Thrombophilia—Hypercoagulable States

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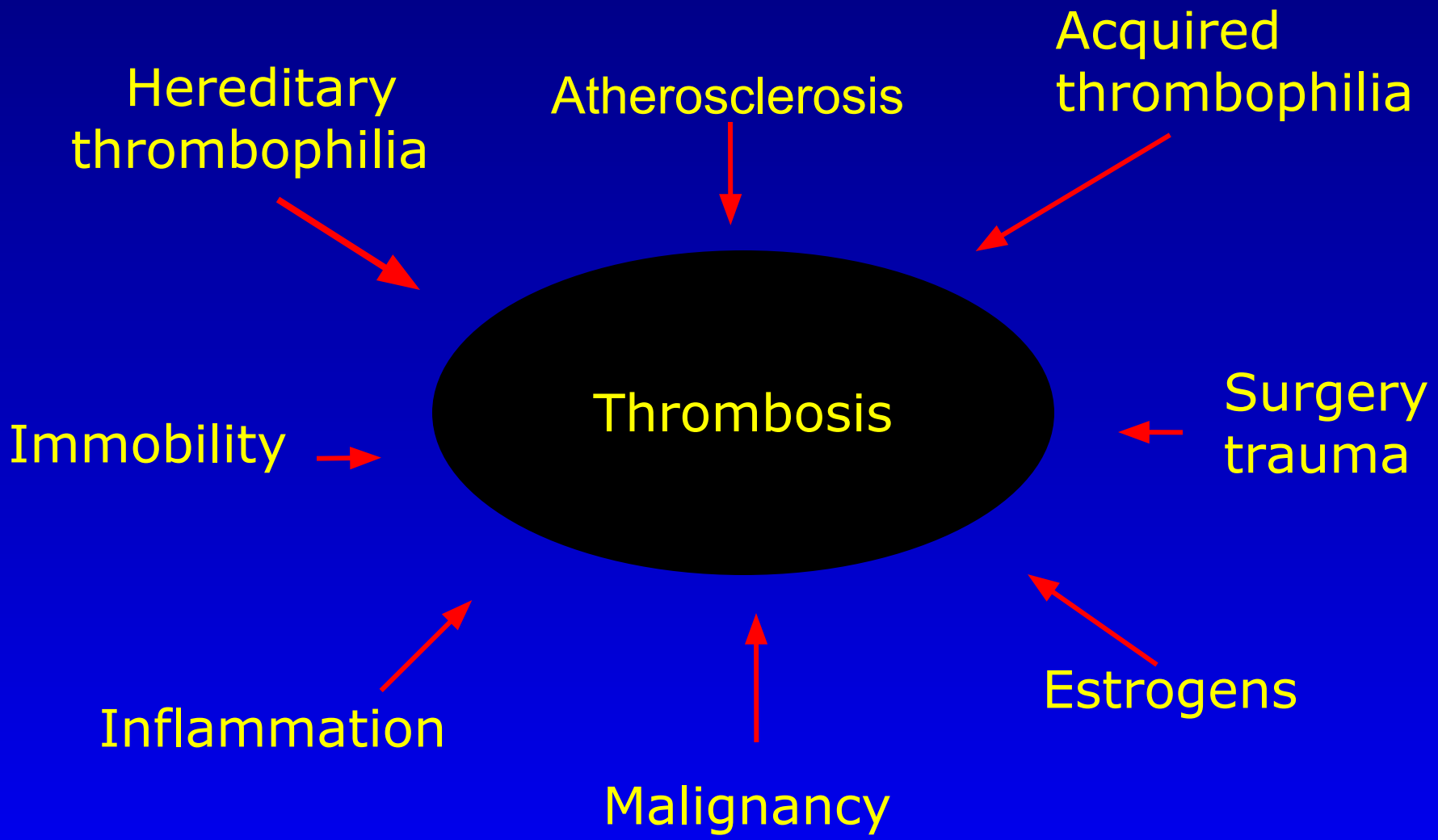
Risk Factors for Thrombosis



Risk Factors for Venous Thrombosis

- Acquired
- Inherited
- Mixed/unknown

Risk Factors—Acquired

- Advancing age
- Prior Thrombosis
- Immobilization
- Major surgery
- Malignancy
- Estrogens
- Antiphospholipid antibody syndrome
- Myeloproliferative Disorders
- Heparin-induced thrombocytopenia (HIT)
- Prolonged air travel

Risk Factors—Inherited

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden mutation (Factor V-Arg506Gln)
- Prothrombin gene mutation (G→A transition at position 20210)
- Dysfibrinogenemias (rare)

Risk Factors—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

Genetic Thrombophilic Defects Influence the Risk of a First Episode of Thrombosis

Risk vs. Incidence of First Episode of Venous Thrombosis

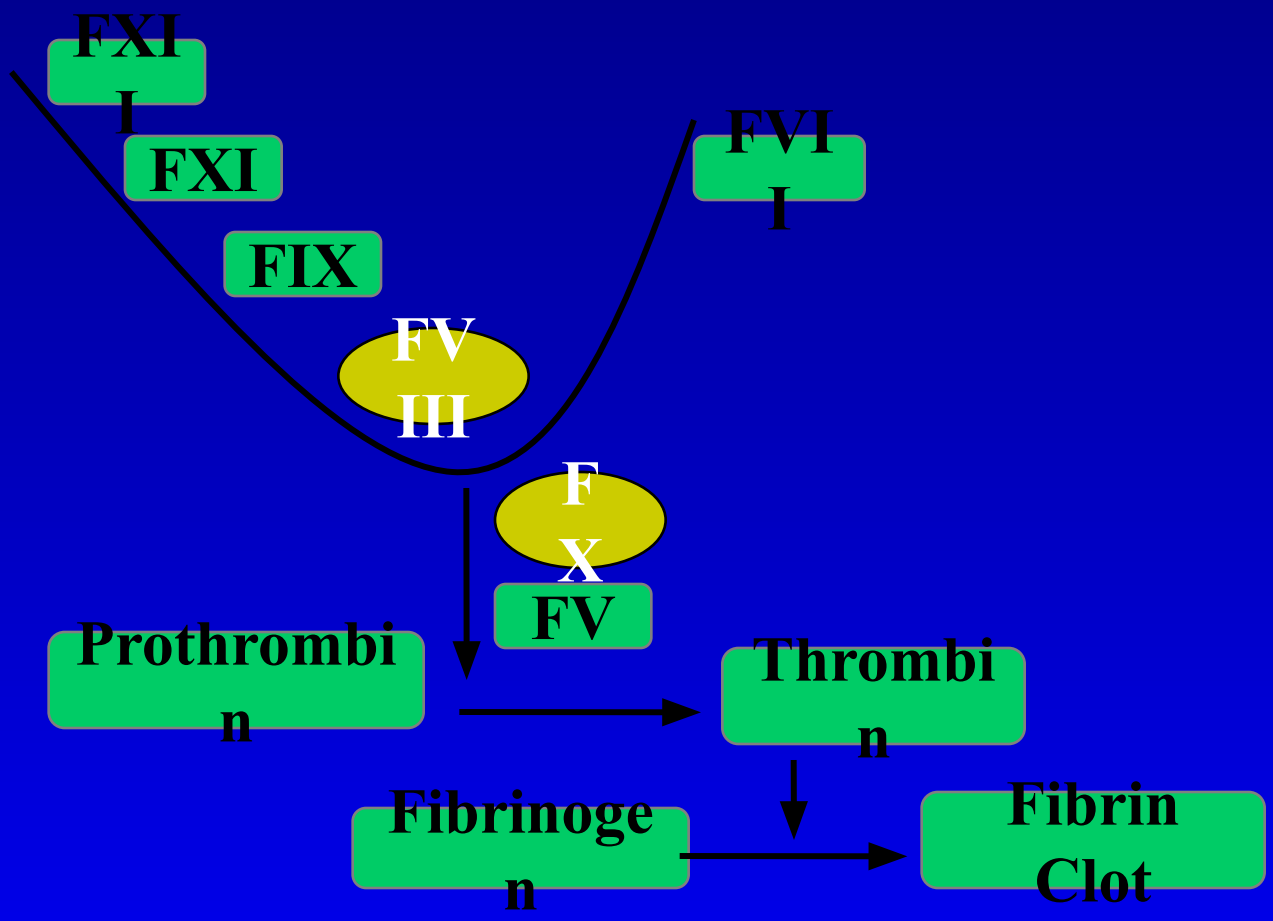
	Risk	Incidence/year (%)
Normal	1	.008
Oral Cont. Pills	4x	.03
Factor V Leiden (heterozygote)	7x	.06
OCP + Factor V L.	35x	.3
Factor V Leiden homozygotes	80x	.5-1

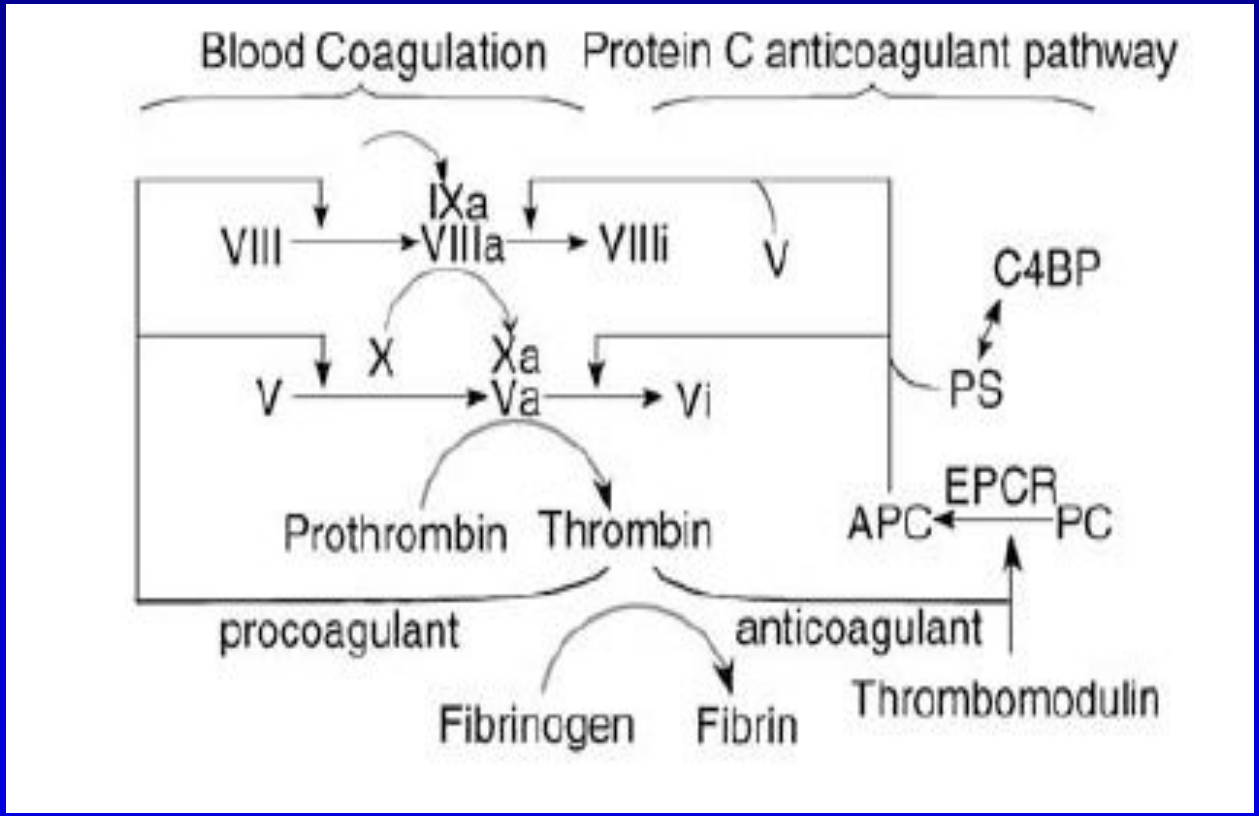
Risk of Recurrent Venous Thromboembolism (VTE) in Thrombophilia Compared to VTE Without a Thrombophilic Defect

Thrombophilic Defect	Rel. Risk
Antithrombin, protein C, or protein S deficiency	2.5
Factor V Leiden mutation	1.4
Prothrombin 20210A mutation	1.4
Elevated Factor VIII:c	6 – 11
Mild hyperhomocysteinemia	2.6 – 3.1
Antiphospholipid antibodies	2 – 9

Other Predictors for Recurrent VTE

- Idiopathic VTE
- Residual DVT
- Elevated D-dimer levels
- Age
- Sex


FXII
FXI
FIX
FVIII
FVIII
FX
FV
Prothrombin
Thrombin
Fibrinogen
Fibrin Clot



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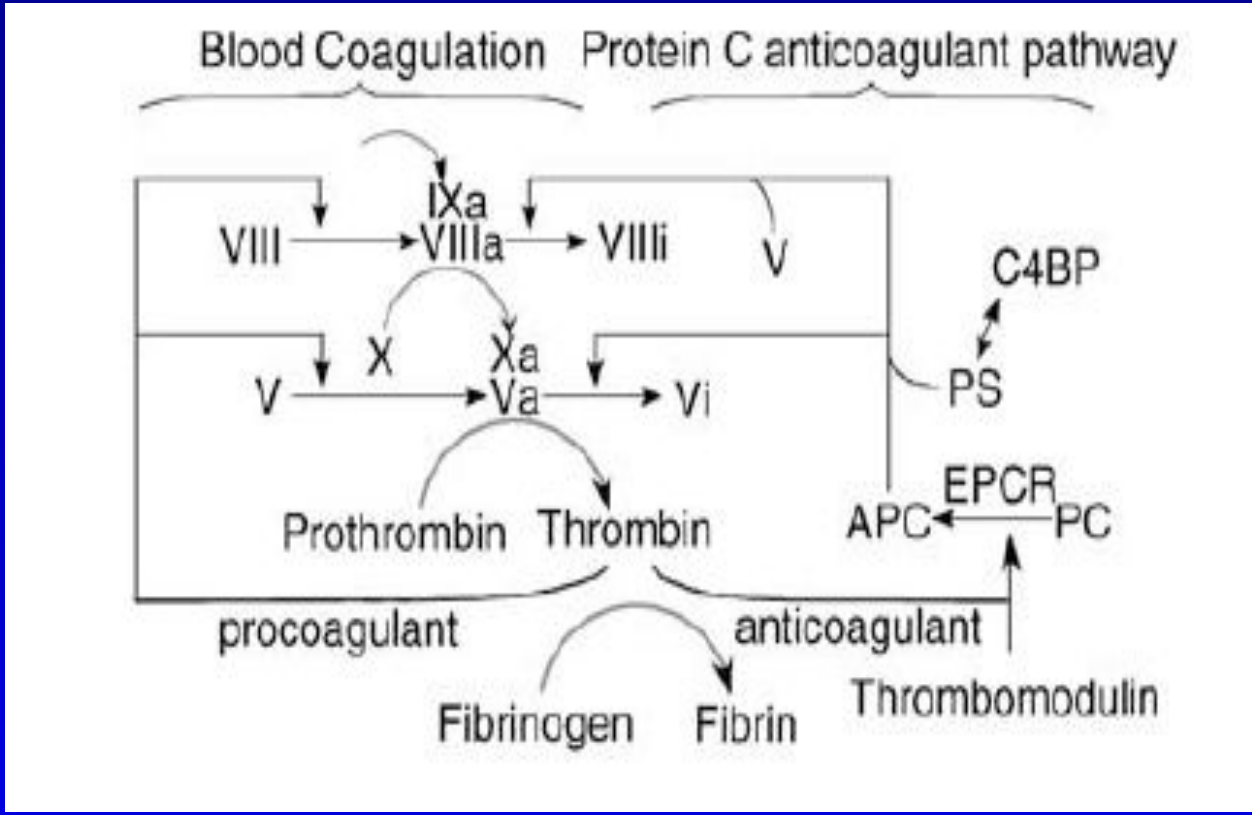
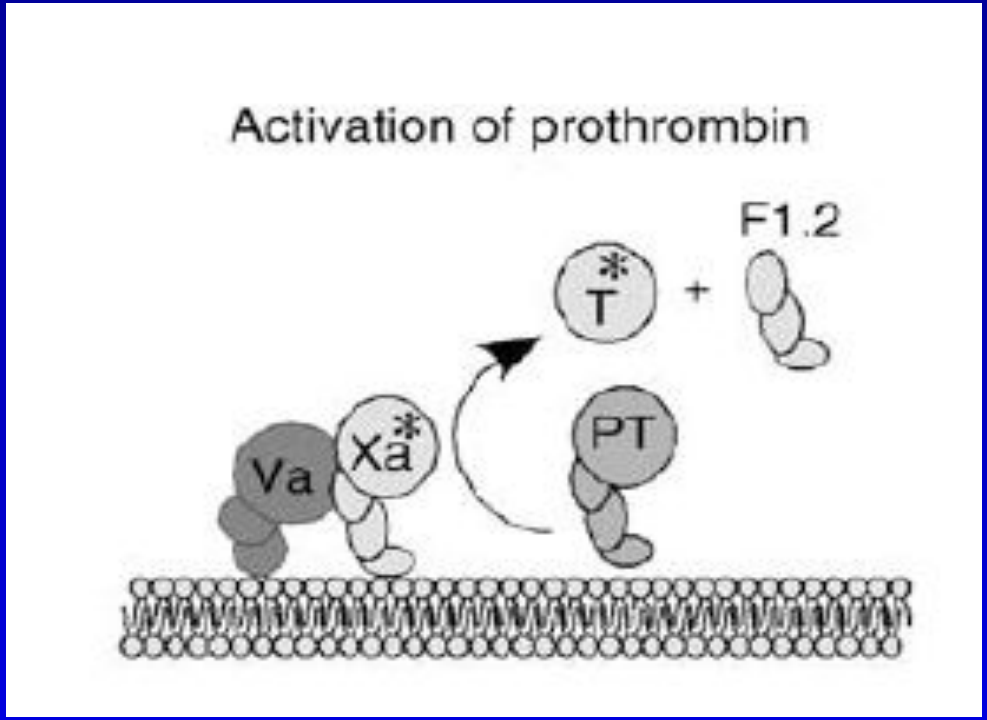
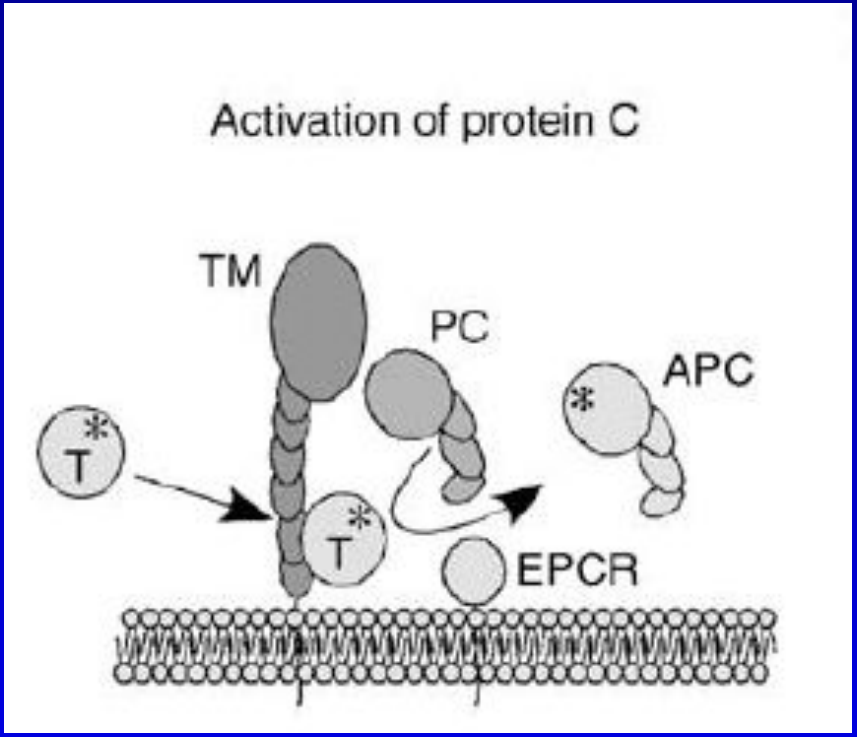
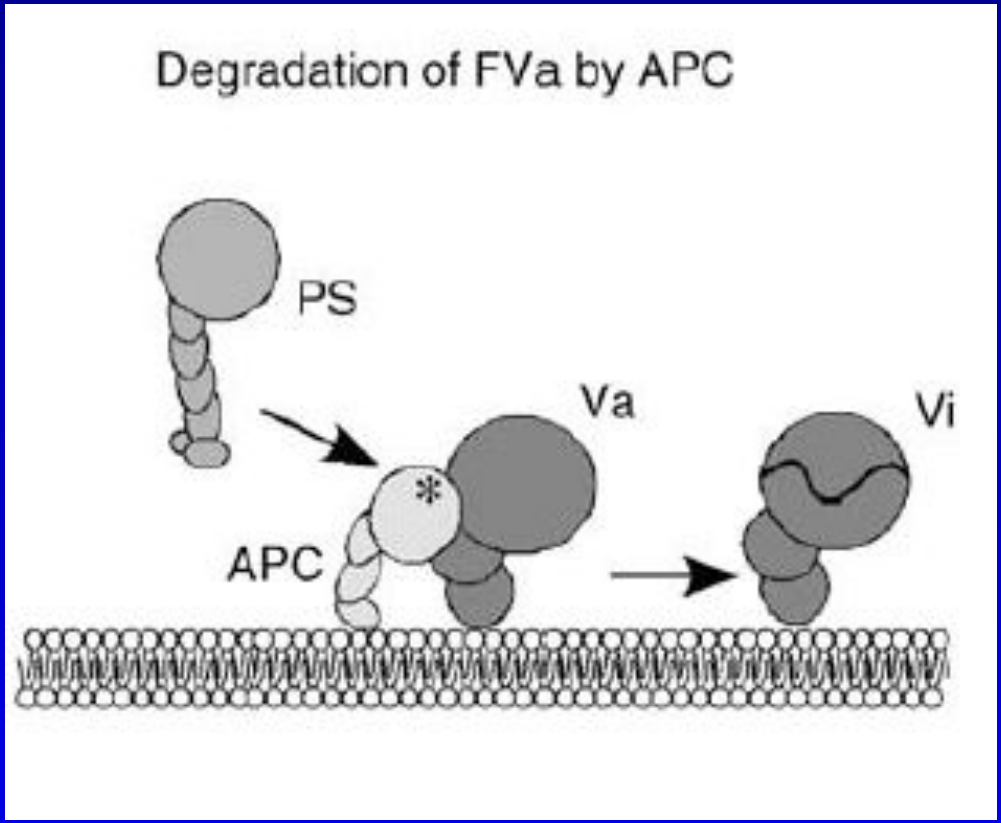
Antithrombin, Antithrombin Deficiency

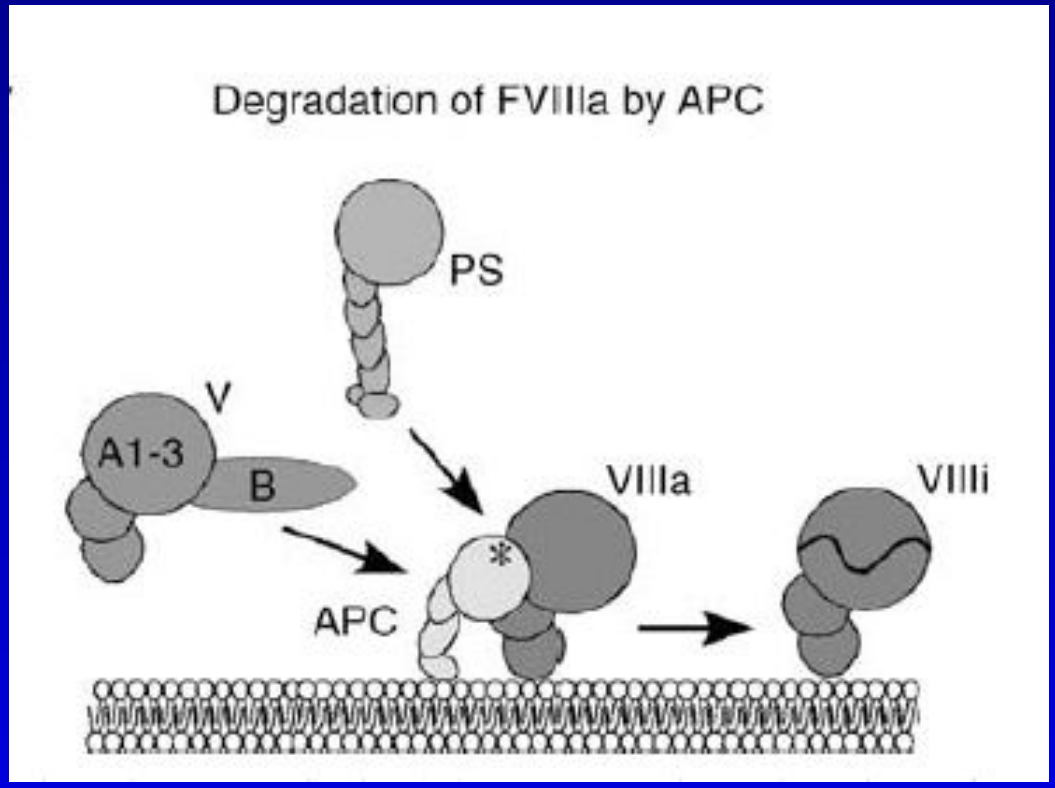
- Also known as Antithrombin III
- Inhibits coagulation by irreversibly binding the thrombogenic :thrombin (IIa), IXa, Xa, XIa and XIIa
- Antithrombin's binding reaction is amplified 1000-fold by heparin, which binds to antithrombin to cause a conformational change which more avidly binds thrombin and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


Blood Coagulation
Protein C anticoagulant pathway
IXa
VIII
VIIIa
VIIIi
V
C4BP
X
Xa
V
Va
Vi
PS
EPCR
Prothrombin
Thrombin
APC
PC
procoagulant
anticoagulant
Thrombomodulin
Fibrinogen
Fibrin


Activation of prothrombin
F1.2
T*
+
PT
Va
Xa*

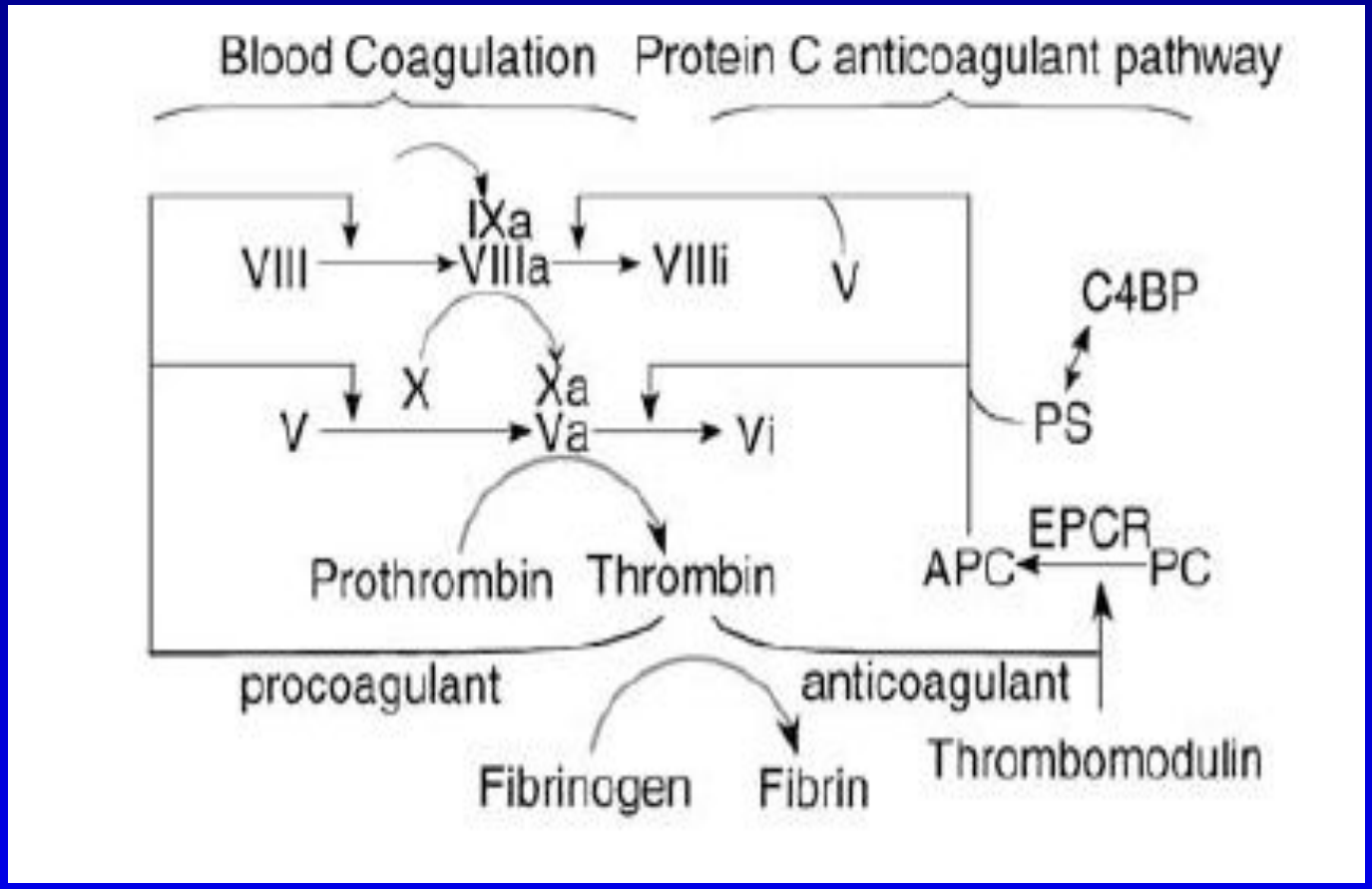

Activation of protein C
TM
PC
APC
T*
T*
EPCR


Degradation of FVa by APC
PS
Va
Vi
APC


Degradation of FVIIIa by APC
PS
V
A1-3
B
VIIIa
VIIIi
APC

Protein C and 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, liver or renal failure, DIC,or warfarin


Blood Coagulation
Protein C anticoagulant pathway
IXa
VIII
VIIIa
VIIIi
V
C4BP
X
Xa
V
Va
Vi
PS
EPCR
Prothrombin
Thrombin
APC
PC
procoagulant
anticoagulant
Thrombomodulin
Fibrinogen
Fibrin

Protein S, C4b Binding Protein, and Protein S Deficiency

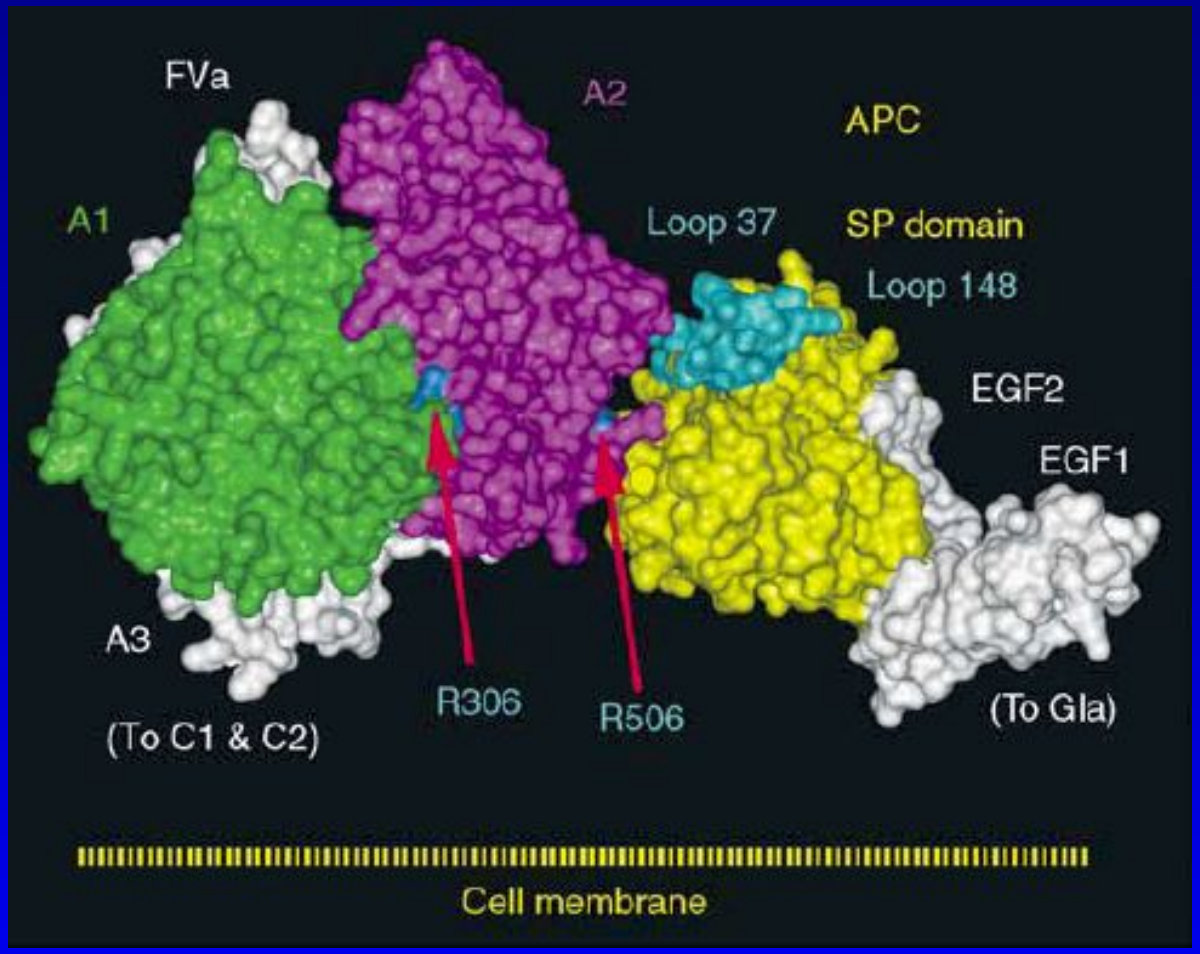
- Protein S is an essential cofactor in the protein C pathway
- Protein S exists in a free and bound state
- 60-70% of protein S circulates bound to C4b binding proten
- The remaining protein S, called free PS, is the functionally active form of protein S
- Inherited PS deficiency is an autosomal dominant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

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

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



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Prothrombin G20210A Mutation

- 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.

Antiphospholipid Syndrome

Antiphospholipid Syndrome—Diagnosis

- Clinical Criteria

  -Arterial or venous thrombosis

  -Pregnancy morbidity

- Laboratory Criteria

  -IgG or IgM anticardiolipin antibody-medium or high titer

  -Lupus Anticoagulant

Antiphospholipid Syndrome—Clinical

- Thrombosis—arterial or venous
- Pregnancy loss
- Thrombocytopenia
- CNS syndromes—stroke, chorea
- Cardiac valve disease
- Livedo Reticularis

Antiphospholipid Syndrome—
The Lupus Anticoagulant (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

Antiphospholipid Syndrome—Anticardiolipin Antibodies

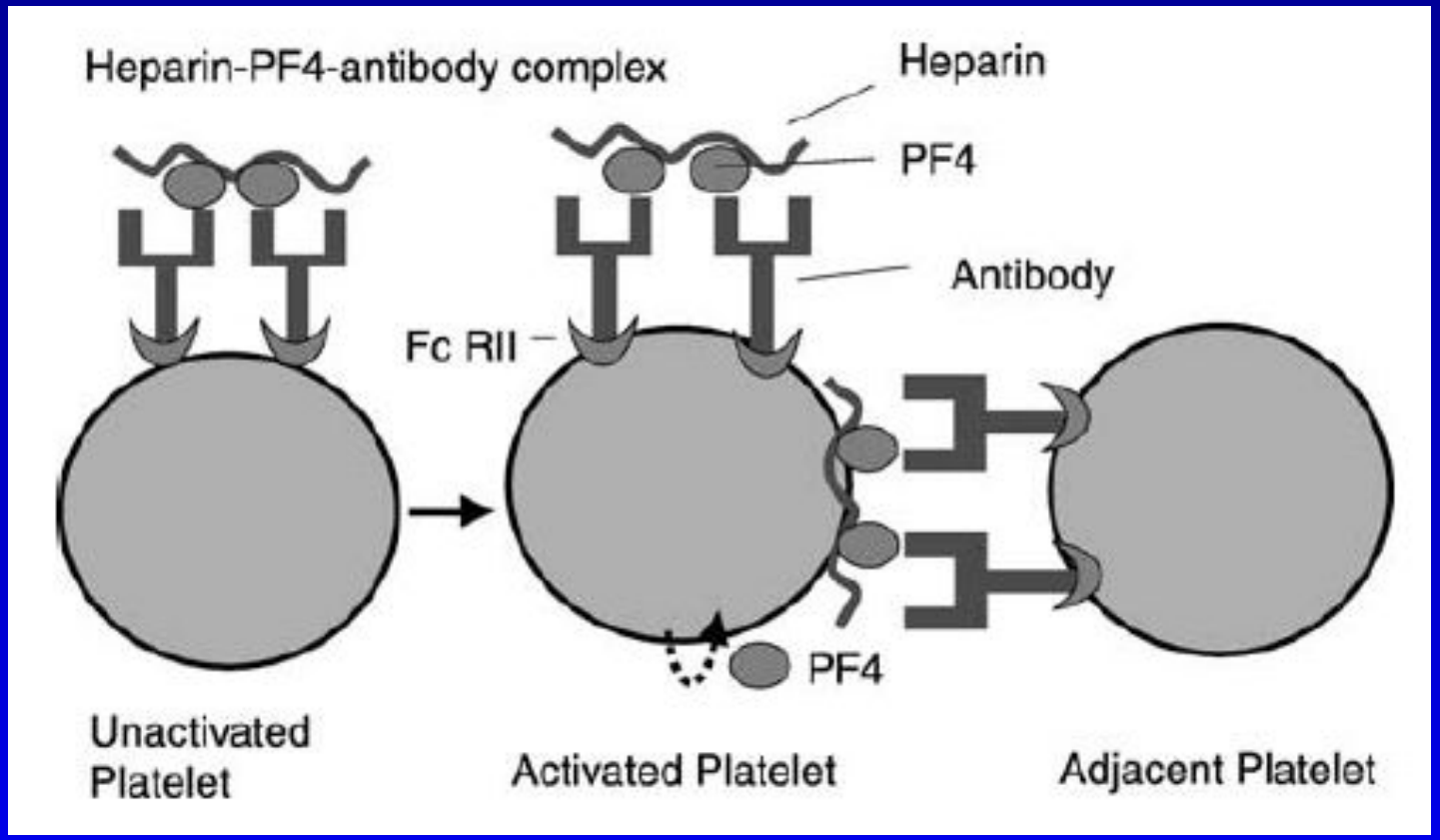
- ACAs are antibodies directed at a protein-phosholipid complex
- Detected in an ELISA assay using plates coated with cardiolipin and B2-glycoprotein

Antiphospholipid Syndrome—Treatment

- Patients with thrombosis- anticoagulation, INR 2- 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 or low-dose heparin during their pregnancies

Heparin-Induced Thrombocytopenia (HIT)

- HIT is mediated by an antibody 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



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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.

Clinical manifestations

- DVT
- PE
- Sagittal vein thrombosis
- Splanchnic vein thrombosis

Management of Patients With Thrombophilia

Risk Classification	Management
High Risk	
2 or more spontaneous events	Indefinite 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	