Team Medicine

4.Thrombophilia

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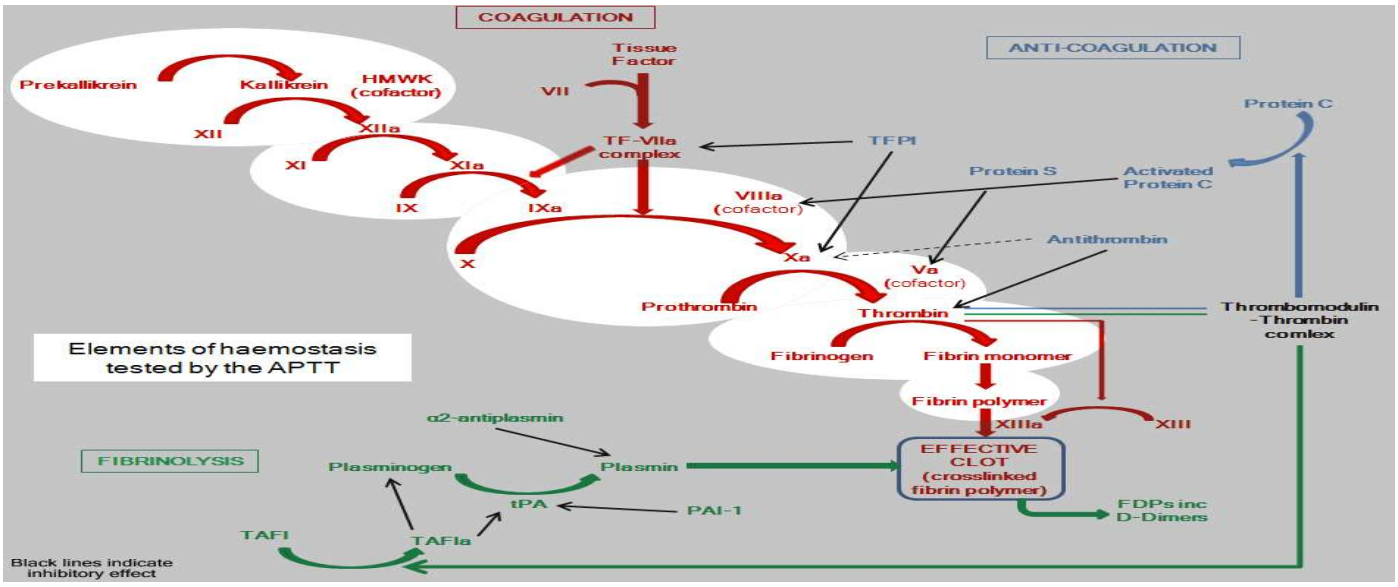
■ Slides ■ Doctors notes ■ Additional

431 Teams

Risk factors for thrombosis:

- Hereditary causes
- Acquired causes→ estrogen, atherosclerosis, trauma, surgery, malignancies, infections, immobility.



Antithrombotic agents:

1.antithrombin→prevents thrombin from converting fibrinogen to fibrin

2.activated protein C → inhibit factor V & VIII

3.protien C action is facilitated and enhanced by protein S

4.TFPI (tissue factor pathway inhibitor)→prevent tissue factor TF (factor III) from activating clotting factors. Tissue factor (TF) is a protein available in sub-endothelial tissue and leukocytes that works as a high affinity receptor for coagulation factor VII. The complex of TF with factor VIIa catalyzes the conversion of the inactive protease factor X into the active protease factor Xa. Tissue factor forms the extrinsic pathway, opposed to the intrinsic pathway, which involves both activated factor IX and factor VIII. Both pathways lead to the activation of factor X (the common pathway) that combines with activated factor V in the presence of calcium and phospholipid to produce thrombin (thromboplastin activity).

Once a clot is formed, fibrinolysis process is aided by plasminogen→plasmin (the activated form), which is catalyzed by Tissue Plasminogen Activator (t-PA) found in endothelial cells

Plasmin may cause a bleeding problem if it spreads to the entire blood→ the presence of alpha2-antiplasmin will deactivate it.

The liver can remove excess thrombin; therefore in liver diseases→ bleeding (low clotting factors) and thrombosis (due to accumulation of thrombin) may occur

Risk factors for arterial thrombosis:

*Smoking. * Hypertension. * Hyperlipidaemia. *Diabetes mellitus

Factor V Leiden is the most common hereditary hypercoagulability disorder amongst Eurasians

Risk Factors for Venous Thrombosis:thrombophiliausually leads to venous thrombosis (DVT or PE) rather than arterial thrombosis.

- **Inherited:**

1. Antithrombin deficiency (reduction of the inhibitor)→thrombinwill continuously be activated and convert fibrinogen to fibrin→clot formation
2. Protein C deficiency
3. Protein S deficiency
4. Factor V leiden mutation (factor V-Arg506Gin
5. Prothrombin gene mutation (G—A transition at G20210A position)
6. Hyperhomocysteinemia

Methionine synthase function: (transferring methyl group to Hcys. to form methionine when transforming 5-methyltetrahydrofolate(N5-MeTHF) into tetrahydrofolate (THF))

- **Acquired:**

1. Antiphospholipid syndrome
2. Myeloproliferative disorder
3. **HIT**heparin induced thrombocytopenia
4. Prolonged air travel/immobilization
5. Advancing age
6. History of thrombosis (prior thrombosis) important to ask when taking history.
7. Major surgery
8. Malignancy
9. Estrogens/ hormonal replacement therapy/OCP

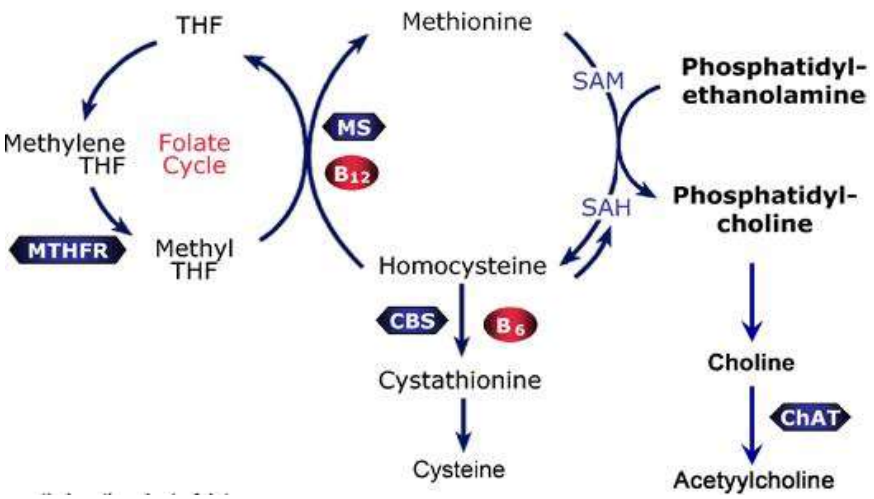
- **Mixed/unknown**→ if a patient has an inherited form and was exaggerated by an acquired cause eg. A female patient with Factor V leiden thrombophilia and uses oral contraceptive pills→ very high risk for thrombosis.

1.Hyperhomocysteinemia→ can cause both:

- (congenital)→e.gmethionine synthase gene mutation leads to inactivation of the enzyme that regenerates homocysteine into methionine → accumulation of homocystiene→homocysteinemia
- (acquired)→e.gadministration of (INH) isoniazid drug for tuberculosis causes the depletion of vitb6 (INH-related vitb6 deficiency) → leading to high levels of homocysteine→that's why we should always give vitB6 supplements when treating TB with INH

2.high levels of factor VIII, IX, XI

3.Aquired protein C resistance (APC resistance) → in factor V leiden(factor V leiden is most common hereditary risk factor for venous thrombosis)



Always give pyridoxine (vitb6) supplements when treating TB with INH isoniazid to prevent neuropathies and elevated homocysteine

Methionine (SAM) works as methyl donor→ all proteins in body are built from methyl group.

Homocysteine causes damage to endothelium leading to:

1.decreased production of vasodilators e.g. nitric oxide, prostacyclin.

2.Protein C cannot be activated

3. Tissue plasminogen activator t-PA won't work

If you have anti-thrombin deficiency you have 8-9 folds more risk to have thrombosis compared to normal person

* Predictors of Thrombosis and Relative Risk

Thrombophilic Factor	Relative Risk
Antithrombin deficiency	8 – 10
Protein C deficiency	7 – 10
Protein S deficiency	8 – 10
Factor V Leiden/APC resistance	3 – 7
Prothrombin G20210A mutation	3
Elevated Factor VIII	2 – 11
Lupus Anticoagulant	11
Anticardiolipin antibodies	1.6-3.2
Mild Hyperhomocysteinemia	2.5

* Site of Thrombosis vs. Risk Factor

Abnormality	Arterial	Venous
Factor V Leiden	-	+
Prothrombin G20210A	-	+
Antithrombin deficiency	-	+
Protein C deficiency	-	+
Protein S deficiency	-	+
Hyperhomocysteinemia	+	+
Lupus Anticoagulant	+	+

Most cases of methionine synthase deficiency are symptomatic within 2 years of birth with many patients rapidly developing severe encephalopathy, blindness birth defects and neurological problems.

- **Other Predictors for Recurrent VTE(venous thromboembolism):**

#Idiopathic VTE # Residual DVT #Elevated D-dimer levels(d-dimer is fibrin fragments caused by degradation of blood clots by fibrinolysis).#Gender #age

Major role: inhibition of thrombin(factor IIa)

Minor role: inhibition of seriene proteinases (factors X,IX,XI and XII).Antithrombin also antagonize factor VII by accelerating the dissociation of the factorVIIa-TF complex and preventing its re-association

common causes ofacquiredantithrombin deficiency:

1.liver disease(reduction in synthesis). 2.kidney disease (nephrotic syndrome)→ lost in urine 3.DIC→ increaseconsumption 4.Utilization of heparin →reduction of antithrombin levels due to rapid clearance of heparin-antithrombin complex

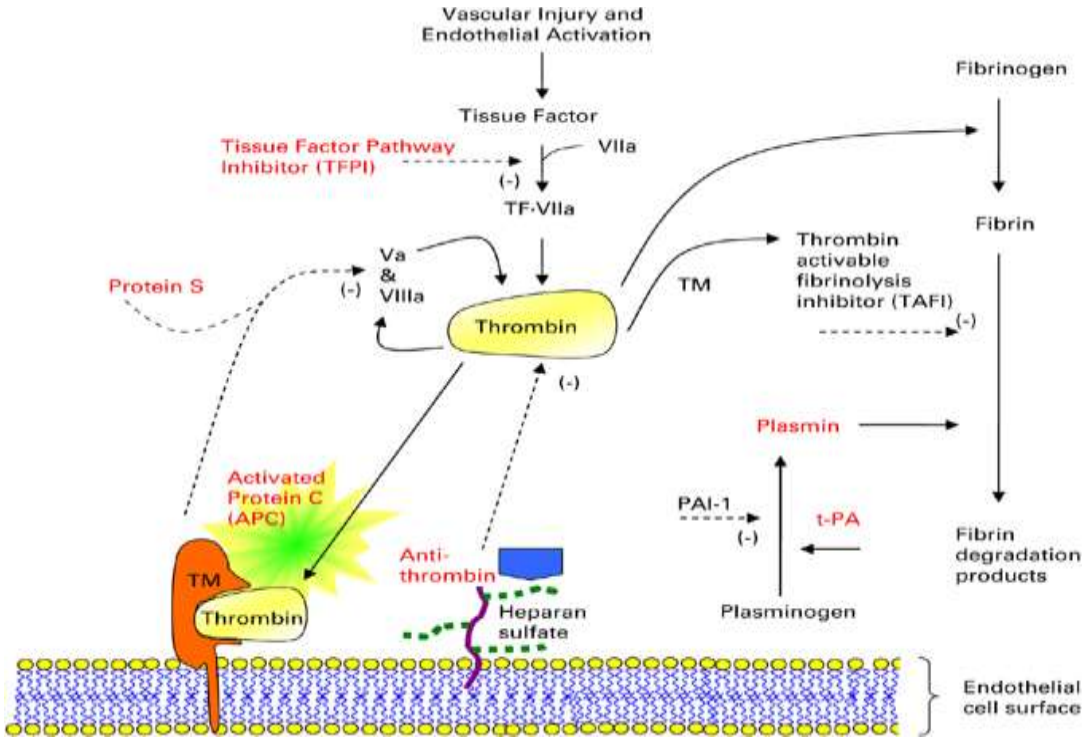
Hereditary Risk Factors:

Antithrombin Deficiency: rare

previously known as Antithrombin III)

Inhibits coagulation by irreversibly binding the thrombogenic proteins thrombin (IIa), IXa, Xa, XIa and XIIa

Antithrombin binding reaction is amplified 1000-fold by heparin, which binds to antithrombin to prevent clot formation by avidly binding thrombin and the other serine proteases (serine protease inhibitor superfamily plays a central role as an anticoagulant in mammalian circulation systems) not only works as an antagonist to thrombin but also inhibits other proteases of the coagulation cascade



The most dangerous factor enhancing thrombosis is thrombin

That's why we have many mechanisms trying to stop it→ remove thrombin and prevent thrombosis → by forming [thrombomodulin- thrombin] complex → this complex will form an activated protein C APC . Slide shows how protein S potentiates protein C to inactivate factor V and VIII.

Associated with increased risk ofvenousthromboembolism, no association with arterial thrombotic disease.

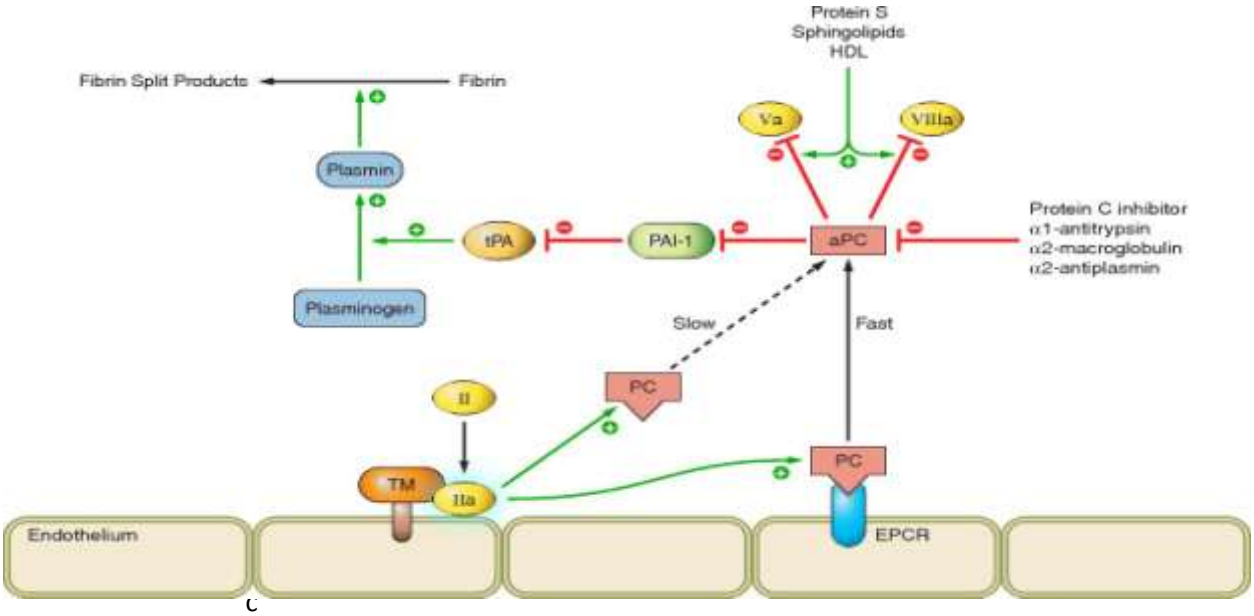
Protein C Deficiency

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



C

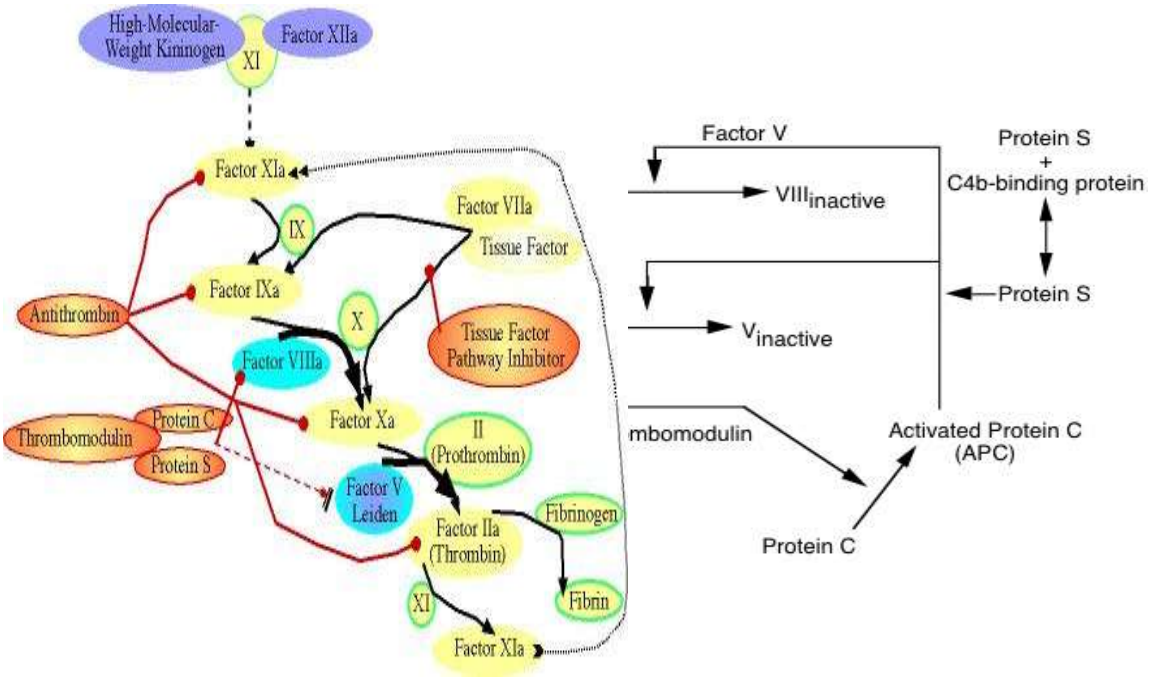
iency, whether inherited or acquired, may cause thrombosis when levels drop to 50% or below

Protein C deficiency also occurs with surgery, trauma, pregnancy, OCP, liver or renal failure, DIC,or warfarin(increased risk for developing skin necrosis)

Protein C has 2 effects:inhibit thrombosis&inhance fibrinolysis

1. Inhibit the activation of proteins Factor Vaand Factor VIIIa→this action can be enhanced by protein S (PROTIEN S is a CO-factor for protein C) → that's why when you have protein S deficiency→ you can have thrombosis→ due to the weak action of protein C

2. Enhancing fibrinolysis → inactivates PAI-1 (plasminogen activator inhibitor) inhibit the inhibitor of plasminogen activation → enhancing plasmin formation



Complement c4 binding protein inhibits the action of c4 in complement system

Causes of Acquired Protein S Deficiency->more important than inherited causes

- 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 (one of the several causes of thrombosis in pregnancy), SLE, causing a drop in free PS(protein S binds to c4bBP in any inflammatory condition) → LEADS to reduction of PS levels.When you measure protein S → activity is low (cause its bound) but availability is high.
- Functional PS activity may be decreased in vitamin K deficiency, warfarin, liver disease→PS is vitK dependent anticoagulant.
- Increased PS consumption occurs in acute thrombosis, DIC, MPD (myeloprolifative disease), sickle cell disease.

Factor V Leiden →Activated Protein C (APC) Resistance: chief cause of inherited thrombophilia

- 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

APC usually binds to Va→Va-PC complex →inactivates and degrades the phospholipid bound factors Va and VIIIa→slows down clotting process

Factor Va has receptors for protein C, when factor V is mutated protein C cannot inactivate factor V>> clot →increasing the chance of developing abnormal clots

Mutation of the receptors in factor V → the cause of APC resistance → increase levels of protein C because it's not consumed, also FIBRINOLYSIS will be inhibited

Condition of factor V leiden strongly enhanced with contraceptive pills in and pregnancy → 3 weeks comes with DVT

50% of people with factor V leiden also have prothrombin mutation, so they can be combined.

They are the 2 most common inherited hypercoagulable disorders.

Prothrombin G20210A mutation (factor II)

The variant causes elevated plasma prothrombin levels (hyperprothrombinemia), possibly due to increased pre-mRNA stability

- 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.

Anti phospholipid syndrome:

is an autoimmune, hypercoagulable state caused by antiphospholipidantibodies. APS provokes blood clots (thrombosis) in both arteries and veins as well as pregnancy-related complications such as miscarriage, stillbirth, preterm delivery, or severe preeclampsia.Note: The majority of the patients with these autoantibodies do not have increased risk of thrombosis because many of these autoantibodies are transient and appear to carry little or no risk of thrombosis.

- **Diagnosis:**

❖ **Clinical Criteria**-Arterial or venous thrombosis-Pregnancy morbidity
❖ **Laboratory Criteria**

-IgG or IgManticardiolipin antibody-medium or high titer -Lupus Anticoagulant

Diagnostic criteria require one clinical event→thrombosis (arterial or venous)or pregnancy complication, and two positive blood tests spaced at least 3 months apart. These antibiodies are: lupus anticoagulant, anti-cardiolipin and anti-β2-glycoprotein-I

clinical:

- Thrombosis—arterial or venous
- Pregnancy loss
- Thrombocytopenia
- CNS syndromes—stroke, chorea
- Cardiac valve disease
- Livedo Reticularis:is a common skin finding consisting of a mottled reticulated vascular pattern that appears like a lace-like purplish discoloration of the skin.The discoloration is caused by swelling of the venulesowing to obstruction of capillaries by thrombi. It can be caused by any condition that makes venules swell

Endothelium can produce 1.prostacyclin works as an antiplatelet and a vasodilator2.heparan sulfate 3.thrombomodulin →activate PC and remove thrombin 4. Nitric oxide(antidote for homocysteine). And so on…

In platelets →thromboxaneA_2 is produced by phospholipids of platelets membrane→ platelet aggregation and vasoconstriction

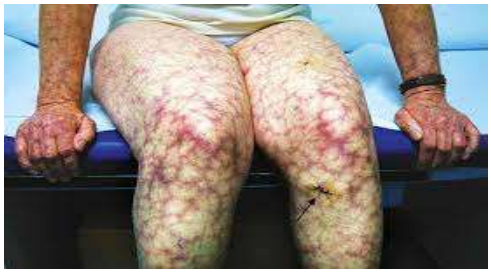
In antiphospholipid syndrome→ thrombosis → damage to the antithrombotic effect of endothelium (prevent prostacyclin form production and enhance platelet aggregation)

Vasoconstriction and thrombosis→ ischemia in placenta→ miscarriages

APS may present in isolation (primary) or in association with RA, SLE, systemic sclerosis,infections and cancers.

LUPUS anti-coagulants (LAC):

- DRVVT- venom activates F. X directly;prolonged by LAC's
- APTT- Usually prolonged, does not correct in 1:1 mix
- Prothrombin Time- seldom very prolonged



Mixing studies:tests performed on blood plasma used to distinguish factor deficiencies from factor inhibitors, such as lupus anticoagulant, or specific factor inhibitors, such as antibodies directed against factor VIII. Mixing studies take advantage of the fact that factor levels that are 50 percent of normal should give normal PT and PTT result.

Take plasma of a patient → do PTT→ prolonged→ either due 1. Low factors 2. Inhibitor to clotting

If you add PLASMA that contains normal factor level and mix it with patient's plasma→ PT/PTT will be normal → mixing study show correction→factors deficiency (hemophilia A or B)

If there is a failure in correction→ prolonged PTT after adding plasma (false prolongation in vivo)→ indicates an inhibitor (LUPUS anticoagulant)

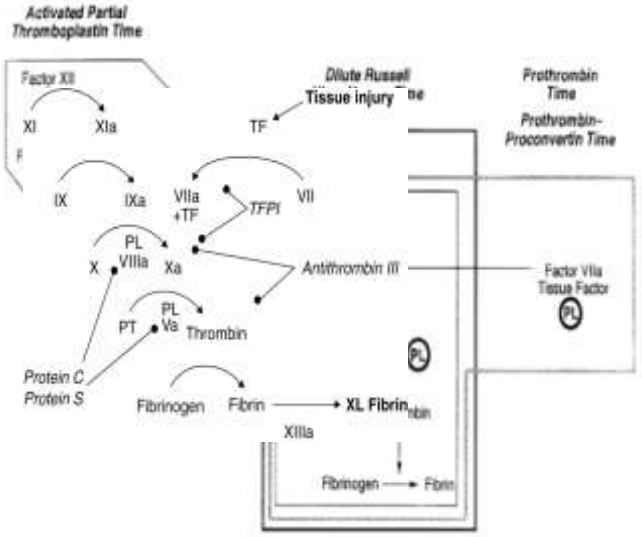
If you have Antiphospholipid syndrome→ prolonged PTT in tube→ gives you the idea that it's a bleeding problem while in the body the opposite is happening (thrombosis)

That's why surgeons and physicians cancel operations→ thinking that the patient is a "bleeder" but if we suspect Antiphospholipid syndrome→ easily diagnosed

Role of phospholipids on coagulation test

Membranes of activated platelets provide a catalytic phospholipid on which both (factor IXa-factor VIIIa)complex and (factor Xa-factor Va) complex can be assembled→calcium is also needed.Tissue-factor, which plays a key role in blood coagulationby initiating the extrinsic coagulation pathway, requires the presence of phospholipids for optimal biological activity

With antibodies→it will take long time to convert prothrombin to thrombin →giving a prolonged PTT



VDRL test for syphilis gives false +ve result in patients with anti-phospholipid syndrome (why??) because the test detects Anticardiolipin antibodies in the blood →we can tell them apart by ELISA assay.

antiphospholipid- anti-cardiolipin antibody:

- ACAs are antibodies directed at a protein-phosholipid complex
- Detected in an ELISA assay using plates coated with cardiolipin and B2-glycoprotein

Treatment:

- **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(enoxaparin 40mg/day for average weight women along with aspirin) and low-dose heparin during their pregnancies. (WE NEVER GIVE WARFARIN IN PREGNANCY)**

HIT- Heparin induced thrombocytopenia

- HIT is mediated by an antibodyIgG that reacts with a heparin-platelet factor 4 complex to form antigen-antibody complexes
- These complexes bind to the platelet via its Fc receptors
- Cross-linking the receptors leads to platelet aggregation and release of platelet factor 4 (PF4)
- the released PF4 reacts with heparin to form heparin-PF4 complexes, which serve as additional sites for HIT antibody binding

Anti-ApoH and a subset of anti-cardiolipin antibodies bind to ApoH, which in turn inhibits Protein C, a glycoprotein with regulatoryfunction upon the common pathway of coagulation (bydegradating activated factor V).

LAC (lupus anticoagulant) antibodies bind to prothrombin, thus increasing its cleavage to thrombin, its active form.

Cardiolipin is a phospholipid.

If patient with APS no symptoms-> no treatment

APS with thrombosis →treat thrombosis+ prophylaxis is needed

For pregnant woman→prophylaxis for thrombosis (aspirin) →very effective → because APS activate platelets leading to vasoconstriction and platelet aggregation→ also improves circulation to the fetus in placenta → if going for delivery when do we stop aspirin and heparin??

If someone with platelets of 300 and we know that they can survive for 5 days → if you give aspirin it will last for 1 hour and disappear but the affected platelets will persist this function until they're dead →20% of our platelets will die within 24 hours and new 20% will be generated→60,000 platelets within 24 hours work →2 days →120,000(40%).→ so we don't have to wait for each single affected platelet to die because we have to see how many platelets we need to work, so we advise to stop aspirin for 2 days only → enough new platelets that can prevent bleeding →depending on the platelet count.

SURGERY AND ANTIPHOSPHOLIPID SYNDROME

What is antiphospholipid antibody?

Antiphospholipid antibody (aPL) is an abnormal blood protein (antibody) that causes blood clots and/or pregnancy losses. It is measured in several different ways, and is named for the way it is measured. In one test, it is called *anticardiolipin* antibody; in another, it is called *lupus anticoagulant*. It can also be called *antibody to beta-2-glycoprotein I*; sometimes, because of a technical aspect of the way the test is done, the antibody causes a *false positive* test for syphilis. (People with a false positive test do not have syphilis, or anything like it.) The term *antiphospholipid* refers to all of these tests. Patients have antiphospholipid syndrome (APS) when they have both blood clots and aPL (or pregnancy loss and aPL).

About 1 of every 3 people with lupus has aPL, but only about half of people with APS have lupus. People with APS, but without lupus, only have the primary antiphospholipid syndrome (PAPS). Those with both lupus and APS have secondary APS. The APS symptoms are the same for both, but people with secondary APS have additional symptoms due to lupus.

Why am I taking anticoagulant medication?

If you have had a blood clot, you will be treated with an anticoagulant medication, such as warfarin (Coumadin) or heparin (including low molecular weight heparin). If you are pregnant, you will be treated with one of the heparin preparations, since warfarin cannot be used in pregnancy.

If you have to undergo a surgical operation or procedure (such as a colonoscopy), **YOU MUST CONTINUE ANTICOAGULATION** except during the surgery or procedure itself!

You should discuss this with the physician prescribing your anticoagulation and with the person performing the procedure, since individual needs differ. Always discuss your plans with your physician.

Common recommendations for anticoagulation for elective procedures:

- *7 days before the procedure,* discontinue warfarin.
- *5 days before the procedure,* start low molecular weight heparin and a dose of 1 mg per kilogram (70 mg of Lovenox for a 145 pound person) twice daily, if kidney function is normal. Use a different dose if kidney function is abnormal.
- *24 hours before the procedure,* stop low molecular weight heparin.
- *24 hours after the procedure,* or when the surgeon gives the OK, restart low molecular weight heparin in the same dose, and start taking warfarin again. (It takes several days for warfarin to have its effect.)
- *On the 4th day after the procedure,* when the warfarin effect has occurred, discontinue the low molecular weight heparin (and continue the warfarin). If there are any questions about this, remember to consult with your surgeon and physician well in advance of the procedure.

What if I need emergency surgery?

If you need emergency surgery, the effect of warfarin or heparin can be reversed very quickly by physicians, but the risk of inducing clotting is high. You should start taking anticoagulation as soon as possible after the surgery:

- *24 hours after the procedure,* or when the surgeon gives the OK, restart low molecular weight heparin (for instance, Lovenox at 1 mg/kg twice daily), and start taking warfarin again. (It takes several days for warfarin to have its effect.)
- *On the 4th day after the procedure,* when the warfarin effect has occurred, discontinue the low molecular weight heparin (and continue the warfarin).

Heparin induced thrombocytopenia is a thrombogenic condition causes platelet aggregation

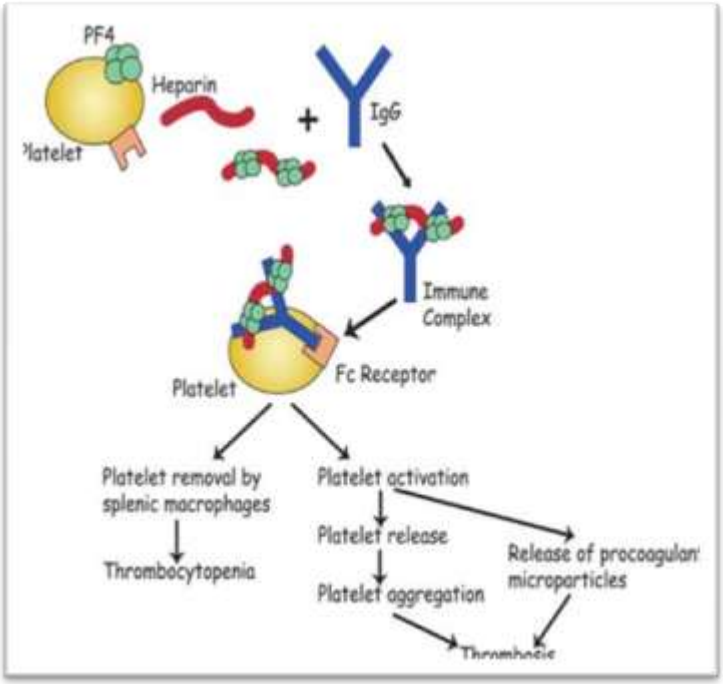
First platlet factor 4 makes a complex with heparin→ antibodies then are made against the complex →the tail of antibodies bind to Fc receptors in platelets → causing platelet aggregation (thrombosis)

Increase consumption throughout the body + platelets removed by splenic macrophages. (thrombocytopenia)→ bleeding

Formation of clots either in arteries (gangrene, ischemia leading to leg or arm amputations) or veins (DVT and PE)

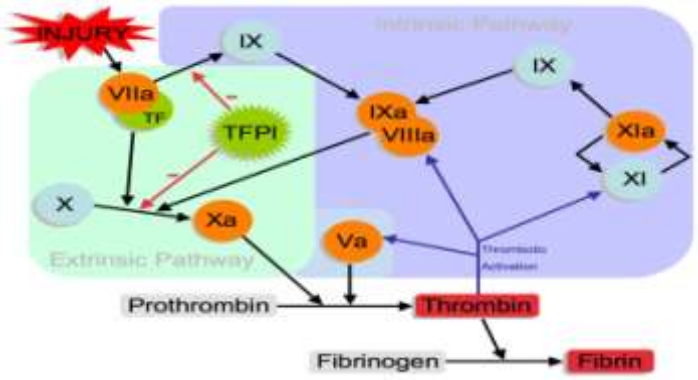
2 types of HIT: 1. Which is mild form→come down to 100 (unnoticed) 2.severe form→ thrombosis and bleeding at the same time

treatment is to stop heparin and use alternatives.



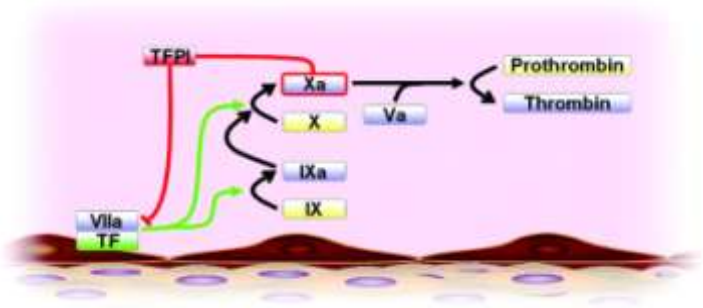
- **Diagnosis of HIT:**
  - Diagnosis made on clinical grounds
  - HIT usually results in thrombosis rather than bleeding
  - Diagnosis should be confirmed by either immunoassay (ELISA) or functional tests (14C serotonin release assay)
  - Treatment involves cessation of heparin, treatment with an alternative drug, e.g. argatroban, and switching to warfarin

↑ Tissue factor (cancer induced thrombosis): several mechanisms one of them is overproduction of TF (activates factor VII), which is expressed by tumor cells and contributes to a variety of pathologic processes, such as thrombosis, metastasis, tumor growth, and tumor angiogenesis.



TFPI: tissue factor pathway inhibitor

Anti thrombotic agent



Clinical implications in treatment of thrombophilia :

- Routine screening of patients with VTE for an underlying thrombophilic defect "is not justified"
- However, the risk of subsequent thrombosis over 5 years in men with idiopathic VTE is 30%
- Any additional defect adds to risk and to possible need for prolongation of anticoagulation
- Furthermore, women with a history of VTE who wish to become pregnant will be treated differently if a defect were found.

Screening EvaluationFor "Strongly Thrombophilic" Patients

- Test for Factor V Leiden
- Genetic test for prothrombin gene mutation 20210A
- Functional assay of Antithrombin
- Functional assay of protein C
- Functional assay of protein S
- Clotting test for lupus anticoagulant/ELISA for cardiolipin antibodies
- Measurement of fasting total plasma homocysteine

Screening Laboratory Evaluation For "Weekly Thrombophilic" Patients

- Test for Factor V Leiden
- Genetic test for prothrombin gene mutation G20210A
- Measurement of fasting total plasma homocysteine
- Clotting assay for lupus anticoagulant/ELISA for cardiolipin antibodies

Screening in young→look forcongenital causes

Screening for middle age→autoimmune

Screening for elderly→malignancies/ vitB6, 12 deficiencies

Management of Patients With Thrombophilia

Risk Classification	Management
High Risk	
2 or more spontaneous events	Indefinite Anticoagulation
Anticoagulation	
1 spontaneous life-threatening event (near-fatal pulmonary embolus, cerebral, mesenteric, portal vein thrombosis)	
1 spontaneous event in association with antiphospholipid antibody syndrome, antithrombin deficiency, or more than 1 genetic defect	
Moderate Risk	
1 event with a known provocative stimulus	Vigorous prophylaxis in high risk settings
Asymptomatic	

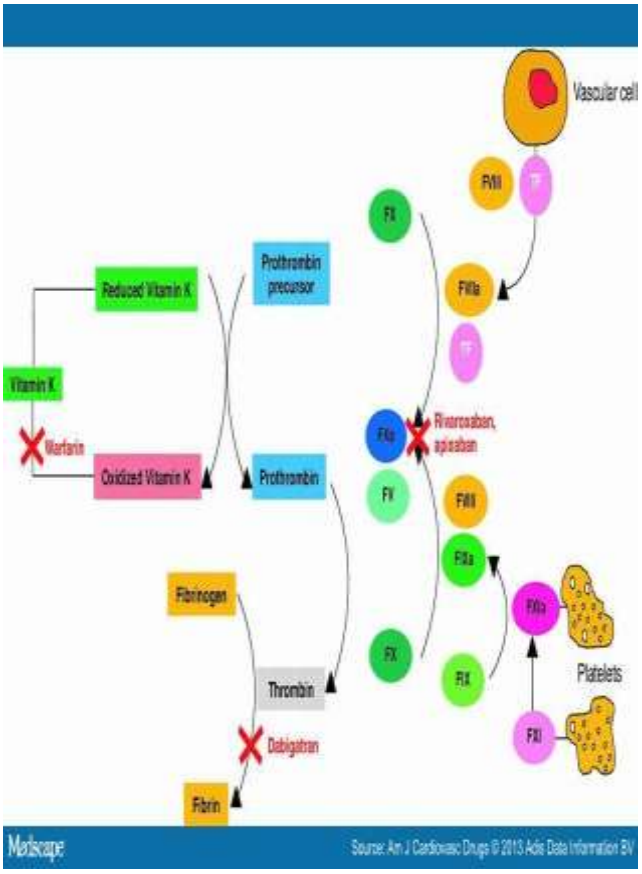
Can we start warfarin without heparin?? **NO!!** Warfarin can cause thrombosis shortly after commencing treatment (skin necrosis is a side effect) why?? The Anticoagulant PROTIEN C is a VitK-dependent and needs carboxylation just like the vit-Kdependentprocoagulants (II, VII, IX and X). Its half-life is 4-6 hours(just like factor VII)(SHORT HALF LIFE)

First warfarin will reduce protein C BEFORE reducing the coagulation factors→ high tendency to coagulate→ leading to skin necrosis and gangrene

Therefore we always overlap and Use heparin in parallel to compact side effects→overlap for 48 hours at least

So we give heparin then give warfarin while they're on heparin→until INR starts to increase and we do not stop it immediately we give further to start working on factor VII (shortest life) and then factor X and factor II (after 2-3days)→longest half life

Overlap for at least 48h-3days→ then stop heparin and continue warfarin alone



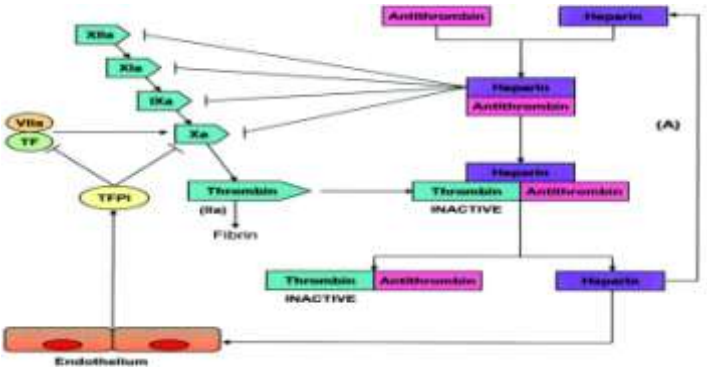
Heparin: activates anti-thrombin does not work by itself, andantithrombin doesn't only prevent thrombin but also inhibit factor X, IX, XI,XII.

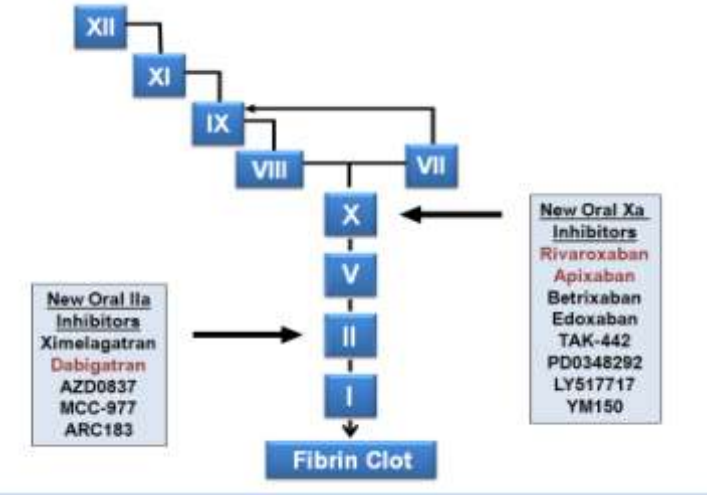
Thrombin can activate factor **XIII to stabilize the clot**→ so by inhibiting thrombin we inhibit many things.

We start treating people with heparin and then warfarin→ when treating with UFH (Heparin)->you give infusion, have to adjust PTT and have to do tests every 6 hours

Now we use LMWH:

- Use according to body weight
- No need for PT/PTT monitoring→ if we want to see the activity→ we can test for factor X activity cause LMWH is Anti-Factor X
- Given once/twice a day
- Can be taken at home no need to admit patients





New agents→ direct thrombin inhibitors(dabigatran)→ only works on thrombin → strongly change PT/PTT

For dabigatran we can check factor II activity

Ximelagtran→withdrawn from market→ causes hepatitis and abnormal LFTs in 60% of patients

Most popular now are the factor X inhibitors→rivaroXaban(Xa) any drug that ends with Xaban is afactor X inhibitor (new agents) quite expensive only used to those with serious conditions.

Advantage of these agents→

- fixed dose: 20mg twice/day for treatment for 2 weeks →then give 20 mg once /day
- oral
- no need for testing PT/PTT
- no need for heparin → no need for bridging → immediately work within 1-2 hours
- THEY DON'T INERTACT WITH FOOD OR DRUGS

Disadvantage: expensive and if you forget a one day dose→ problem→ the drug maximally works for 24 hours → effect of drug is gone.

Summary:

 # Hypercoagulable state (Thrombophilia) is a group of inherited and acquired conditions predispose to venous thrombosis, arterial thrombosis or both.

 # Inherited thrombophilia:

1) **ATIII deficiency:**
   - An autosomal dominant inheritance.
   - **Most thrombogenic disorder.**(IMP)
   - What is normal function of ATIII?
     It binds to heparin sulfate and inactivate (Thrombin),(IXa),(Xia) and (XIIa) in which it acts as anticoagulant.
     So, when ATIII is deficient, more (Thrombin),(IXa),(Xia) and (XIIa) are available in the circulation inducing the coagulation cascade that ends up with fibrin strands. So when ATIII is deficient it acts as (procoagulant).

2) **Protein C Deficiency:**
   - What is the normal function of protein C in the circulation?
     * It is Vitamin K dependent glycoprotein produced in the liver.
     * First of all there is thrombomodulin is found of the top of the endothelium in which thrombin will bind and forms (Thrombomodulin-thrombin complex), this complex then converts protein C to activated protein C (APC), which degrades factors Va and VIIIa (Anticoagulant).
     So when protein C is deficient it acts as (procoagulant).
   - May cause thrombosis when levels drop to 50% or below.

3) **Protein S Deficiency: (**could be inherited or acquired)
   - Inherited PS deficiency is an autosomal dominant disorder.
   - Acquired protein S deficiency due to:
     a) Elevated C4bBP: inflammation, pregnancy, SLE
     b) Decreased PS synthesis: vitamin K deficiency, warfarin, and liver disease.
     c) Increase PS consumption: acute thrombosis, DIC, MPD, sickle cell diseas.
   - What is the normal function of protein S:
     * It is Vitamin K dependent
     * An essential cofactor in the protein C pathway.
     * Two forms : 1) free (active)
     2) Bound (to C4b binding protein) 60-70 %

4) **Factor V Leiden:**
   - Mutation that prevents APC (activated protein C) inactivate of (Va) How?
     - This mutation alternates factor V molecule at APC binding sites.
   - (APC) Resistance.

5) **Prothrombin G20210A Mutation:**
   - Associate with increase prothrombin plasma level.

6) **Hyperhomocysteinemia:** (could be inherited or acquired)
   - Implicated in both arterial and venous thrombosis.
   - Acquired is more common.

 # Acquired thrombophilia:

1) **Antiphospholipidsyndrome :**
   - Positive test of antiphospholipid Ab.
   - antiphospholipidAb encompasses both (Lupus anticoagulant) and (Anticardiolipin ab)

   *** clinical features:**
   - Thrombosis—arterial or venous
   - Pregnancy loss
   - Thrombocytopenia
   - CNS syndromes—stroke(the most common arterial event), chorea
   - Cardiac valve disease
   - Livedo Reticularis

   * **in clinical practice there 2 types of test are used which detect:**
   - Anticardiolipin antibody test
   - Lupus anticoagulant test.

2) **Heparin-Induced Thrombocytopenia:**
   - Antibody that reacts with a heparin-platelet factor 4 complex to form antigen-antibody complexes.
   - Cause thrombosis rather than bleeding.
   - **Diagnosis** : - immunoassay
     - functional tests
   - **Treatment:** (cessation of heparin + and replace it by Argatroban)

 # Dignosis of thrombophilia :

(manifestations of the same disease: VTE and PE)

Treatment:
(same treatment of DVT and PE : **Anticoagulation,Thrombolysis and Thrombectomy**)

Questions:

1.Low molecular weight heparins (LMWH) are distinct from unfractionated heparin in several ways. Which of the following is the primary target?

A) Antithrombin III
B) Factor IIa
C) Factor VII
D) Factor Xa
E) Factor II,IX and X

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2. A 45-year-old woman comes to the emergency department because of acute shortness of breath and hemoptysis. Pulmonary angiography confirms a pulmonary embolus. On further questioning, the patient denies smoking or using birth control pills. She has not been on a prolonged journey during which she was immobilized. She denies recent trauma. She had a recent negative mammogram and Pap smear. She reports a strong family history of miscarriages. She had a deep venous thrombosis when she was pregnant at ages 23 and 28 years. Her mother died of pulmonary embolus at age 48 years. The patient has no other medical history. She denies having allergies. Laboratory studies are positive for a high D-dimer. Which of the following is the most appropriate additional study at this time?

A. Activated protein C level

B. Activated protein S level

C. Factor V Leiden mutation

D. Lactate dehydrogenase level

E. Lupus anticoagulant level

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3. A 35-year old woman comes to the urgent care clinic with a 3-day history of right lower extremity swelling. She first noticed the swelling after returning from Spain via a transatlantic flight. She also reports mild shortness of breath, exacerbated with ambulation. At baseline, she leads an active lifestyle and enjoys bowling and sailing. Her past medical history is significant only for tobacco abuse, with a 20-pack-year history. Her only medication is oral contraceptive pills. Her vitals signs are: blood pressure 132/61 mm Hg, pulse 71/min, respiratory rate 14/min, temperature 37.0 C (98.6 F), and room air saturation of 94% on ambient air. Physical examination reveals lungs clear to auscultation bilaterally and 2+ right lower extremity edema to her knee.. Her chest x-ray is unremarkable. Her d-dimer is significantly elevated. You obtain a V/Q scan that demonstrates a segmental pulmonary embolism. You admit the patient and begin an unfractionated heparin drip and warfarin. On hospital day 5 with continued heparin and warfarin, you notice that her platelet count has decreased from an admission count of 250,000/ml to the current value of 50,000/ml. Her hematocrit remains stable at 38%, her stool guaiac continues to be negative, she has negative orthostatics, and she has no evidence of bleed. The patient has not been started on any other medications. Which of the following is the mechanism that accounts for the thrombocytopenia?

A. Bleed from an undetermined site because of the heparin and warfarin

B. Decreased megakaryocyte production in the bone marrow

C. Direct effect of heparin on platelet activation

D. Formation of antibodies against platelet factor 4 complex

E. Formation of antibodies against platelet factor 8 complex

Answers:

1) Answer is A. LMWH act mainly by activating antithrombin III→ leading to conformational changes to which accelerates its inhibition of activated factor X (Factor Xa).

2) The correct answer is C. This patient has a hereditary thrombophilia and a predisposition to thrombosis. The most likely cause of this condition is a factor V mutation. This is seen in 4% of the general population presenting with such thrombosis.
Activated protein C deficiency (choice A) is very rare and less common than conditions such as hyperhomocysteinemia.
Similarly, activated protein S deficiency is very rare (choice B).
Any patient presenting with an unexplained thrombosis should be worked up for a malignancy. This includes a mammogram, pelvic examination, colonoscopy, and testicular examination. This patient also has had a thrombosis more than 20 years ago. This makes a malignancy unlikely. Furthermore, the family history leads to a diagnosis of a hereditary thrombophilia. Lactate dehydrogenase level (choice D) seeks to determine if there might be a lymphoma.
Lupus anticoagulant level (choice E) seeks to determine if the patient has an antiphospholipid syndrome. This should be on the differential diagnosis. Given the presentation, however, the aforementioned syndromes should be ruled out first.

3) The correct answer is D. There are two types of heparin-induced thrombocytopenia (HIT), HIT I and HIT II. HIT I is the more benign form and occurs from a direct effect of heparin on platelet activation. Additionally, HIT I occurs in 10 to 20% of patients exposed to heparin and occurs 1 to 4 days after exposure to heparin. The nadir platelet count is typically around 100,000/ml. In contrast, HIT II is mediated by the formation of antibodies against platelet factor complex 4, not platelet factor 8 (choice E) complex. The Fc portion of these antibodies then binds to receptors present on platelets, leading to further release of factor 4 and further positive feedback. Additionally, HIT II is characterized by an incidence of 1 to 3% of patients exposed to unfractionated heparin and a nadir platelet count of 35,000 to 55,000/ml. Further, HIT II occurs after 5 to 10 days of exposure to heparin. In this case the presentation is classical for HIT II, with thrombocytopenia developing after 5 days of heparin exposure and the patient having a platelet count of 50,000/ml.
Bleed from an undetermined site with the overlap of heparin and warfarin (choice A) is unlikely given a stable hematocrit, stable orthostatics, guaiac-negative stool, and otherwise no evidence of bleed.
HIT II occurs by the formation of antibodies against platelet factor complex 4, not by decreased megakaryocyte production in the bone marrow (choice B).
As stated previously, HIT I, not HIT II, occurs from a direct effect of heparin on platelet activation (choice C).