Thrombophilia

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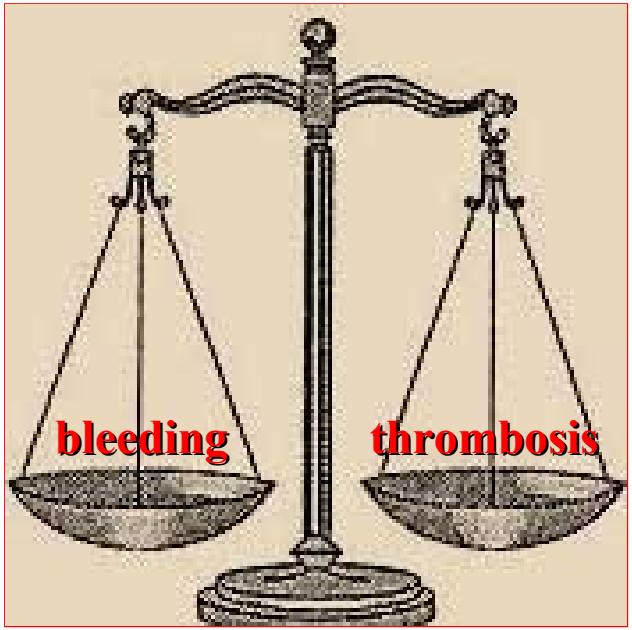
Definition:

Thrombophilia is a condition where the blood has an increased tendency to form clots.

Normal hemostasis: helps to stop bleeding if there is an injury.



Inhibitors: natural chemicals in the blood which act against the clotting system, to stop the blood clotting too much.

Thrombophilia occurs if the normal balance of the clotting system is upset: *- too much of a clotting factor*, or

- too little of a factor that opposites clotting.

Virchow triad

Rudolf Virchow categorized *abnormalities in the consistency of the blood* as a factor in the development of thrombosis.

(1821-1902)

HYPERCOAGULABLE STATE

- Malignancy
- Pregnancy and peri-partum period
- Oestrogen therapy
- Trauma or surgery of lower extremity, hip, abdomen or pelvis
- Inflammatory bowel disease
- Nephrotic syndrome
- Sepsis
- Thrombophilia

VASCULAR WALL INJURY

- Trauma or surgery
- Venepuncture
- Chemical irritation
- Heart valve disease or replacement
- Atherosclerosis
- Indwelling catheters

CIRCULATORY STASIS

- Atrial fibrillation
- Left ventricular dysfunction
- Immobility or paralysis
- Venous insufficiency or varicose veins
- Venous obstruction from tumour, obesity or pregnancy

Venous thromboembolism (VTE) /deep vein thrombosis (DVT) and pulmonary embolism (PE) together/ is a leading cause of death and disability.

There are more death each year due to VTE than death due to breast cancer, AIDS, and traffic accidents, combined **(BMJ, 334, 1017-18, 2007).**

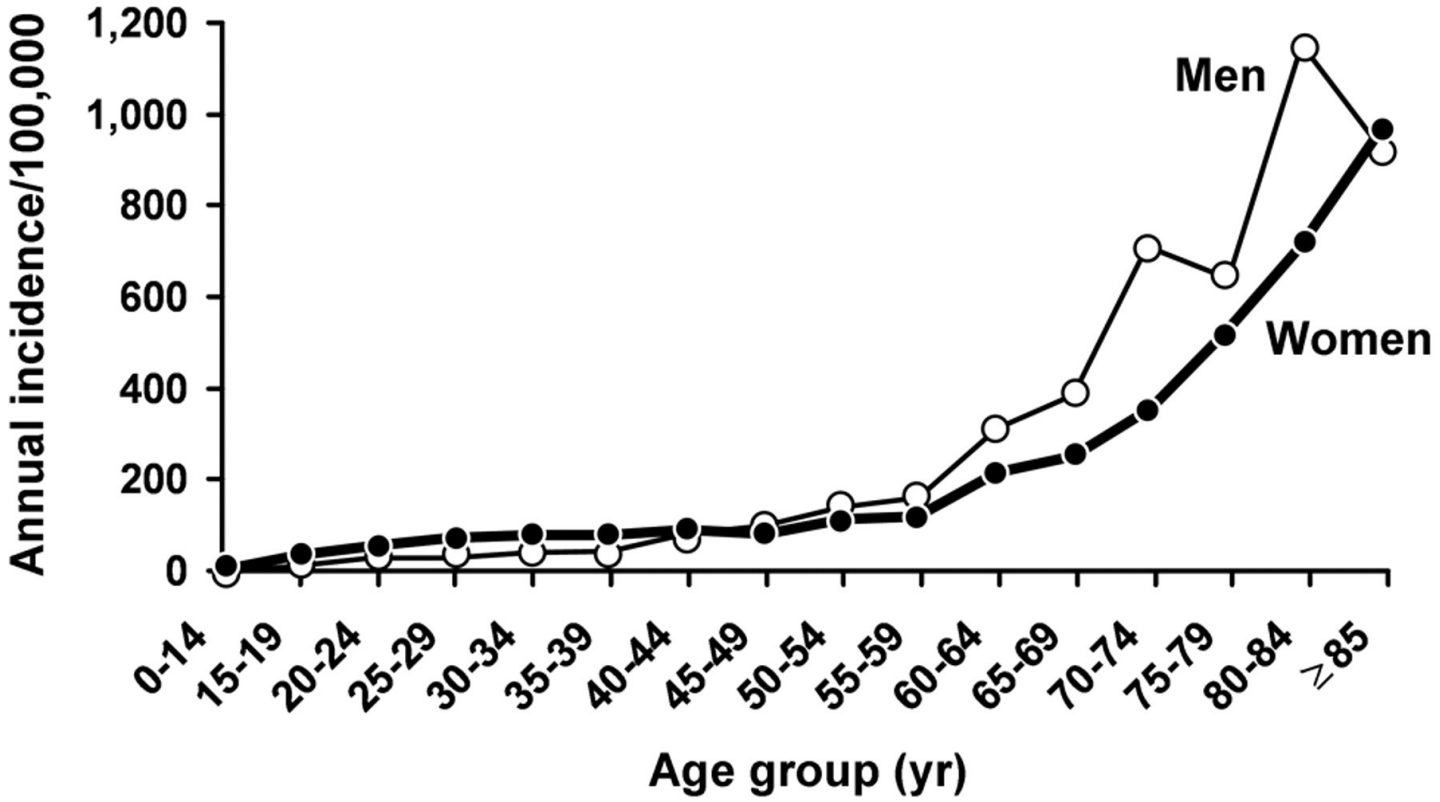
Up to 15% of patients hospitalized for an acute medical illness develop VTE.

Age is an important risk factor for VTE:

- in children under 15: <5/100000/year

- adults over 80: ~ 500/100000/year

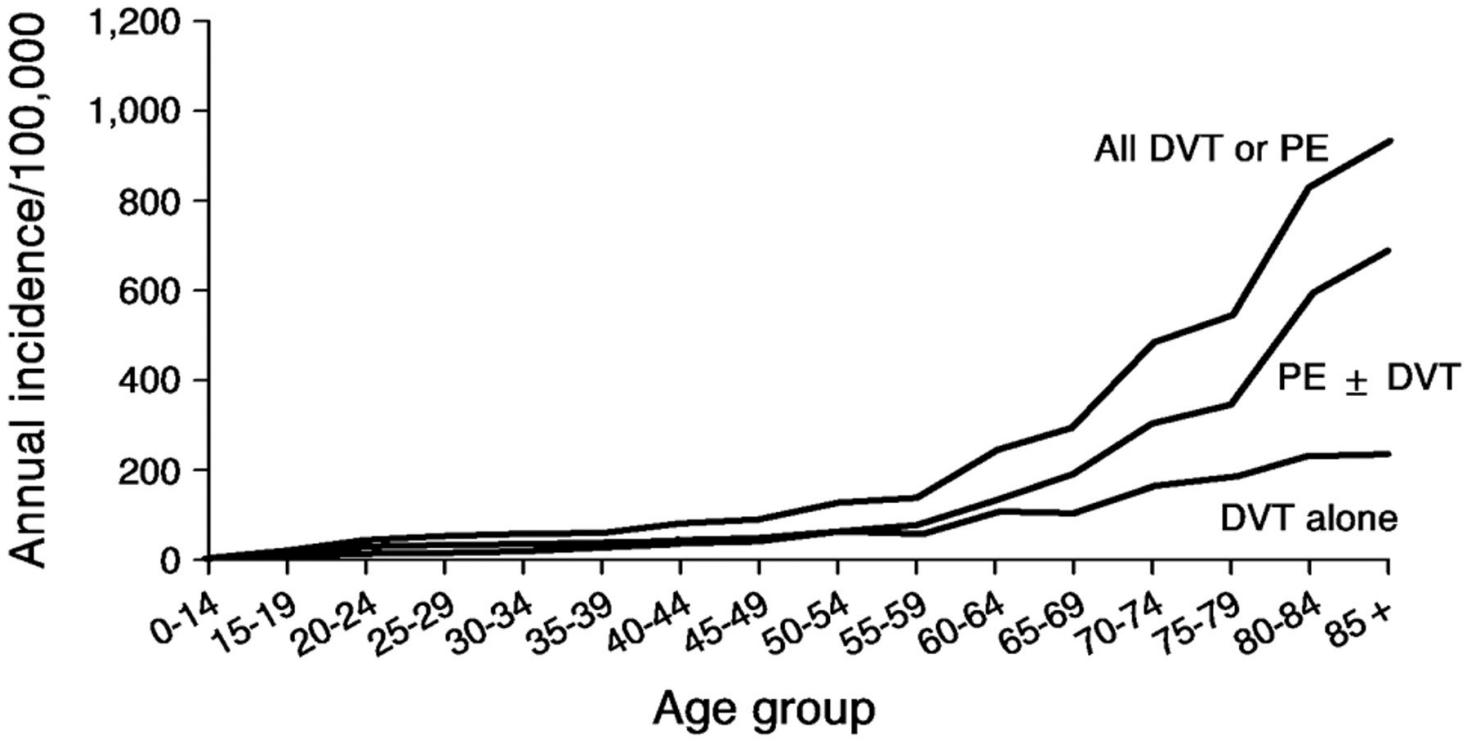
Annual incidence of venous thromboembolism by age and sex



Heit, J. A. Hematology 2007;2007:127-135

Women after menopusal age: the incidence increases exponentially.

Annual incidence of all venous thromboembolism, deep vein thrombosis (DVT) alone, and pulmonary embolism with or without DVT (PE +/- DVT)



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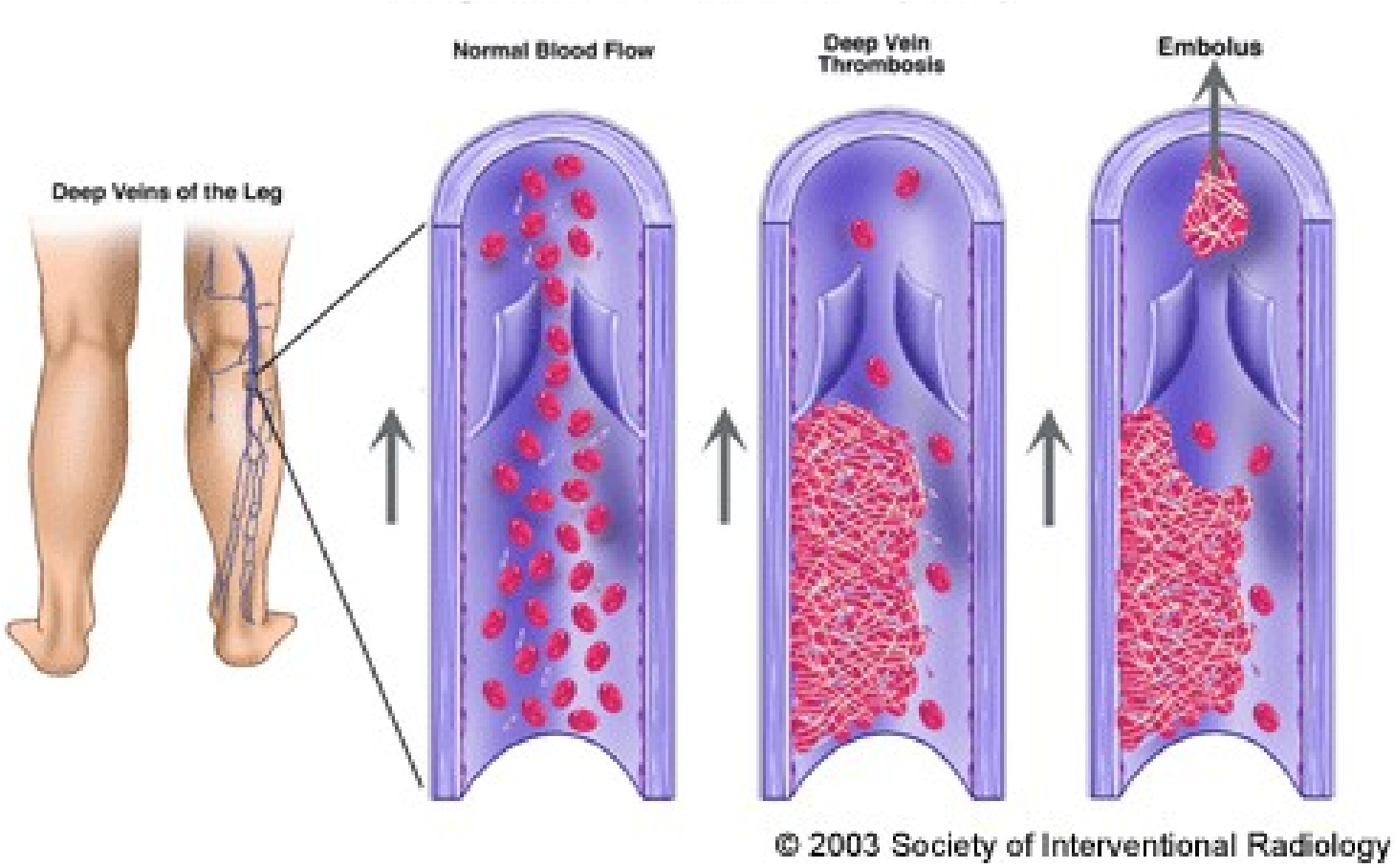
Deep vein thrombosis (DVT):

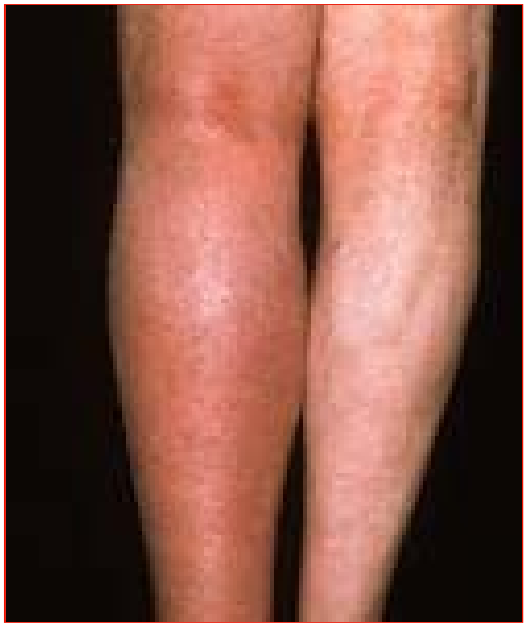
blood clot (thrombus) develops in one or more of deep veins, usually in the legs or arms.

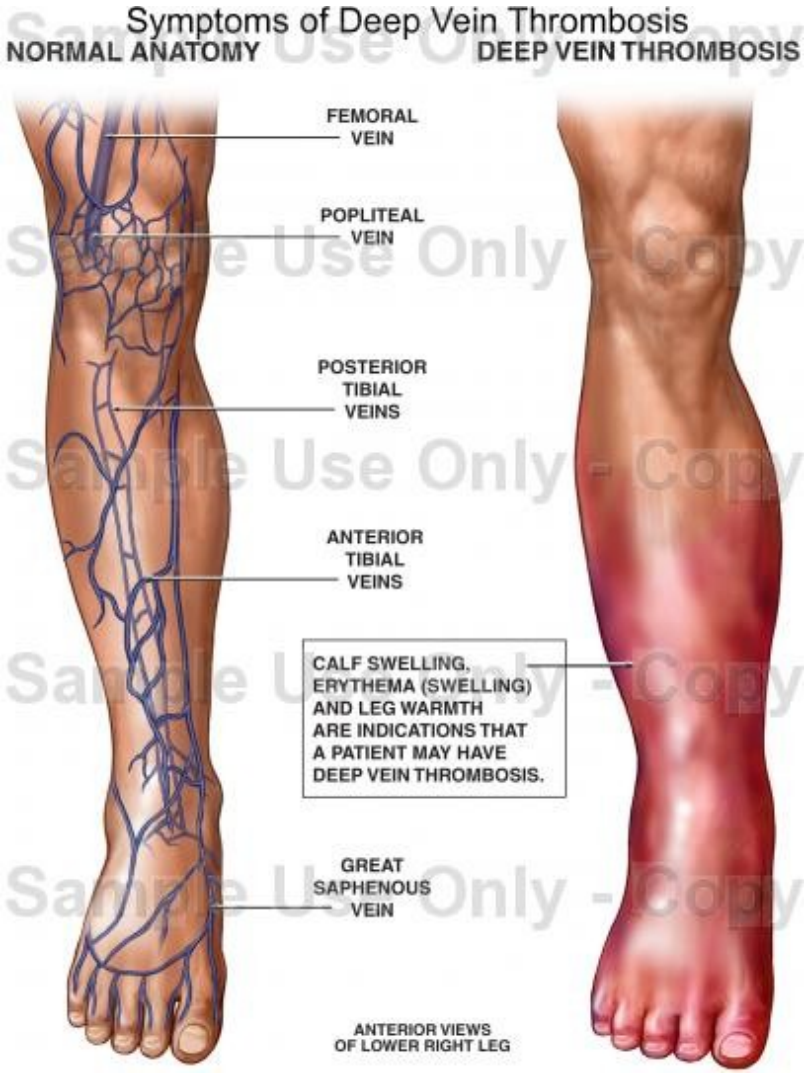


Symptoms of DVT:

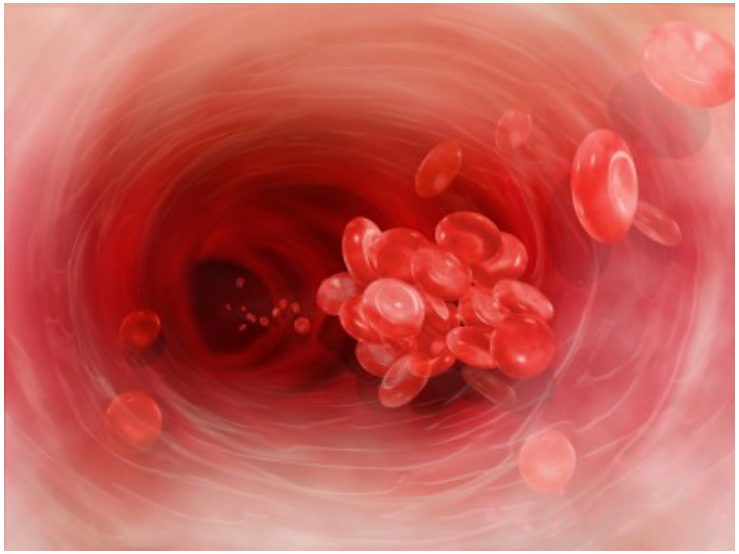
swelling of the affected leg or arm,
the area feel warm and look redder,
it may ache or feel tender,

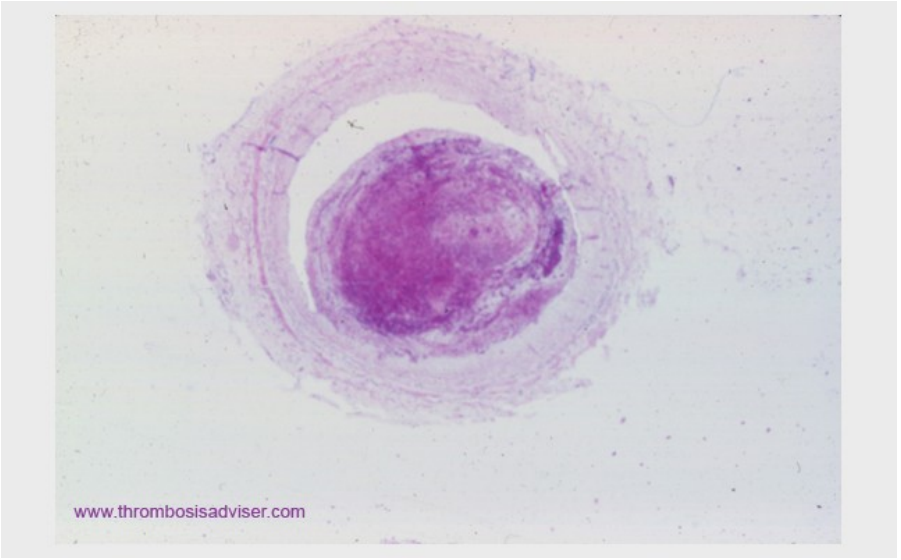
although occasionally there are no symptoms at all, particularly with smaller clots!

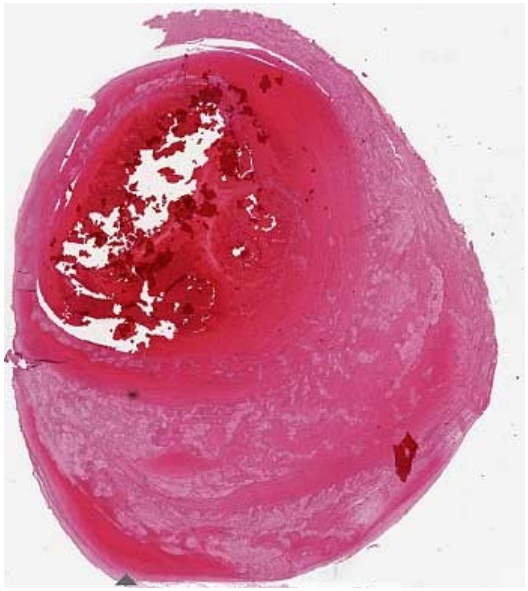




Deep vein thrombosis







Diagnosis of DVT:

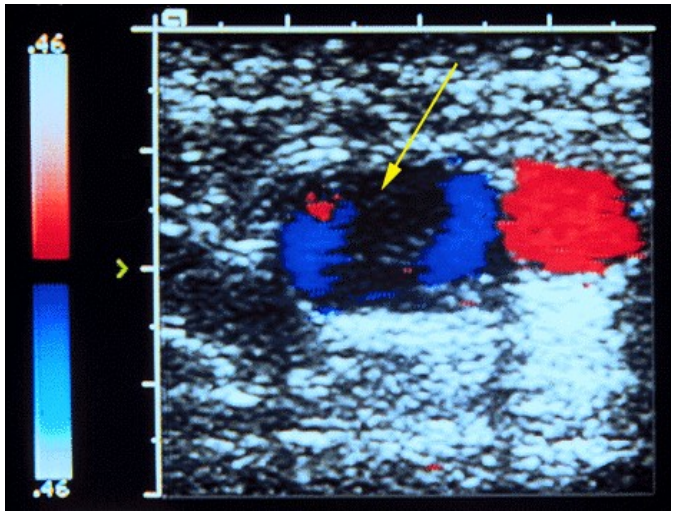
- Clinical signs and symptoms
  (non-occlusive thrombosis may be asymptomatic)

- Positive Homan's sign

- Blood test: D-dimer positivity
  - cross-linked fibrin degradation product is an indication that thrombosis is occurring, and that the blood clot is being dissolved by plasmin.

- Doppler ultrasound

Homan's sign involves the forced plantar flexion of the ankle and may be positive for pain.



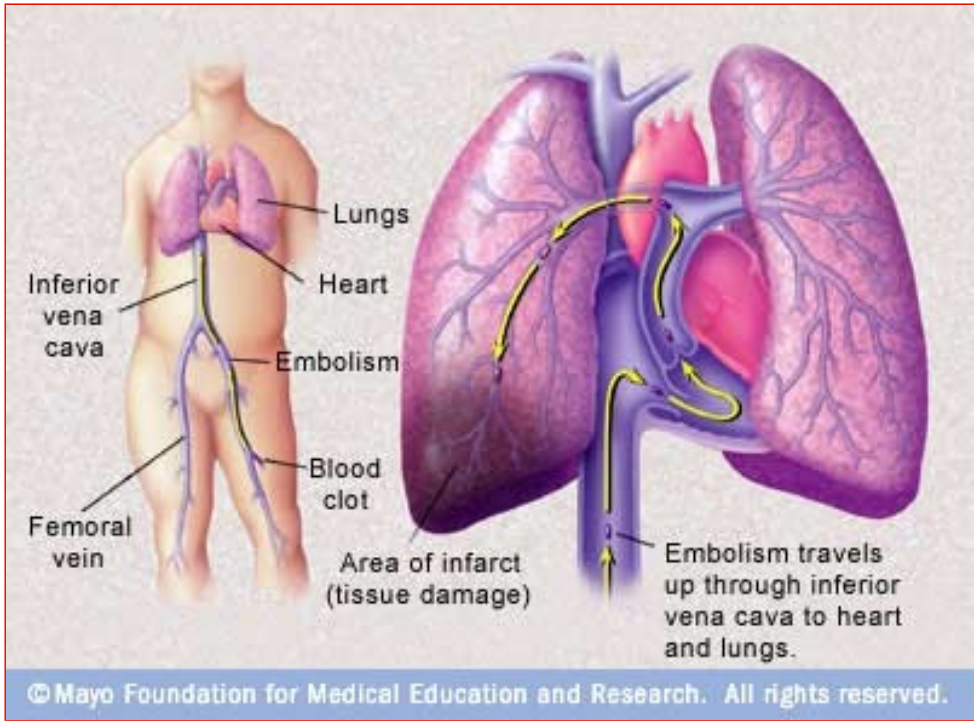
Pulmonary embolism:

Blood clot or a portion of the clot can travel to the lung and block one of the branches of the pulmonary artery.

Most clinically important PEs originate from proximal DVT of the leg (popliteal, femoral, or iliac veins)

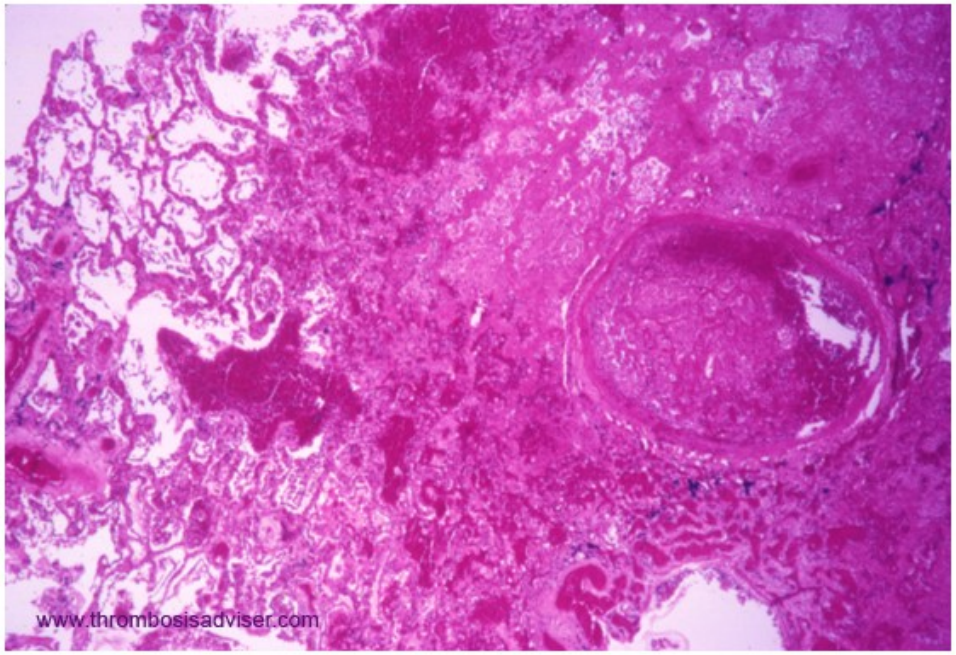
(PE in 67 % of proximal DVT, 46% of distal DVT, 77 % of pelvic vein thrombosis).

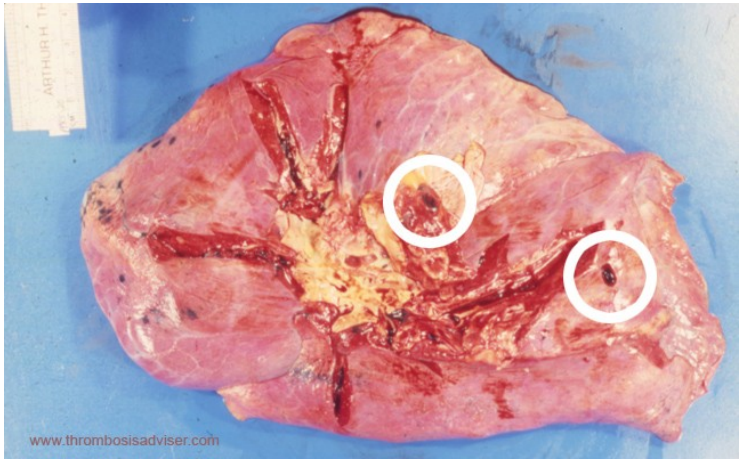
Upper extremity DVT is less common but also may lead to PE.



Pulmonary embolism

For about one-quarter of patients with acute PE, the initial clinical presentation is sudden death!





Section of pulmonary parenchyma with middle right (round) blood vessel containing embolus. The surrounding lung parenchyma has undergone haemorrhagic infarction.

Symptoms of PE:

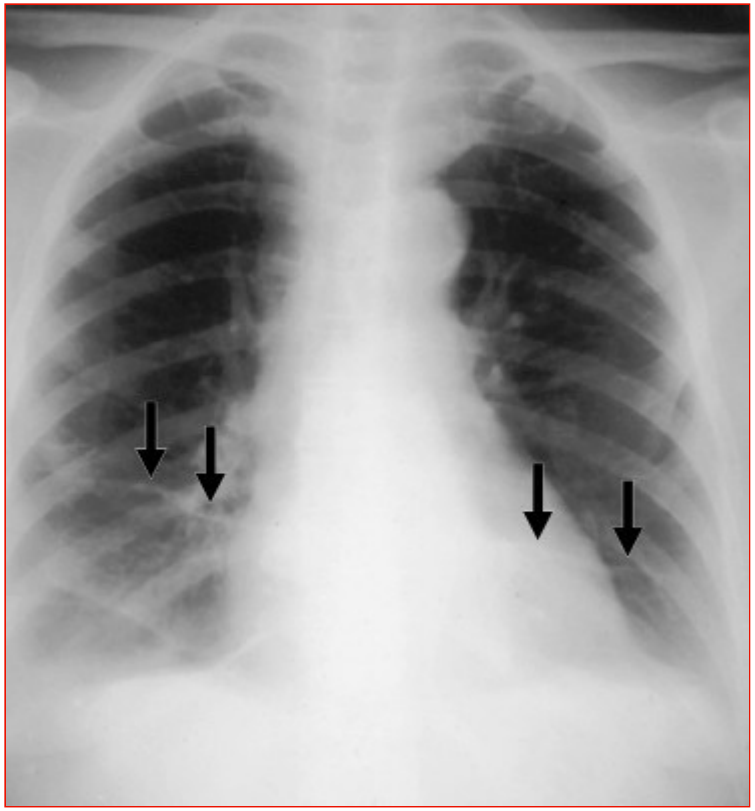
chest pain
breathlessness
coughing up blood
fainting, sweating, rapid pulse

Incidence: 50-100/100000/year.

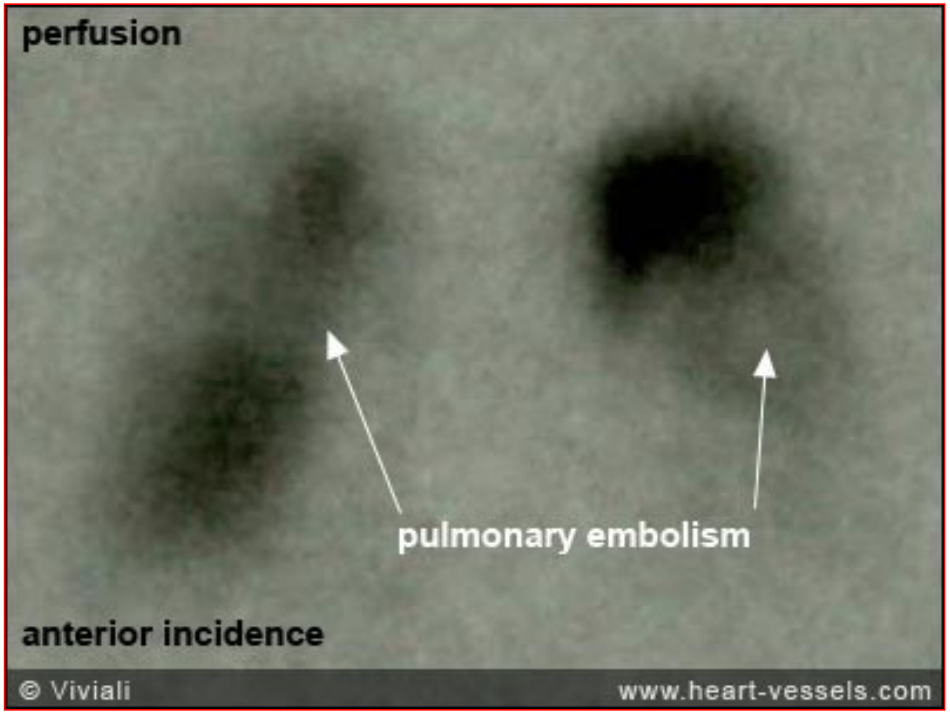
At autospy of the patients dying in hospital: 12-25 % PE.
1/100 patients with DVT die due to PE.

Mortality: without treatment: 30%
with appropriate therapy: 2-8 %

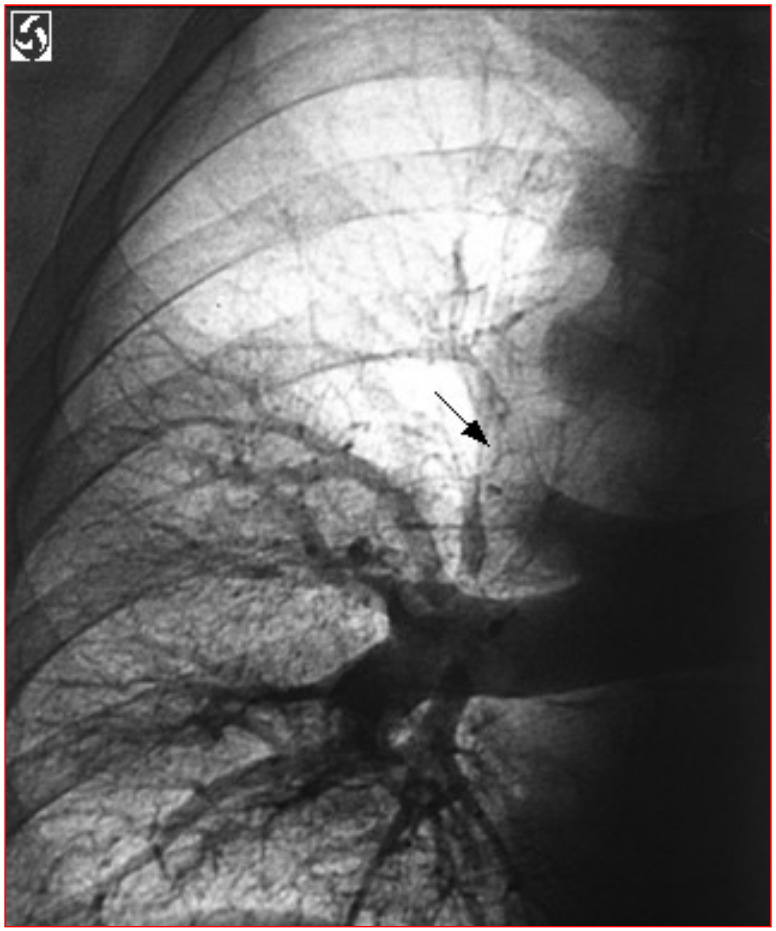
Diagnosis: clinical signs and symptoms, D-dimer test
chest radiograph
ventilationperfusion scintigraphy
pulmonary angiography (invasive procedure)
contrast-enhanced computed tomography (CT)



Chest radiograph:
bilateral pleural effusion and long linear bands of atelectasis (Fleischner lines) (arrows).

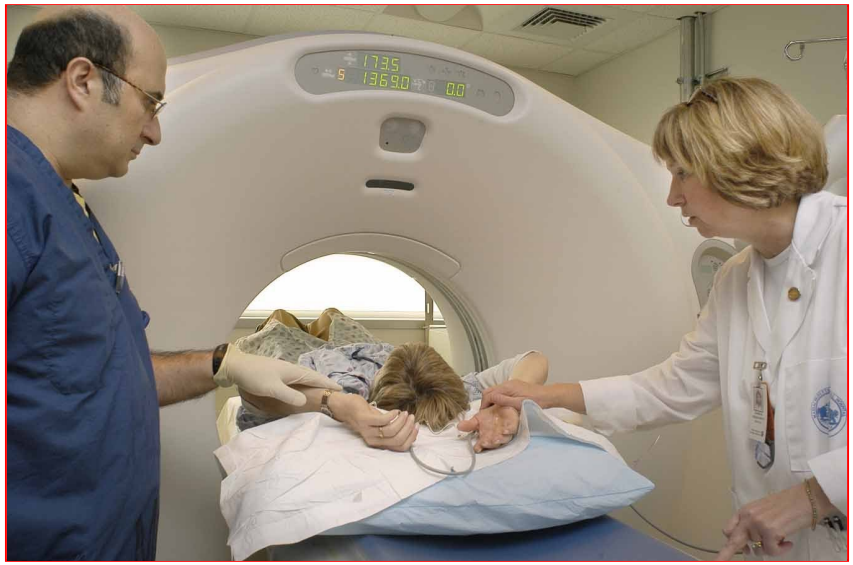


Pulmonary scintigraphy:
a perfusion failure of the right and left superior lobe exists, corresponding to a bilateral pulmonary embolism.

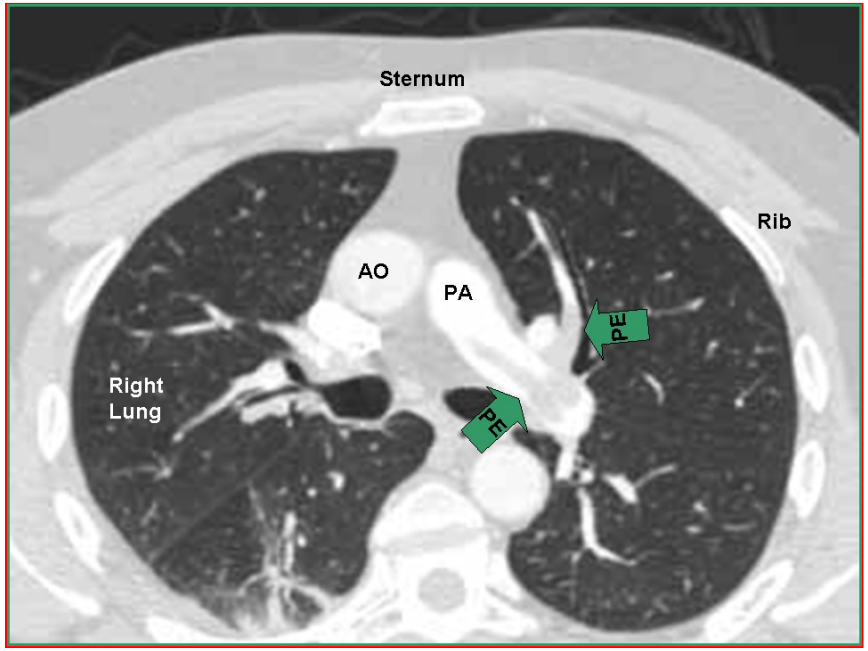


Pulmonary angiography: reveals an abrupt termination and occlusion (arrow) of the ascending branch of the right pulmonary artery, the truncus anterior.

(Angiography is invasive and has achieved only limited patient and physician acceptance.)



Computed tomographic pulmonary angiography (CTPA).



PE in the left branch of the pulmonary artery (PA) is shown.

The long-term complications of VTE:

I. Recurrence of DVT:

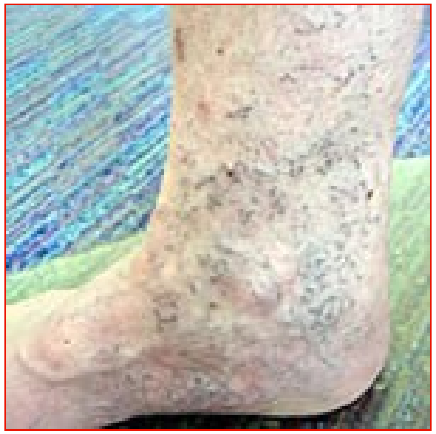
Risk: varies depending on the initial treatment.

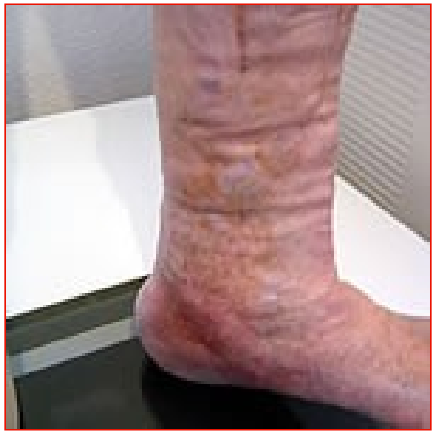
- no treatment: 50 % within 3 months
- inadequate treatment of proximal DVT: 40 %
- adequate treatment: 4 %

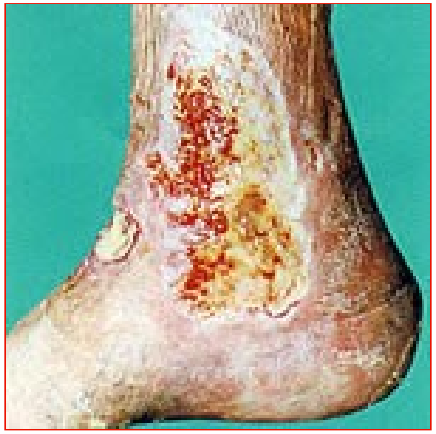
II. Post-thrombotic syndrome: 20-50 %

III. Chronic pulmonary hypertension: 3-4 % after PE

(Chronically elevated blood pressure in the pulmonary circulation. 5-year survival rate is 30 % when pulmonary artery pressure reaches 40 mmHg)





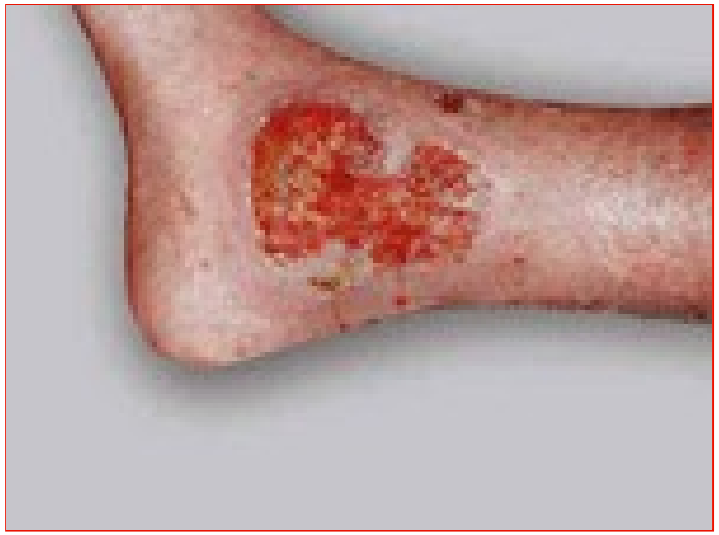


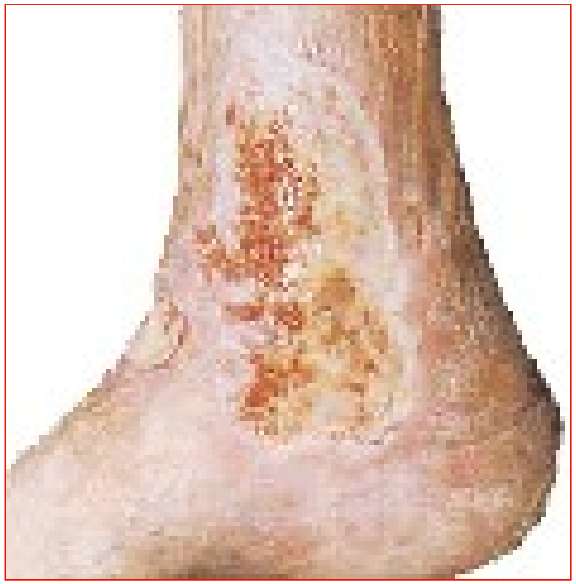
Post-thrombotic syndrome

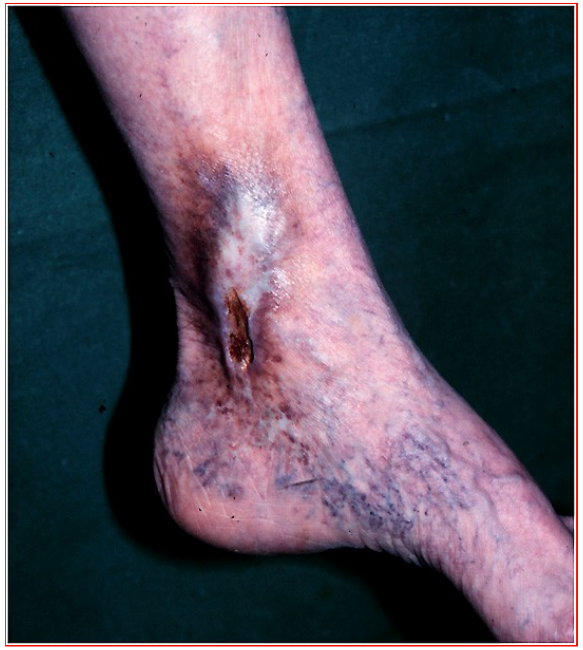
A significant proportion of these patients develop permanent irreversible damage in the affected leg veins and their valves, resulting in abnormal pooling of blood in the leg.

Signs and symptoms:

- **chronic pain**
- **swelling**
- **discoloration of leg**
- **skin ulcer**

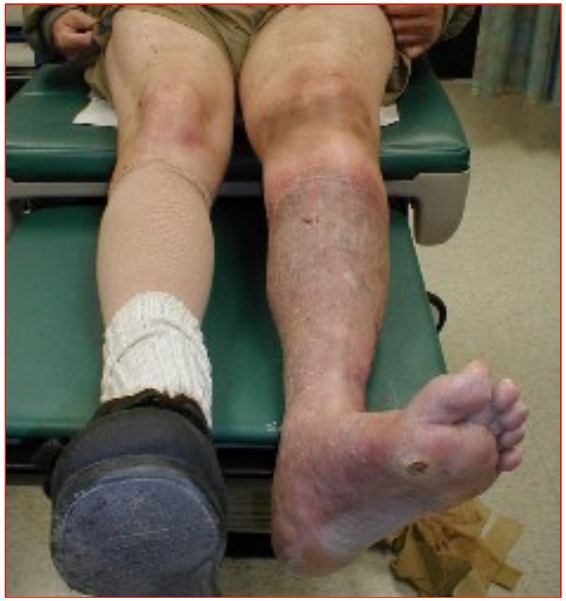






Leg ulcer

(over 40 year olds: 2 %)



Causes of thrombophilia:

- **A. Acquired:**
  - Transient or acquired conditions that increase the tendency to clot.

- **B. Inherited:**
  - Hereditary conditions that increase the tendency to clot.

A. Acquired disorders:

- **Malignancy: 10-20-fold increased risk**
  - **Pancreatic, gastric, colon, brain, kidney, ovarian, prostate, hematologic, lung cancers.**
  - **Metastatic disease confers a greater risk than primary tumours.**
- **Major surgery: 6x**
- **Immobilization: 11x**
- **Antiphospholipid antibody syndromes (anticardiolipin antibody, lupus anticoagulant): 10x**
- **Oral contraceptive use: 4x**
- **Pregnancy: 5x**

- **Thalidomide use (especially with dexamethasone): 10-20x**
- **Heparin induced thrombocytopenia: 50x**
- **Trauma**
- **Myeloproliferative disorders**
- **Inflammatory bowel disease**
- **Nephrotic syndrome**
- **Paroxysmal nocturnal hemoglobinuria**
- **Smoking: 2-3 fold increased risk**
- **Obesity: 2-3x**
- **Age: VTE more common with advanced age**
- **Sex: more common in women**

B. Inherited disorders: genetic defects

- **Antithrombinopathy**
  (Egeberg, 1965)
- **Protein C deficiency**
  (Griffin, 1981)
- **Protein S deficiency**
  (Comp, 1984)
- **Factor V Leiden**
  (Dahlback, 1993)
- **Prothrombin gene mutation (G20210A)**
  (Poort, 1996)

- **Others:**
  plasminogen deficiency, dysfibrinogenemia, FXII↓, FVIII↑, FIX ↑, FXI ↑, t-PA↓, PAI↑, TFPI↓, heparin cofactor II ↓, thrombomodulin deficiency, lipoprotein(a)↑, HRG↑, endothel cell damage, platelet receptor dysfunction …???

(t-PA: tissue plasminogen activator
PAI: plasminogen activator inhibitor
TFPI: tissue factor pathway inhibitor
HRG: histidin rich glycoprotein)

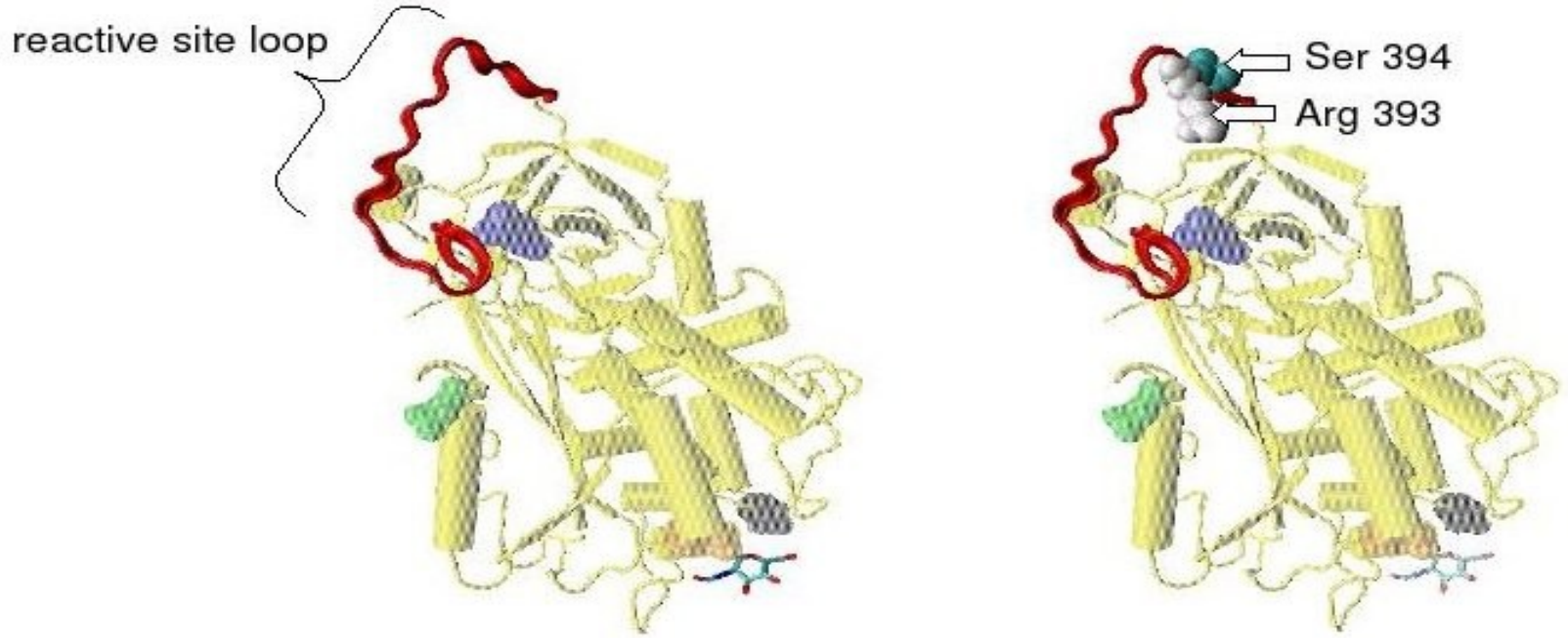
Antithrombin (AT)

Antithrombin (AT) a potent inhibitor of the coagulation cascade.

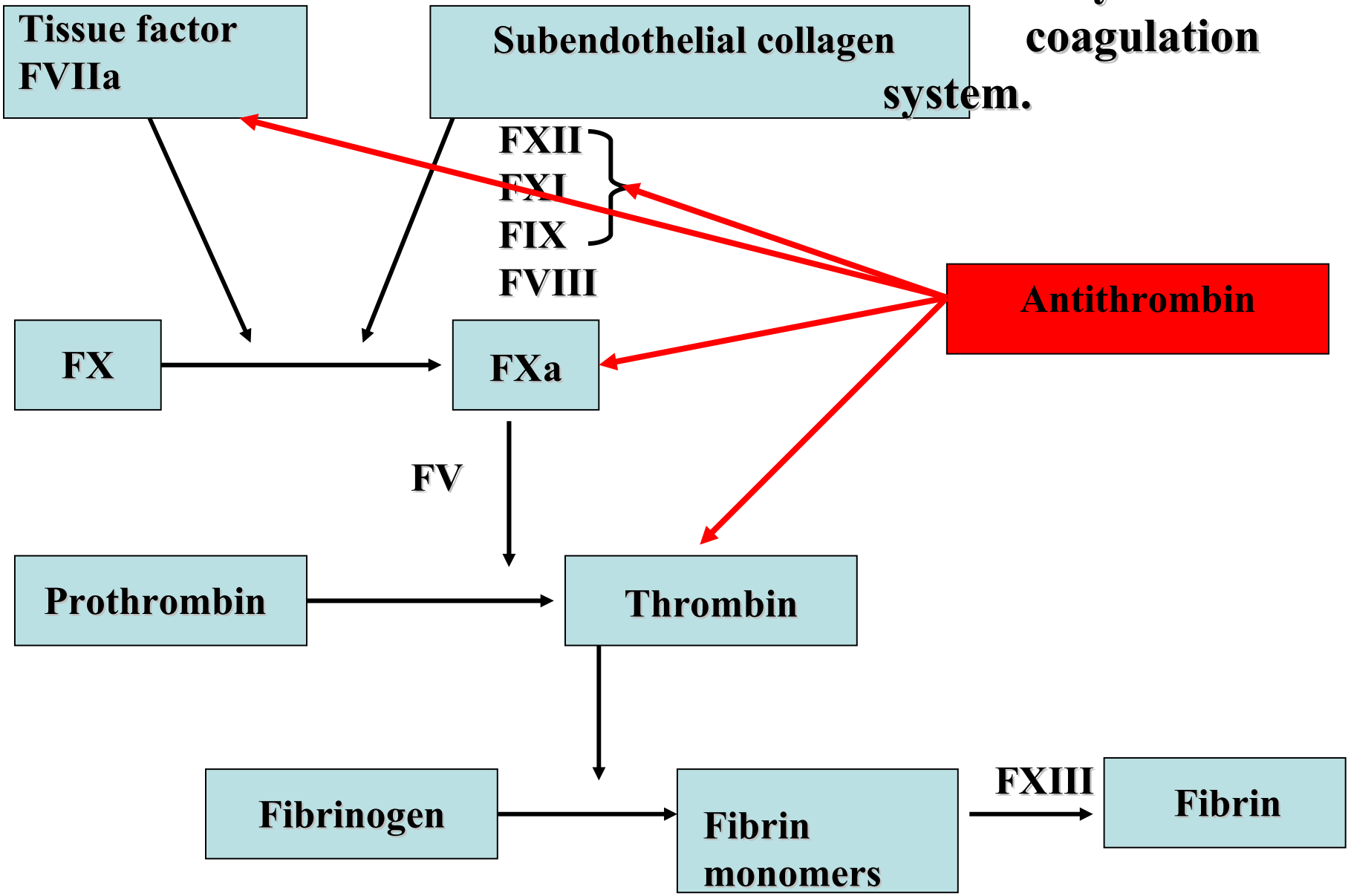
It is a glycoprotein produced by the liver and consists of 432 amino acids.

Mol. weight: 58 kDa.

AT activity is markedly potentiated by heparin.



Antithrombin anticoagulant system: It inactivates several enzyms of the coagulation system.



Antithrombin deficiency I.

The first family suffering from AT deficiency being described in 1965 by Olav Egeberg, a Norwegian hematologist.

(10 family members with AT deficiency: 6 thrombosis,
7 healthy members: 0 thrombosis.)

Olav Egeberg (1906-1977)

This was the first observation linking a hereditary defect in the control of blood coagulation to the occurrence of thrombotic disease.

Antithrombin deficiency II.

Congenital AT deficiency:

- autosomal dominant inheritance
  (rare autosomal recessive condition is rarely compatible with life)
- increased risk of venous and arterial thrombosis
- clinical manifestations appearing in young adulthood
- most of thrombotic events occurs spontaneously

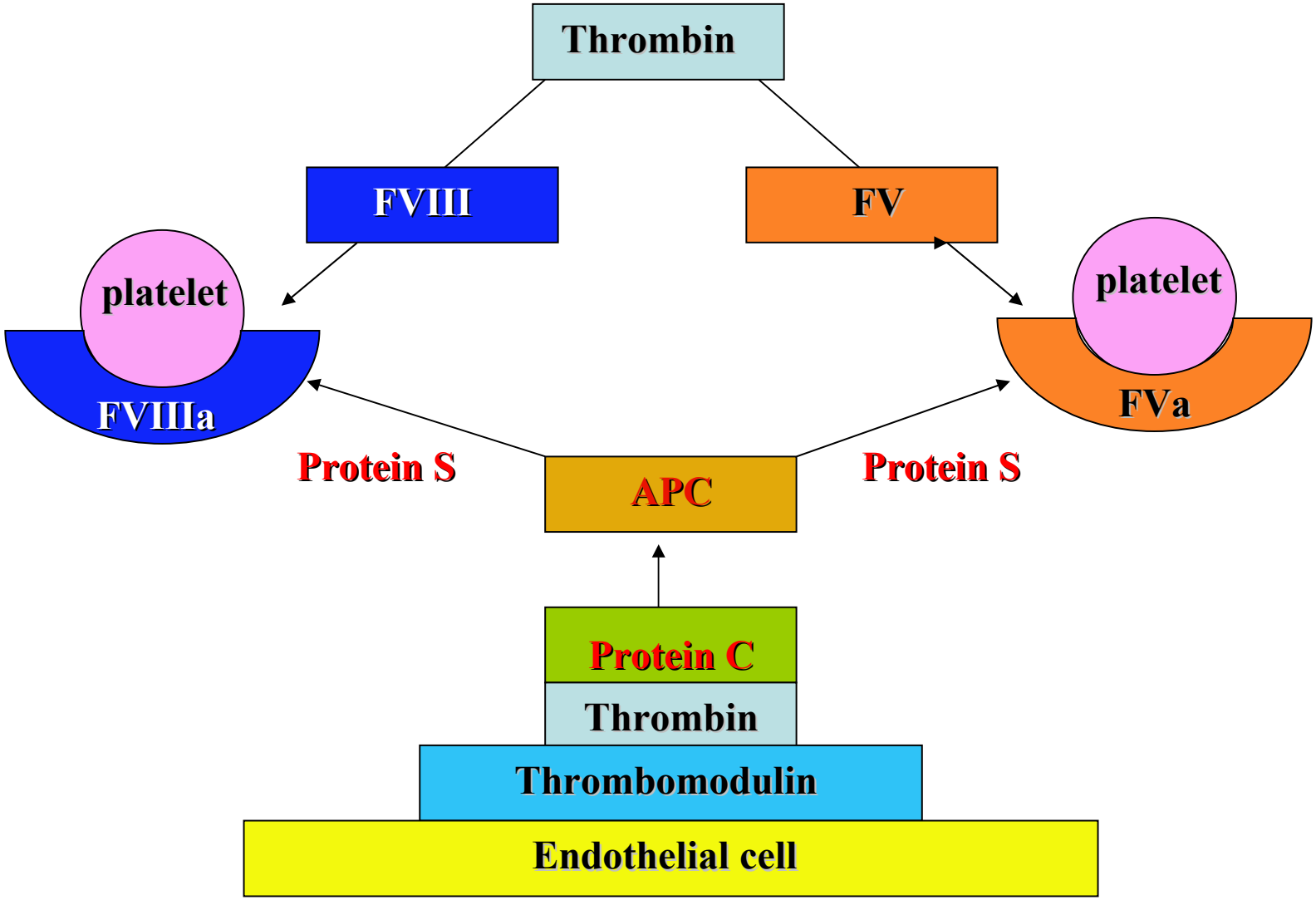
Acquired AT deficiency: DIC, cirrhosis, nephrotic sy.

Two types of AT deficiency:

- **I. type: *quantitatív defect***
  - **Both antigen and activity levels are similarly low (~ 50 % of the normal value).**
  - **It is the most common phenotype.**
- **II. type: *qualitatív defect***
  - **Antigen level is within the normal range, functional activity is reduced.**
    - **Type II RS (reactive site abnormality)**
    - **Type II HBS (heparin- binding site abnormality)**
    - **Type II PE (pleiotropic abnormalities)**

Deficiency may be due to several different genetic defects.

Anticoagulant effects of Protein C, Protein S system



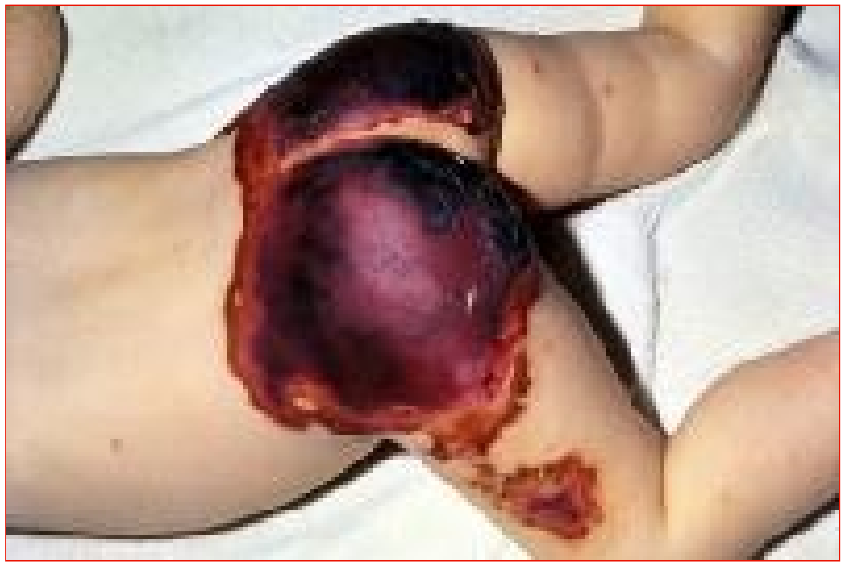
Thrombomodulin enhances the capacity of thrombin to activate protein C.

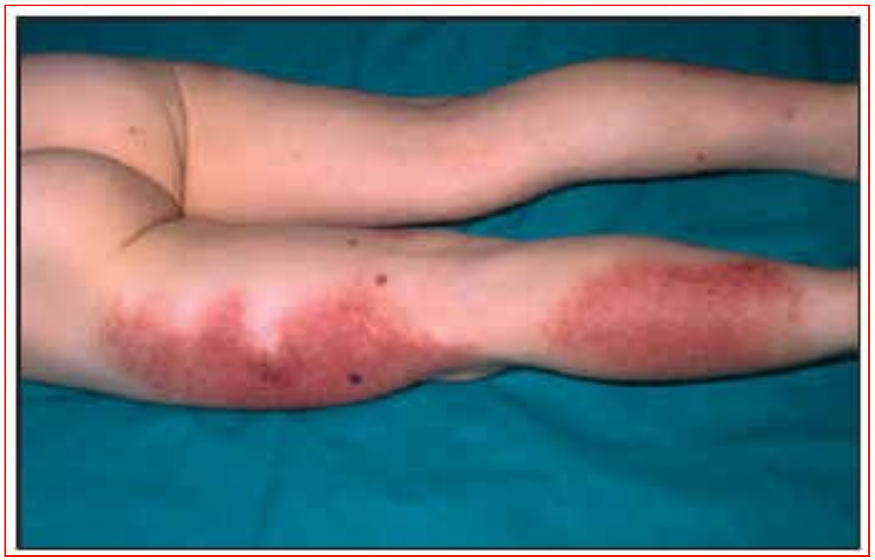
Protein C deficiency

- PC is a vitamin K-dependent glycoprotein that is synthesised in the liver.
  It circulates in an inactive form, it is activated by the thrombin-thrombomodulin complex on endothelial cells.
- **Activated PC (APC) degrades the activated clotting factors Va and VIIIa.**
- Aethiology:
  - **Inherited PC deficiency:** autosomal dominant (rarely: autosomal recessive) inheritance.
    - Type I: quantitative defect: decreased level of PC
    - Type II (less common): decreased functional activity
  - **Acquired PC deficiency:**
    - Severe infection, DIC, liver disease, vitamin K deficiency, warfarin therapy, hemopoietic stem cell transplantation
- Clinical signs:
  - Increased risk of venous TE (no association with arterial thrombosis)
  - Homozygotes: neonatal purpura fulminans (NPF)
  - Warfarin induced skin necrosis (WISN)

Purpura fulminans in the newborn (homozygous protein C deficiency)

A life-threatening emergency, it usually present in the first week of life. There is thrombosis of cutaneous vessels.

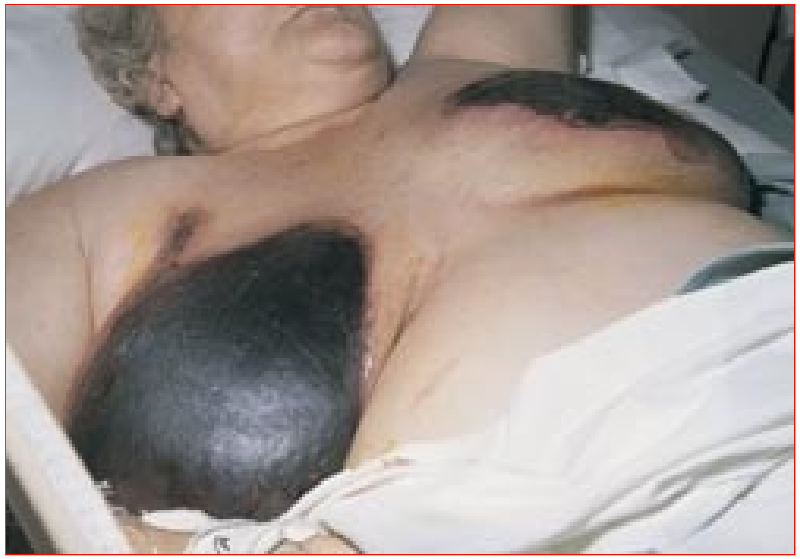


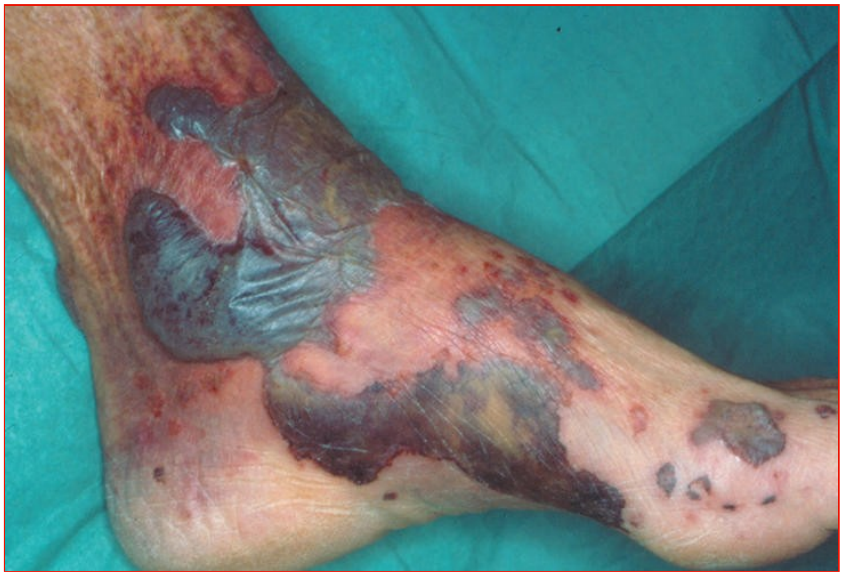


Warfarin-induced skin necrosis (PC deficiency)

A rare complication of initiating warfarin therapy with relatively large loading dose.

/Protein C levels fall faster than the levels of vitamin-K dependent clotting factors (FII, VII, IX, X). This creates a transient hypercoagulable state when warfarin therapy is started → cutaneous vessel thrombosis, ischaemic necrosis./





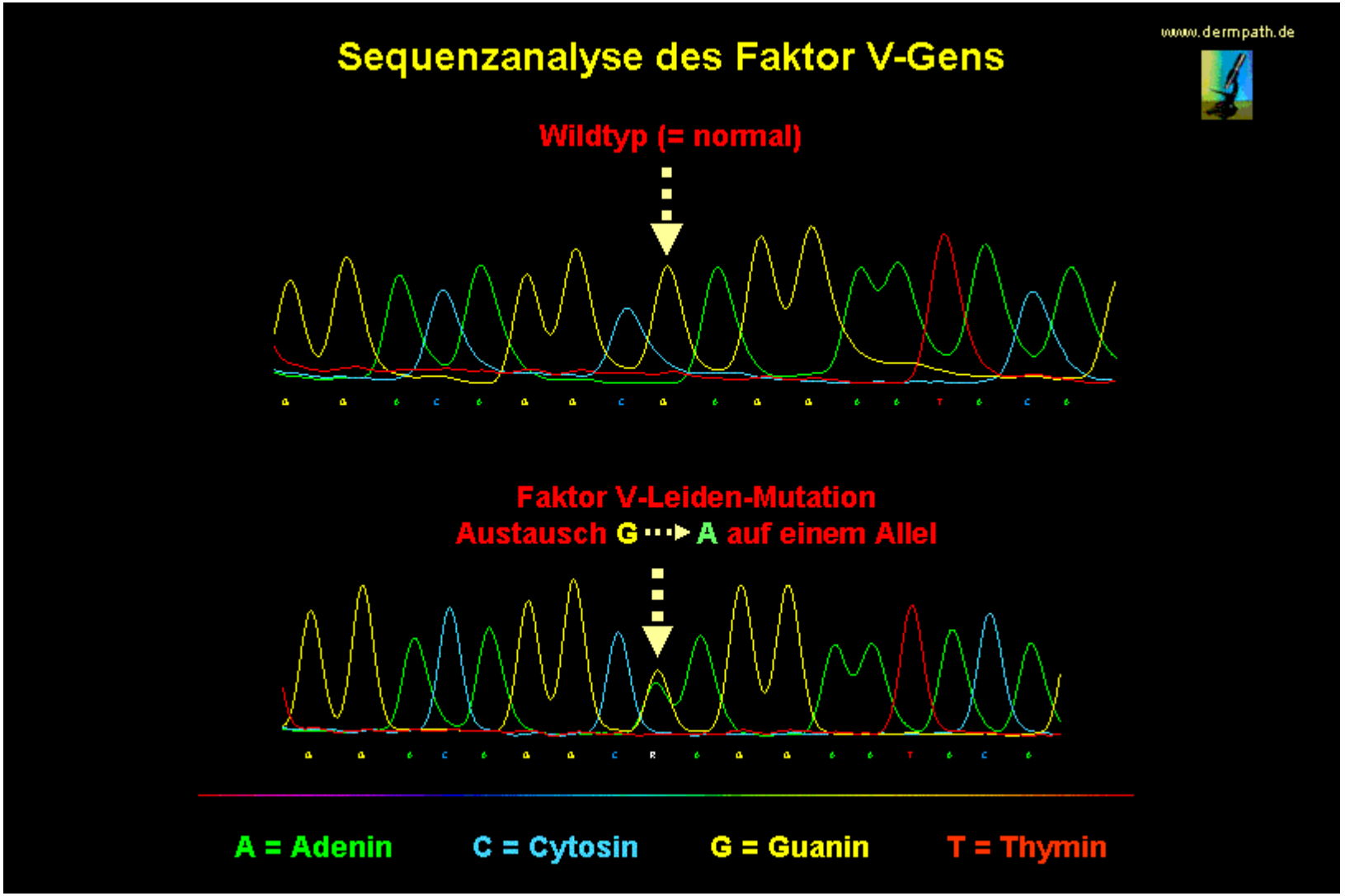
Protein S deficiency

- PS is a vitamin K-dependent anticoagulant protein that is synthesised in the liver.
- PS is a **co-factor** for the action of APC on FVa and FVIIIa.
- 60 % of PS in the plasma is inactive (being bound to a binding protein), 40 % is free. *Only free PS has APC co-factor activity.*
- Aethiology:
  - **Inherited PS deficiency:** autosomal dominant (rarely: autosomal recessive) inheritance.
    - Type I: quantitative defect (both total and free PS levels are reduced)
    - Type II: qualitative defect (decreased functional activity)
    - Type III: total PS level is normal, free PS level is reduced.
  - **Acquired PS deficiency:**
    - Acute thrombosis, DIC, liver disease, vitamin K deficiency, warfarin therapy, nephrotic syndrome, antiphospholipid antibodies
- Clinical signs: similar to the PC deficiency.

Activated Protein C (APC) resistance: Factor V Leiden mutation (FV:G1691A)

- **Congenital APC resistance is the consequence of a point mutation in the gene for clotting factor V.**
- **The most common cause (99%) is the so called „Factor V Leiden mutation”:**
  - **a single amino acid substitution (arginine 506 to glutamine) at the APC cleavage site.**

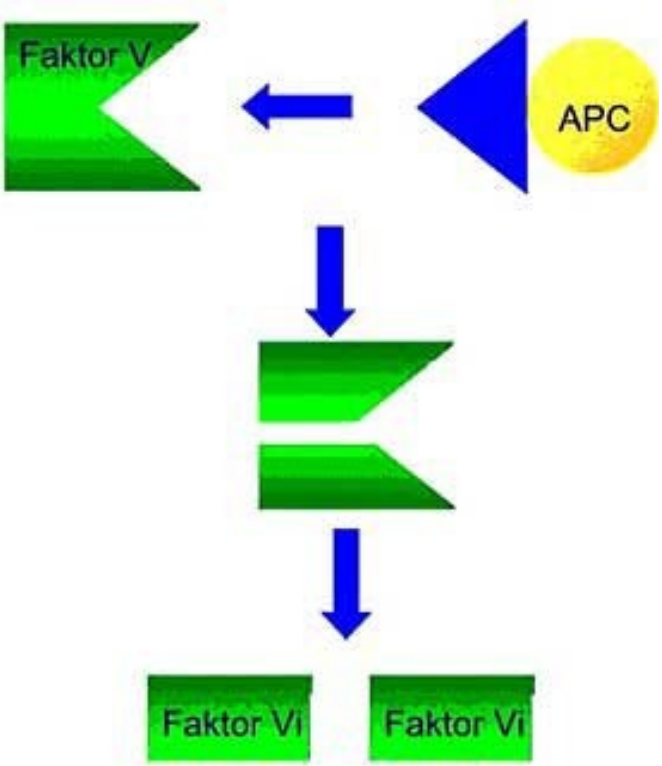
    (This mutation is named after the city Leiden, where it was first identified by Prof R. Bertina, 1994.)

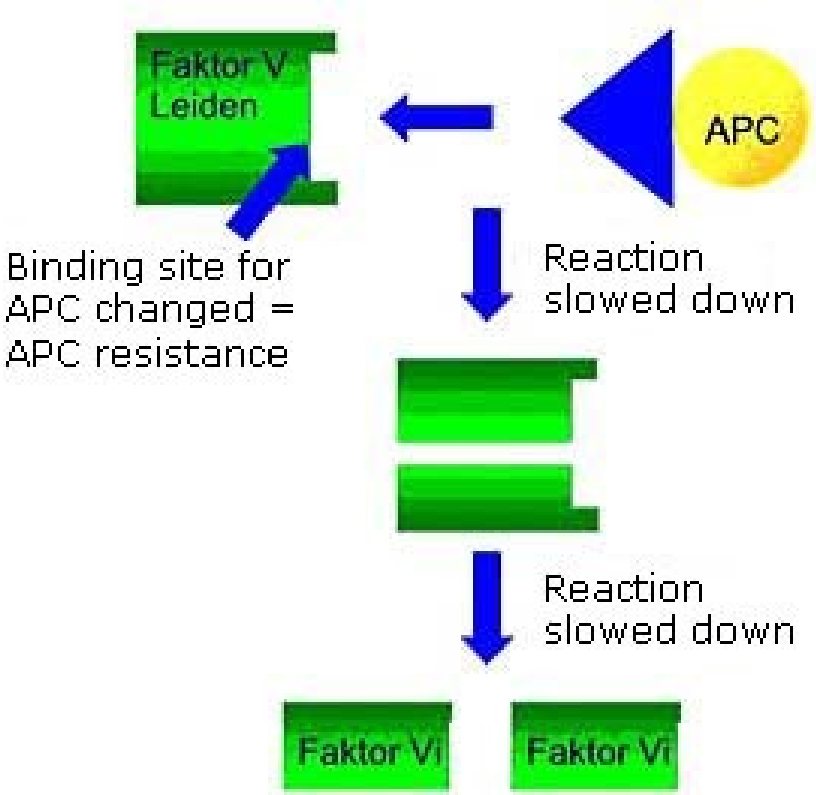


Guanine (G)-to adenine (A) substitution at nucleotide 1691 in exon 10, which predicts the replacement of arginine at amino acid residue 506 by glutamine.

Normal Factor V:

APC binds to FV and cleaves it into 2 inactive fragments.





Factor V Leiden:

As a result of the mutation of FV, the APC can cleave factor V only slowly (10 x slower), as the factor V cleavage site has changed. The coagulation equilibrium shifts towards greatly increased coagulability of the blood.

An individual may be:

heterozygote **(4 to 8 fold increased risk of VTE), or** ***homozygote*** **(80-fold risk) for the FV Leiden mutation.**

Clinical signs: VTE, women: increased risk of miscarriage and stillbirth, rarely formation of clots in arteries (stroke, heart attack).

The presence of major risk factors for thromboembolism (obesity, immobility, surgery, pregnancy) interacts with the thrombotic tendency caused by FV Leiden mutation.

VTE without co-existing risk factors are relatively infrequent.

FV Leiden mutation should be distinguished from FV deficiency (Owren disease, parahemophilia), which is a rare inherited coagulopathy!

Prothrombin gen mutation (G20210A)

- **The common genetic variant: a single guanine (G) to adenine (A) nucleotid substitution at position 20210 of the prothrombin gene. This change makes the blood clot more easily.**

- **Plasma prothrombin level may be elevated.**

- **It increases the risk of a VTE (low risk).**

- **Many people with prothrombin gene mutation do not get clots.**

Prevalence of major thrombosis risk factors

	Healthy:	First VTE:	Recurrent VTE:
APC-R: - heterozygous: - homozygous:	 3 -7% 0,1%	 >20% 1,5%	 >50%
Antithrombino-pathy:	0,02%	1%	5-10%
Protein C def.:	0,2-0,4%	3%	5-10%
Protein S def.:	1-3%	2%	5-10%
Prothr. gen mut.:	2%	6,2%	18%

Relative risk of venous thrombosis I.

- **Healthy: 1**
- **Oral contraceptive use (OC): 4**
- **FV Leiden heterozygous: 5 - 7**
- **- „ - + OC: 30 - 35**
- **FV Leiden homozygous: 80**
- **- „ - + OC: > 100**
- **Prothrombin G20210A, heterozygous: 3**
- **- „ - + OCP: 16**
- **Prothrombin G20210A , homozygous: ? may be arterial thrombosis**

Relative risk of venous thrombosis II.

- **Protein C heterozygous:** 7
- **Protein C homozygous:** purpura fulminans

- **Protein S heterozygous:** 6
- **Protein S homozygous:** purpura fulminans

- **AT deficiency, heterozygous:** 20
- **AT deficiency, homozygous :** rarely compatible with life

- **FVIII ↑ :** 3 - 5

Symptoms of thrombophilia:

- Many people with thrombophilia do not get clots and have no symptoms.

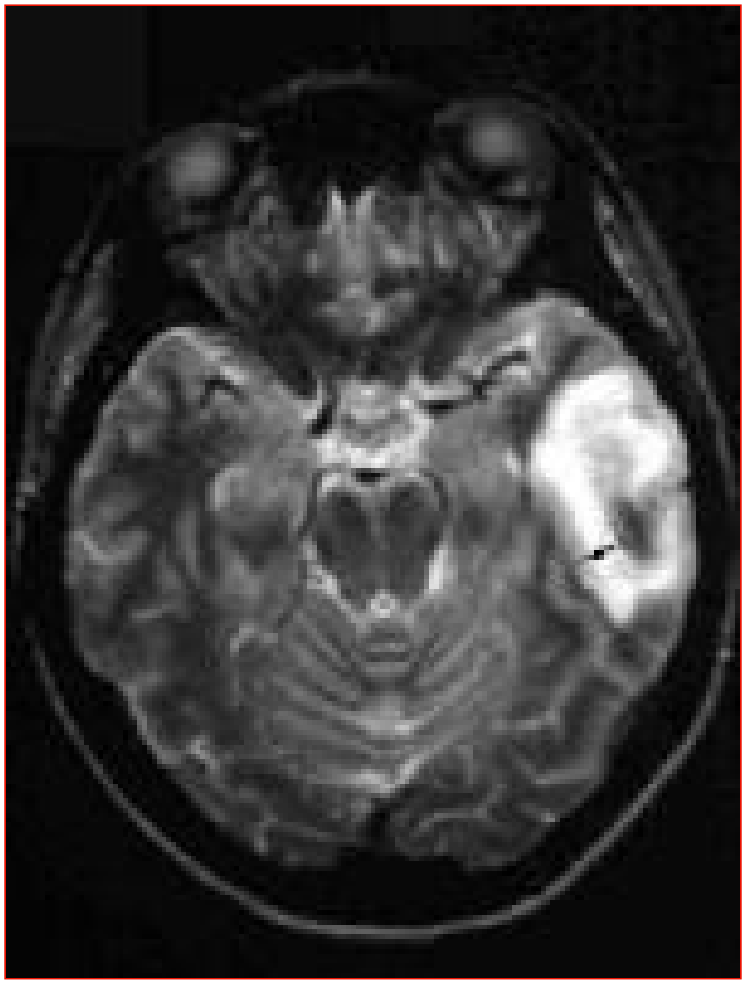
- The most common symptoms:
Deep vein thrombosis (DVT)
Pulmonary embolism (PE)
(together venous thromboembolism, VTE)

- May be clots in arteries:
stroke
heart attack
placental thrombosis during pregnancy

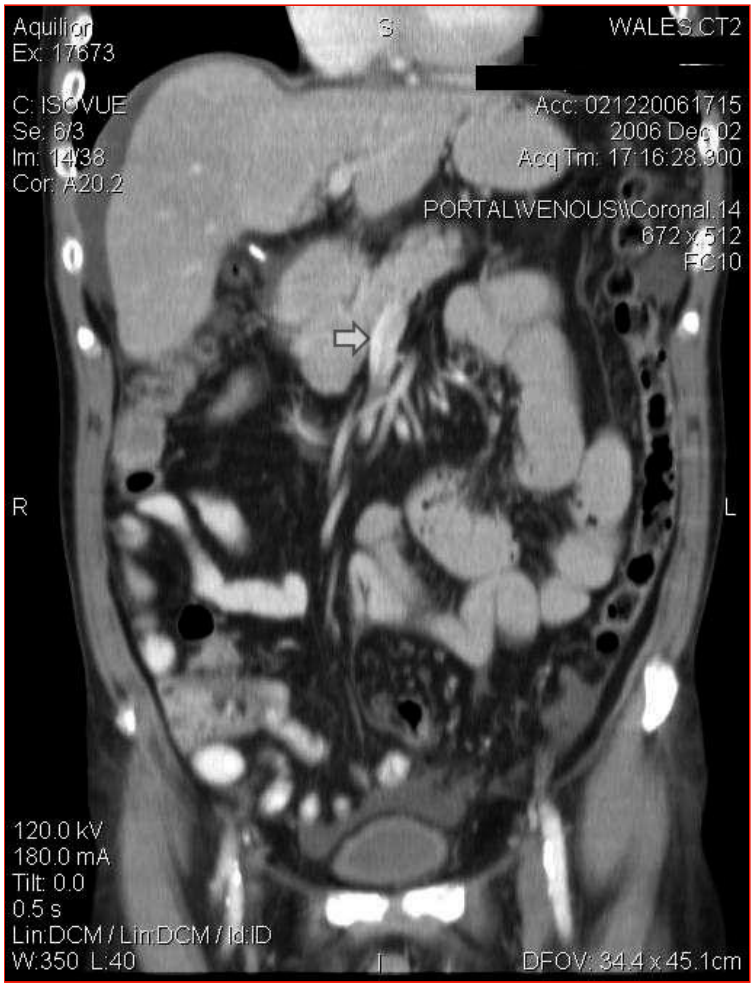
Thrombophilia is possible in the following situations:

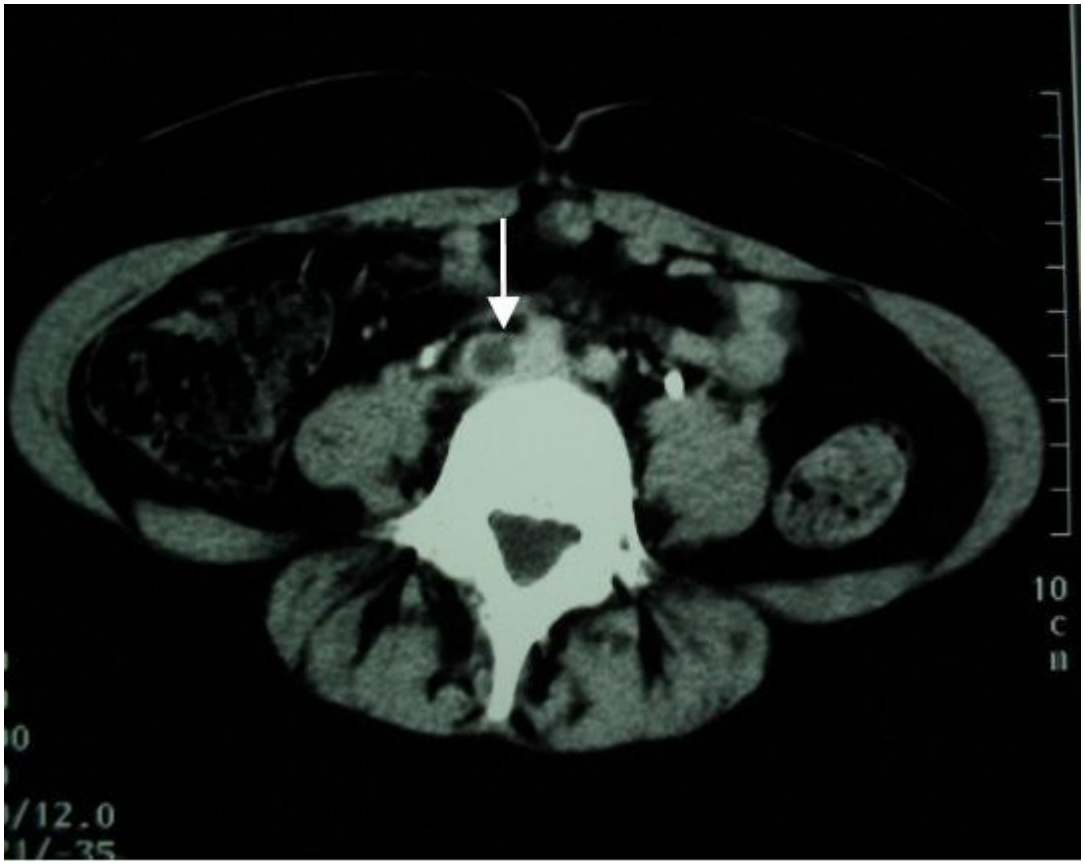
- **Venous thrombosis or pulmonary embolism (PE) under age of 45 years**
- **Repeated episodes of venous thrombosis or PE or thrombophlebitis**
- **Venous thrombosis in an unusual site (cerebral, hepatic, renal veins, arm, portal, ovarian veins)**
- **Unexplained blood clots in newborn babies**
- **Skin necrosis (warfarin induced)**
- **Arterial thrombosis under the age of 40 years (stroke, acute myocardial infarction)**
- **Relatives of patients with thrombophilia**
- **Patients with clear history of venous thrombosis**
- **Possible complications of pregnancy (recurrent miscarriage or fetal death, stillbirth, intrauterine growth restriction, pre-eclampsia, abruptio placentae)**

Cerebral sinus thrombosis



Thrombosis of vena mesenterica superior



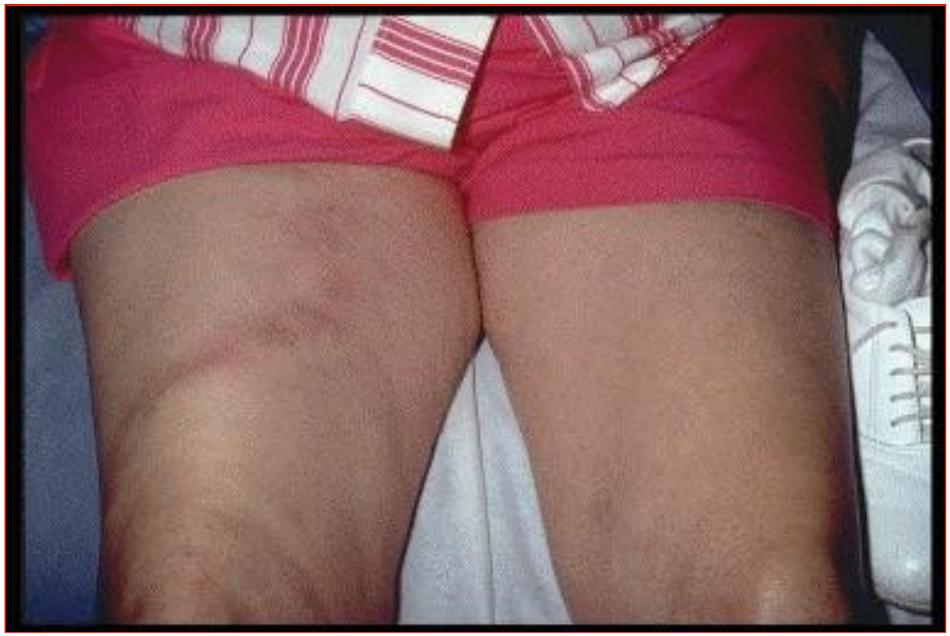


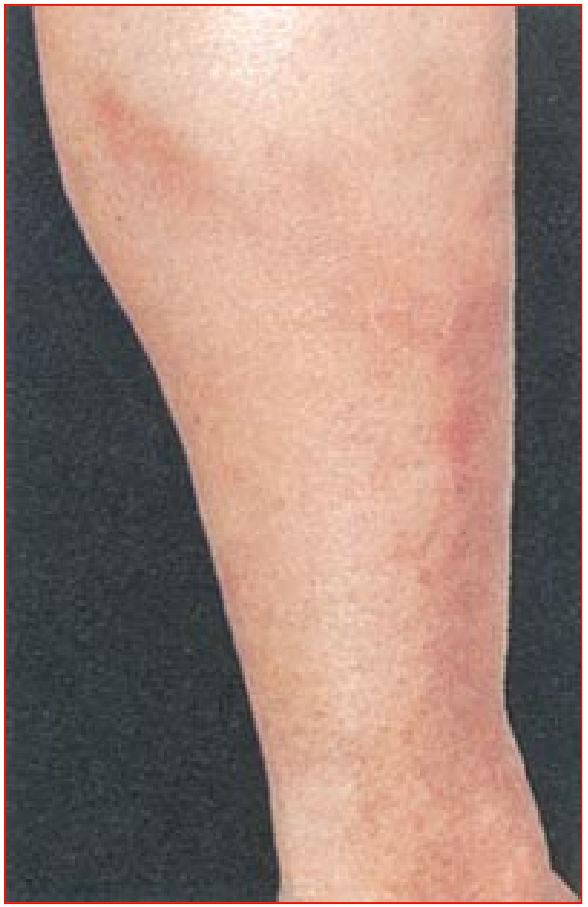
Abdominal computed tomographic scan: showing a common iliac vein thrombosis.

(The arrow indicates the filling defect in the vein visualised using radiocontrast.)

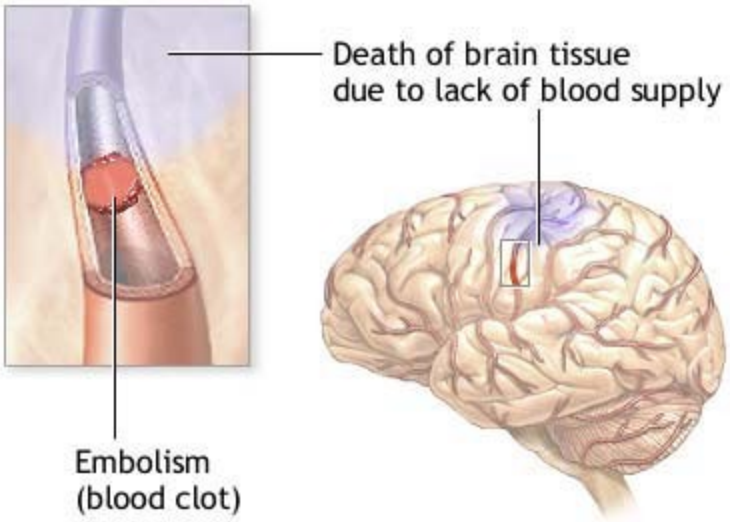
Thrombophlebitis

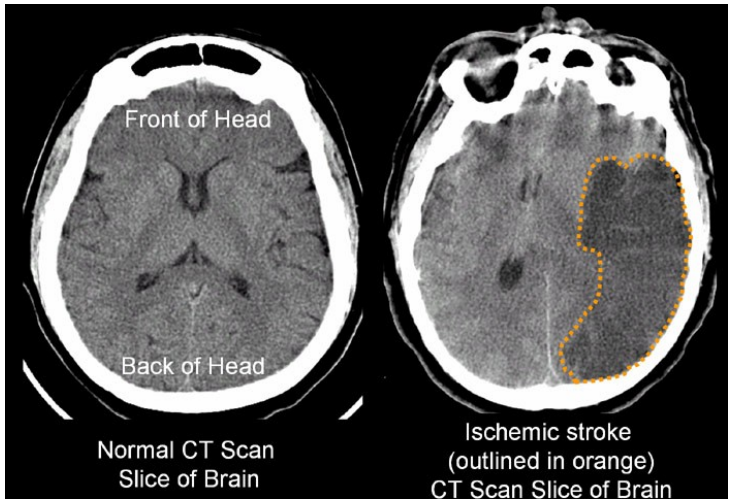
Blood clots form in veins that are near the skin's surface. Superficial blood clots do not cause PE. There is inflammation of the vein in conjunction with a blood clot.



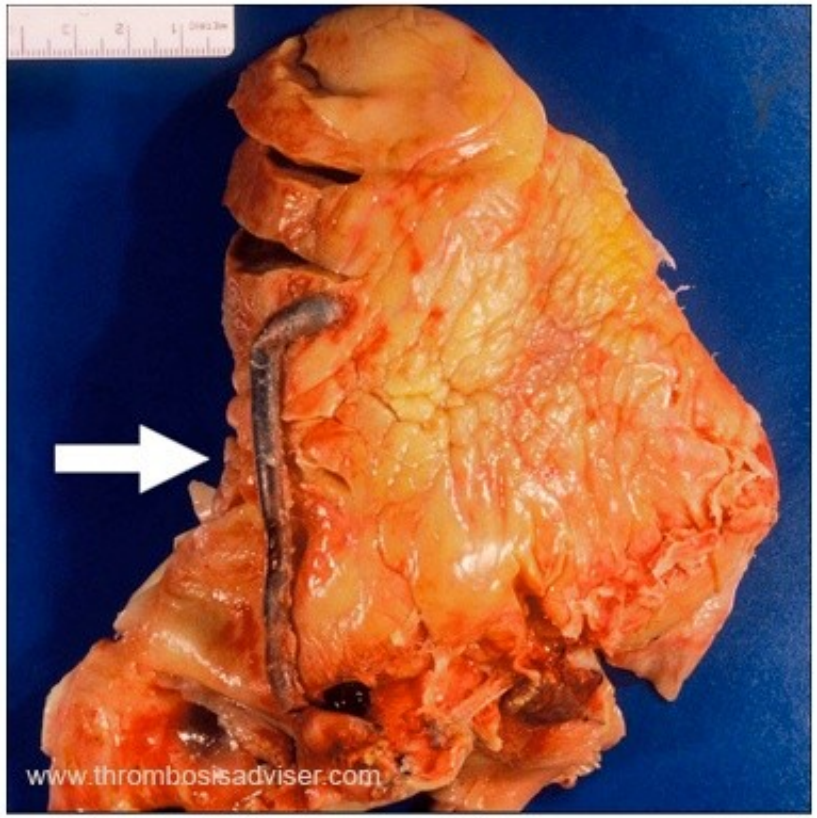


At a young age myocardial infarction and/or stroke may occur without any additional risk factors.





Ischemic stroke



Coronary thrombosis

How is thrombophilia diagnosed?

- **Generally screening of the population is not necessary.**
- **When an individual is thought to have hereditary form of thrombophilia, it is possible to perform a range of laboratory tests.**
- **Usually blood tests are done in two stages:**
  - **First: thrombophilia screen (clotting tests), together with coagulation tests (APTT, PT, TT, fibrinogen), and assays to detect antiphospholipid antibodies.**
    Complete blood count.
  - **More detailed tests (polymerase chain reaction /PCR/ to detect genetic defect)**
- **Not all thrombophilias be diagnosed on tests (there are some kinds which we cannot yet identify or test for).**

Blood tests for thrombophilia: there is no single laboratory assay that will identify all thrombophilias.

- Generally recommended panel of tests:
  - **Activated protein C (APC) resistance test** (functional test with FV-deficient plasma). When APC-R is abnormal: **direct mutation test (DNA analysis)** is necessary.
  - **Antithrombin activity**
  - **Protein C activity**
  - **Protein S activity**
  - **Prothrombin G20210A** (diagnosis is only possible by DNA analysis)
  - **Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies)** (acquired hypercoagulable state)

Timing of diagnostic thrombophilia testing:

- **Not testing in acute phase!**
  - **Acute thrombosis and its management affect the results of coagulation tests (AT, PC, PS: ↓, fibrinogen, FVIII:↑)**
  - **Thrombophilia testing should be delayed for at least 6 weeks.**
- **Heparin therapy: AT↓, impairs interpretation of LA**
- **Warfarin: PC, PS ↓ (change warfarin to heparin, but the effect of warfarin on PS levels may not resolve for 4-6 weeks)**

Screening asymptomatic family members:

- **Searching for the same genetic defect in relatives of patient with thrombophilia allows the identification of still asymptomatic carriers, *who might be at risk of DVT or PE in high-risk situations:***
  - **major surgery**
  - **prolonged immobility or plaster casts**
  - **use of combined oral contraceptive pills containing oestrogen**
  - **hormone replacement therapy.**
- **Prophylaxis with LMWH or UFH should be given during high-risk situations.**
  Long term anticoagulation is not indicated.
- **Young children (<15 years) should not be tested. Screening teenage daughters of thrombophilic patients is considered.**

All patients with a thrombophilic state *need to be given advice as to how to minimise their risk of thrombotic episodes.*

This should include advice on:

- **mobilisation (immobility helps venous thrombosis)**
- **adequate hydration (dehydration can contribute to blood clots)**
- **the use of graduated compression stockings or mechanical compression devices during period of immobility**
- **the use of combined oral contraceptives and HRT (increases the risk of thrombosis)**
- **pre-pregnancy councelling**
- **stop smoking, avoid overweight**

Treatment

First step: to consider *how much risk there is of an unvanted clot?*

It depends on:

- **thrombophilia type**
- **combined defects have higher risk for thrombosis than a single defect**
- **age, weight, lifestyle, other medical condition**
- **pregnancy**
- **previous VTE**
- **positive family history**

Possible treatments for thrombophilia

- **Low dose aspirin: inhibits platelet function**
  - **150 mg/day *for prevention in some patients* with thrombophilia with no previous TE.**

- **Anticoagulants: *to prevent or treat* DVT and PE.**
  - **Heparin: LMWH, UFH inj. (1-2 x daily)**
  - **Oral anticoagulant agents: Warfarin**
    - **The dose has to be adjusted on individual basis, need a blood test (Prothrombin INR) which checks the clotting speed.**

Thrombophilia and pregnancy

Pregnancy I.

- **Pregnancy and the puerperium are risk factors for VTE.**
- **Women with previous VTE *should be screened* for thrombophilia before pregnancy.**
- **Recommandation:**
  - **Women with previous VTE and thrombophilia: thromboprophylaxis with LMWH antenatally for at least 6 weeks postpartum.**
  - **Women with thrombophilia and no previous VTE: should be stratified to the level of risk associated with their thrombophilia.**

Pregnancy II.

- *Warfarin is avoided* due to its teratogen potential.

- **Heparin** does not harm the child as it does not cross the placenta.
  - LMWH or UFH inj.
- Pregnant women and APS: heparin and low-dose aspirin is indicated to prevent miscarriage.

- Both heparin and warfarin are safe for breastfeeding.

Duration of the anticoagulation treatment after DVT or PE

Patient categories	Duration (months)	Comments
First episode of DVT/PE to a transient risk factor	3	Both proximal and calf vein thrombosis
First episode of idiopathic DVT/PE	6-12	Continuation after 6-12 months may be considered
First episode of DVT/PE with documented thrombophilia (single defect)	6-12	Continuation after 6-12 months may be considered
First episode of DVT/PE with APS, or two or more thrombophilic abnormality	12	Continuation after 12 months may be considered (life-long)

Harrison's Principles of Internal Medicine, 2008.