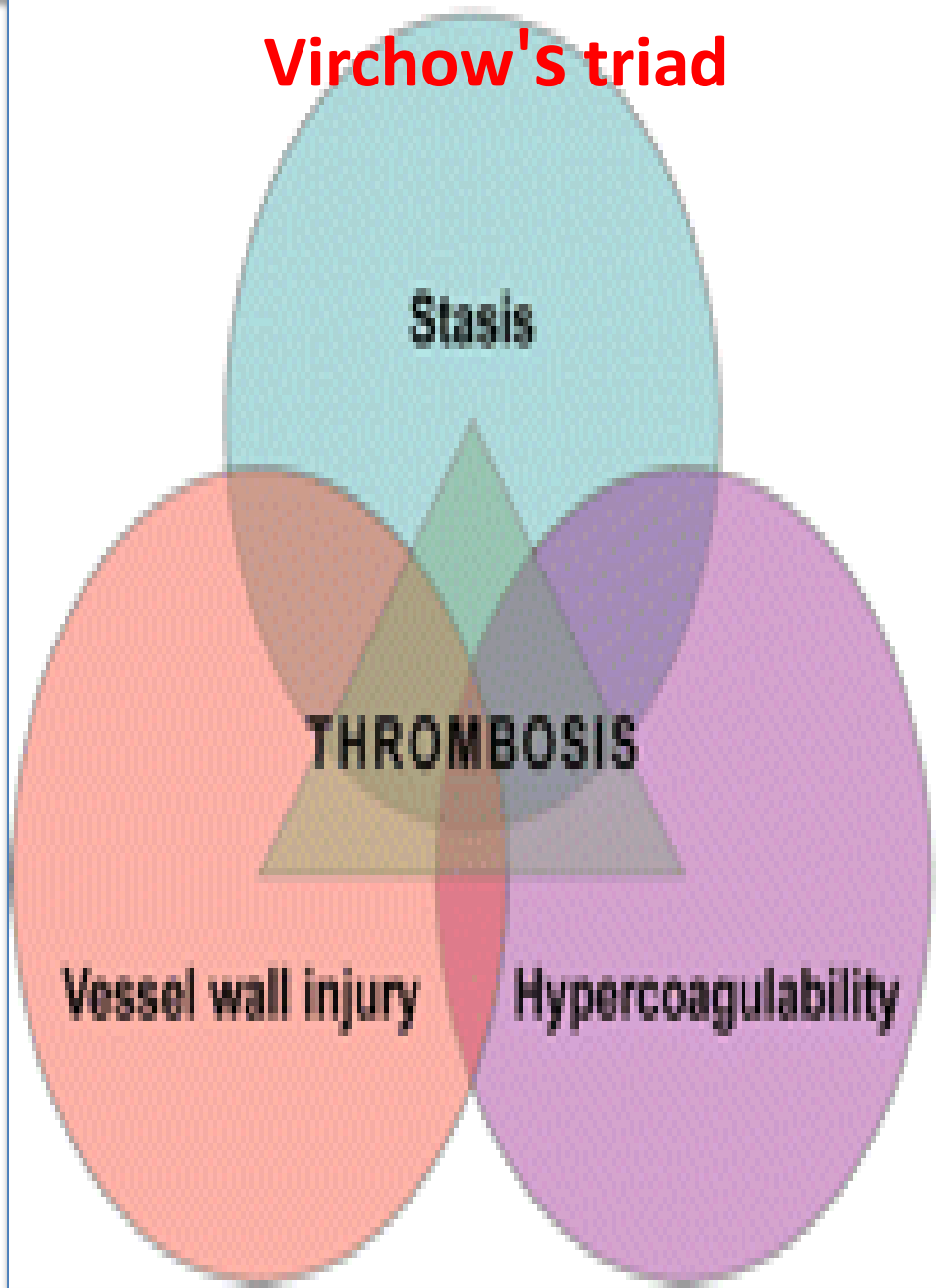
- Thrombosis: formation of blood clot at site of endothelial injury and coagulation system activation
- Embolism: migration of clot through the vasculature to a distant site

The Virchow's triad: Virchow recognized three predisposing factors for VTE:

(1) Endothelial damage

(2) Venous stasis

(3) Hypercoagulation



Venous thromboembolism (VTE) include:

- **Commonly: deep vein thrombosis (DVT) of the leg and/or pulmonary embolism (PE).**
- **Rarely: jugular vein thrombosis, upper limb DVT, cerebral sinus thrombosis and intra-abdominal venous thrombosis (e.g. Budd–Chiari syndrome).**

DVT has an annual incidence of approximately 1 : 1000 in Western populations and the case mortality is 1–3%.

The risk for a subsequent PE is much higher with proximal DVT (clot involving the popliteal vein or above) than those of distal DVT (clot involving calf vessels) (40% to 50% versus 5% to 10%, respectively).

Factors predisposing to venous thrombosis

1- Patient factors:

- Increasing age
- Obesity
- Varicose veins
- Previous DVT
- Family history, especially of unprovoked VTE when young
- Pregnancy/puerperium
- Oestrogen-containing oral contraceptives and HRT
- Immobility, e.g. long distance travel (> 4 hrs)
- IV drug use (femoral vein)

2- Surgical conditions:

- Major surgery, especially if > 30 mins' duration
- Abdominal or pelvic surgery, especially for cancer
- Major lower limb orthopaedic surgery, e.g. joint replacement and hip fracture surgery

3- Medical conditions:

- Myocardial infarction/heart failure
- Inflammatory bowel disease
- Malignancy
- Nephrotic syndrome
- Pneumonia
- Neurological conditions associated with immobility, e.g. stroke, paraplegia, Guillain–Barré syndrome

4- Haematological disorders:

- Polycythaemia rubra vera
- Essential thrombocythaemia
- Deficiency of anticoagulants: antithrombin, protein C, protein S
- Paroxysmal nocturnal haemoglobinuria
- Prothrombotic mutations: factor V Leiden, prothrombin gene *G20210A*
- Myelofibrosis

5- Antiphospholipid syndrome:

Lupus anticoagulant (more strongly associated with thrombosis than anticardiolipin antibodies)

Deep venous thrombosis (DVT)

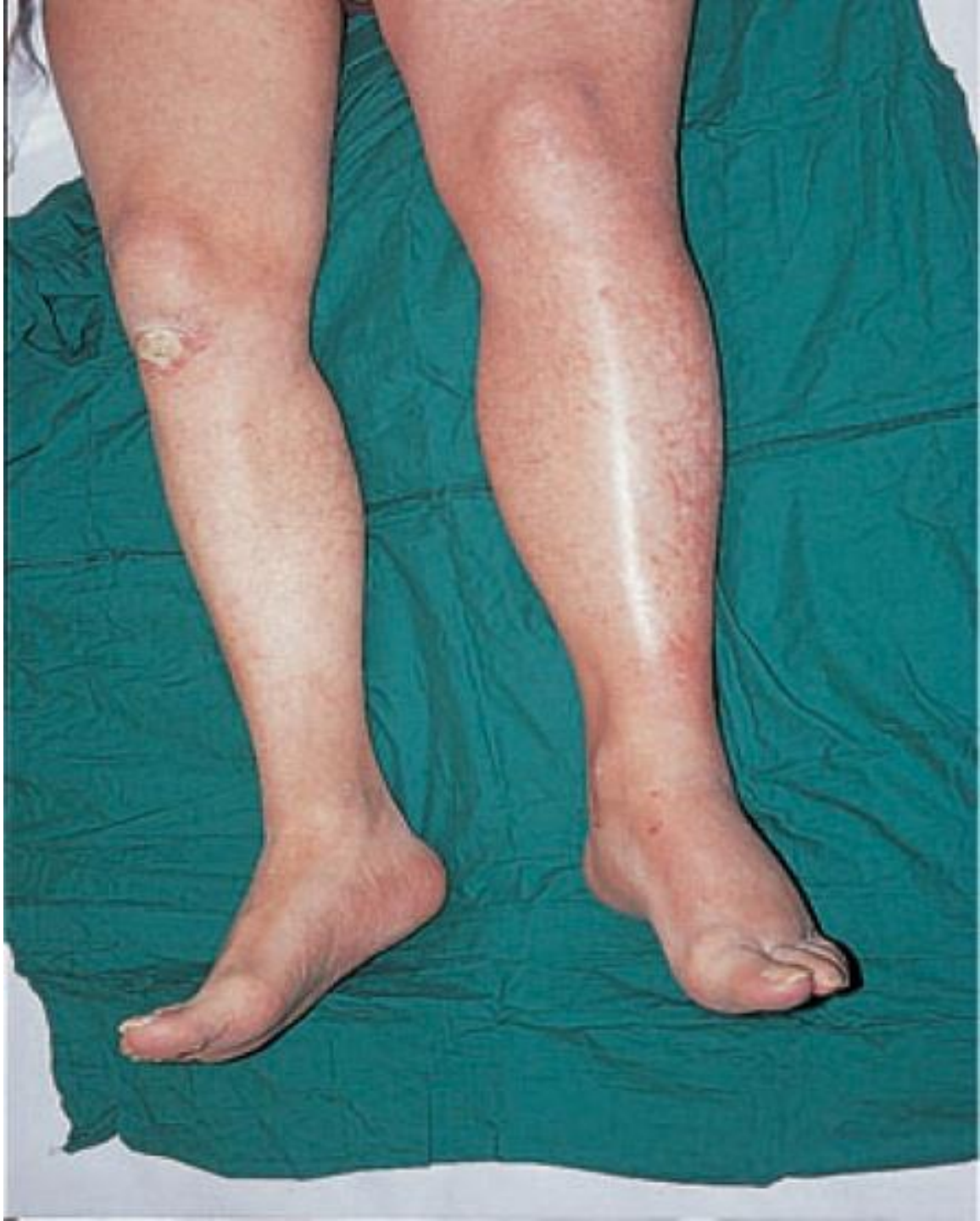
DVT: which is the most important disease affecting the peripheral veins, has an estimated annual incidence of 0.1% in white populations.

Clinical presentation: Lower limb DVT characteristically starts in the distal veins, causing pain, swelling, an increase in temperature and dilatation of the superficial veins. It is typically unilateral but may be bilateral, and clot may extend proximally into the inferior vena cava.

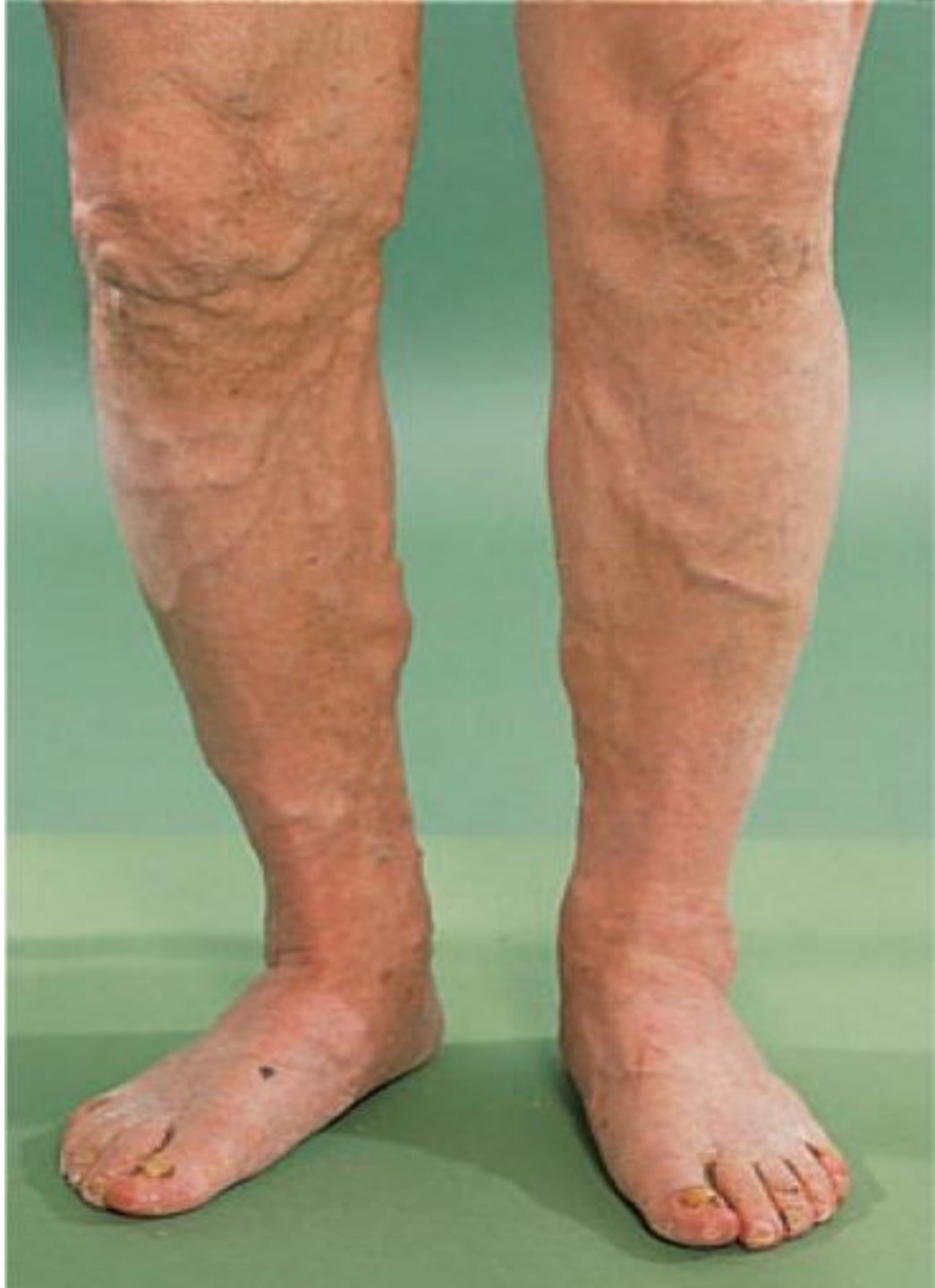
Differential diagnosis of unilateral leg swelling includes:

- **Spontaneous or traumatic calf muscle tear or a ruptured Baker's cyst, both characterised by sudden onset and localised tenderness.**
- **Infective cellulitis is usually distinguished by marked skin erythema and heat localised within a well-demarcated area of the leg and may be associated with an obvious source of entry of infection (e.g. insect bite, leg ulcer).**

Deep venous thrombosis (DVT) presenting as an acutely swollen left leg. Note the dilation of the superficial veins. The leg was hot to the touch, and palpation along the line of the left popliteal and femoral veins caused pain. Less than 50% of DVTs present in this way, and other conditions may mimic DVT, so further investigation is always indicated. Note the coincidental psoriatic lesion below the patient's right knee.



Varicose veins are a risk factor for deep venous thrombosis and may result from it.



The pre-test probability of DVT using the Wells score

Clinical feature	Points
Active cancer (treatment within 6 months, or palliation)	1
Paralysis, paresis, or immobilization of lower extremity	1
Bedridden for more than 3 days because of surgery (within 4 weeks)	1
Localized tenderness along distribution of deep veins	1
Entire leg swollen	1
Unilateral calf swelling of greater than 3 cm (below 10 cm tibial tuberosity)	1
Unilateral pitting edema	1
Collateral superficial veins	1
Alternative diagnosis as likely as or more likely than DVT	-2
Total points	

Risk score interpretation (probability of DVT):
>/=3 points: high risk (75%);
1 to 2 points: moderate risk (17%);
<1 point: low risk (3%).

Investigations:

1- Wells score pre-test probability of DVT: rank the patients likelihood of DVT.

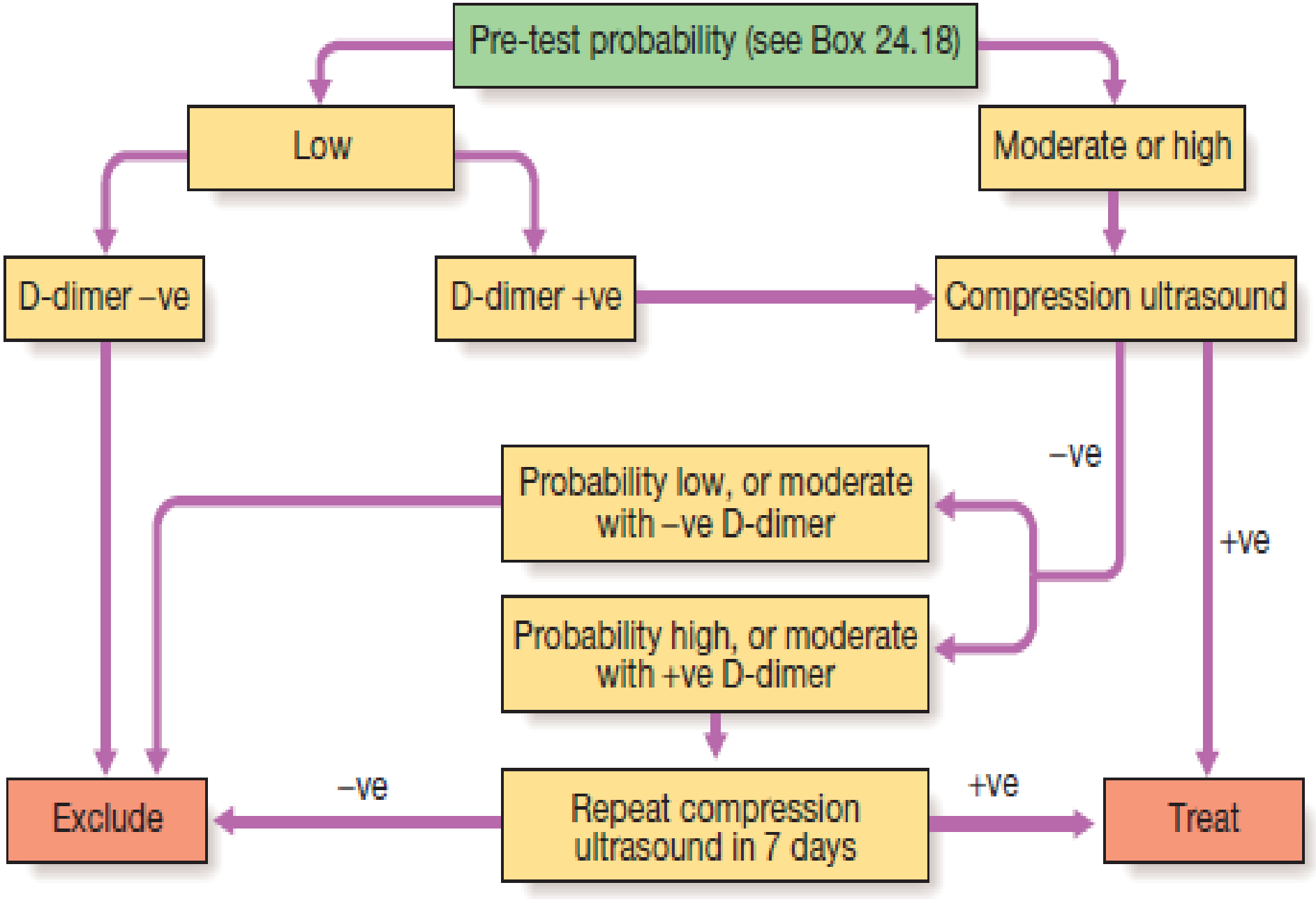
2- D-dimer: which are fibrin degradation products. D-dimer elevation is a highly sensitive indicator of DVT.

In patients with a low Wells score and D-dimer level is normal (less than 500 ng/mL), DVT is unlikely so further investigation for DVT is unnecessary.

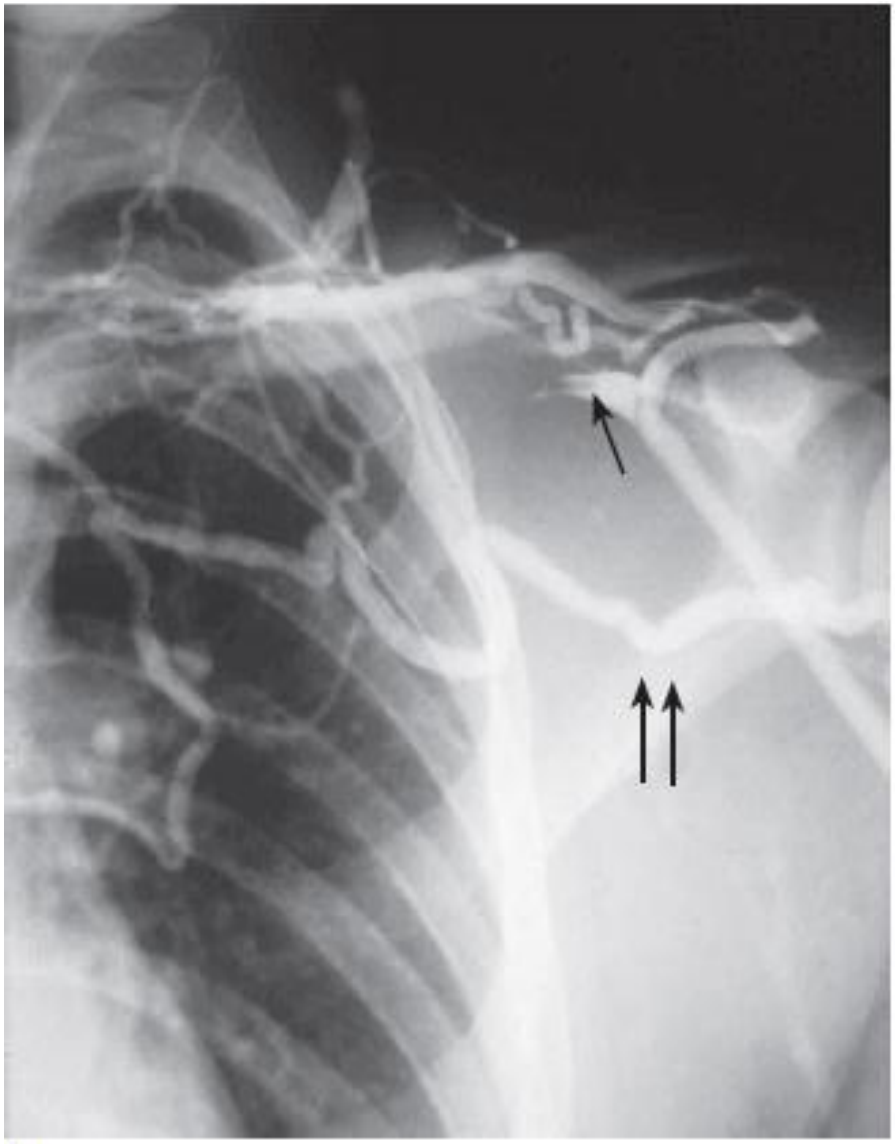
3- Doppler ultrasound is the imaging modality of choice. It has a sensitivity for proximal DVT (clot involving the popliteal vein or above) of 99.5%, but (40% to 90%) for distal DVT (clot involving calf vessels).

4- Other diagnostic invest.: MR angiography and contrast venography in difficult cases.

5- Investigations of predisposing factors, particularly pelvic malignancy and thrombophilic conditions.



Investigation of suspected deep vein thrombosis.



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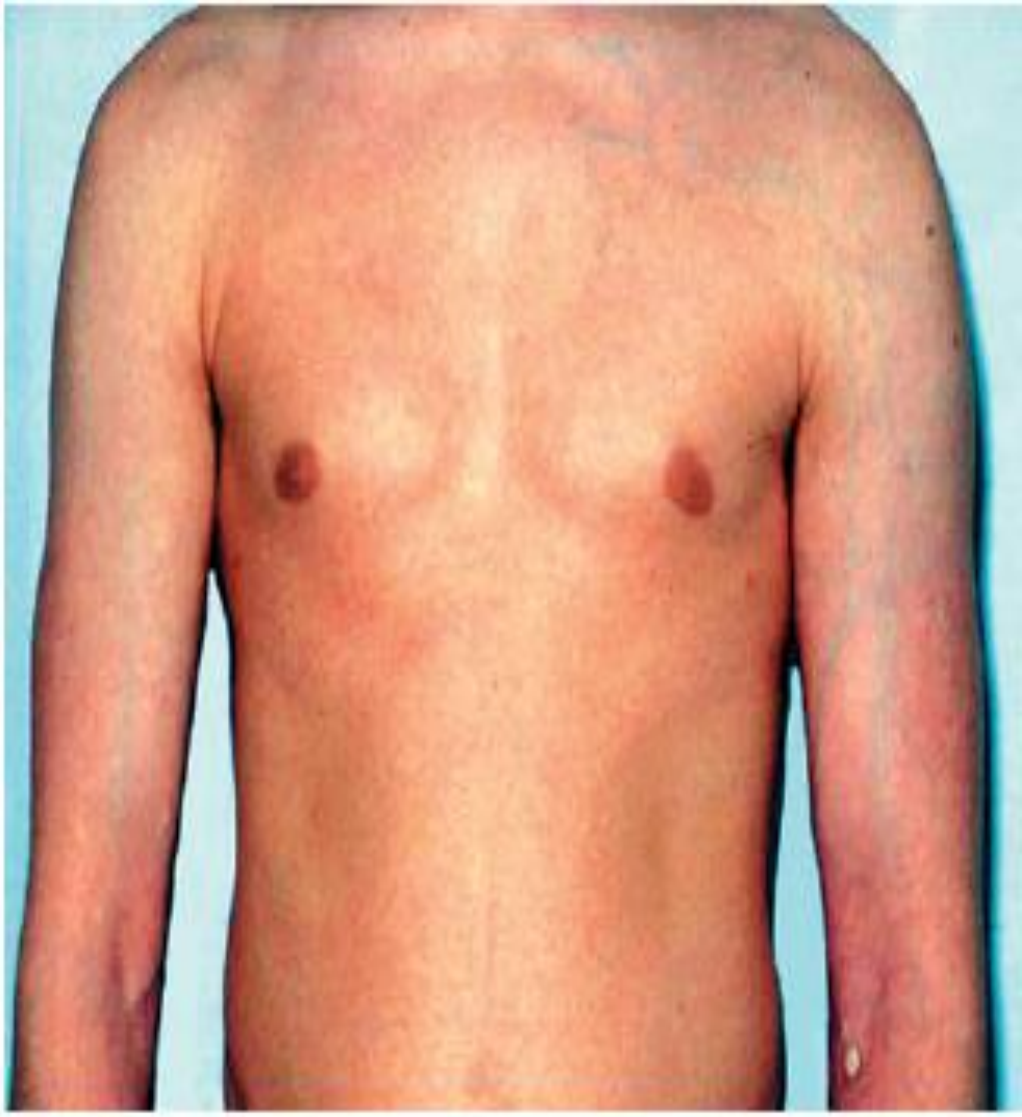


B

Axillary vein thrombosis. (A) Angiogram. Single arrow shows site of thrombosis. Double arrows show dilated collateral vessels. (B) Clinical appearance with swollen left arm and dilated superficial veins.

PULMONARY EMBOLISM

The majority (75%) of pulmonary emboli arise from the propagation of lower limb DVT.

Amniotic fluid, placenta, air, fat, tumour (especially choriocarcinoma), and septic emboli (from endocarditis affecting the tricuspid or pulmonary valves) are rare causes.

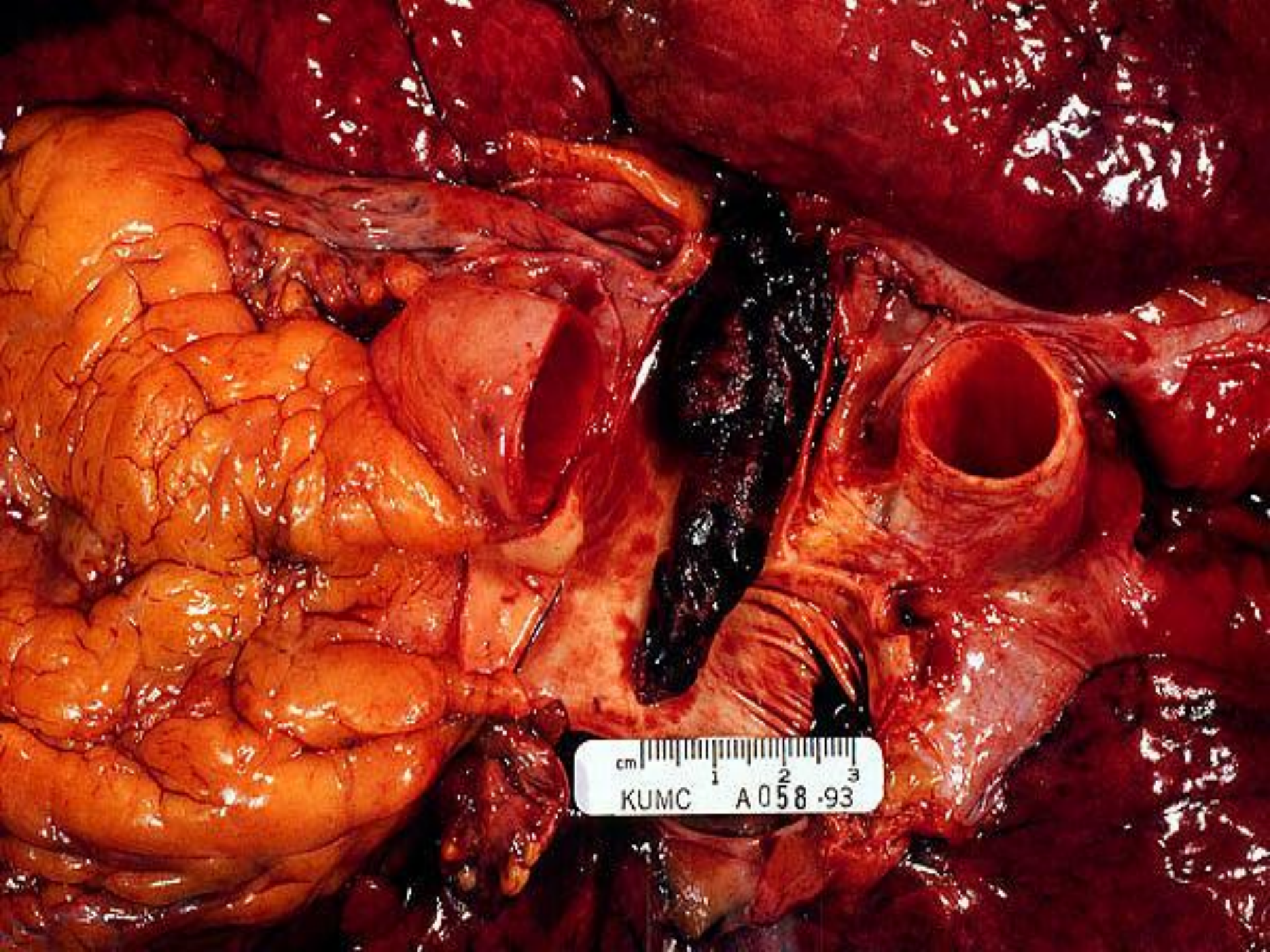
PE occurs in around 1% of all patients admitted to hospital and accounts for around 5% of in-hospital deaths.

The clinical features of PE depend largely upon the size of embolism and co-morbidity. They encompass a spectrum from cardiovascular collapse to small emboli with few or no hemodynamic consequences.

A recognized risk factor is present in 80% - 90% of patients.

Acute massive PE

Pathophysiology	Major hemodynamic effects: ↓ cardiac output; acute right heart failure
Symptoms	Faintness or collapse, central chest pain, apprehension, severe dyspnea
Signs	Major circulatory collapse: tachycardia, hypotension, ↑ JVP, right ventricular gallop rhythm, split P_2 , Severe cyanosis, ↓ Urinary output
Chest X-ray	Usually normal. May be subtle oligaemia
ECG	S_1 Q_3 T_3 anterior T-wave inversion Right bundle branch block (RBBB)
Arterial blood gases	Markedly abnormal with ↓ PaO_2 and ↓ $PaCO_2$. Metabolic acidosis
Alternative diagnoses	Myocardial infarction; pericardial tamponade; aortic dissection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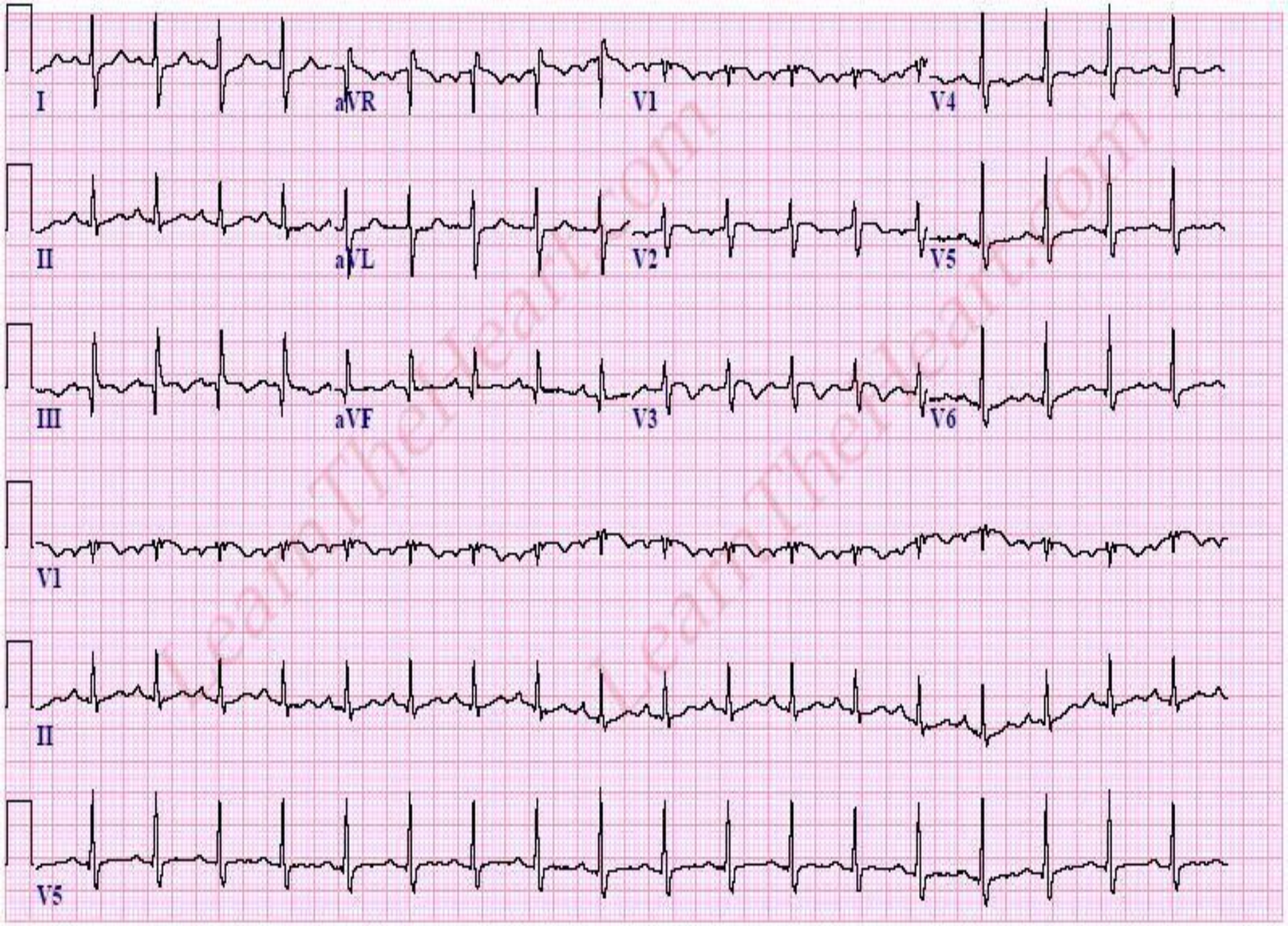
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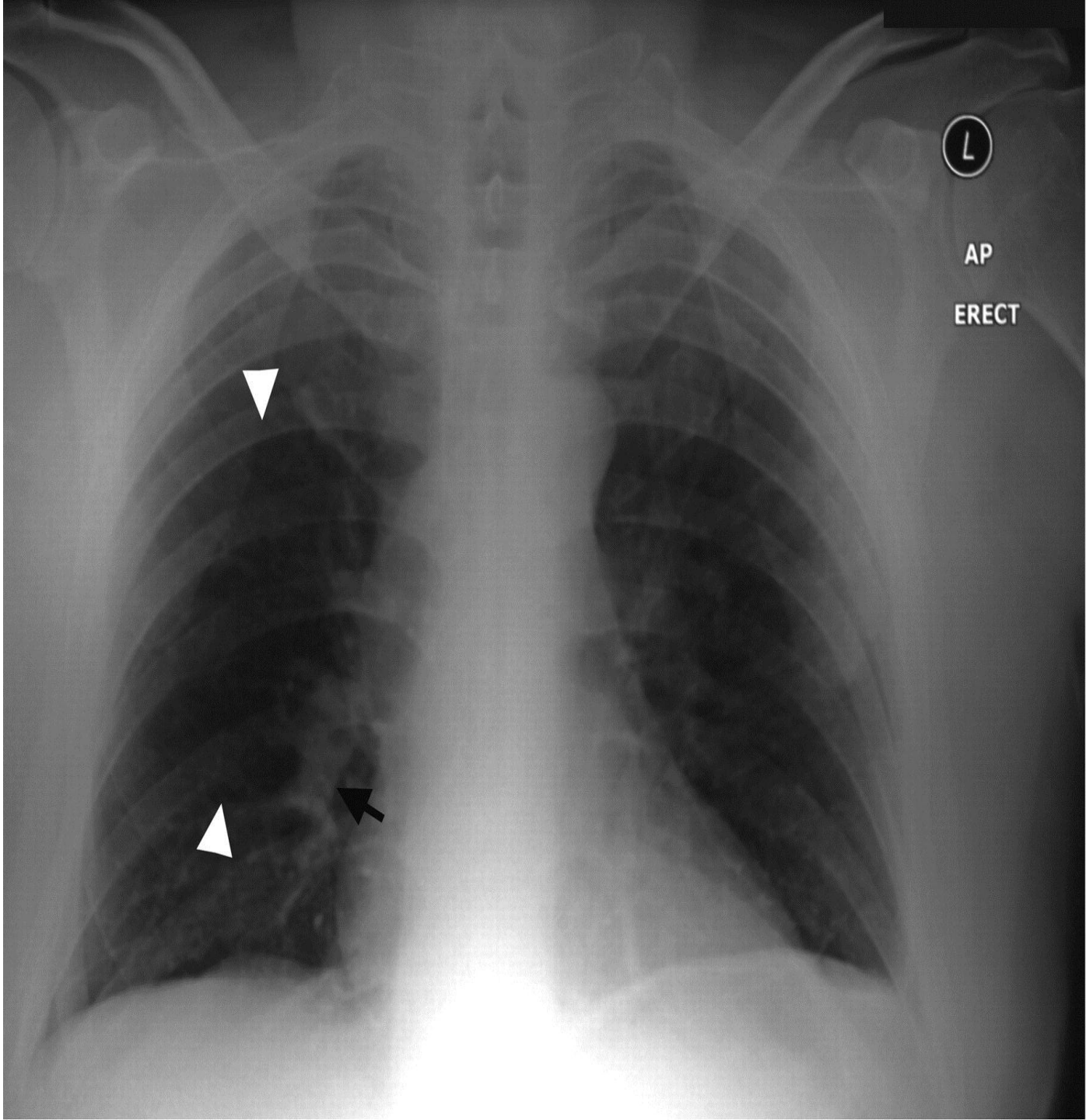
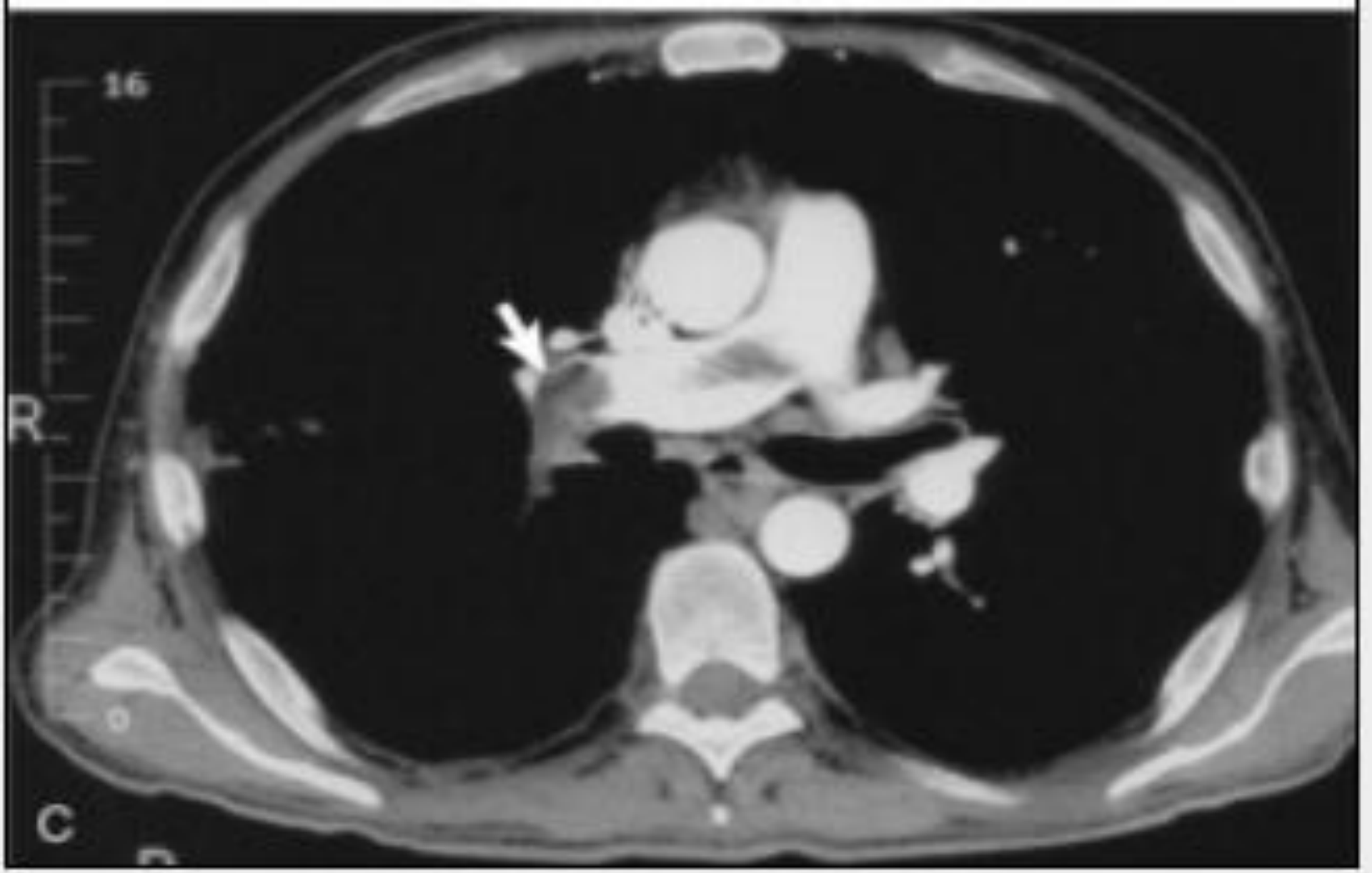
Chest radiograph demonstrating focal oligemia in the right lung (area between white arrowheads) and a prominent right descending pulmonary artery (black arrow).





Large central pulmonary embolism. A contrast-enhanced computed tomography (CT) scan of the chest shows the pulmonary artery with a large clot (arrow) obstructing the right main pulmonary artery.

Acute small/medium PE

Pathophysiology	Occlusion of segmental pulmonary artery → infarction ± effusion
Symptoms	Pleuritic chest pain, restricted breathing, haemoptysis
Signs	Tachycardia Pleural rub, raised hemidiaphragm, crackles, effusion (often blood-stained) Low-grade fever
Chest X-ray	Pleuropulmonary opacities, pleural effusion, linear shadows, raised hemidiaphragm
ECG	Sinus tachycardia
Arterial blood gases	May be normal or ↓ $PaCO_2$
Alternative diagnoses	Pneumonia, pneumothorax, musculoskeletal chest pain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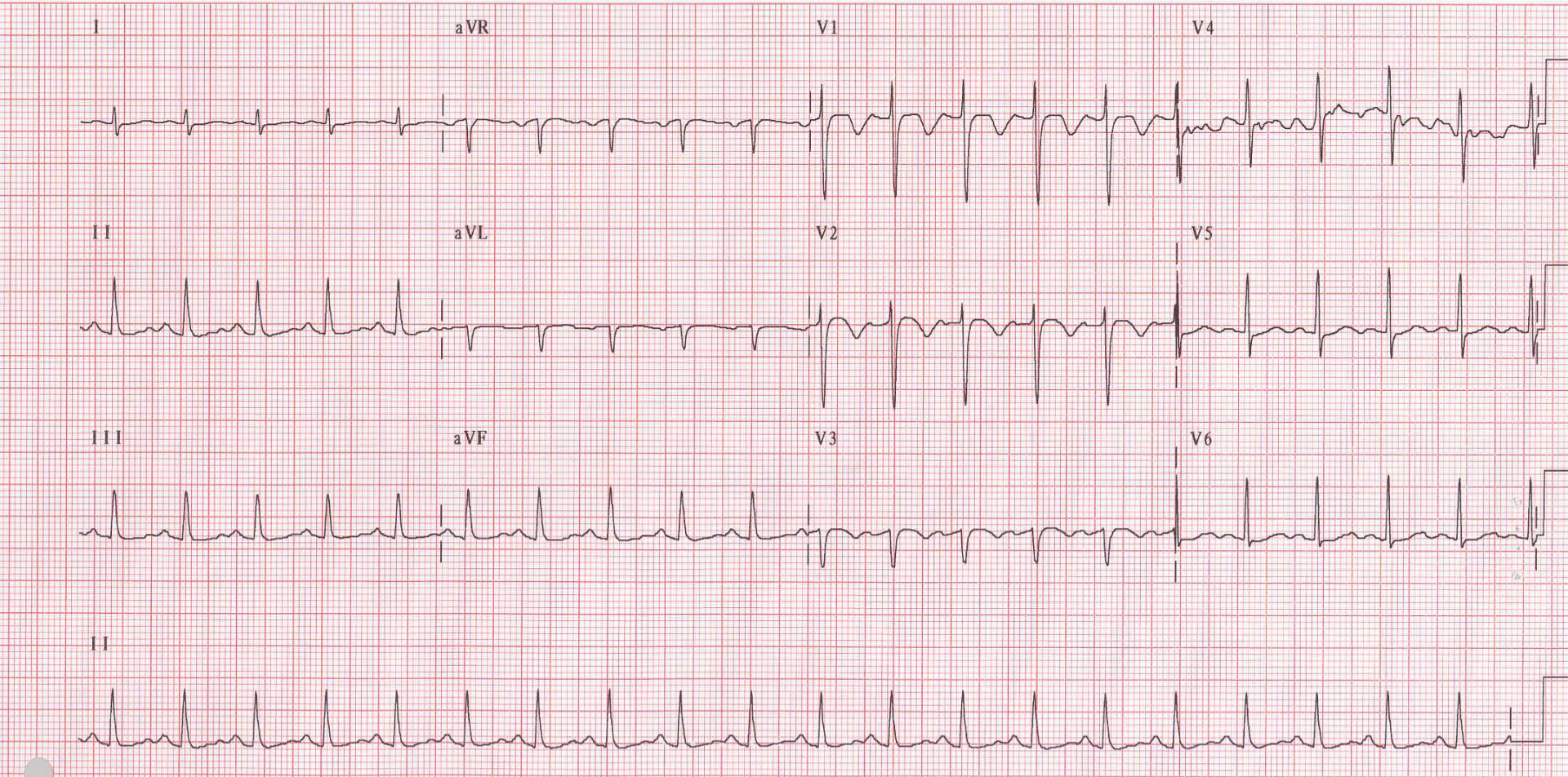
Rate	122	. Sinus tachycardia, rate 122	.Normal P axis, rate >= 100	DX
PR	166	. Vertical axis, unusual for age	.QRS axis 81 to 90 & age > 40	ER
QRSD	69	. Consider Anterior infarct	.Q wave in V3	DOB
QT	256	. Nonspecific Inferior T abnormalities	.T neg or T/QRS ratio <.05 2,3,F	07/01/45
QTc	365			

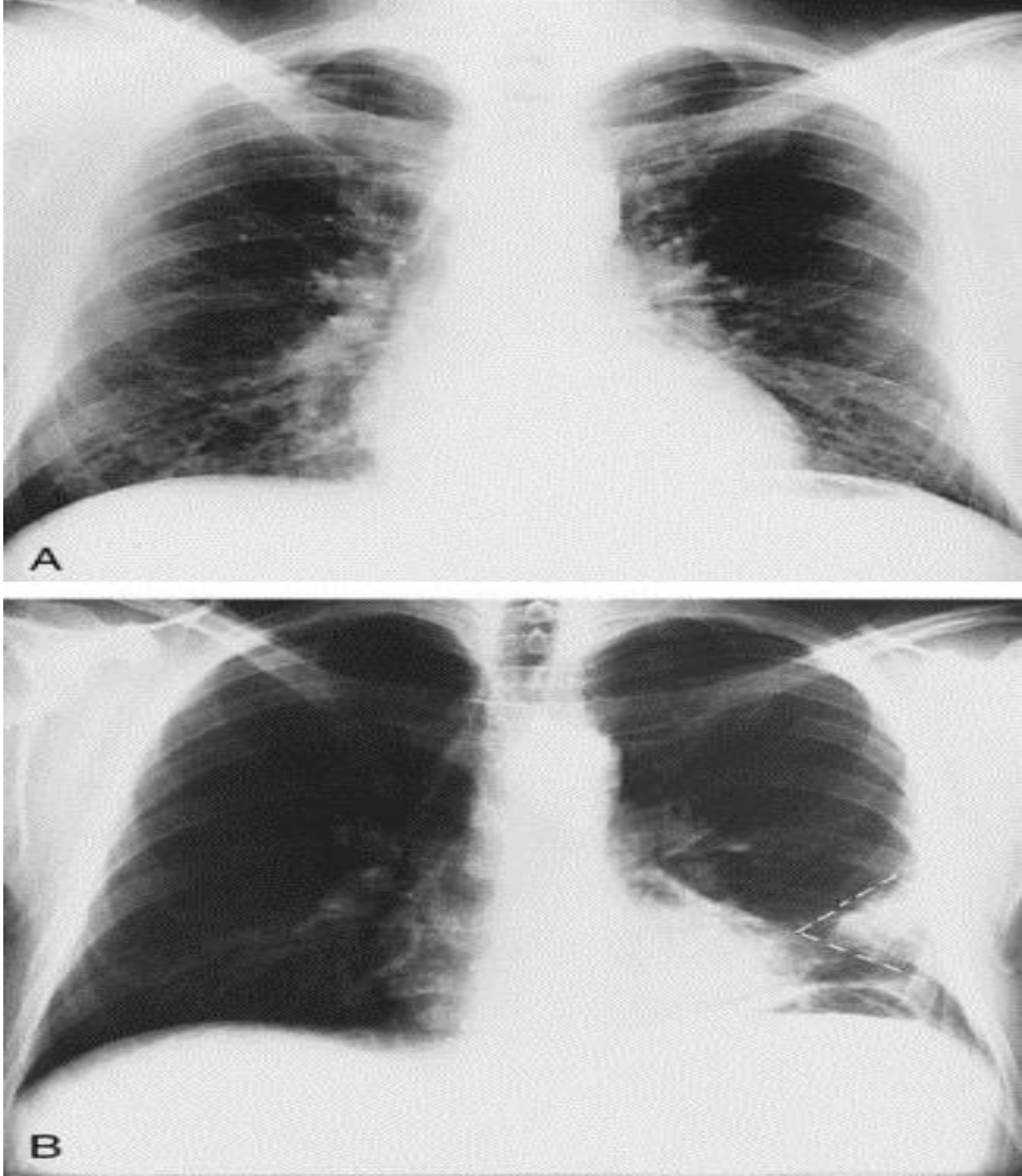
P	70
QRS	88
T	-68

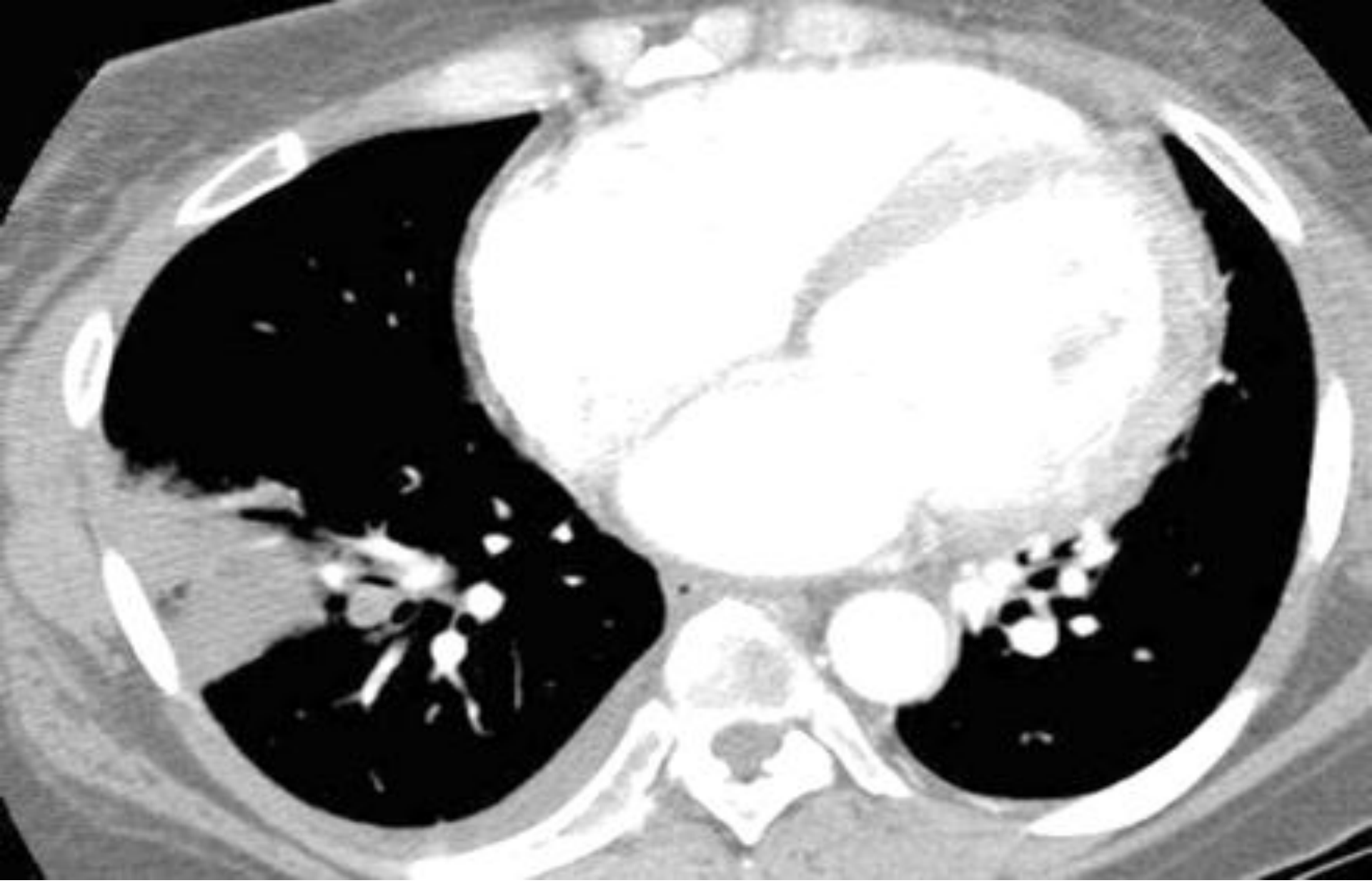
- ABNORMAL ECG -

PRELIMINARY-MD MUST REVIEW



Pulmonary infarction. Immediately after an acute episode of shortness of breath due to a pulmonary embolism, the posteroanterior chest x-ray is essentially normal (A). If the pulmonary embolism actually leads to infarction, a peripheral wedge-shaped infiltrate develops (B).





CT scans= A pulmonary infarct is typically triangular or dome-shaped, with the base abutting the pleura and the apex directed toward the hilum. The opacity represents local hemorrhage with or without central tissue necrosis.

Pre-test clinical probability score of Wells for PE

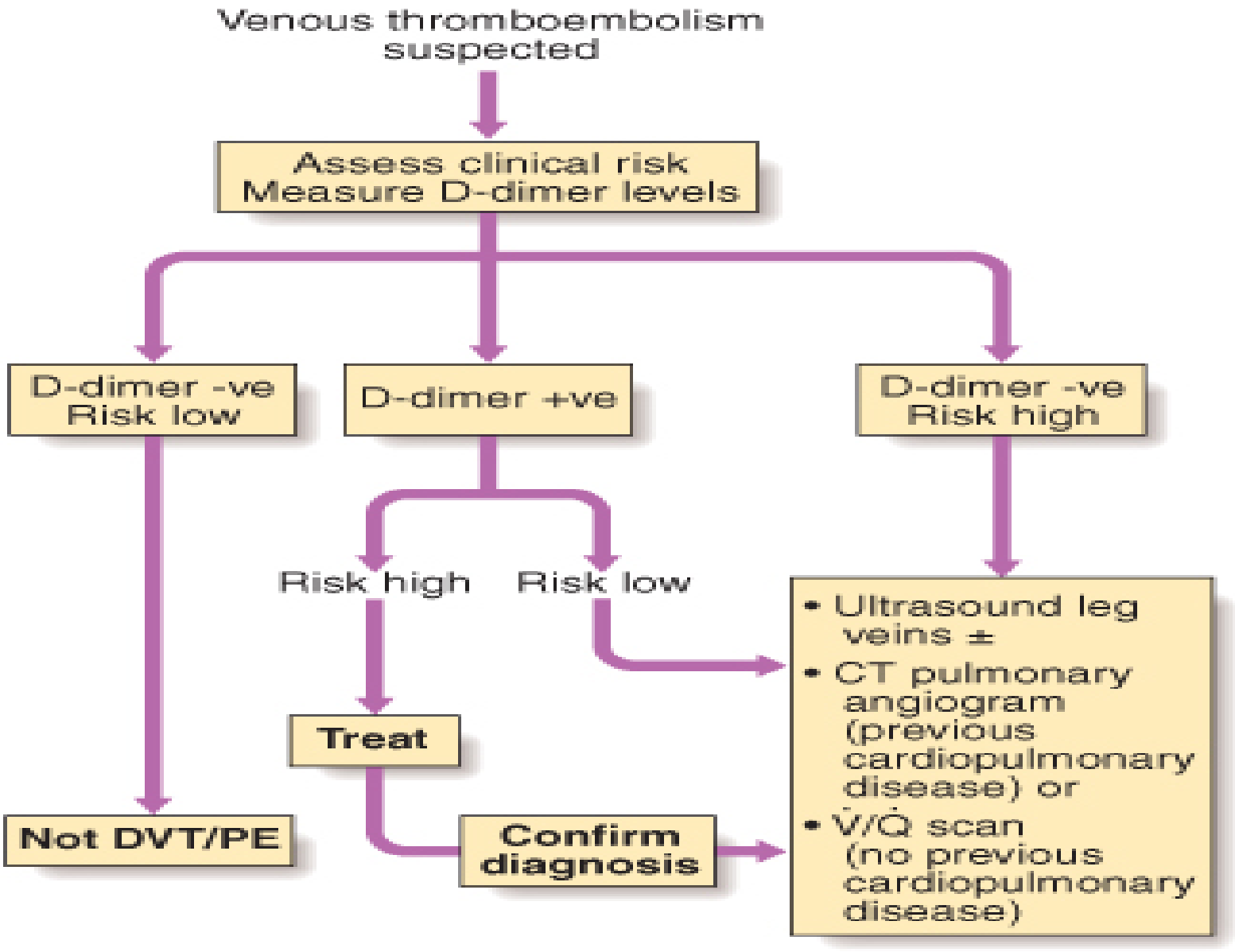
Clinical feature	Points
Clinical symptoms of DVT	3
Other diagnosis less likely than PE	3
Heart rate greater than 100 beats per minute	1.5
Immobilization or surgery within past 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Malignancy	1
Total points	

Risk score interpretation (probability of PE):
>6 points: high risk (78.4%);
2 to 6 points: moderate risk (27.8%);
<2 points: low risk (3.4%)

Investigations

- Pre-test clinical probability score of Wells for PE.
- D-dimer: An elevated D-dimer is of limited value, as it may be raised in a variety of conditions including PE, myocardial infarction, pneumonia and sepsis. However, low levels (< 500 ng/mL), particularly where clinical risk is low, have a high negative predictive value and further investigation is usually unnecessary.
- Chest radiography: Normal radiographic appearances in an acutely breathless and hypoxaemic patient should raise the suspicion of PE.
- ECG: The most common findings are a sinus tachycardia and anterior T-wave inversion.

- CT pulmonary angiography (CTPA) is the first-line diagnostic test. It has the advantages of visualising the distribution and extent of the emboli.
- Ventilation-perfusion scanning is seldom used nowadays.
- Doppler ultrasound of the leg veins remains the investigation of choice in patients with suspected DVT.
- Echocardiography; is extremely helpful in the differential diagnosis and assessment of acute circulatory collapse.
- Arterial blood gases typically show a reduced PaO_2 and a normal or low $PaCO_2$.



Algorithm for the investigation of patients with suspected pulmonary thromboembolism. Clinical risk is based on the presence of risk factors for VTE and the probability of another diagnosis.

Management of venous thromboembolism

1- General measures:

DVT: elevation and analgesia.

Pulmonary embolism:

- Oxygen should be given to all hypoxaemic patients
- Opiates may be necessary to relieve pain and distress but should be used with great caution in the hypotensive patient.
- Hypotension should be treated by giving intravenous fluid or plasma expander.
- Resuscitation by external cardiac massage may be successful in the moribund patient by dislodging and breaking up a large central embolus.

2- Anticoagulation of VTE: preventing additional thrombus formation and permitting endogenous fibrinolytic mechanisms to lyse clot that has already formed.

A- Immediate Parenteral Anticoagulation:

1- Unfractionated heparin (UFH): anticoagulates by binding to and accelerating the activity of antithrombin III, bolus and continuous infusion, to achieve aPTT 2–3 times the upper limit of the laboratory normal. Given as intravenous bolus is 5000–10,000 units (80 units/kg) followed by a continuous infusion of 1000–1500 units/h(18 units/kg per hour).

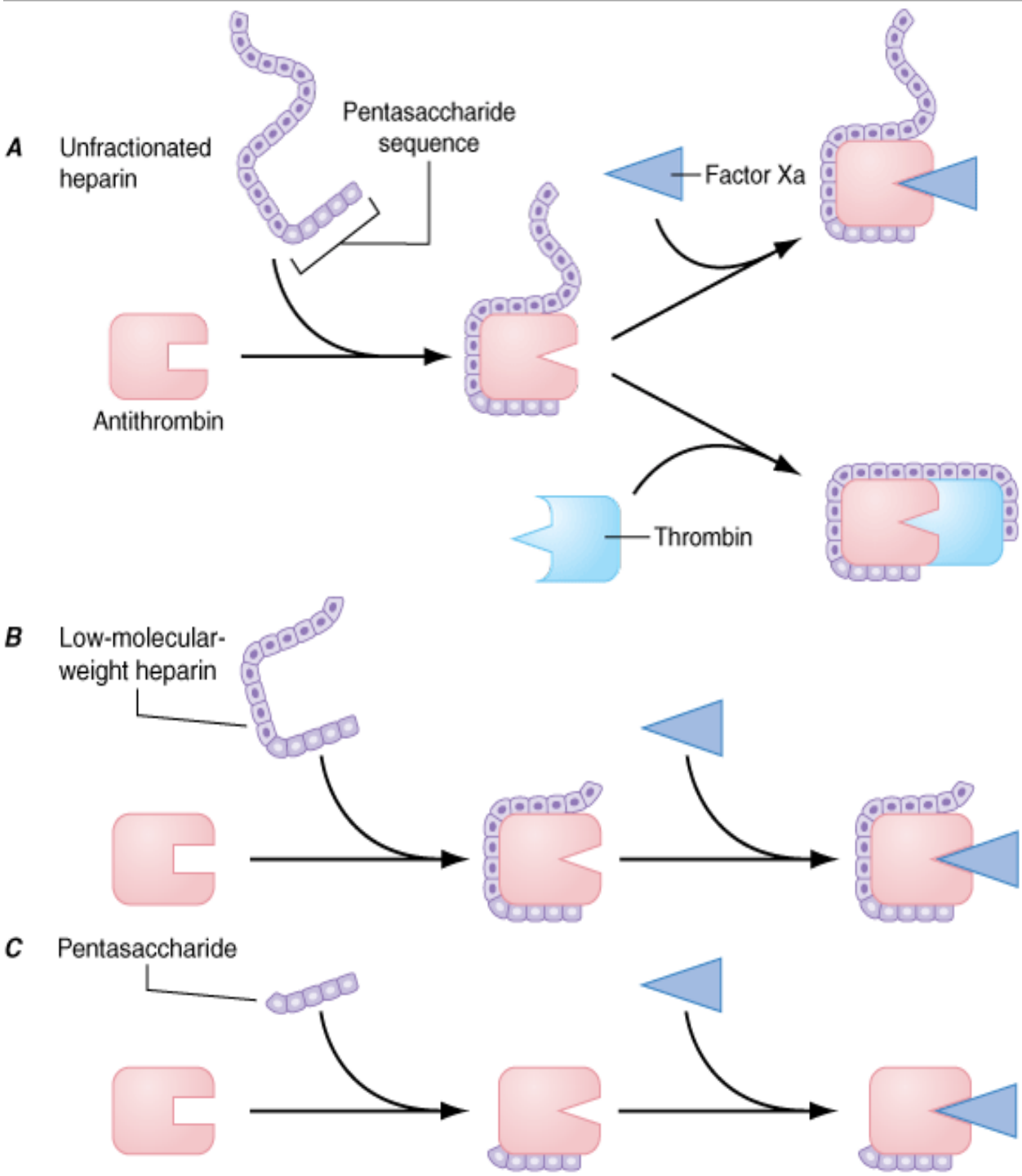
2- Low Molecular Weight Heparins: These fragments of UFH, and a longer half-life than UFH. No monitoring or dose adjustment is needed.

Enoxaparin 1 mg/kg twice daily and tinzaparin 175 units/kg once daily. Other: dalteparin, nadroparin. The weight-adjusted doses must be adjusted downward in renal insufficiency because the kidneys excrete LMWH.

3- Fondaparinux: an anti-Xa pentasaccharide, is administered by once-daily subcutaneous injection adjust for impaired renal function and no laboratory monitoring is required.

B- Warfarin Anticoagulation: This vitamin K antagonist prevents carboxylation activation of coagulation factors II, VII, IX, and X. The full effect of warfarin requires at least 5 days. usually initiated in a dose of 5 mg with continue parenteral anticoagulation for a minimum of 5 days , until the target INR is 2.5, with a range of 2- 3.

Mechanism of action of heparin, low-molecular-weight heparin (LMWH), and fondaparinux, a synthetic pentasaccharide.
A. Heparin binds to antithrombin via its pentasaccharide sequence.
B. LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin.
C. The pentasaccharide only accelerates factor Xa inhibition by antithrombin because the pentasaccharide is too short to bridge antithrombin to thrombin.



Duration of anticoagulation:

- In the presence of a temporary risk factor (provoked DVT), which is then removed, for upper extremity or calf DVT, 3 months of anticoagulation is sufficient.
- For provoked proximal leg DVT or PE, 6 months of anticoagulation is sufficient.
- Patients with "idiopathic," unprovoked DVT or PE, patient at high risk of recurrent VTE: thrombophilia (e.g., factor V Leiden, antiphospholipid syndrome, deficiency of antithrombin, protein C, or protein S, or the prothrombin gene mutation) recommend anticoagulation for an indefinite long duration.
- In patients with active cancer and VTE, there is evidence that LMWH should be continued for 6 months rather than being replaced by a warfarin.

3- Inferior Vena Caval (IVC) Filters: The two principal indications are (1) active bleeding that precludes anticoagulation, and (2) recurrent venous thrombosis despite intensive anticoagulation.

4- Thrombolytic therapy:

In DVT: Thrombolysis may be considered for limb threatening DVT.

In pulmonary embolism: Thrombolysis appears to improve outcome when acute massive PE is accompanied by shock. In the absence of shock, the benefits are less clear but thrombolysis may be considered in those presenting with right ventricular dilatation and hypokinesis or severe hypoxaemia.

Treatment of Deep Venous Thrombosis in Pregnancy

Warfarin cross the placenta and have the potential to cause warfarin embryopathy if the newborn is exposed to warfarin between 6 and 12 weeks of gestation. Consequently, parenteral unfractionated heparin and LMWH, which do not cross the placenta and are safe for the fetus, are the agents of choice.

The easiest approach is to initiate therapy with weight-adjusted “treatment” doses of LMWH continued for the duration of the pregnancy.

Venous thromboembolism prophylaxis

Patients at high risk are indicated for VTE prophylaxis:

- **Congestive heart failure**
- **Acute respiratory illness**
- **Acute inflammatory diseases**
- **Immobilized for 3 days or longer**
- **Patients with previous VTE**
- **Major surgery, either elective or emergent**

Those patients should receive :

- **unfractionated heparin, 5000 units subcutaneously twice daily or low-molecular-weight heparin, typically in the dose of enoxaparin, 40 mg once daily, or dalteparin, 2500 or 5000 units once daily**
- **Intermittent pneumatic compression**

Intermittent pneumatic compression (IPC) devices are used to help prevent blood clots in the deep veins of the legs. The devices use cuffs around the legs that fill with air and squeeze the legs. This increases blood flow through the veins of legs and helps prevent blood clots.

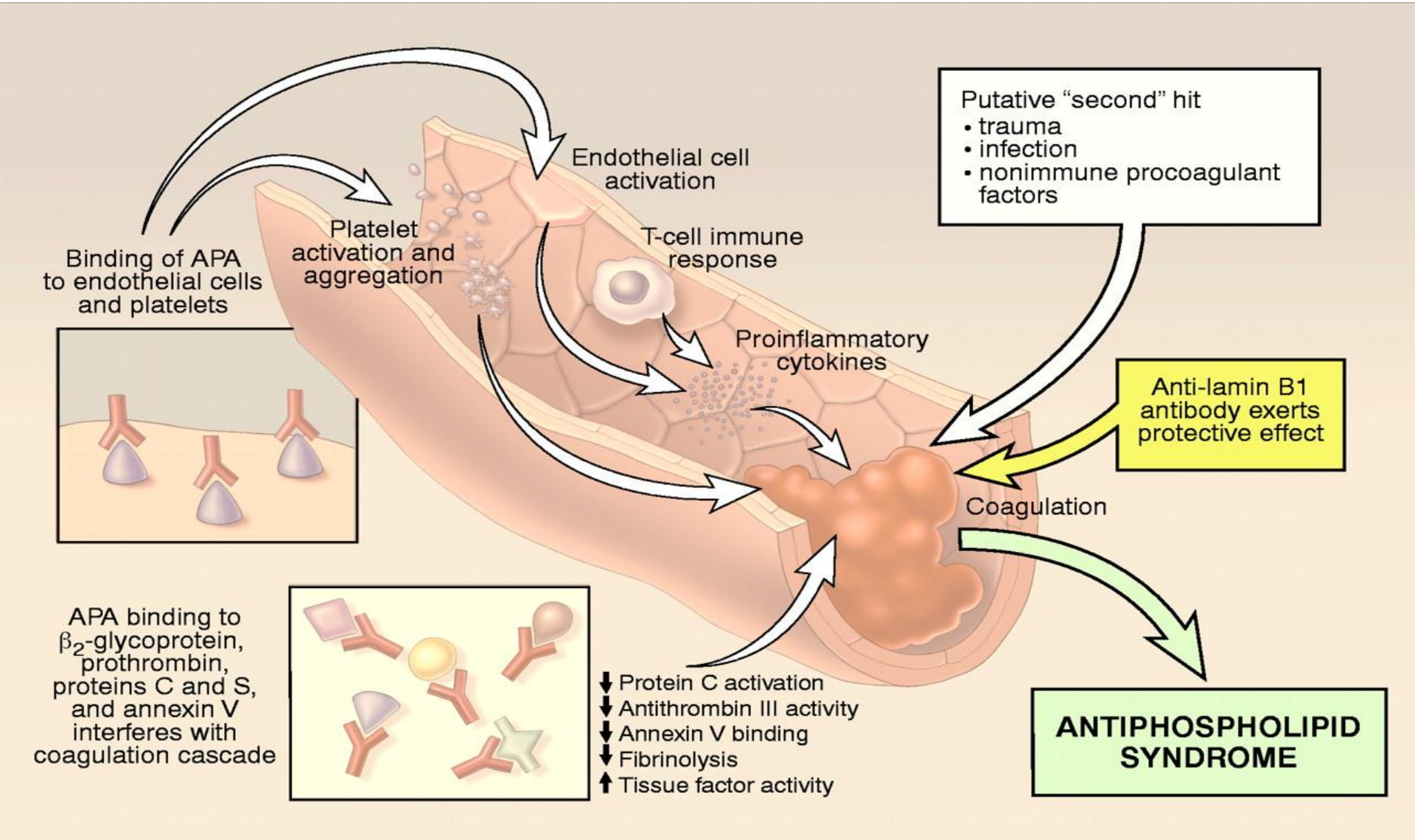
Antiphospholipid Syndrome (APS)

APS is characterized by venous and arterial thrombosis, recurrent spontaneous abortions (which may also be due to thrombosis), thrombocytopenia, and a variety of neuropsychiatric manifestations.

It is associated with a heterogeneous group of autoantibodies that bind to phospholipid-protein complexes, a **β2-glycoprotein I**. β2-GPI antibodies potentiate the risk of thrombosis through:

1. Endothelial activation and secretion of proinflammatory cytokines.
2. Platelet activation, leading to increased platelet adhesion and thromboxane synthesis.
3. Acquired resistance to the anticoagulant properties of protein C.

Annexin A5, further contributing to the increased risk of thrombosis. APS displaces annexin A5 from the trophoblastic surface of placenta, which may contribute to pregnancy loss.



Clinical Features:

- APS either primary (occurs in isolation) or secondary (associated with other autoimmune diseases such as SLE).
- Venous thrombotic complications: Deep vein thrombosis and pulmonary embolism.
- Arterial thrombotic complications: Cerebrovascular events such as stroke and transient ischemic attacks.
- Obstetric complications: Recurrent spontaneous abortions and fetal growth retardation, which are probably due to thrombosis of placental vessels.
- Mild thrombocytopenia, with platelet count usually above 50,000/mL.
- About a third of these patients have nonbacterial heart valve vegetations (Libman-Sacks endocarditis).

Diagnosis: The presence of clinical features with laboratory evidence of APS antibodies:

1. Lupus anticoagulant antibody
2. Anticardiolipin antibody

With Prolonged APTT because it interfere with phospholipid-dependent coagulation tests.

Treatment:

- Acute management of thrombosis in these patients is essentially the same as in other individuals.
- The use of low-molecular-weight heparin is better, which does not require monitoring. Warfarin is effective in preventing recurrent thrombosis but usually requires prolonged therapy with doses to achieve an INR of 2.0 to 3.0.
- Risk of recurrent pregnancy loss in APS can be reduced with combination treatment of low-dose aspirin and heparin.


Thanks