Hypercoagulable state

Objectives:

- (Not given)

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Resources: 435 team + Davidson's Principles of Practice of Medicine + Slides + 500 Best Single Answers in Medicine.

- Editing file
- Feedback

Introduction (you can skip this)

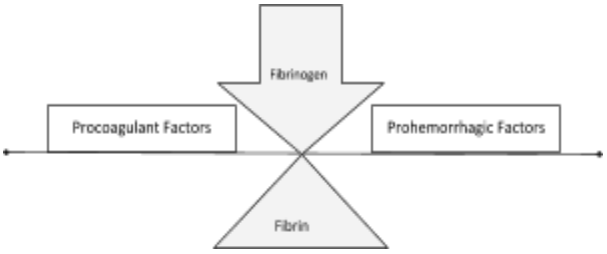
For your exam, you'll probably get a case asking about its management.

★ **History..** (only in Dr.Farjah's slides, Click here for more), Incidence and prevalence

Balance of homeostasis:

- Balance of bleeding and clotting.
- Imbalance in one direction can lead to:

1. Bleeding tendency[1] state → bleeding
2. Hypercoagulable state → thrombosis



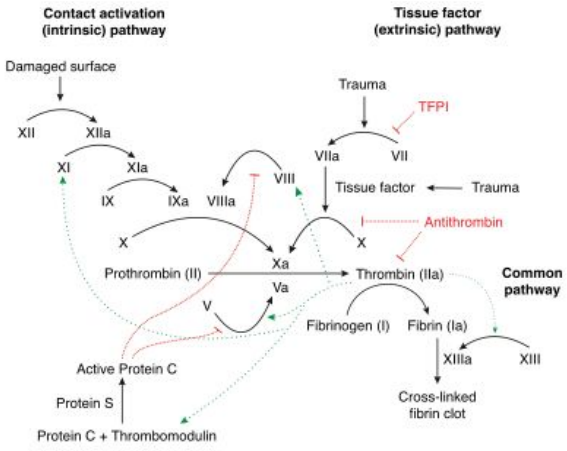
The major components of the hemostatic system are:

1. The vessel wall.
2. Platelets (and other blood elements).
3. Plasma proteins (coagulation and fibrinolytic factors).

Stages of normal hemostasis			
Pre-injury	Fibrin clot formation	Limiting clot formation	Fibrinolysis
The endothelium produces anti-thrombotic agents. (thus platelets & coagulation factors circulate in non-activated state)	- The endothelium is injured. - Platelets are activated. - Then Coagulation cascade is activated. - Fibrin clot forms.	- Once hemostasis has been secured, the propagation of clot is halted by natural anticoagulants.	- The insoluble clot needs to be broken down for vessel recanalization. - Plasminogen is activated by tissue plasminogen activator (t-PA)→plasmin. - Plasmin hydrolyse the fibrin clot, producing fibrin degradation factors including D-dimer.

Natural anticoagulants		
Antithrombin	Tissue factor pathway inhibitor	Protein C & S
- Serine protease inhibitor synthesized by the liver. - Destroys activated factors such as XIa, Xa & thrombin (IIa).	- Binds to and inactivates VIIa & Xa.	- Protein C is activated through binding of thrombin to thrombomodulin (structure on the endothelium), activated protein C binds to its co-factor protein S → then cleaves Va & VIIIa. - Both protein C & S are K-dependent and are depleted by warfarin.

[1] Dr.Amer said that (HYPOcoaguable) is incorrect there no such thing and replaced it with (bleeding tendency)



how does the coagulation cascade start?
all our vessels are lined by tissue factor,so whenever there's endothelial injury tissue factor will be released. what will activate factor 7 to its active form will activate factor 10 to 10 a, and starts the process...
*so tissue factor is very imp ,and it might be increased in some conditions like cancer causing thrombosis .
so what's the job of tissue factor phosphate inhibitor?when the initial activation and release of tissue factor,it will inhibit any further activation(check in between "feedback" mechanism)

Antithrombotic functions of endothelium: [2]

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

Coagulation factors :					
I	Fibrinogen	**II**	Prothrombin	**III**	Thromboplastin
IV	Calcium	**V**	Proaccelerin (Labile factor)	**VII**	Proconvertin (Stable factor)
VIII	Antihemophilic globulin A	**IX**	Christmas factor	**X**	Stuart-power factor
XI	Plasma thromboplastin antecedent	**XII**	Hageman factor	**XIII**	Fibrin stabilizing factor

Thrombophilia

Definition:

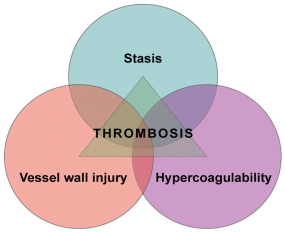
- Alteration in the hemostatic balance between blood fluidity and clot formation due to genetic or acquired disorders which shift the balance toward excessive platelet aggregation and thrombin generation (clot formation) that lead to thrombosis. (Hypercoagulable state). Synonyms are : Hypercoagulable state, prothrombotic state and thrombogenic state.

[2] (Substances that are released from endothelial cells and have physiological antithrombotic effects)

★ Risk factors for thrombosis:

In 1856, Rudolf **Virchow** postulated a **triad** of factors that leads to intravascular coagulation :

1. Local trauma to the vessel wall.
2. Hypercoagulability (Thrombophilia).
3. Stasis.



Stasis	Endothelial injury	Hypercoagulable states
1. Immobility. 2. Paralysis (e.g. CVA). 3. Obesity. 4. Postoperative & casting. 5. Heart & Respiratory Failure.	1. Trauma & major surgery. (especially orthopedic hip & knee replacement) 2. Central venous catheters.	1. Conditions that predispose to an increased risk for thrombosis either venous (most common), arterial or both. 2. These conditions are being identified more frequently and may be classified as inherited or acquired.

- Prothrombotic states:
  - Vascular (endothelial dysfunction)
  - Platelets (↑activity and/or number)
  - Coagulation factors (↑)
  - Natural anticoagulants (↓ and/or dysfunction)
  - Fibrinolytic system (↓)
  - Pathological conditions (cancer, CCF, antiphospholipid syndrome, OCP...)

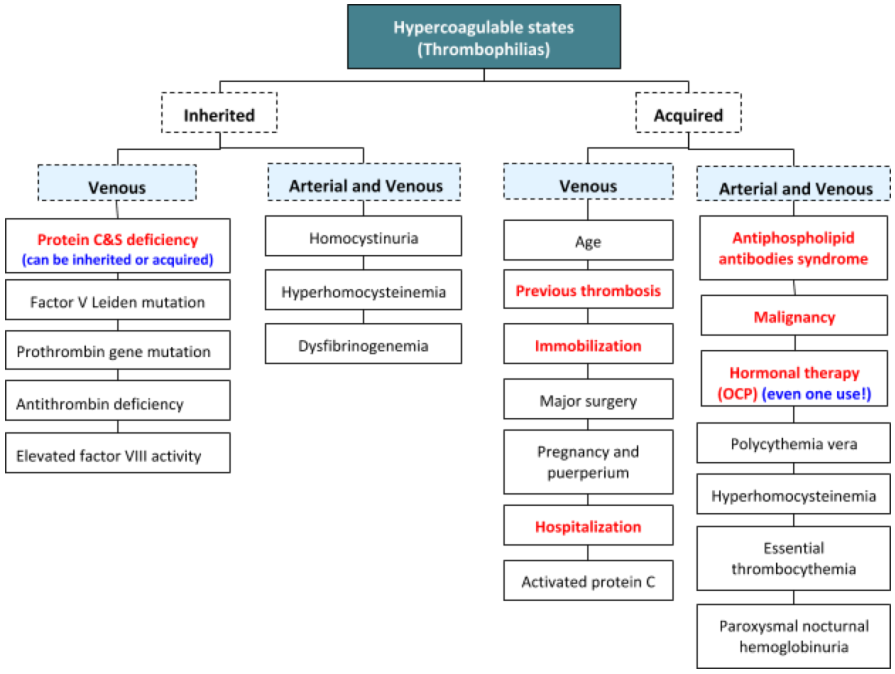


Diagram from 435teamwork >

- 50% 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). Patients with more than one inherited thrombophilia or more than one acquired thrombophilia are at greater risk for thrombosis.

Acquired	Inherited	Mixed/Unknown
1. Advancing age. (>60) 2. Prior Thrombosis very important in Hx 3. Immobilization 4. Recent Major surgery especially abdominal surgeries where the portal vein might be somehow involved (do not exclude laparoscopic surgeries for being minor) 5. Presence of a CENTRAL venous catheter 6. Malignancy 40% of idiopathic DVTs are associated with malignancies 7. Estrogens, OCP or HRT 8. Antiphospholipid antibody syndrome 9. Myeloproliferative Disorders Polycythemia vera or essential thrombocythemia. 10. Heparin-induced thrombocytopenia (HIT) especially unfractionated, you have to monitor platelet count. 11. Prolonged air travel 12. Pregnancy (very important) 13. Have a lower limb cast (very important) 14. Hyperviscosity syndromes (multiple myeloma or Waldenstrom's macroglobulinemia).	1. Antithrombin deficiency 2. Protein C deficiency 3. Protein S deficiency 2,3> They could be heterozygous or homozygous. homozygous cases are more severe. 4. Factor V Leiden mutation (Factor V-Arg506Gln) [Estrogen + FV Leiden → ↑↑↑ thrombosis]. 5. Prothrombin gene mutation (G→A transition at position 20210) 6. Dysfibrinogenemias (rare in literature but locally it is reported a lot) **Important note: WE shouldn't look for an inherited cause if an acquired one is clearly present.** There is little evidence that the detection of these abnormalities predicts recurrence of VTE	1. Hyperhomocysteinemia 2. High levels of factor VIII 3. Acquired Protein C resistance in the absence of Factor V Leiden 4. High levels of Factor IX, XI

In inherited deficiencies, you should consider your local's "most commons". They differ between nations. The most common deficiency causing thrombophilia in the west is **Factor V Leiden**. Locally, they are **S & C.**

Venous thrombosis :

- Venous thrombosis could be inherited, acquired or mixed/unknown.
- Risk factors below are the most important thing to acknowledge in this lecture.
- Females are more prone to, and more commonly seen with venous thrombosis.
- Patients in medical wards have higher mortality rates due to thrombosis than those in surgical wards. That is because surgeons are more precautious in terms of thrombotic prevention.

Inherited thrombophilia (Dr.Farjah skipped this)

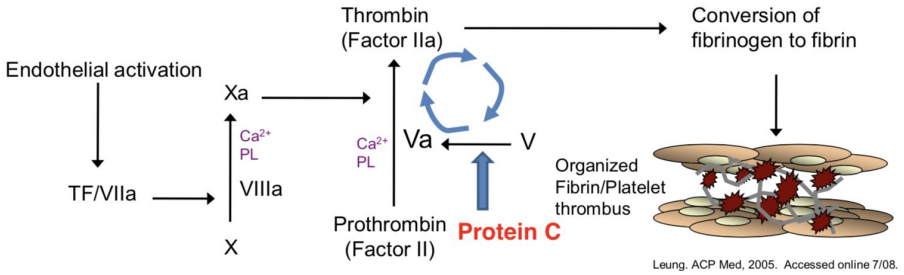
1. Antithrombin deficiency :

- Also known as Antithrombin III deficiency. overall incidence is low.
- Normally antithrombin III Inhibits coagulation by irreversibly binding the thrombogenic proteins thrombin (IIa), IXa, Xa, XIa and XIIa.
- Antithrombins' binding reaction is amplified 1000-fold by heparin, which binds to antithrombin to cause a conformational change which more avidly binds thrombin and the other serine proteases.

- Antithrombin deficiency is **autosomal dominant,** thereby affecting both sexes equally. but females are at a higher risk for VTE during pregnancy. (DVT occured in 18% of pts with AT deficiency, and in 33% i the postpartum period.

2. Factor V Leiden:

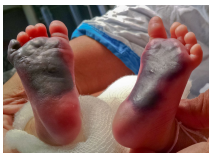
- Factor V Leiden (=Factor V mutation → **activated protein C resistance**)– Most common form of inherited thrombophilia (~50% of cases)



3. Protein C deficiency:

- Protein C is a **vitamin K dependent** glycoprotein produced in the liver.
- In the activation of protein C, thrombin binds to thrombomodulin, a structural protein on the endothelial cell surface.
- This complex then converts protein C to activated protein C (APC), which degrades factors Va and VIIIa, limiting thrombin production
- For protein C to bind, cleave and degrade factors Va and VIIIa, protein S must be available.
- Protein C deficiency, whether inherited or acquired, may cause thrombosis when levels drop to 50% or below.
- Protein C deficiency also occurs with surgery, trauma, pregnancy, OCP, Vit. K deficiency, liver/renal failure, DIC,or warfarin.
- Vitamin K deficiency causes hemophilia most of the time but it can cause thrombophilia because of protein c deficiency.

4. Protein S, C4b Binding Protein and Protein S Deficiency:



- Protein S is an essential cofactor in the protein C pathway.
- Protein S exists in a free and bound state.
- 60-70% of protein S circulates bound to C4b binding protein.
- The remaining protein S, called free PS, is the functionally active form of protein S.
- Inherited PS deficiency is an autosomal dominant disorder, causing thrombosis when levels drop to 50% or lower.

❖ Protein C & S deficiency: Heterozygous or homozygous, congenital or acquired. clinical expression of the hypercoagulability variable, and do not necessarily correspond with absolute concentration of protein C.

5. Prothrombin G20210A Mutation:

- Normal Prothrombin (factor II) circulates as vitamin K-dependent cofactor with 1/2life of 3-5 days.
- Prothrombin G20210A mutation (the 2nd most common prothrombotic mutation) leads to decrease in thrombin activation.
- A G-to-A substitution in nucleotide position 20210 is responsible for a factor II polymorphism.
- The presence of one allele (heterozygosity) is associated with a 3-6 fold increased for all ages and both genders.
- The mutation causes a 30% increase in prothrombin levels

❖ **Combined effect of inherited thrombophilias on tendency for VTE. (click here)**

Mixed/Acquired/ unknown thrombophilia (Dr.Farjah skipped this)

1. Causes of Acquired Protein S Deficiency:

- May be due to elevated C4bBP, decreased PS synthesis, or increased PS consumption.
- C4bBP is an acute phase reactant and may be elevated in inflammation, pregnancy, SLE, causing a drop in free PS.
- Functional PS activity may be decreased in vitamin K deficiency, warfarin, liver disease.
- Increased PS consumption occurs in acute thrombosis, DIC, MPD, sickle cell disease.
- It may be induced by OCPs, pregnancy or nephrotic syndrome.
- Pregnancy: a protective mechanism against bleeding during delivery.

2. Activated Protein C (APC) Resistance due to Factor V Leiden:

- Activated protein C (APC) is the functional form of the naturally occurring, vitamin K dependent anticoagulant, protein C.
- APC is an anticoagulant which inactivates factors Va and VIIIa in the presence of its cofactor, protein S.
- Alterations of the factor V molecule at APC binding sites (such as amino acid 506 in Factor V Leiden) impair, or resist APC's ability to degrade or inactivate factor Va.
- Mutant Leiden gene product is not susceptible to cleavage by APC.

3. Hyperhomocysteinemia:

- Homocysteinuria or severe hyperhomocysteinemia is a rare autosomal recessive disorder characterized by developmental delay, osteoporosis, ocular abnormalities, VTE, and severe premature CAD.
- Less marked elevations of homocysteine are more common, occuring in 507% of the population, associated with clinical factors such as vitamin deficiencies (i.e. folate, vit B6, and/or vit B12).
- Homocysteine has primary atherogenic and prothrombic properties.

4. Antiphospholipid Syndrome (APS): [Thrombosis + multiple abortions]

Antiphospholipid syndrome (APS) is an autoimmune multisystem disorder, either primary or secondary, characterized by venous, arterial, or small vessel thromboembolic events**.** The antiphospholipid antibodies are heterogeneous and typically are directed against phospholipid binding proteins. Can be MS or chorea like in presentation.

Diagnosis [you need at least: 1 of the clinical criteria to be positive + 1 positive antibody] click here	
A.Clinical Criteria	• Thrombosis—arterial or venous • Pregnancy loss [why? bc APS acts directly on the placental vein causing thrombosis → placental ischemia → abortion] in the form of Early spontaneous abortions or Stillbirths. • Thrombocytopenia • CNS syndromes—stroke, chorea, TIA • Cardiac valve disease • **Livedo Reticularis** • Deep vein thrombosis • Pulmonary embolism • Skin Rash

B. Laboratory Criteria -Any one of the antibodies Positive (should be done twice, 12 weeks apart)	**The Lupus Anticoagulant (LAC)**	**Anticardiolipin Antibodies**
	• Initially found in patients with SLE (Usually prolonged APTT and/or PT) paradoxically, usually increased APTT indicates hemophilia but not in lupus anticoagulant antibodies. History is very important to differentiate here, ask about bleeding history, surgeries, tooth extraction. If negative, patient probably doesn't have hemophilia even if APTT is increased, does not correct in 1:1 mix • DRVVT - venom activates FX directly; prolonged by LAC's • Prothrombin Time - seldom very prolonged.	• IgG or IgM anticardiolipin antibody-medium or high titer • ACAs are antibodies directed at a protein-phospholipid complex • Detected in an ELISA assay using plates coated with cardiolipin & B2-glycoprotein

Treatment

- The aim is to open the clot, and prevent further clot formations.
- Patients with thrombosis- anticoagulation, INR 3
- Anticoagulation is long-term—risk of thrombosis is 50% at 2 years after discontinuation
- Women with recurrent fetal loss and APS require LMW heparin and low-dose heparin during their pregnancies.
- NOACs are contraindicated with APS patients of high risk (INR >2) because it causes a stroke. Other than APS, give NOACs.

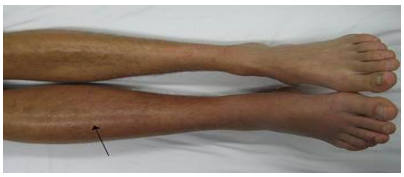
★ Malignancy:

- Risk for thrombosis is multifactorial.
- Predominantly venous thrombosis - stasis, tumor invasion of vessels, chemotherapy effects superimposed on acquired or primary defects in hemostasis.
- Increased production of tissue factor by tumors found in many patients which can activate FX directly.

★ VTE:

- Incidence of VTE 2-3 per 1000
- Incidence is higher in men than women (above the age of 45)
- Overall adjusted incidence in men is 130:100,000 vs 110:100,000 in women (1.2:1)
- Risk of early death in DVT+PE is 18x higher than in DVT alone.
- ¼ of PE cases present with sudden death
- Other predictors of poor survival in DVT are older age, male gender, confinement to hospital, CHF, chronic lung disease, neurological disease and active malignancy.

★ Thrombosis manifestations :

<table>
<tr><th colspan="2">Venous – superficial vein or deep veins</th></tr>
<tr><th>Clinical presentation: DVT (Deep vein thrombosis)</th><th>Clinical presentation: Pulmonary embolism (PE)</th></tr>
<tr><td>- Swollen, painful extremity.
- Can happen in upper limb, abdominal veins, cerebral veins & sinuses.
- Lower limb most common site
- Symptoms & signs depend on the site.
- Often, however, symptoms and signs are minimal. .
 
Pic : A right-sided acute deep vein thrombosis.The leg is swollen and red due to venous outflow obstruction.</td><td>- 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.</td></tr>
<tr><th colspan="2">Arterial – coronary, carotid and femoral</th></tr>
<tr><td colspan="2">- Acute MI, Angina
- CVA, TIA
- Claudication</td></tr>
</table>

Investigations & Diagnosis

★ Hypercoagulability Workup / diagnosis :

- No consensus on who to test
- Increased likelihood if:
  - Age <50 y/o without immediate identifiable risk factors (idiopathic or provoked)
  - Family history
  - Recurrent clots
  - If clot is in an unusual site (portal, hepatic, mesenteric, cerebral)
  - Unprovoked upper extremity clot (no catheter, no surgeries)
  - Patients with warfarin induced skin necrosis (they may have protein C deficiency
- DVT and pulmonary embolism are the two most common manifestations of the same entity: 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.
- Consider pre-test probability for VTE before proceeding further in diagnostic evaluation
  - Among those with suspected DVT of the LE, a minority (17-32%) actually have the disease.
- Clinical criteria can be used to rank patients according to their likelihood of DVT or PE: for example, by using scoring systems such as the Wells score. It is the most practical and widely used diagnostic tool.

Wells Clinical Prediction Rule

Clinical Feature	Points
Active cancer (treatment ongoing or within previous 6 months or palliative	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Unilateral calf swelling of greater than 3 cm (below tibial tuberosity)	1
Unilateral pitting edema	1
Collateral superficial veins	1
Previous Hx DVT	1
Alternative diagnosis as likely as or more likely than DVT	-2
Total Points	

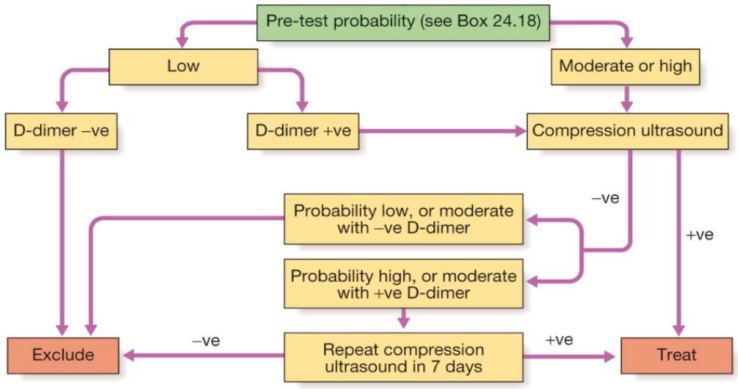


Diagram: investigation of suspected DVT based on initial Wells score. In patients with a low ('unlikely') pre-test probability of DVT, **D-dimer** levels can be measured; *if these are normal, further investigation for DVT is unnecessary.* In those with a moderate or high ('likely') probability of DVT or with elevated D-dimer levels, objective diagnosis of DVT should be obtained using appropriate imaging.

Diagnosis	
Clinical Examination (Non-Specific)	• The most common and important presentation is pain • Palpable cord over the calf • Ipsilateral edema, warmth • and/ or Superficial venous dilatation

Non-Invasive Testing	• Impedance plethysmography
	• Compression ultrasonography Gold standard
	  - Recommended in moderate to high pre-test probability
	• D-dimer
	  - Useful in low pre-test probability to exclude diagnosis of VTE
	  - Sensitivity and negative predictive value are high (~99%)
	  - HIGH D-dimer in: trauma, pregnancy and malignancy, one of the test's limitations. That is why these groups of patients are excluded from being diagnosed by D-dimer.
	  - Medicolegally, the patient should be cleared of DVT suspicion once there is the slightest increase in D-dimer, even if the history was not suggestive.
	• Magnetic resonance venography
	• Computed tomography
	• Echocardiography, ventilation-perfusion (V/Q) scanning and pulmonary angiography

Invasive Testing	• Contrast venography, very cumbersome, not used anymore.

★ Aim of Management :

- Initially; to prevent propagation of thrombus
- Chronic anticoagulation to allow fibrinolysis and recanalization.

Management

Treatment of Venous thromboembolism(VTE)	
Anticoagulation	1) 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 2) Vitamin K antagonists (warfarin) - Heparin + warfarin is more effective than warfarin alone; all cases of Venous thromboembolism should be "bridged" with heparin 3) Factor Xa inhibitors (fonduparinux) 4) Hirudins (lepirudin, bivalirudin) 5) Direct oral Anticoagulants (DOACs).
Thrombolysis	Usually reserved for massive PE - Tissue plasminogen activators (t-PA, u-PA, urokinase, alteplase)
Thrombectomy (arterial)	

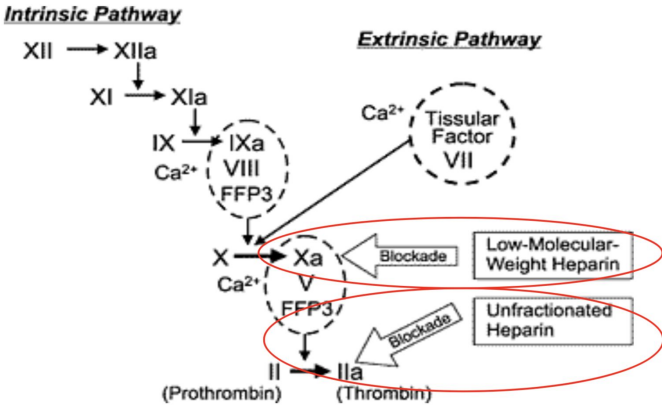
★ Anticoagulation :

- Start during resuscitation phase itself
- If suspicion high, start empiric anticoagulation
- Evaluate patient for absolute contraindication (i.e.: active bleeding)

Duration of Anticoagulation for DVT or PE*

Event	Duration	Strength of Recommendation
First Time event of Reversible cause (surgery/trauma)	At least 3 mos	A
First episode of idiopathic VTE	At least 6 mos	A
Recurrent idiopathic VTE or continuing risk factor (e.g., thrombophilia, cancer)	At least 12 mos	B
Symptomatic isolated calf-vein thrombosis	6 to 12 weeks	A

*From American College of Chest Physicians



Anticoagulation

Conventional Anticoagulation

important to give as soon as you suspect DVT.

- 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(aka prothrombin time) 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.[3]
- COUMADIN , new oral anticoagulant more feasible, no need for follow up

Heparin (LMWH)

1. Lovenox(one brand of LMWH): if hemodynamically stable, no renal function impairment(1 mg/kg BID OR 1.5mg/kg QDay) it has a longer half-life and doesn't respond quickly to antidote(protamine). So if the patient is unstable and may need a procedure or surgery we avoid LMWH.
2. Heparin gtt: if hypotension, renal failure (80 units/kg bolus then 18 units/kg infusion_Goal PTT 1.5 to 2.5 times the upper limit of normal)
3. Antidote: protamine sulphate
4. LMWH inhibits factor Xa, unfractionated inhibits factor IIa

Warfarin

- Warfarin will inhibit vit k dependent clotting factors (II, VII, XI and X). (click here)
- No fixed dose of warfarin, every patient needs a different dose (loading dose + maintenance)
- INR (International normalized ratio) Therapeutic INR 2-3 in most cases
- Initially heparin is a must as warfarin is slow to act and initially prothrombotic treatment continued for 3-12 months mostly but longer or life long anticoagulation may be needed in RECURRENT cases of VTE.
- Dose:
  - 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, >10mg) is not recommended.
  - starting dose od <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)

How to treat warfarin overdose?

- Antidote: vitamin K but may take time (many hours) to act
- An actively bleeding patient may also need fresh frozen plasma (FFP) or ,prothrombin complex

[3] UFH: is the IV anticoagulant, the rest are Oral or SC . UFH: is Suitable for unstable patient because the absorption won't be good from SC root (LMWH)

<table>
<tr><td></td><td>Fluctuations in INR may occur because of any one or more of the following conditions:
- Patient non-compliance
- Changes in vitamin K intake (diet)
- Effect(s) of concomitant drug(s) use
- Changes in warfarin metabolism
- Changes in vitamin K dependent coagulation factor synthesis or metabolism
- Inaccuracy in INR testing</td></tr>
<tr><td rowspan="4">Direct oral anticoagulants (DOACs)[4]</td><td>Indications</td></tr>
<tr><td>● Treatment of venous thromboembolism.
● TE prevention in atrial fibrillation.
● Prophylaxis in orthopedic surgery.
● Treatment of VTE in cancer patients.
● VTE prophylaxis in cancer patients.</td></tr>
<tr><td>● Direct thrombin inhibitors (DTI): Dabigatran
○ The reversal (antidote) is by Idarucizumab.
○ It 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.
● Factor X inhibitors : Rivaroxaban, Apixaban, Edoxaban
○ The reversal (antidote) is by 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.</td></tr>
<tr><td><table><tr><th>Pros</th><th>cons</th></tr><tr><td>● Fixed daily dose
● No need for monitoring
● Quick onset of action .
● Bleeding risk similar to warfarin (GI bleed more common),
● Smaller doses can be used as prophylaxis.</td><td>● More expensive
● Reversal a problem (Antidote available now)
● Can not be used in end stage renal failure and Not suitable for AC for prosthetic valves</td></tr></table></td></tr>
</table>

[4] AKA new oral anticoagulants(NOACs).

IVC filter [5]
Indications: - Absolute contraindication to anticoagulation (i.e. active bleeding) - Recurrent PE during adequate anticoagulation - Complication of anticoagulation (severe bleeding) - Pts with poor cardiopulmonary reserve - Recurrent P.E. will be fatal - Patients who have had embolectomy - Prophylaxis against P.E. in select patients (malignancy) It prevents large clots, we don't do it unless theres proven DVT, ACUTe and within the first month.
Embolectomy (Surgical or catheter)
Indications: - Those who present severe enough to warrant thrombolysis - In those where thrombolysis is contraindicated or fails

Notes
- In pregnancy, we use Heparin. Why? because it cannot cross the placenta = safe. - Thrombosis in cancer patients? LMWH. - Side effect of heparin? Thrombocytopenia (low platelet count).

Complications of DVT

★ **Post thrombotic syndrome:** (important)

- **Risk factors for PTS:**
  - Inadequate initial anticoagulation
  - Recurrent DVT
  - Higher BMI
  - Distal vein thrombosis
  - Recently, persistently elevated D- dimers
  - Not impact for long – term anticoagulation.
- **PTS Impact:** **(click here)**

  It's a chronic syndrome

[5] Patients who have had a DVT and have a strong contraindication to anticoagulation, and those who, despite therapeutic anticoagulation, continue to have new pulmonary emboli, should have an **inferior vena cava filter** inserted to prevent life-threatening PE.

Summary

- **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 (1st 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).

Clinical case scenario *(From Dr.farjah slides)*

- **Case 1 (John) :**

John is a 75-year old man with a recent (4 weeks ago) admission to hospital for hip replacement. The procedure was performed under general anaesthetic. During admission, John received the following VTE prophylaxis (to be continued until John no longer had significantly reduced mobility):

(1) anti-embolism stockings
(2) pharmacological VTE prophylaxis.

John reports that his right leg has been swollen for over 2 weeks. He thought it was healing after the operation, which is why he has not told anyone sooner. He presented to his GP and the GP has referred him to your accident and emergency (A&E) department.

1.1 Question

You believe John has symptoms of DVT. What would you do next?

Carry out an assessment of John's general medical history and a physical examination to exclude other causes.

1.2 Question

John reports that he had a DVT 20 years ago and that he has osteoarthritis. On admission, he is apyrexial with a temperature of 37°C and his right calf and ankle are red, blotchy and swollen with pitting oedema. His heart rate is 80 beats per minute, respiratory rate 15 breaths per minute, blood pressure is 136/80 mmHg and SpO2 96% in air. You suspect DVT: **what would you do next?**

Even though John received VTE prophylaxis, the diagnosis of DVT should still be highly considered. Use the two-level DVT Wells score to estimate the clinical probability of DVT.

1.3 Question

John's two-level DVT Wells score is 3 (DVT likely):

(1) Major surgery within 12 weeks requiring general or regional anaesthesia = 1.
(2) Pitting oedema confined to symptomatic leg = 1.
(3) Previously documented DVT = 1.

You do not consider that an alternative diagnosis is at least as likely as DVT.

You suspect DVT: **what would you do next?**

Organise a proximal leg vein ultrasound scan. Unfortunately, in your organisation, this scan is not available within 4 hours of being requested. Therefore, you offer a D-dimer test, an interim 24-hour dose of a parenteral anticoagulant and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.The D-dimer test is positive and the proximal leg vein ultrasound scan is also positive.

1.4 Question

What would you do next?

Diagnose DVT and start treatment with low molecular weight heparin (LMWH) or anticoagulant as soon as possible.

Questions

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 | unaffected

   Partial thromboplastin time | prolonged

   Bleeding time | prolonged

   Platelet count | 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