Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Hypercoagulable states / DVT

Objectives :

- Definition
- Physiology of Hemostatic system
- Etiology of thrombosis (venous)
- Inherited thrombotic conditions
- Acquired thrombotic condition
- Clinical manifestations and diagnosis of thrombosis
- Treatment of thrombosis

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Resources :

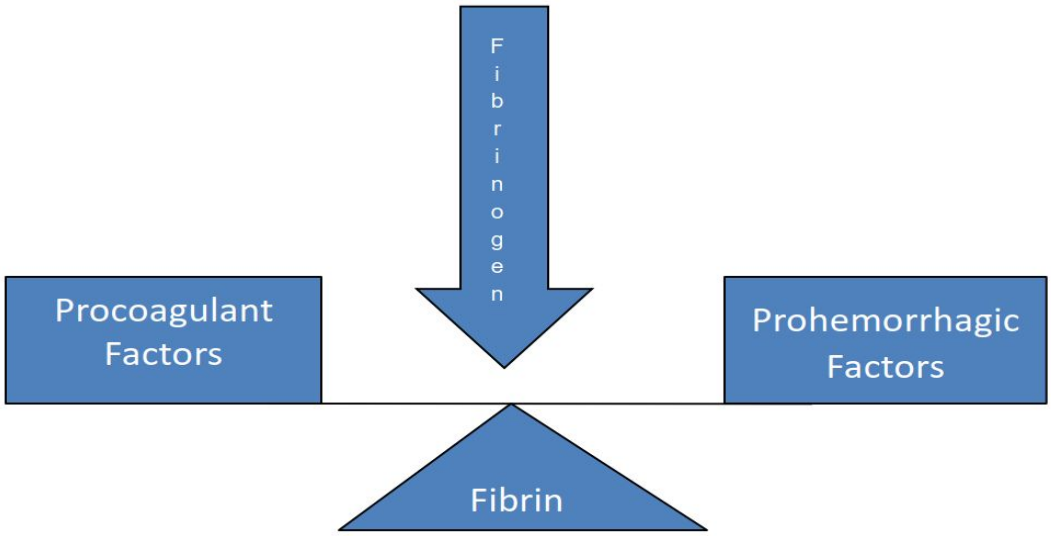
- 437 slides | Same 436's slides
- Teamwork 436
- Doctor notes | Prof. Aamer Aleem

Definitions:

- Thrombophilia: Characterized by clinical tendency to thrombosis or molecular abnormalities of hemostasis that predisposes to thromboembolic disease.
- Thrombophilia: **Alteration** in the hemostatic balance between blood fluidity and clot formation due to genetic or acquired disorders which shift the balance toward excessive clot formation that lead to thrombosis.
- Inherited Thrombophilia: Inherited thrombophilia is a genetic/inherited tendency to venous thromboembolism, and is usually seen in pediatric age group.
- Acquired Thrombophilia: **e.g DVT, PE, fractures and pregnancy.**

Balance of Homeostasis:

Balance of bleeding and clotting, imbalance in either would lead to:
Hypocoagulable state -> bleeding
Hypercoagulable state -> thrombosis



Pro-Hemorrhagic Factors = Anticoagulants

Synonyms:

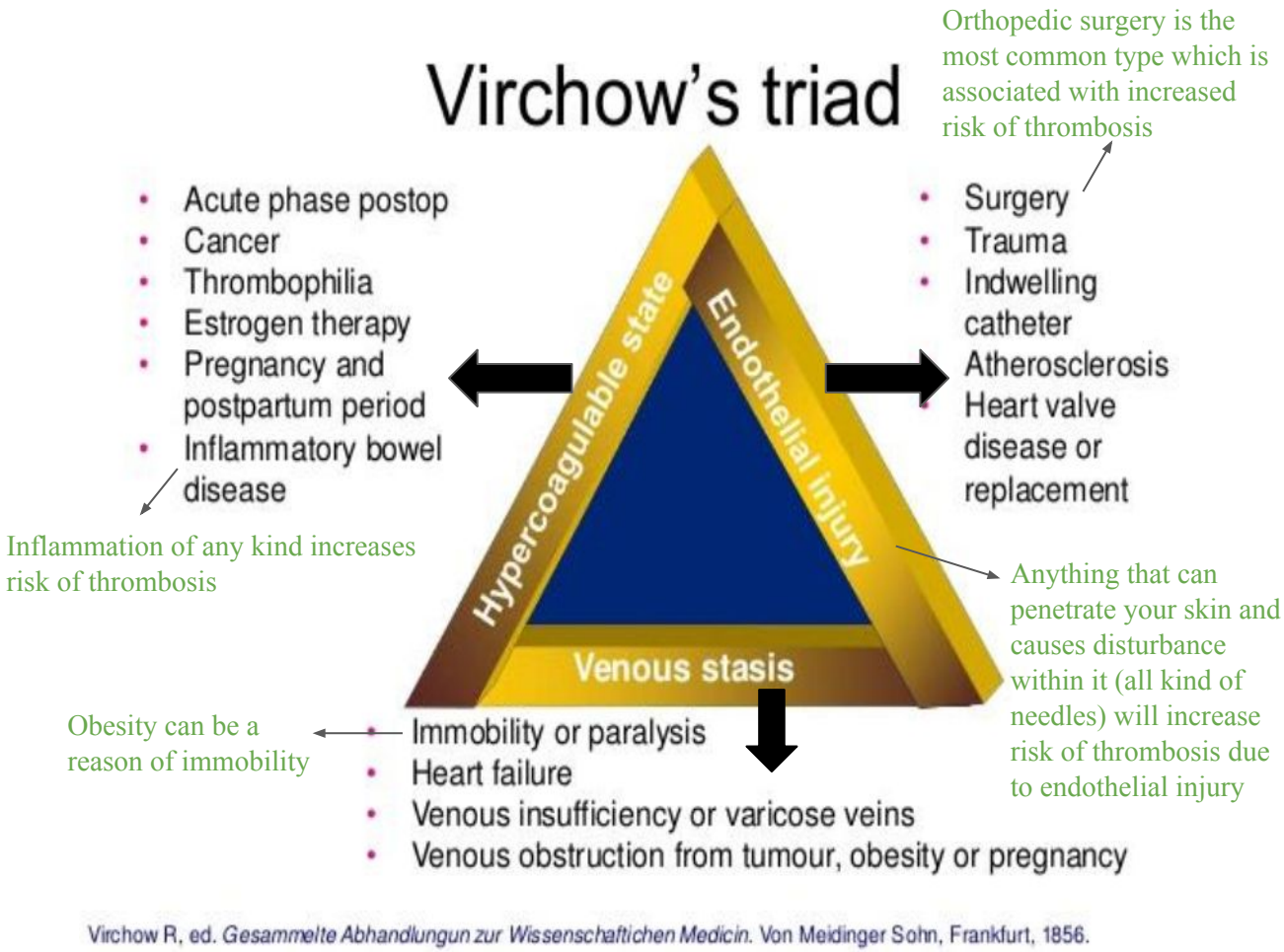
Hypercoagulable state = Prothrombotic state = Thrombophilia = Thrombogenic state t

Virchow's triad:

- **Alterations in blood flow (stasis):**
  -Disrupted laminar flow allows greater interaction between platelets and endothelial surface
  -Prevents dilution of locally activated clotting factors
  -Prevents inflow of clotting factor inhibitors
  -Promotes endothelial cell damage and activation

- **Vascular endothelial injury**
  -Causes exposure of sub-endothelium and release of tissue factor, thereby activating coagulation cascade

- **Alterations in constituents of blood (i.e., hypercoagulability)**
  -Acquired vs inherited coagulopathies
  -Predisposing factors for thrombus formation



Virchow R, ed. *Gesammelte Abhandlungun zur Wissenschaftichen Medicin*. Von Meidinger Sohn, Frankfurt, 1856.

Antithrombotic functions of endothelium:

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

Mechanisms associated with prothrombotic states:

- Vascular (Endothelial dysfunction)
- Platelets (↑ activity and/or numbers)
- Coagulation factors (↑) **Like during pregnancy**
- Natural anticoagulants (↓ and/or dysfunction) Such as: Protein C,S and Antithrombin
- Fibrinolytic system (↓)
- Pathological conditions (e.g.: cancer, CCF, antiphospholipid syndrome, Contraceptive pills, etc.)

Causes of venous thrombo-embolism:

The causes of venous thrombo-embolism (VTE) can be divided into two groups:

- Inherited thrombophilia
- Acquired thrombophilia

and are often multiple in a given patient.

Ex for multiple factors:Patient have Factor V Leiden and undergoing a surgery for his cancer so the pt may develop thrombosis because of theses factors

Prothrombotic states:

- Inherited risk factors
  - Factor V Leiden
  - Prothrombin gene mutation 20210A
  - Protein S deficiency
  - Protein C deficiency
  - Antithrombin deficiency
  - Hyperhomocysteinemia

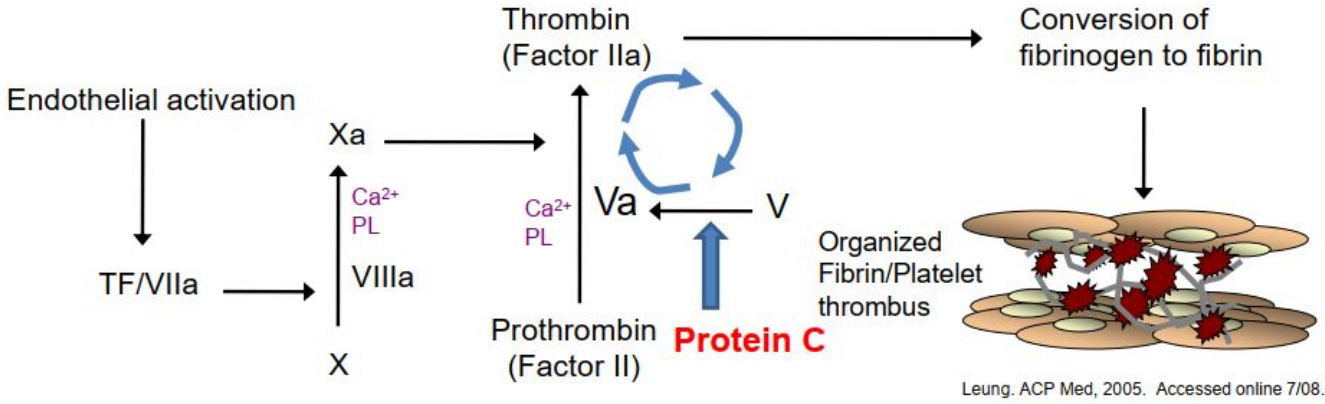
Protein S deficiency and protein C deficiency are the most common inherited disorders in Saudi Arabia, but in the west it is Factor V Leiden

- As a group, the inherited thrombophilias have a prevalence of around 10-50%
- Total incidence of an inherited thrombophilia in subjects with DVT range from 24 – 50%

Factor V Leiden

- Factor V Leiden (=Factor V mutation → **activated protein C resistance**)
  - Most common form of inherited thrombophilia (~50% of cases)

Normally Protein C inhibits Factor V



Leung. ACP Med, 2005. Accessed online 7/08.

- Activated Protein C (APC) resistance
  - Discovered in Leiden, the Netherlands (1993) amongst a group of subjects with unexplained VTE
  - **Mutant Leiden gene product is not susceptible to cleavage by APC**

- **Dual prothrombotic state of Factor V Leiden**
  - **Increased coagulation**

FV Leiden → ↑ thrombin generation, (↓ anticoagulation) and ↓ inactivation of factor FVIIIa (also ↓ PAI inactivation → ↓ fibrinolysis)

Protein C & S deficiency:

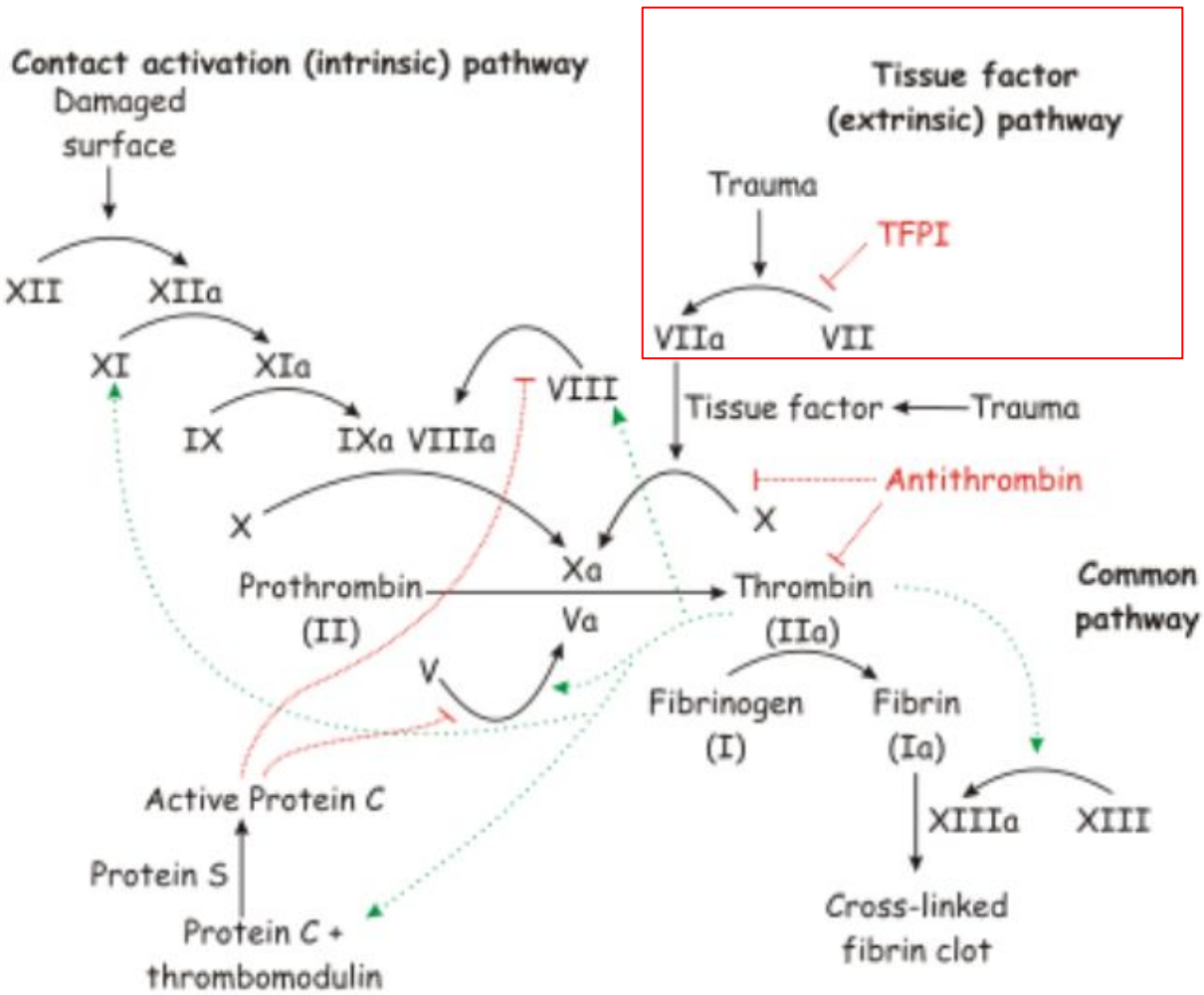
- Protein C and S inhibit activated cofactors Va and VIIIa, respectively.
- **Protein C is consumed and levels are low in vitamin K deficiency, DIC,liver disease, etc**
- Protein C & S deficiency ;
- **-They are inherited conditions(autosomal recessive)**
  – Heterozygous or homozygous,
  – Congenital or acquired **(In case of Liver diseases or Taking OCP)**
  – Clinical expression of hypercoagulability variable, and **do not necessarily correspond with absolute concentration of Protein C**
- **Acquired Protein S deficiency may be induced by OCPs, pregnancy, or nephrotic syndrome**
- **Tests done to measure the levels of these proteins must be repeated multiple times and in each result they must be low so we can be confident this is a deficiency**

Prothrombin gene mutation:

- Normal prothrombin (Factor II) circulates as Vitamin K-dependent cofactor w/ ½ life of 3-5 days
- Mutation discovered in 1996 as a **transition (G→A) at nucleotide 20210,** resulting in elevated plasma levels of Factor II
  – Heterozygotes have a 30% higher plasma prothrombin level compared to normals
- **Prothrombin G20210A mutation is the 2nd most common**
- **Prothrombotic mutation (→ ↓ thrombin inactivation)**

Antithrombin (AT) deficiency:

- AT is a potent inhibitor of thrombin and other serine proteases of the coagulation cascade (e.g., FXa, FIXa)
- AT deficiency typically occurs in a **AD inheritance pattern,** thereby affecting both sexes equally
- Overall incidence of AT deficiency is low
- **Females with AT deficiency are at particularly high-risk for VTE during pregnancy**
  – DVT occurred in 18% of pts with AT deficiency, and in 33% in the postpartum period



****Remember the first step in the external coagulation cascade is the release if tissue factors**

Hyperhomocysteinemia:

- Homocystinuria or severe hyperhomocysteinemia is a rare autosomal **recessive disorder characterized by developmental delay, osteoporosis, ocular abnormalities, VTE, and severe premature CAD.** Try to look for dysmorphic features in these patients, they can be part of the clinical presentation.
- Less marked elevations of homocysteine are more common, occurring in 5-7% of the population, and are associated with a number of clinical factors
  – V**itamin deficiencies (i.e., folate, Vit B6, and/or Vit B12)** and the other way around, these deficiencies could lead to hyperhomocysteinemia, it can happen in both ways
- Homocysteine has primary atherogenic and prothrombotic properties
- Meta-analyses of case-control studies have found an odds ratio of 2.5-3 for VTE in pts with homocysteine levels > 2 standard deviations above the mean value of control groups

Combined effect of inherited thrombophilias on tendency for VTE:

- Pooled analysis of 2310 cases and 3204 controls amongst 8 case-control studies (from UK, Denmark, France, Italy, Sweden, Brazil) evaluating the risks in patients with FVL and/or prothrombin 20210A

- Of patients with VTE,
  - 23% were heterozygous for prothrombin gene mutation
  - 12% were heterozygous for Factor V Leiden
  - 2.2% were double heterozygotes

Inherited hypercoagulable state	Odds ratio for VTE
Prothrombin gene mutation 20210A heterozygotes	3.8
Factor V Leiden mutation heterozygotes	4.9
Combined Prothrombin and Factor V Leiden heterozygotes	20.0

Odds ratio is a measure of association between an exposure and an outcome.

- **Fifty percent of thrombotic events** in patients with inherited thrombophilia are **associated with the additional presence of an acquired risk factor (eg, surgery, prolonged bed rest, pregnancy, oral contraceptive).**
- **Females are at higher risk of being exposed to secondary factors than males do.**

- Some patients have more than one form of inherited thrombophilia or more than one form of acquired thrombophilia and appear to be at even greater risk for thrombosis

Acquired prothrombotic States Risk Factors:

- **Prior thrombotic event or family H/O VTE**
- Recent major surgery **(the longer the surgery, the higher the risk)**
  - Especially orthopedic (hip & knee replacement **and Spine surgery)**
- Immobilization
- Heart failure
- **Malignancy: You think of cancer when there is unexplained thrombosis.**
- Trauma
- **Presence of a central venous catheter**
- **Obesity & older age (>60)**
- **Pregnancy**
- Oral contraceptive or **hormone replacement therapy**
- **Antiphospholipid antibody syndrome**
- **Myeloproliferative disorders**
  - Polycythemia vera or essential thrombocythemia
- Heparin induced thrombocytopenia & thrombosis (HIT)
- Hyperviscosity syndromes
  - Multiple myeloma or Waldenstrom's macroglobulinemia

In case of Multiple myeloma they will have high level of abnormal proteins such as IgG or IgM which will increase the viscosity and cause thrombosis.

Cancers of the brain, ovary, pancreas, colon, stomach, lung and kidney have the highest risk of DVT/PE. Lymphomas, leukemia and liver cancer are also more likely to lead to DVT/PE

Malignancy (cancer):

- Risk for thrombosis is multi-factorial.
- Predominantly venous thrombosis - stasis, tumor invasion of vessels, chemotherapy effects superimposed on acquired or primary defects in hemostasis.
  -**Chemotherapy will cause damage toward the endothelium and release of tissue factors.**
- **Increased production of tissue factor by tumours found in many patients which can activate FX directly.**

Antiphospholipid Syndrome

Definition

- Antiphospholipid syndrome (APS) is an **autoimmune multisystem disorder, either primary or secondary(SLE ,scleroderma and Leukemia), characterized by venous, arterial, or small vessel thromboembolic events**
- **And/or recurrent abortions in the presence of persistent antiphospholipid antibodies (aPL). aPLs are a heterogeneous group of autoantibodies which are directed against phospholipid-binding proteins.**

Antiphospholipid Syndrome cont:

Clinical manifestations:

- **Deep vein thrombosis (31.4%) The most common**
- Pulmonary embolism (23.8%)
- Stroke (14.9%)
- Transient ischemic attack (11.9%)
- **Early spontaneous abortions (67.1%)**
- Stillbirths (62.5%)
- Skin rash
- **Livido reticularis (indicates multiple micro-thrombi)**
- Thrombocytopenia

Types of antibodies:

- **Anticardiolipin antibodies**
- **Anti-beta 2 glycoprotein**
- **Lupus anticoagulant (initially found in patients with SLE (usually prolonged APTT and/or PT).**

The pt might have anyone of theses and it could be in combination

Diagnostic criteria: *You need to have clinical manifestations and Ab persistent*

- Clinical:
  Thrombosis (venous, arterial, small vessel)
  And/or recurrent abortions
- Laboratory:
  Any one of the antibodies positive (should be done twice, 12 weeks apart)

Thrombosis Manifestations

Clinical presentation: Pulmonary embolism (PE)

- **Shortness of breath that may occur suddenly.**
- **Sudden, sharp chest pain that may become worse with deep breathing or coughing (can be pleuritic type).**
- Palpitation (tachycardia).
- Rapid breathing (tachypnea).
- Sweating & anxiety.
- **Hemoptysis or pink, foamy sputum.**
- Dizziness and fainting (low BP).
- **PE with low BP (<90 mmHg) is called massive PE (most serious condition and the management will be different) .**

Clinical presentation: Arterial

coronary, carotid and femoral

- Acute MI, Angina
- CVA, TIA
- Claudication

Clinical presentation: Venous

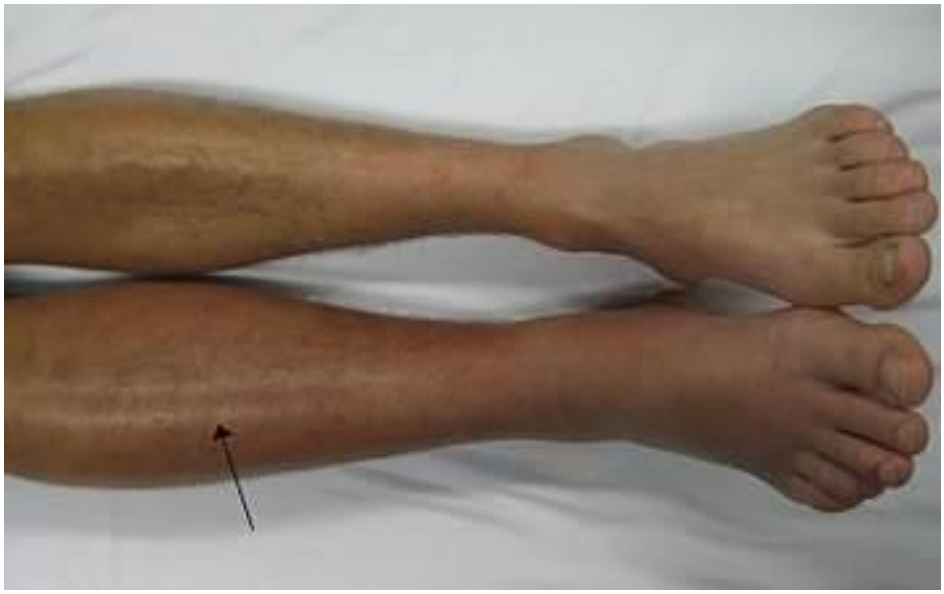
Superficial vein or deep veins

- Deep vein thrombosis: Swollen, painful extremity
- Pulmonary embolus

Thrombosis Manifestations cont:

Clinical presentation: DVT

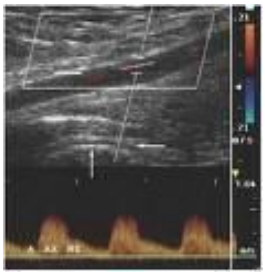
- Lower limb most common site
- Can happen in upper limb, abdominal veins, cerebral veins & sinuses
- **Symptoms & signs depend on the site (Limb swelling, Pain, Redness, Skin changes like shiny skin)**



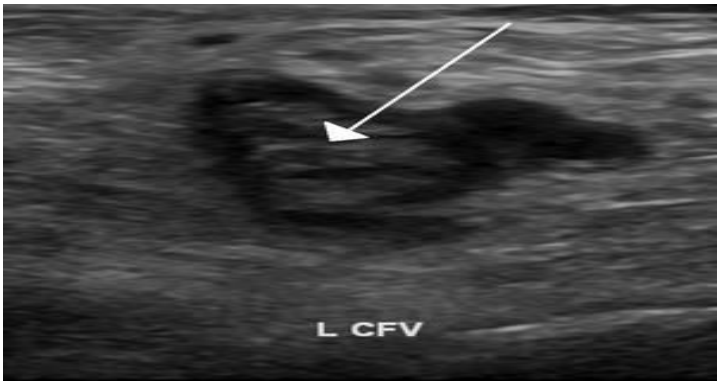
A right-sided acute deep vein thrombosis. The leg is swollen and red due to venous outflow obstruction

Diagnosis of Thrombosis:

- Clinical examination (non-specific)
  – Physical findings may include **a palpable cord over the calf**, ipsilateral edema, warmth, and/or superficial venous dilatation
- Contrast venography
- Non-invasive testing
  – Impedance plethysmography
  – Compression ultrasonography: Recommended in moderate to high pre-test probability its Imp in DVT
  – D-dimer: Useful in low pre-test probability to exclude diagnosis of VTE, Sensitivity and negative predictive value are high (~99%)
  – Magnetic resonance venography
  – Computed tomography
  – Echocardiography, ventilation-perfusion (V/Q) scanning, and pulmonary angiography



Start with D-dimer and pre test if they were negative then proceed with invasive tests



An ultrasound image demonstrating a blood clot **(which produces hyperechogenicity on US)** in the left common femoral vein

Diagnosis of Thrombosis:

- **DVT and pulmonary embolism are the two most common manifestations of the same disease: VTE**
  - 90% of cases of acute PE are due to emboli emanating from the proximal veins of the lower extremities; proximal DVTs are clinically most significant due to high morbidity and mortality

- **Consider the differential diagnosis of DVT**
  - Popliteal (Baker) cyst, superficial thrombophlebitis, muscle pulls/tears, chronic venous insufficiency, cellulitis (you have to consider them becauses the treatment will be different)

- Consider pre-test probability for VTE before proceeding further in diagnostic evaluation
  - Among those with suspected of DVT of the LE, a minority (17-32%) actually have the disease

Modified Wells Prediction Rule (criteria) for Diagnosing Pulmonary Embolism

Clinical characteristic	Score
Previous pulmonary embolism or DVT	+1.5
Heart rate >100 beats per minute	+1.5
Recent surgery or immobilization (within the last 30 days)	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than pulmonary embolism	+3
Hemoptysis	+1
Cancer (treated within the last 6 months)	+1

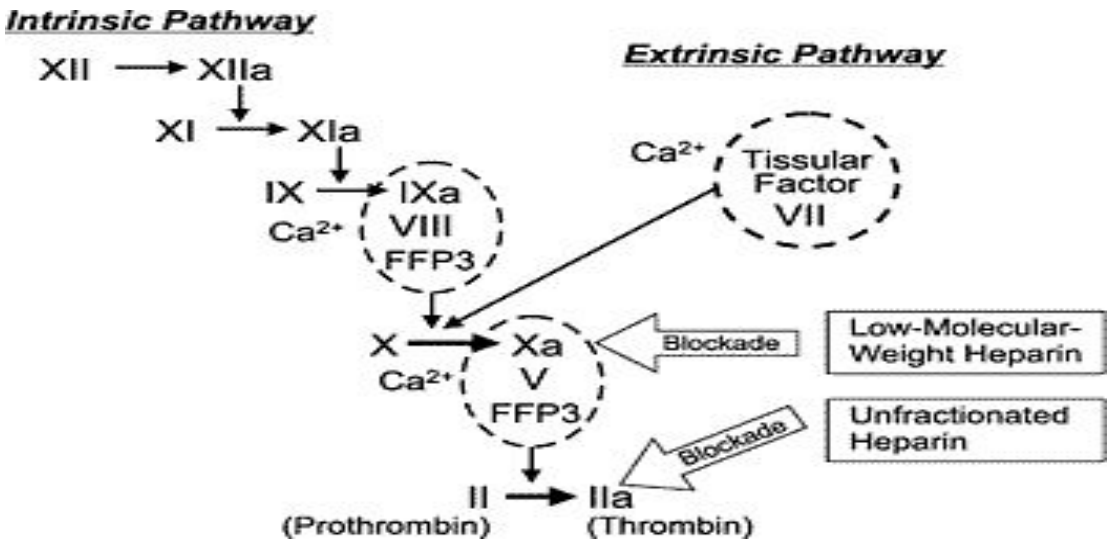
If the score is 0-1, then there is low probability of pulmonary embolism **and we don't need to investigate**
2-6 = intermediate probability **we need to invistigate**
≥6 = high probability

Treatment of Venous Thromboembolism (VTE)

- Anticoagulation
  – Unfractionated (UFH) and low-molecular weight heparin (LMWH, ie, enoxaparin, tinzaparin, dalteparin, etc)
    •Enable antithrombin to accelerate many-fold its inactivation of thrombin
    • LMWH should be avoided in CKD; contraindicated in Stage-V CKD

  – Vitamin K antagonists (warfarin)
    • **Heparin + warfarin is more effective than warfarin alone; all cases of VTE should be "bridged" with heparin**
  – Factor Xa inhibitors (fonduparinux)
  – Hirudins (lepirudin, bivalirudin) **used in pt who develop HIT especially for those pt with renal failure who cant tolerate Fondaparinux**
  – Direct oral Anticoagulants (DOACs)
- Thrombolysis (Usually reserved for massive PE)
  – Tissue plasminogen activators (t-PA, u-PA, urokinase, alteplase)
- Thrombectomy (arterial) **used when thrombolytic drugs cant be used.**

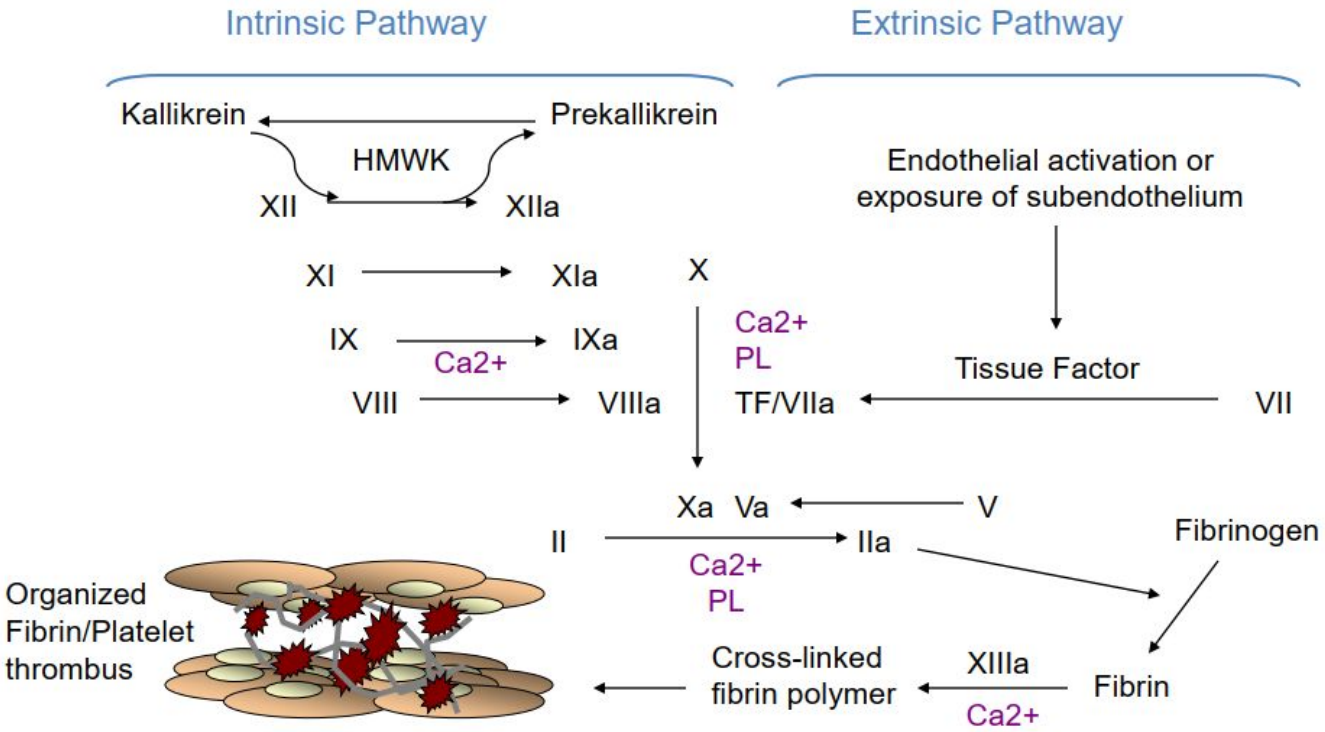
- **Conventional Anticoagulation**
  - Treatment **always started with heparin** (immediate action)
  - Warfarin can be started at the same time
  - Warfarin takes time to work & may increase the tendency to further thrombosis initially (reduces level of Protein C & S)
  - Around 4 days of warfarin & heparin overlap needed
  - Heparin can be stopped when INR reaches therapeutic levels (2-3)
  - **LMWH (SC) in stable cases of VTE but UNH (IV) needed in hemodynamically unstable patients or pts who need procedures**



Warfarin-mechanism of action

Warfarin inhibits vitamin-K dependent **coagulation factors (II, VII, XI and X)**

Sites of Vitamin-K antagonism:



How to Remember Warfarin Color & strengths

Warfarin Treatment & Monitoring:

- **No fixed dose of warfarin, every patient needs different dose (loading dose + maintenance)**
- Therapeutic INR (International normalized ratio) **2-3 in most cases**
- Initially heparin is a must as warfarin slow to act and initially pro-thrombotic
- **Treatment continued for 3-12 months mostly but longer or life long AC may be needed in recurrent cases of VTE**

- In patients starting warfarin therapy for initiation of oral anticoagulation, doses between 5 and 10 mg for the first 1 or 2 days are recommended for most individuals and subsequent dosing based on the INR response
- A loading dose (ie, > 10 mg) of warfarin is not recommended
- A starting dose of < 5 mg might be appropriate in elderly patients; in patients with impaired nutrition, liver disease, or congestive heart failure (CHF); and in patients who are at high risk of bleeding e.g have had recent major surgery

- Fluctuations in INR may occur because of any one or more of the following conditions:
  - Patient non-compliance **(most important cause)**
  - Changes in vitamin K intake (diet)
  - **Effect(s) of concomitant drug(s) such as antibiotics**
  - Changes in warfarin metabolism **bc of liver diseases**
  -Changes in vitamin K dependent coagulation factor synthesis or metabolism
  - **Inaccuracy in INR testing**

Overdose & Anti-dotes:

- For heparin…protamine sulphate
- For warfarin…vitamin K but may take time (many hours) to act
- An actively bleeding patient on warfarin may also need fresh frozen plasma (FFP) or prothrombin complex

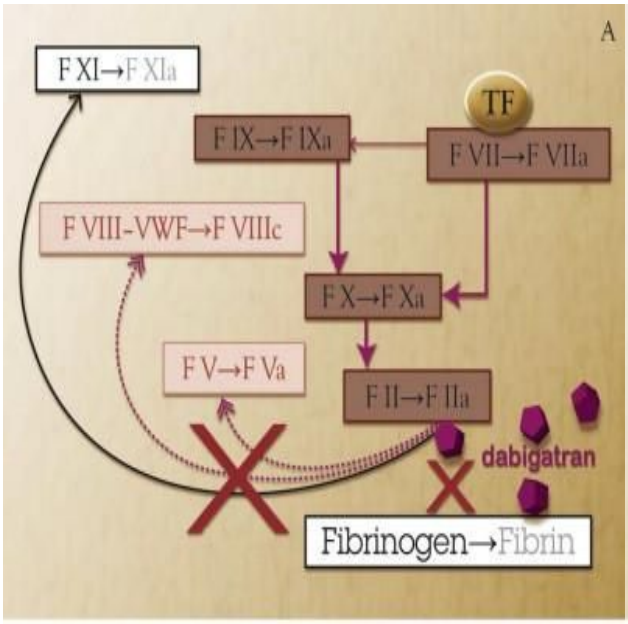
Direct oral anticoagulants (DOACs)

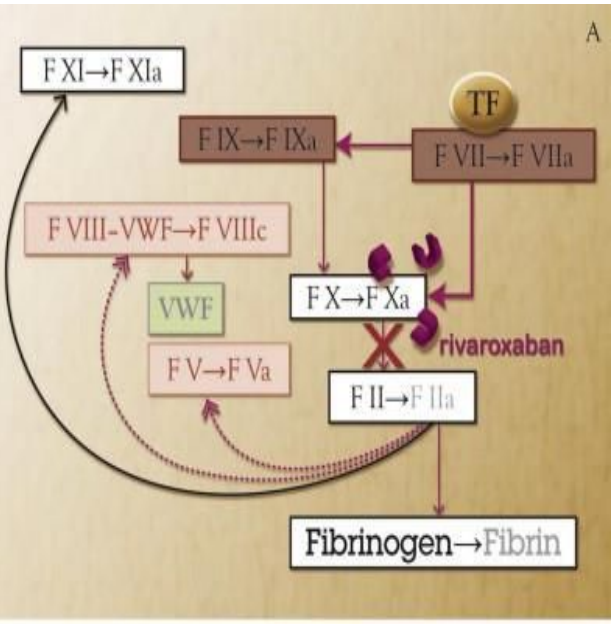
- Direct thrombin inhibitors (DTI): Dabigatran (Pradaxa, Boehringer)

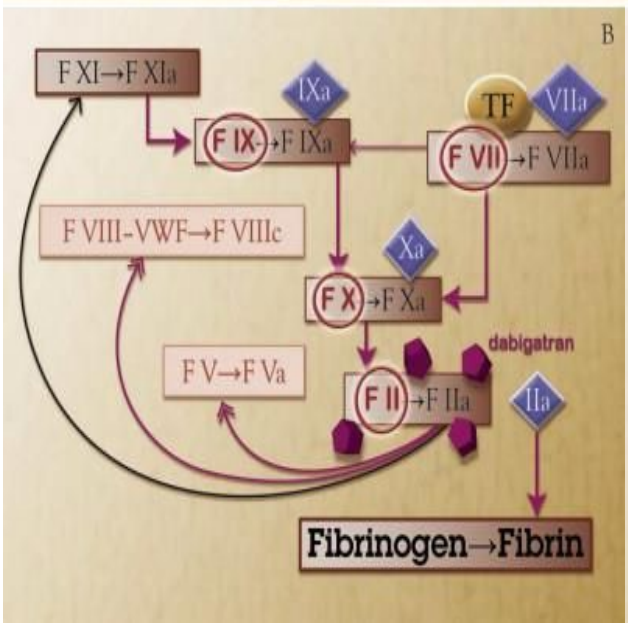
- Factor X inhibitors
  - **Rivaroxaban** (Xarelto, Bayer/Janssen)
  - Apixaban (Eliquis, Pfizer/BMS)
  - Edoxaban (Savaysa, Daichii Sankyo)
  - Betrixaban (Bevyxxa, Portola)

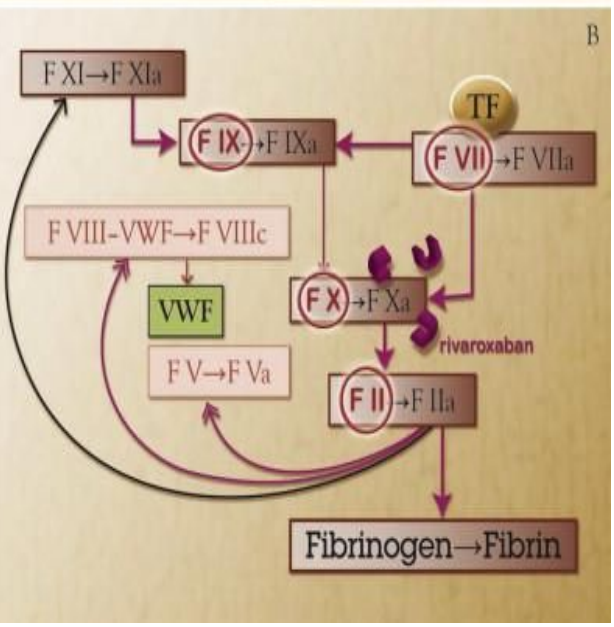
DOACs indications:

- Treatment of venous thromboembolism (TE) **with no renal failure.**
- TE prevention in atrial fibrillation
- Prophylaxis in orthopedic surgery
- Treatment of VTE in cancer patients
- VTE prophylaxis in cancer patients









DOACs Advantages:

Advantage	Clinical implications
Rapid onset of action	No need for bridging
Predictable anticoagulant effect	No need for routine coagulation monitoring
Low potential of food interactions	No dietary precautions
Low potential for drug interactions	Few drug restrictions
Specific coagulation enzyme target	Low risk of off-target adverse effects
Prophylactic dose	Smaller doses can be used as prophylaxis?

DOACs Disadvantages:

- More expensive (Cost of drug/year $3000)
- Reversal a problem (Antidote available now)
- Can not be used in end stage renal failure
- Not suitable for AC for prosthetic valves

Warfarin and its Indications

- Warfarin is still the treatment of choice for longer term AC
- Patients with end stage renal failure
- Patients with prosthetic heart valves
- Antiphospholipid syndrome (high risk)

Some Important Facts about DOACs

- The risk of bleeding with the DOACs, and particularly intracranial bleeding, is less with the DOACs than with VKA therapy
- Based on patients with atrial fibrillation, GI bleeding may be higher with dabigatran, rivaroxaban, and edoxaban than with VKA therapy, although this has not been seen in patients with VTE
- Based on indirect comparisons, the risk of bleeding may be lower with apixaban than with the other DOACs
- Despite the lack of specific reversal agents for the DOACs, the risk that a major bleed will be fatal appears to be no higher for the DOACs than for VKA therapy

Anticoagulants in VTE: Current Recommendation Statements & Remarks:

- The minimum duration of anticoagulant therapy for DVT or PE is usually 3 months; this period of treatment is referred to as "long-term therapy."
- Treatment longer than 3 months but for a limited period "longer time-limited period" (eg, 6, 12, or 24 months).
- A decision to treat patients for longer than 3 months, which we refer to as "extended anticoagulant therapy," usually implies that anticoagulant therapy will be continued indefinitely.
- Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy
- In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).
- Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy. In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

Reversal of Direct Thrombin inhibitors (Dabigatron)

- Idarucizumab:

  - Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with 350-fold higher affinity than that of dabigatran for thrombin.
  - In addition to binding dabigatran, idarucizumab also binds the active glucuronide metabolites of dabigatran to form essentially irreversible 1:1 stoichiometric complexes.
  - Idarucizumab and idarucizumab-dabigatran complexes are cleared by the kidneys, as is dabigatran.
  - After intravenous infusion, the half-life of idarucizumab is about 45 min in subjects with normal renal function.

Reversal of Factor-X Inhibitors

- Andexanet alfa:
  - Andexanet alfa is a recombinant human FXa variant with the active-site serine residue replaced with alanine to eliminate catalytic activity and with the membrane-binding domain deleted to prevent incorporation into the prothrombinase complex.
  - Andexanet serves as a decoy for the oral FXa inhibitors because it binds them with affinities similar to those of native FXa. Because andexanet also binds tissue factor pathway inhibitor (TFPI) to form a non-productive andexanet–TFPI complex, it reduces TFPI activity

- **Hypercoagulable state (Thrombophilia):** it is the 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.

- **Virchow's triad (risk factors for thrombosis):** Hypercoagulable state, endothelial injury, and venous stasis.

- **Causes for venous thrombosis can be:** acquired, inherited, or mixed/unknown.

- **Acquired:**
  - Advancing age
  - Previous Thrombosis
  - Immobilization
  - Major surgery
  - Presence of a CENTRAL venous catheter
  - Malignancy
  - Estrogens
  - Antiphospholipid antibody syndrome
  - Myeloproliferative Disorders
  - Heparin-induced thrombocytopenia (HIT)
  - Prolonged air travel
  - Pregnancy
  - Have a lower limb cast
  - Hyperviscosity syndromes

- **Inherited:**
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Factor V Leiden mutation (Factor V-Arg506Gln)
  - Prothrombin gene mutation
  - Dysfibrinogenemia (rare)

- **Mixed/Unknown:**
  - Hyperhomocysteinemia
  - High levels of factor VIII
  - Acquired Protein C resistance in the absence of Factor V Leiden
  - High levels of Factor IX, XI

- **Diagnosis of thrmobosis:**
  - Clinical picture (1 st step)
  - Non-invasive testing; Impedance plethysmography, compression ultrasonography, D-dimer, Magnetic resonance venography, Computed tomography and Echocardiography.
  - Invasive testing; contrast venography (not used anymore).

- **Treatment:** by anticoagulation, thrombolysis or thrombectomy

- **Anticoagulation:**
  - Conventional anticoagulants; Heparin (LMWH), Coumadin, Warfarin.
  - DOACs: Direct thrombin inhibitors (Dabigatran) and FX inhibitors (Rivaroxaban, Apixaban, Edoxaban)

- **Thrombolysis:** · Tissue plasminogen activators (t-PA, u-PA, urokinase, alteplase)

- **Surgical:**
  - IVC filter.
  - Embolectomy (surgical or catheter).

Questions

Team 436

1. **22-year-old Caucasian woman presents with a 1-day history of a painful right leg which is erythematous on appearance and tender on palpation. She states that she has had this problem many times in the last few years and her family has also suffered from similar problems. Her grandmother died of a pulmonary embolism. The most likely diagnosis is:**

A. Antithrombin Deficiency
B. Factor V Leiden mutation
C. Protein S deficiency
D. Lupus Anticoagulant
E. Protein C deficiency

2. During a busy ward round you are asked to visit a patient the consultant has not had an opportunity to see. The only details you are given are that the patient is female and was admitted the previous day with bleeding abnormalities, you are given the results of her blood investigations: Prothrombin time is unaffected, Partial thromboplastin time is prolonged, Bleeding time is prolonged, Platelet count is unaffected. What is the most likely diagnosis?

A. Factor V deficiency
B. Warfarin therapy
C. Glanzmann's Thrombasthenia
D. Bernard Soulier syndrome
E. Von Willebrand disease

3. All the following are vitamin K–dependent coagulation factors except?

a. factor X
b. factor VII
c. protein C
d. protein S
e. factor VIII

4. **23-year-old woman is diagnosed with a lower extremity deep venous thrombosis. Which of the following medical conditions represent a contraindication to therapy with low-molecular-weight heparin (LMWH)?**

a. Pregnancy
b. Obesity
c. Dialysis-dependent renal failure
d. Uncontrolled diabetes mellitus
e. Jaundice

5. The most common inherited prothrombotic disorder is?

a. activated protein C resistance
b. prothrombin gene mutation
c. protein C deficiency
d. protein S deficiency
e. antithrombin deficiency

6. A 16-year-old male has recurrent thigh hematomas. He has been active in sports all of his life and has had 3 episodes of limb-threatening bleeding with compartment syndrome. A family history is notable for a maternal grandfather with a similar bleeding history. Paternal family history is not available. Laboratory analysis in clinic reveals a normal platelet count, a normal activated partial thromboplastin time (22 s) and a prolonged prothrombin time (25 s). He takes no medications. What is the most likely reason for his coagulation disorder?

a. Factor VIII deficiency
b. Factor VII deficiency
c. Factor IX deficiency
d. Prothrombin deficiency
e. Surreptitious warfarin ingestion

7. A 52-year-old man is admitted with recurrent hemarthrosis of his knees. He is an electrician who is still working but over the last year has had recurrent hemarthrosis requiring surgical evacuation. Before one year ago, he had no medical problems. He has no other past medical history and seldom sees a physician. He smokes tobacco regularly. His platelet count is normal, erythrocyte sedimentation rate is 55 mm/hr, hemoglobin is 9 mg/dL and albumin is 3.1 mg/dL. Coagulation studies show a prolonged activated partial thromboplastin time (aPTT) and a normal prothrombin time (PT). Adding plasma from a normal subject does not correct the aPTT. What is the cause of his recurrent hemarthrosis?

a. Acquired inhibitor
b. Factor VIII deficiency
c. Factor IX deficiency
d. Secondary syphilis
e. Vitamin C deficiency

8. During a pre-employment physical and laboratory evaluation, a 20-year-old male is noted to have a prolonged activated prothromboplastin time (aPTT). On review of systems, he denies a history of recurrent mucosal bleeding and has never had an issue with other major bleeding. He has never had any major physical trauma. A family history is limited because he doesn't know his biologic family history. Mixing studies correct the aPTT when normal serum is used. You suspect an inherited hemorrhagic disease such as hemophilia. Which other laboratory abnormality would you most likely expect to find if this patient has hemophilia?

a. Low Factor VIII activity
b. Low factor IX activity
c. Prolonged bleeding time
d. Prolonged prothrombin time
e. Prolonged thrombin time

Answers: 1.B/ 2.E/ 3.E/ 4.C/ 5.A/ 6.B/ 7.C/ 8.A