433 Teams

MEDICINE

8| Hypercoagulable

433medicine.team@gmail.com

جامعة الملك سعود
King Saud University

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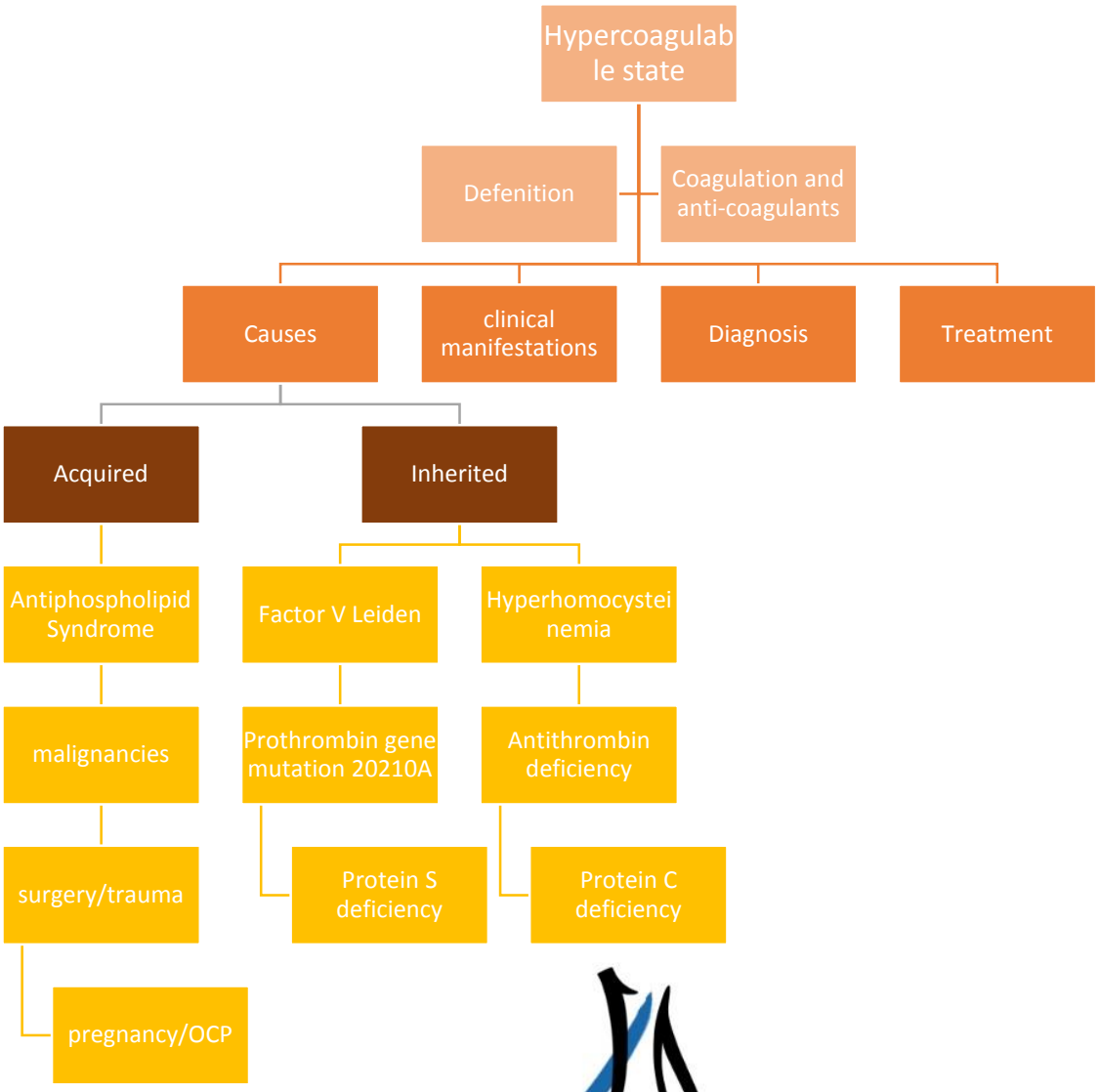
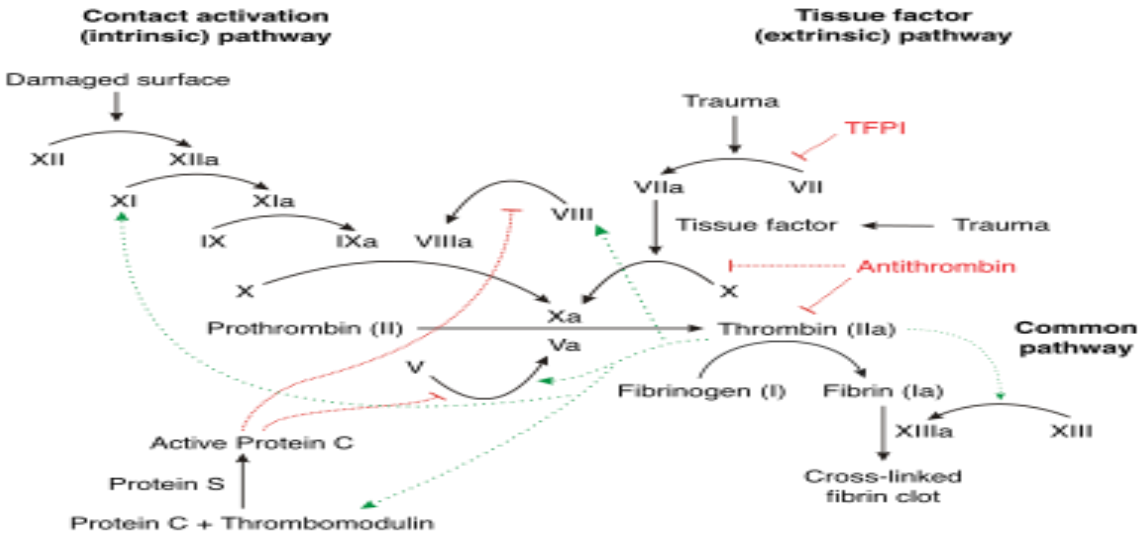
Objectives: were not given.

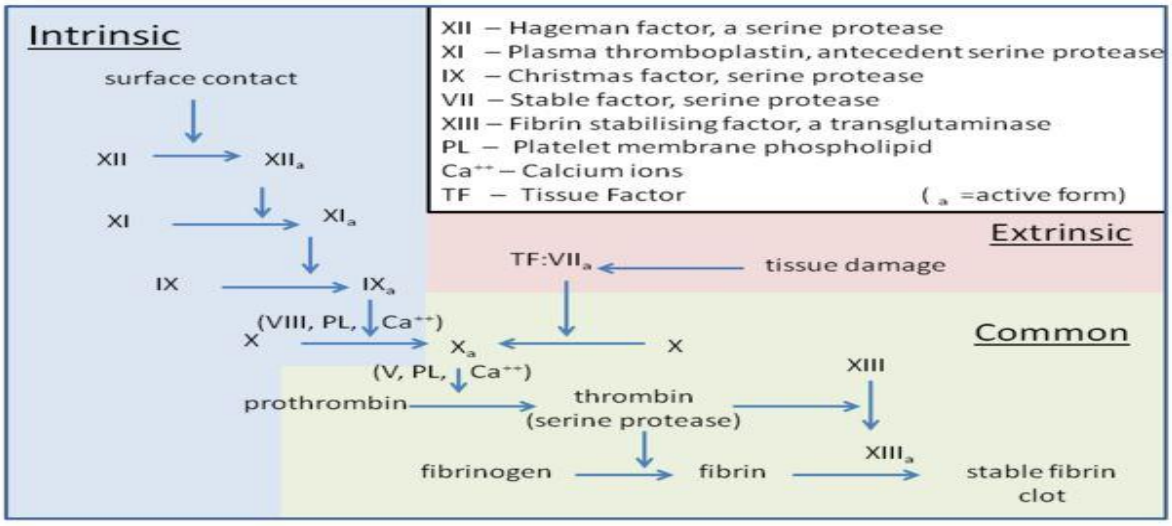


Definition:

Alteration in the hemostatic balance between blood fluidity and clot formation due to genetic or acquired disorders which shift the balance toward excessive platelet aggregation and thrombin generation (clot formation) that lead to thrombosis.



The three pathways that makeup the classical blood coagulation pathway

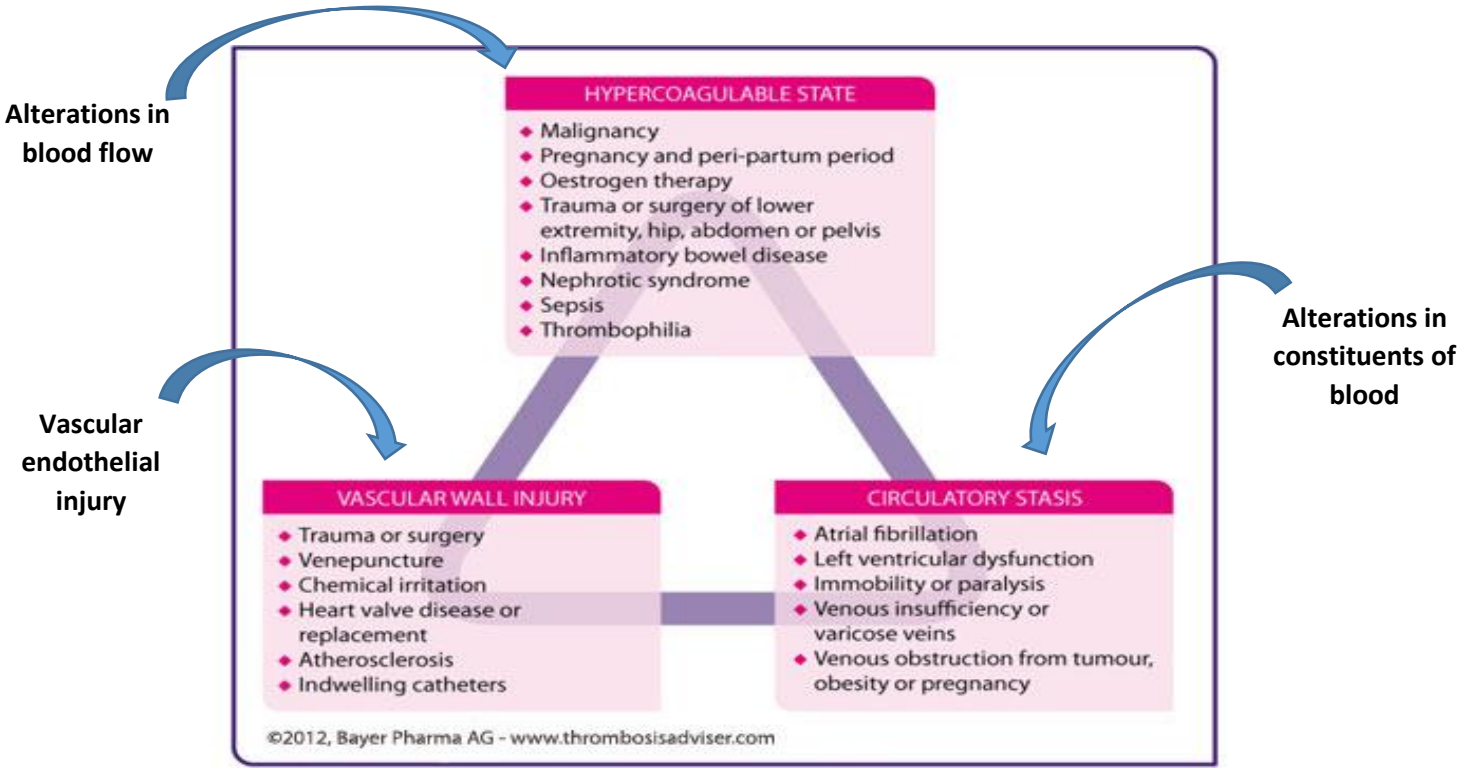


Antithrombotic functions of endothelium:

Prostacyclin(PGI2), Nitrous oxide(NO2), Thrombomodulin, Heparans(proteoglycans), Tissue factor pathway inhibitors(TFPI), Plasminogen activator inhibitors(PAI-1).

Virchow's triad:

Trio of elements essential to thrombosis.



Coagulation factors	Natural inhibitors
• Nearly all are synthesised by the liver • Most require calcium to bind to substrates • II, VII, IX and X are vitamin K dependent	• Antithrombin • Protein C • Protein S • Proteins C and S are vitamin K dependent

Prothrombotic states:

Vascular (Endothelial dysfunction) (hypertension, hypercholesterolemia, obesity, lipid abnormalities, diabetes, smoking tobacco products and exposure to air pollution)	**Platelets** (↑ activity and/or numbers) (essential thrombocytosis, allergic reactions, cancer, chronic kidney failure)	**Coagulation factors (↑)**
Natural anticoagulants (↓ and/or dysfunction)	**Pathological conditions (e.g.: hyperhomocysteinemia, antiphospholipid syndrome, Contraceptive pills, etc.)**	**Fibrinolytic system (↓)**

Thrombosis:

A thrombus is a mass in the vascular lumen which is made up of fibrin and blood constituents. Proportions of red cells, white cells and platelets in the thrombus vary enormously

There are two types of thrombi:

- **Venous thrombi - largely red cells**
- **Arterial thrombi - largely platelets**

Arterial thromboembolism

Characters	1-Almost invariably associated with atheromatous plaques 2-Platelets central to thrombus formation 3-Thrombi – platelet rich, pale, friable 4-Anti-platelet agents central to treatment
Main risk factors	Common: Smoking , Hypertension, Diet Hypercholesterolaemia, Diabetes mellitus ,Personal or family history Less common : Hyperhomocystinaemia, Anti-phospholipid syndrome , Raised fibrinogen , Raised factor VII , Raised factor VIII
Clinical syndromes of arterial thromboembolism	Unstable angina , Myocardial infarction ,Transient ischaemic attack ,Thrombotic stroke , Acute peripheral vascular occlusion

Venous thrombosis (VTE)

Characters	• Stasis plays a bigger part • Thrombus red cell rich, platelet poor • Antiplatelet agents have limited role in treatment Warfarin is commonest drug for long-term management
Main risk factors	1-Exposing risk factors (acute conditions or trauma, surgery, Central venous catheterisation) 2-Predisposing risk factors (patient characteristics) E.g. Chronic heart failure , Advanced age, Obesity Varicose veins, Immobility or paresis Pregnancy/peripartum period Inherited or acquired thrombophilia Hormone therapies
Clinical syndromes of venous thrombosis	Deep Vein Thrombosis (DVT) Pulmonary Embolism (PE)

Etiology of thrombosis:

The causes of venous thrombosis can be divided into two groups: **Hereditary, Acquired.** In many cases, inherited hypercoagulable diseases cause thrombotic events when other risk factors.

Inherited thrombophilia.

1) Factor V Leiden (activated protein C resistance)

Mutation in factor V gene, Protein C can no longer inactivate factor V, leading to unregulated prothrombin activation, and thus an increase in thrombotic events.

(that mutated gene produces products that can't be degraded by protein C, so continues thrombosis will occur).

Dual prothrombotic state of Factor Va Leiden

Increased coagulation FVa Leiden → ↑ thrombin generation, (↓ anticoagulation) ↓ inactivation of factor FVIIIa
Decreased fibrinolysis (also ↓ PAI inactivation → ↓ fibrinolysis

2) Hyperhomocysteinemia:

Homocysteinuria or severe hyperhomocysteinemia is a rare autosomal recessive disorder characterized by developmental delay, osteoporosis, ocular abnormalities, VTE, and severe premature CAD. Homocysteine has primary atherogenic and prothrombotic properties.

3) Prothrombin gene mutation 20210A:

Normal prothrombin (Factor II) circulates as Vitamin K-dependent cofactor w/ ½ life of 3-5 days.
Prothrombin 20210A mutation is the 2nd most common prothrombotic mutation (→ ↓ thrombin inactivation).

4) Antithrombin (AT) III deficiency

AT is a potent inhibitor of thrombin and other serine proteases of the coagulation cascade (e.g., FXa, FIXa)
Autosomal dominant inheritance,
AT III is an inhibitor of thrombin, so a deficiency leads to increased thrombosis.Females with AT deficiency are at particularly high-risk for VTE during pregnancy.
*Patients with Antithrombin III deficiency do not respond to heparin. (Heparin requires the presence of AT III).

5) Protein S deficiency:

Protein S is a cofactor of protein C, so a deficiency leads to decreased protein C activity.

6) Protein C deficiency

Autosomal dominant inheritance
Protein C is an inhibitor of factors V and VIII, so a deficiency leads to unregulated fibrin synthesis

Protein C and S deficiency.

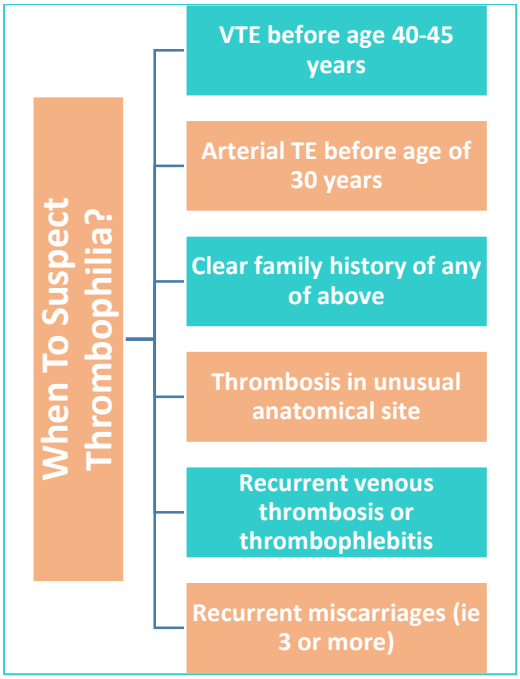
Protein C and S are Vitamin K-dependent natural anti-coagulants involved in switching off coagulation factor activation(Va and VIIIa) and thrombin generation. Inherited deficiency of either protein C or S results in a prothrombotic state with a fivefold relative of VTE compared with the background population.

Surgery/trauma. Mechanisms:

(1) Release of tissue factor from injured tissue (2) Decreased plasma level of anticoagulants

• Particularly common in orthopedic surgery. • Hip and knee surgery without anticoagulant prophylaxis 45~70% DVT. • The incidence of new post-surgical DVT cases is decreasing, because usually surgeons give DVT prophylaxis post surgeries.

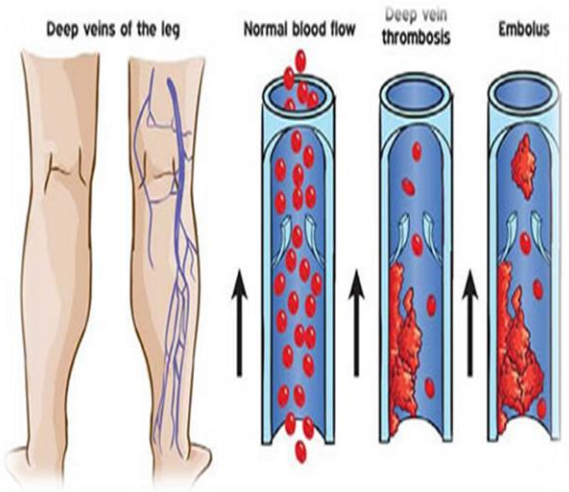
Anti-phospholipid syndrome Autoimmune disorder, either primary or secondary, associated with an increased risk for arterial and venous thrombosis.



***Consider the differential diagnosis of DVT**
Cellulitis, Popliteal (Baker) cyst, superficial thrombophlebitis, muscle pulls/tears, chronic venous insufficiency

DVT : Formation of thrombi within the lumen of the vessels that make up the deep venous system

- **Distal** vein thrombosis refers to DVT of the calves
- **Proximal** vein thrombosis refers to DVT of the popliteal vein or the femoral vein. These thromboses are termed 'proximal' because they are closer to the heart



DVT – Clinical features				
Pain, swelling and redness of affected limb	Calf muscle induration and tenderness	Local increase in temperature	Unilateral oedema	Accentuation of venous pattern

Wells' score is a validated system for estimating pre-test probability of DVT

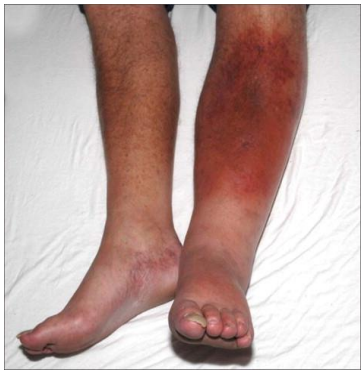
>90% of cases of acute PE due to emboli from proximal DVTs

DVT – Complications:

- **Pulmonary Embolism – main complication**
- **Post-thrombotic syndrome: chronic pain, swelling**

venous ulceration of skin

- **Severe acute venous obstruction**



Wells' score

Pulmonary embolism (PE)

Table 2 Two-level PE Wells score[a]

Clinical feature	*Points*
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified score	
PE likely	**More than 4 points**
PE unlikely	**4 points or less**

PE - clinical features Massive PE				
Sudden severe breathlessness	Shock – hypotension, fast, small volume pulse	Local increase in temperature	Cyanosis	Raised JVP

PE - clinical features Non-Massive PE				
Pleuritic chest pain, cough, dyspnoea, haemoptysis	Tachypnoea	Tachycardia	Signs of right ventricular failure	Symptoms or signs of DVT often absent

Diagnosis of thrombosis:

Consider pre-test probability for VTE before proceeding further in diagnostic evaluation.

There is no single, uncomplicated diagnostic test for aPE. Chest x-ray, EKG, and ABG are the best initial tests. Angiography is the most accurate test, but can be fatal in 0.5% of cases.

***Gold standard of PE is spiral-CT.**

1-Chest x-ray: Usually normal in PE. The most common abnormality is atelectasis.Wedge-shaped infarction, pleural-based lesion (Hampton hump), and oligemia of one lobe (Westermark sign) are much less common than simple atelectasis.

2-EKG: Usually shows sinus tachycardia. The most common abnormality is nonspecific ST-T wave changes. Only 5% will show right axis deviation, RV hypertrophy or right bundle branch block.

3-ABG: Hypoxia and respiratory alkalosis (high pH and low p C02) with a normal
chest x-ray is extremely suggestive of PE.

4-**Spiral CT scan**: Also called a CT angiogram, the spiral CT has become the standard of care in terms of diagnostic testing to confirm the presence of a PE after the x-ray, EKG, and ABG are done. The specificity is excellent (over 95%).

5- **Ventilation/Perfusion (V/Q) scan:** is first only in pregnancy.

6- D-dimer: D-dimer is a poor choice when the presentation is clear because its specificity is poor. -dimer is the answer when the pretest probability of PE is low

7- Lower extremity (LE) Doppler study

IMPORTANT:

When the history and initial labs are suggestive of PE, it is far more importantto start therapy than to wait for the results of confirmatory testing such as thespiral CT or V/Q scan.

Treatment and monitoring:

(Heparin, Warfarin, inferior vena cava (IVC) filter, Thrombolytic)

Heparin is the best initial therapy. Warfarin should be started at the same time

as the heparin in order to achieve a therapeutic INR of 2 to 3 times normal as quickly as possible.

Fondaparinux is an alternative to heparin.

When is an inferior vena cava (IVC) filter the right answer?

• Contraindication to the use of anticoagulants (e.g., melena, CNS bleeding)

• Recurrent emboli while on heparin or fully therapeutic warfarin (INR of 2-3)

• Right ventricular (RV) dysfunction with an enlarged RV on echo. In this case, disease is so severe that an IVC filter is placed because the next embolus, even if seemingly small, could be potentially fatal.

When are thrombolytics the right answer?

• Hemodynamically unstable patients (e.g., hypotension [systolic BP <90] and tachycardia)

• Acute RV dysfunction

(Usually reserved for massive PE, limb threatening condition, stroke, acute MI).

When are direct-acting thrombin inhibitors (argatroban, lepirudin) the answer? Heparin-induced thrombocytopenia

Disadvantages of warfarin:

1-takes few days to start.
2- increased tendency to thrombosis.
3- teratogenic.
4- Many drug interactions.
5- Fluctuations on INR.
6- No fixed dose (different dose for each person).
7-Need for monitoring (INR)

* Warfarin started within 24 hr after initiation of heparin. Heparin should be given for at least 4 days and not discontinued until the INR in the therapeutic range (2.1 to 3.1) for 2 consecutive days.

Overdose & Anti-dotes:

*For heparin…protamine sulphate

*For warfarin…vitamin K

(but may take time (many hours) to act so an actively bleeding patient may also need fresh frozen plasma (FFP) or prothrombin complex)

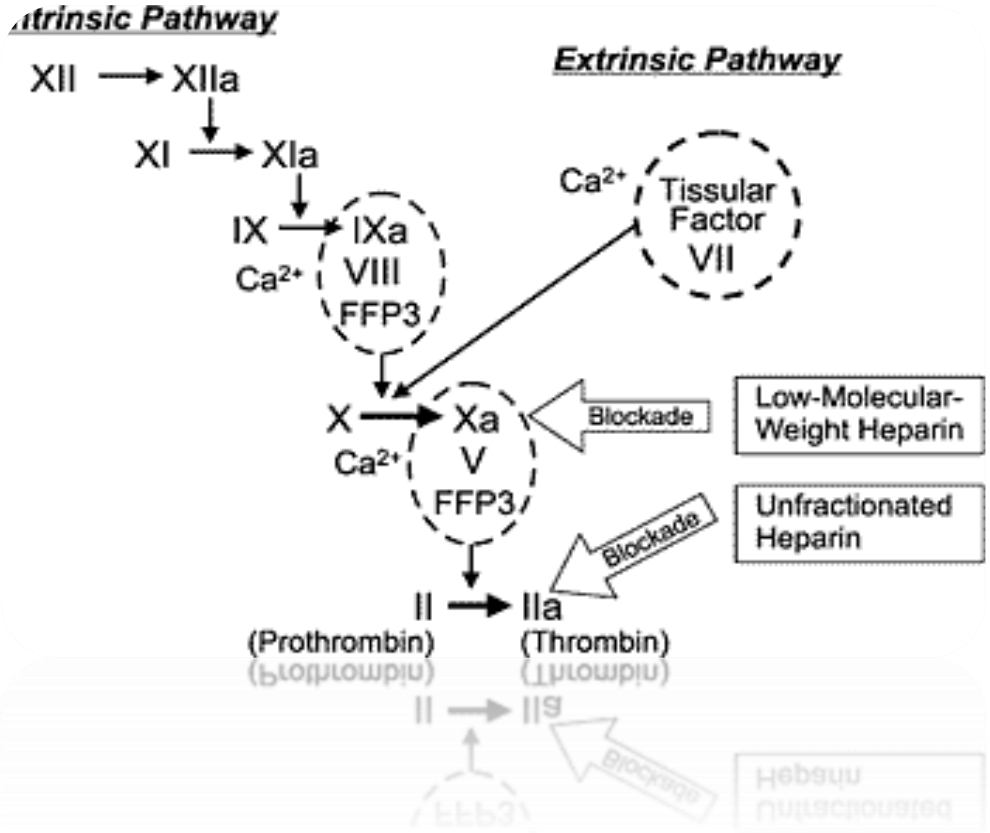
New oral anticoagulants:

1- Direct thrombin (factor II) inhibitors. E.g Dabigatran
2- Rivaroxaban.
3- Apixaban.
4- Edoxaban.
5- Dabigatran Factor X inhibitors. E.g Fondaparinux

Disadvantages of new oral anticoagulants:

Expensive.

No available anti-dote.



MCQ

Q1: a 42-year-old woman who smokes tobacco is found to have acute-onset respiratory distress and tachycardia 4 hours after a non-emergent cholecystectomy. She is subsequently treated for a symptomatic pulmonary embolism. She is begun on low-molecular-weight heparin and warfarin while in the hospital, and is supplied with subcutaneous doses of low-molecular weight heparin to take at home for a total course of 5 days, in addition to the warfarin that she will take for at least 6 months. The initial 5 days of overlap of both heparin and warfarin is necessary because at the beginning of treatment, warfarin actually leads to hypercoagulability. What is the underlying reason for this?

(A) There is an initial increase in vitamin K-dependent coagulation factors
(B) Venous valvular insufficiency is exacerbated during the first 3 days of warfarin therapy
(C) Warfarin causes a more rapid drop in the levels of proteins C and S than factors II, VII, IX, and X
(D) Warfarin induces resistance of factor V to degradation by activated protein C
(E) Warfarin leads to an initial increase in platelet aggregation

Q2: A 69-year-old woman has been in the intensive care unit for 7 days following complicated hip replacement surgery. The patient is currently receiving heparin subcutaneously and wears intermittent pneumatic compression devices on her lower extremities bilaterally. The patient has developed new-onset right calf pain, edema, tenderness, and a positive Homans' sign. A Doppler ultrasound revealed a deep vein thrombosis. Her platelet count is 78,000/ mm^3, and there has been no evidence of spontaneous bleeding. Which of the following will best help prevent future complications?

(A) Beginning warfarin therapy
(B) Discontinuation of bilateral pneumatic compression devices
(C) Discontinuation of heparin
(D) Performing venography
(E) Placing an inferior vena cava filter
(F) Transfusing platelet

Q3: A 32-year-old woman presents to the emergency department with edema and pain of the right lower extremity that began after a 6-hour car ride. A Doppler ultrasound was completed in which a deep vein thrombosis (DVT) was noted. The patient has no prior history of DVT or pulmonary emboli. The patient has been taking oral contraceptive pills for the past 2 years and is currently compliant with her medication. Her family history is significant for a maternal grandmother, mother, and sister with recurrent DVT. Her temperature is 36.2°C (97.2°F), blood pressure is 112/78 mm Hg, heart rate is 86/min, and respiratory rate is 14/ min. There is no clinical evidence indicating a pulmonary embolism. Which of the following is the most likely cause of her DVT?

(A) Antithrombin deficiency
(B) Coagulation factor V gene mutation
(C) Protein C excess
(D) Protein S deficiency
(E) Prothrombin gene mutation

Q4: A 73-year-old woman is admitted for deep venous thrombosis and concern for pulmonary embolism. She has a history of type 2 diabetes mellitus, hypertension, and coronary artery disease. She had been admitted for a three-vessel coronary artery bypass graft 2 weeks prior to this admission. She did well and was dismissed 5 days after the procedure. Pain and swelling of the right leg began 2 days before this admission; she has noticed mild dyspnea but no chest pain. The clinical suspicion of deep vein thrombosis (DVT) is confirmed by a venous Doppler, and the patient is started on unfractionated heparin. Her initial laboratory studies, including CBC, are normal. The next day her pain has improved, and helical CT scan of the chest reveals no evidence of pulmonary embolism. She is instructed in the use of low-molecular-weight heparin and warfarin; she is eager to go home. Her serum creatinine is normal. Her predischarge CBC shows no anemia, but the platelet count has dropped to 74,000. An assay for antibodies to heparin-platelet factor 4 complexes is ordered. What is the best next step in her management?

(A) Dismiss the patient on low-molecular heparin, warfarin, and close outpatient follow-up.
(B) Obtain a liver-spleen scan to look for platelet sequestration.
(C) Discontinue all forms heparin, continue warfarin, and add aspirin 162 mg daily until INR becomes therapeutic.
(D) Keep the patient in the hospital, discontinue unfractionated heparin, add low-molecular-weight heparin, and monitor the platelet count daily.
(E) Keep the patient in the hospital, discontinue all forms of heparin, and start the patient on lepirudin by intravenous infusion

1:C 2:C 3:B 4:E

- The correct answer is C. Along with the coagulation factors (II, VII, IX, and X), the anticoagulant proteins C and S are also vitamin K dependent, and therefore affected by warfarin, which is a vitamin K analog. Proteins C and S have shorter half-lives than the coagulation factors, and therefore a faster turnover in the body. Thus, for a brief window of approximately 3 days after the initiation of warfarin therapy, the body has normal function of its coagulation factors, but loss of anticoagulant proteins C and S, rendering the patient hypercoagulable. Negative consequences of this are avoided by administering heparin with warfarin for the first 5 days.

- The correct answer is C. The patient in this clinical scenario most likely has heparin-induced thrombocytopenia (HIT), which commonly occurs within 4–10 days after the initiation of unfractionated heparin treatment. Unlike other drug-induced thrombocytopenia, HIT is associated with thrombosis due to platelet activation rather than bleeding. Because platelet counts typically remain >20,000/mm^3, spontaneous bleeding is rarely seen. Pathophysiology of this disorder includes the presence of platelet antibodies that cause limb- and life-threatening thrombosis, often at unusual sites including arteries. The first intervention in cases of HIT is immediate cessation of any heparin and immediate initiation of a direct thrombin inhibitor such as argatroban or lepirudin.

- The correct answer is B. Although DVTs in this population are often attributed to the use of oral contraceptives, there is a strong family history of recurrent DVTs and therefore we must consider hereditary disorders of the coagulation system. Factor V Leiden is an autosomal dominant disorder in which coagulation factor Va (the activated form of coagulation factor V) is resistant to degradation by activated protein C. Factor Va remains active and allows for the conversion of prothrombin to thrombin, thereby promoting a hypercoagulable state in patients. Factor V Leiden accounts for 40%– 50% of venous thromboemboli in cases in whom a genetic predisposition is found. A patient with a heterozygous mutation of the gene encoding factor V carries a relative risk of 7 for DVTs, while a patient with the mutation in conjunction with oral contraceptive use carries a relative risk of 35 for DVTs

- The answer is e. (Fauci, p 721.) Heparin is the commonest cause of drug-induced thrombocytopenia. Between 10% and 15% of patients receiving unfractionated heparin develop thrombocytopenia. The drop in platelet count is attributed to the production of an antibody against a complex of heparin and platelet factor 4. Low-molecular-weight heparin can also cause thrombocytopenia, although less frequently than unfractionated heparin. Usually the platelet count drops 5 to 10 days after heparin is started. In this case, however, the patient likely had been exposed to heparin at the time of her CABG. With previous exposure, the thrombocytopenia can begin within hours of the reinstitution of any form of heparin. Although low-molecular-weight heparin causes HIT less frequently than unfractionated heparin, all heparin products must be discontinued in the patient with HIT. In all patients with an active clot and those with HITT (heparin-induced thrombocytopenia with thrombosis), a direct thrombin inhibitor must be started and used as a bridge to full-potency warfarin therapy. The chief consequence of HIT is not bleeding but accelerated clotting resulting from the aggregation of platelet-heparin complexes in the circulation. HITT is a feared complication of HIT. Even with proper treatment, the amputation rate (owing to intra-arterial clotting) is as high as 40%, and the death rate as high as 25%.

Done By:

Abdullah Alasmari	Sara Habis
Majed Altolian	Abdulrhman Alfahadi
Faroq Abdulfattah	Areej Alwahaib