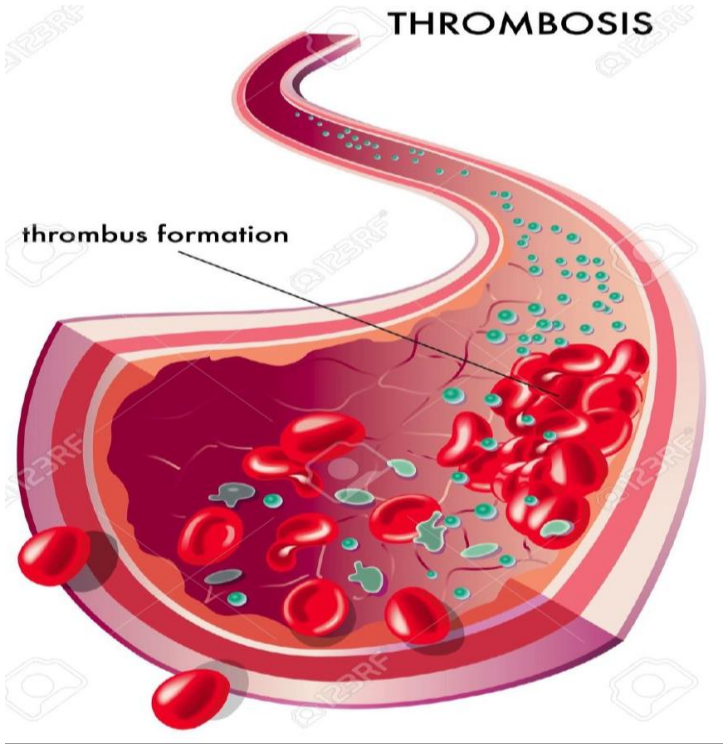
VENOUS THROMBOSIS

Dr. Muhannad R. M. Salih
B.Sc, M.Pharm (Clinical Pharmacy), Ph.D, RPH
Pharmacy Department, Al-Rasheed University College
muhanad_rmk@yahoo.com

BACKGROUND

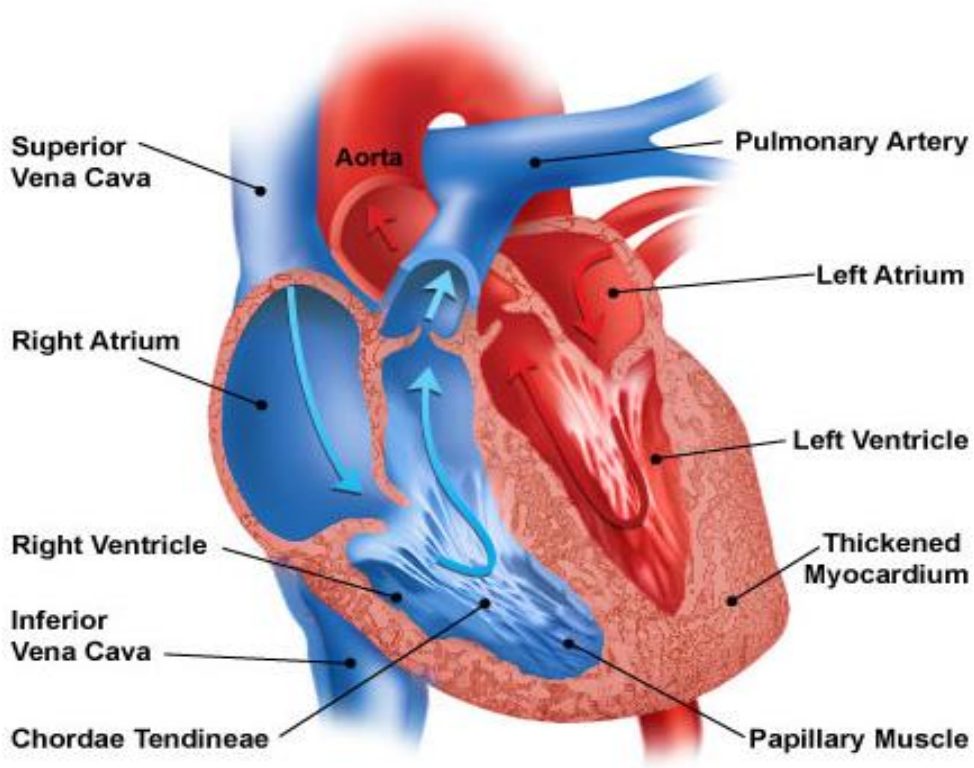
- **Thrombosis** is the development of a thrombus consisting of platelets, fibrin, red cells, and white cells in the arterial or venous circulation.



BACKGROUND

- If a part of this thrombus in the **venous circulation** breaks off and enters the right heart, it may lodged in the pulmonary arterial circulation, causing **pulmonary embolism** (PE).

- In the left- sided circulation, an embolus may result in peripheral arterial occlusion, either in the lower limbs or in cerebral circulation (where it may cause thromboembolic stroke).



VENOUS THROMBOEMBOLISM

- Venous thromboembolism (VTE) occurs primarily due to a combination of
  - **stagnation of blood flow**
  - **hypercoagulability**

- **Vascular injury** is also a recognized causative factor but is not necessary for the development of venous thrombosis.

- In **VTE**, the structure of the thrombus is different from that in **arterial thromboembolism**.

VENOUS THROMBOEMBOLISM

- Stagnation of blood flow may be related to
  - bed rest
  - surgery
  - reduced cardiac output, e.g., heart failure

VENOUS THROMBOEMBOLISM

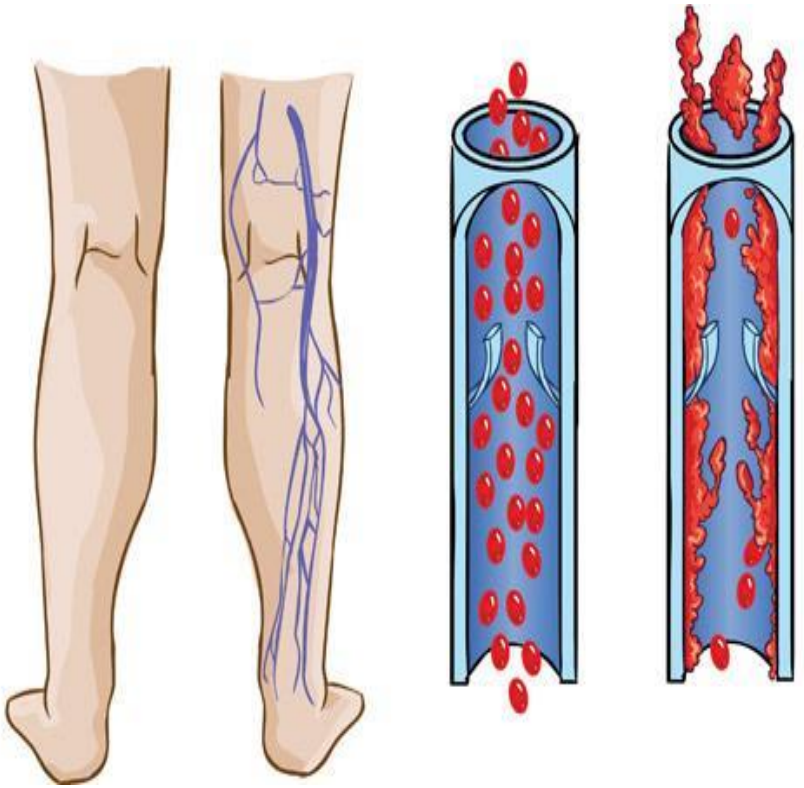
- Factors increasing the risk of hypercoagulability include
  - surgery
  - pregnancy
  - estrogen administration
  - malignancy
  - myocardial infarction
  - acquired or inherited disorders of coagulation

CLINICAL MANIFESTATION

Deep Venous Thrombosis (DVT)

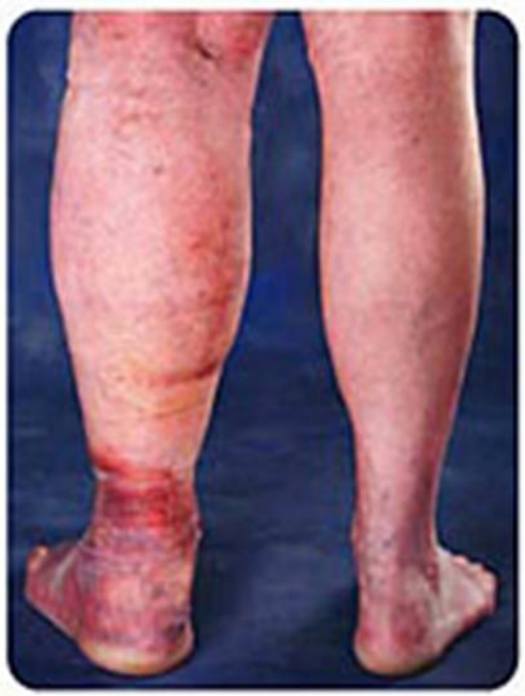
- In 90% of patients, deep vein thrombosis occurs in the veins of the **lower limbs** and **pelvis**.

- **In up to half of cases**, this may not result in local symptoms, and the **onset of PE may be the first evidence of the presence of VTE**.

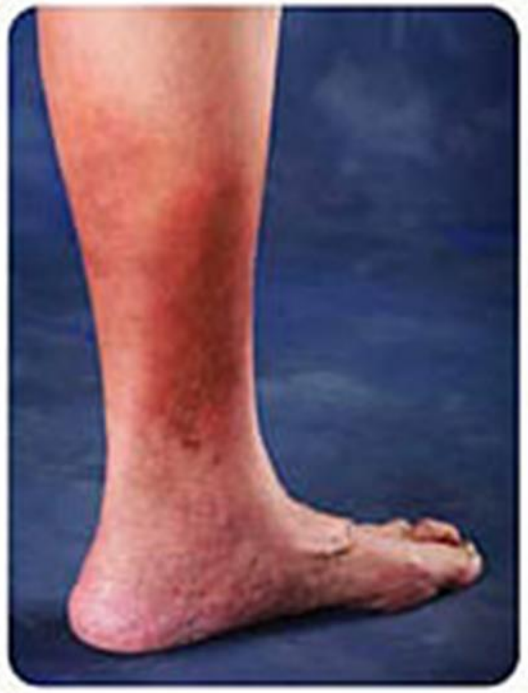


DEEP VENOUS THROMBOSIS (DVT)

- In other cases, patients classically present with
  - **pain involving the calf or thigh associated with swelling**
  - **redness of the overlying skin increased warmth**



Swelling

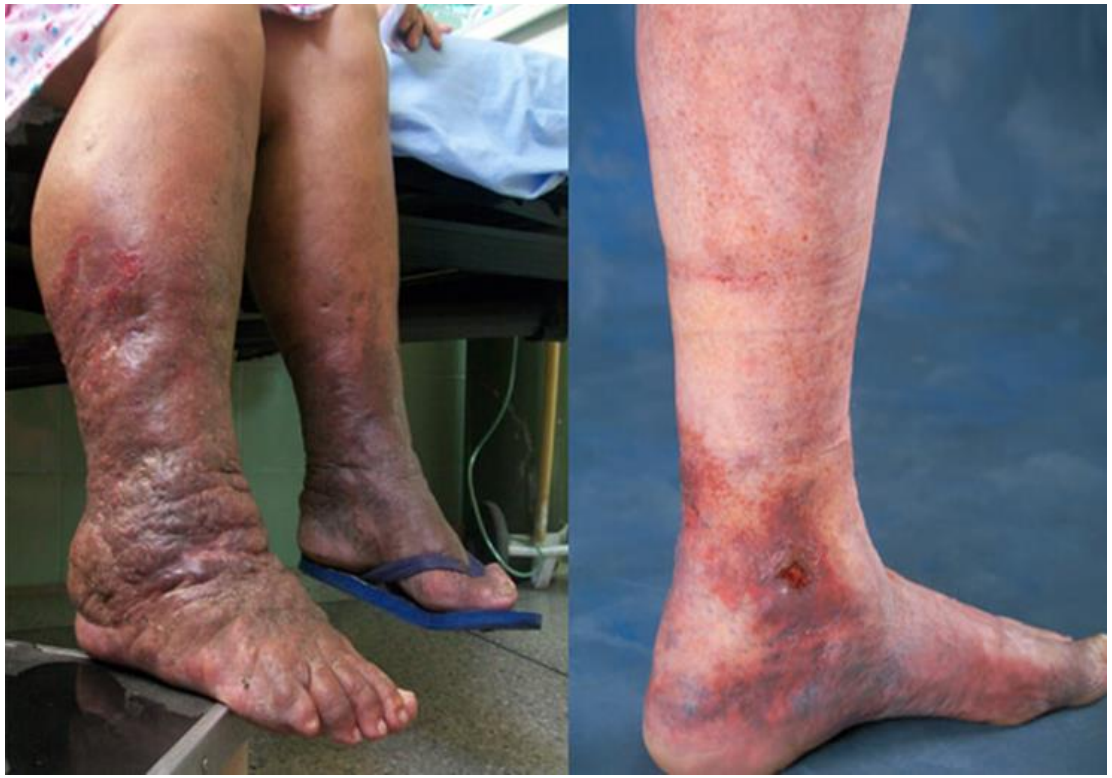


Skin Changes

DEEP VENOUS THROMBOSIS (DVT)

- In a **large deep venous thrombosis**, the leg may become
  - **discolored**
  - **edematous**

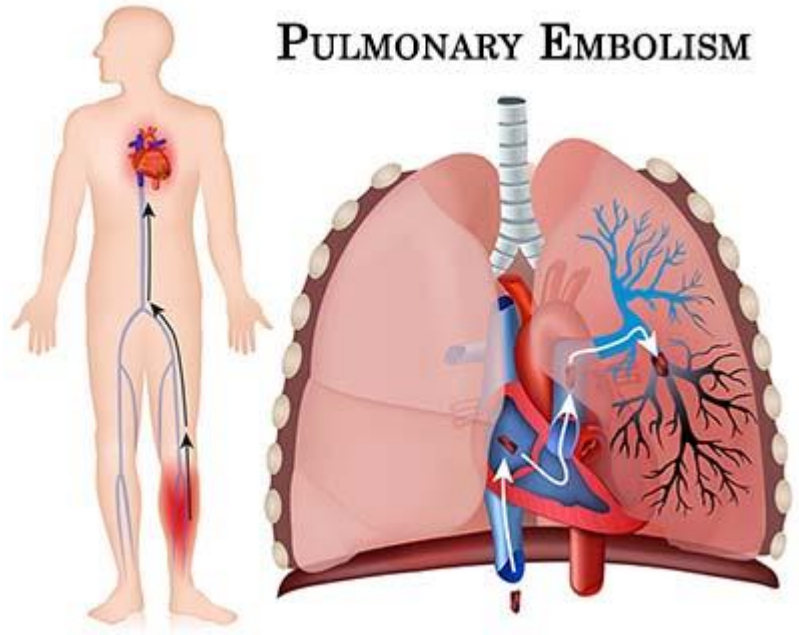
- **Massive venous thrombus** can occasionally result in **gangrene**, although this occurs very rarely now because effective drug therapies are available.



PULMONARY EMBOLISM

- Pulmonary embolism may occur in the absence of **clinical signs** of **venous thrombosis**.

- It may be very difficult to diagnose because there **is no specific** symptoms and signs.



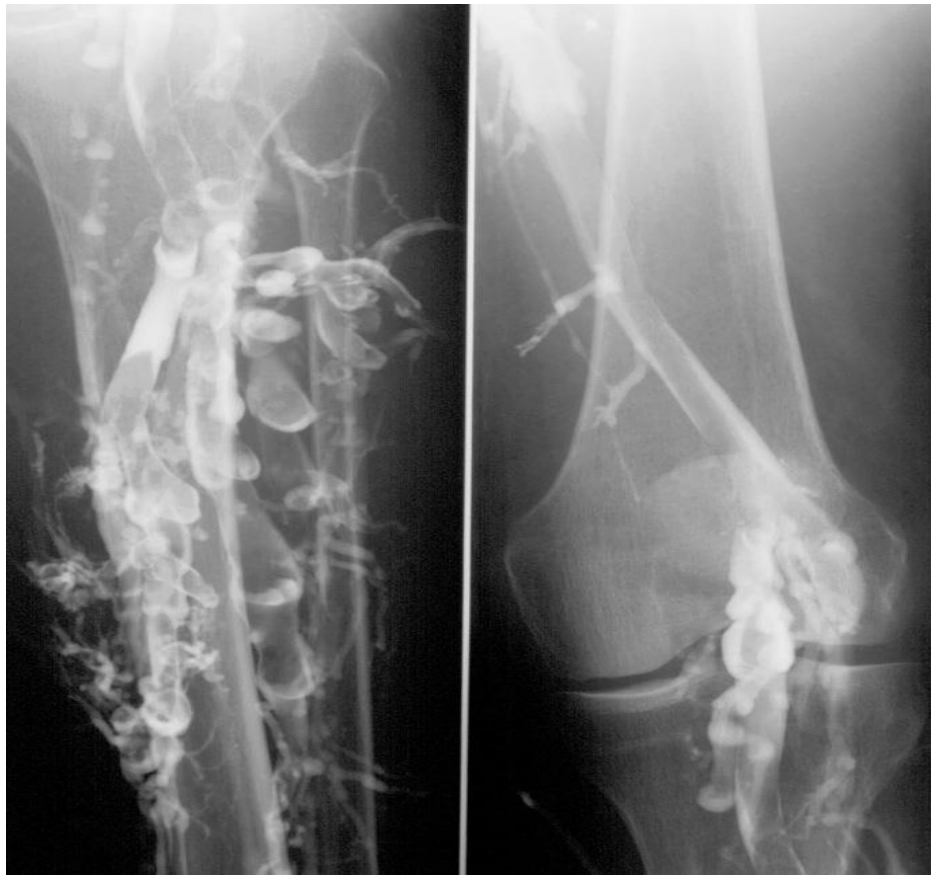
PULMONARY EMBOLISM

- Obstruction with a **large embolus** of a major pulmonary artery may present with sudden
  - **shortness of breath**
  - **central chest pain**
  - **severe hypotension**
  - **right ventricular failure**
  - **sometimes death** due to acute circulatory failure unless rapidly treated.

INVESTIGATIONS - DVT

- The clinical diagnosis of venous thrombosis is relatively unreliable, and **venography** is the most specific diagnostic test.

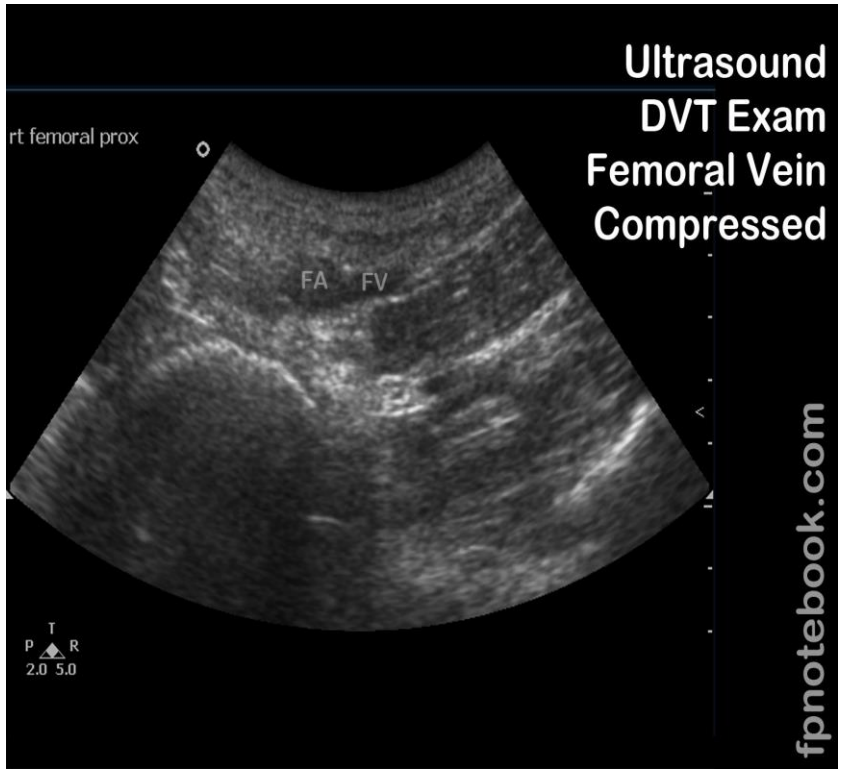
- **Venography** involves injection of radio contrast material, normally into a vein on the top of the foot, and subsequent radiography of the venous system.



INVESTIGATIONS - DVT

- **Ultrasound** is a non-invasive alternative to **venography** that does not involve exposure to radiation or potentially allergenic contrast material.

- It is now the initial **investigation of choice** in clinically suspected deep vein thrombosis, although it is less sensitive for below-knee and isolated pelvic deep vein thrombosis.



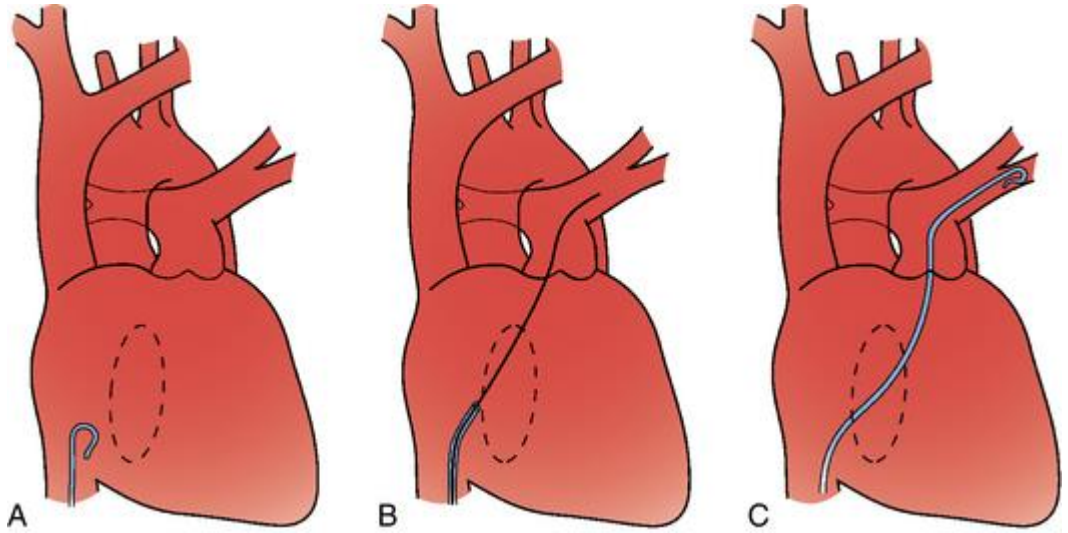
INVESTIGATIONS - DVT

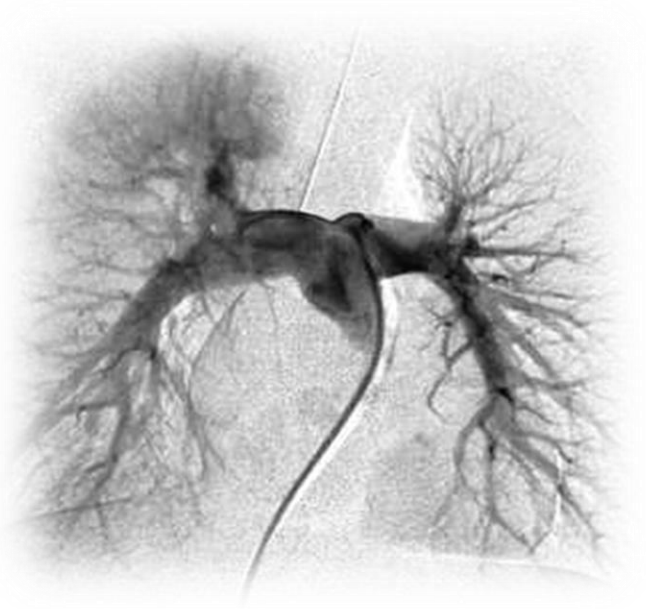
- **Magnetic resonance imaging (MRI)** is also non-invasive and avoids radiation exposure. It is sensitive and specific, even with below knee and isolated pelvic deep vein thrombosis.

- However, it is not widely clinically available and ultrasound remains the primary initial investigation.

INVESTIGATIONS - PE

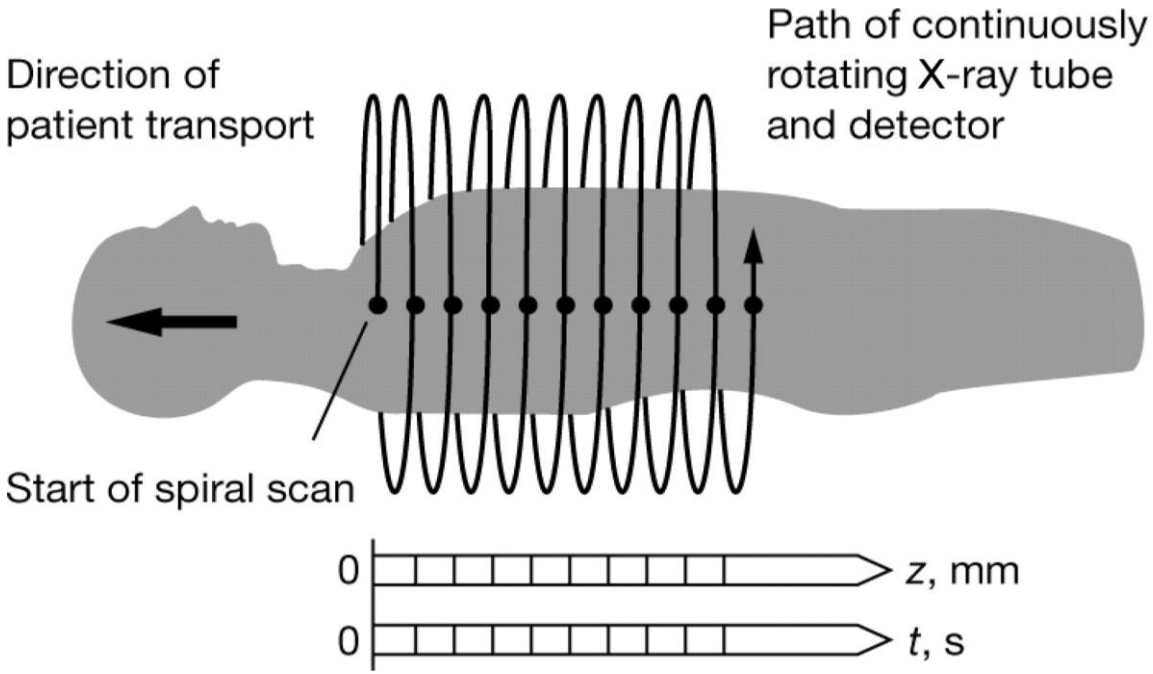
- **Pulmonary arteriography** is the most specific test. This requires catheterization of the right side of the heart and an injection of contrast medium into the pulmonary artery.

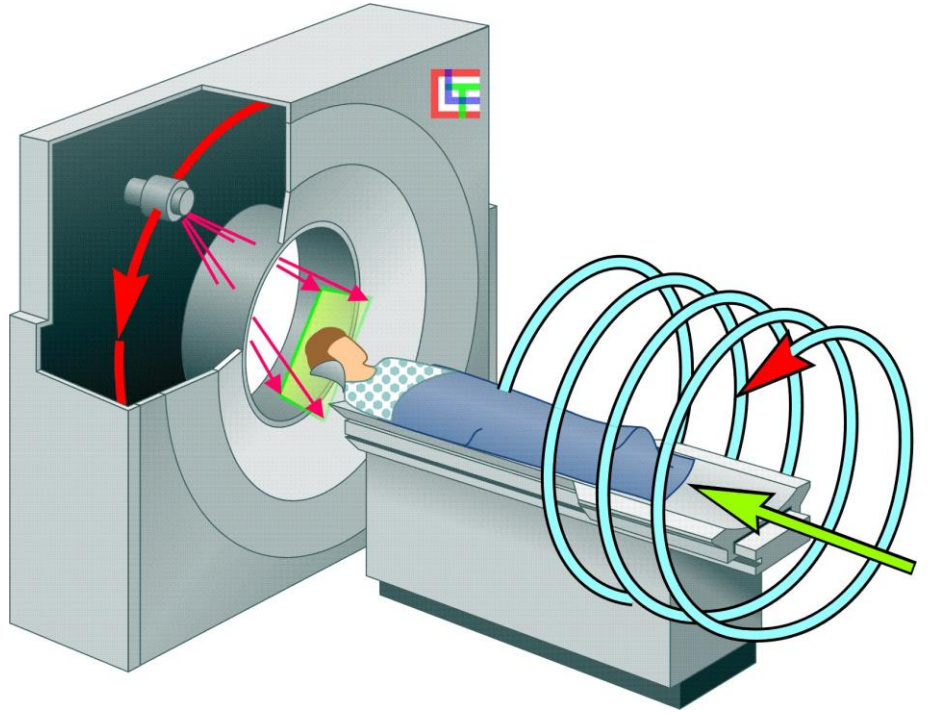




INVESTIGATIONS - PE

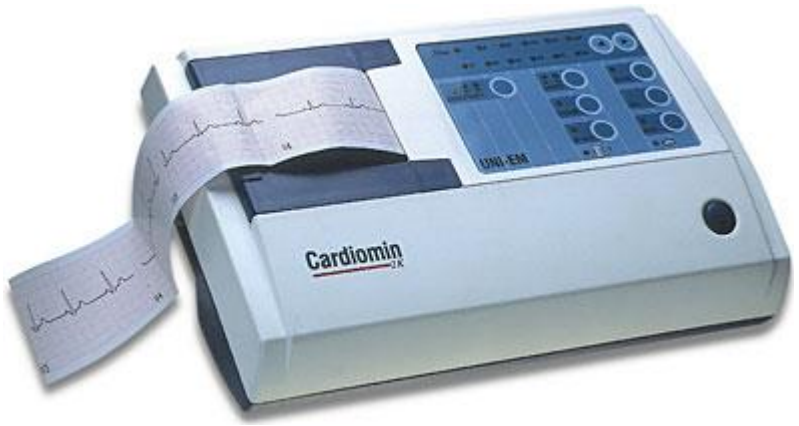
- **Spiral computed tomography (CT)** is a computed tomography technology involving helical movement for the purpose of increasing resolution. Most modern hospitals currently use spiral CT scanners.





INVESTIGATIONS - PE

- Other non-specific investigation may include chest radiography, ECG changes and arterial blood gas measurement (Hypoxia).



AIM OF TREATMENT

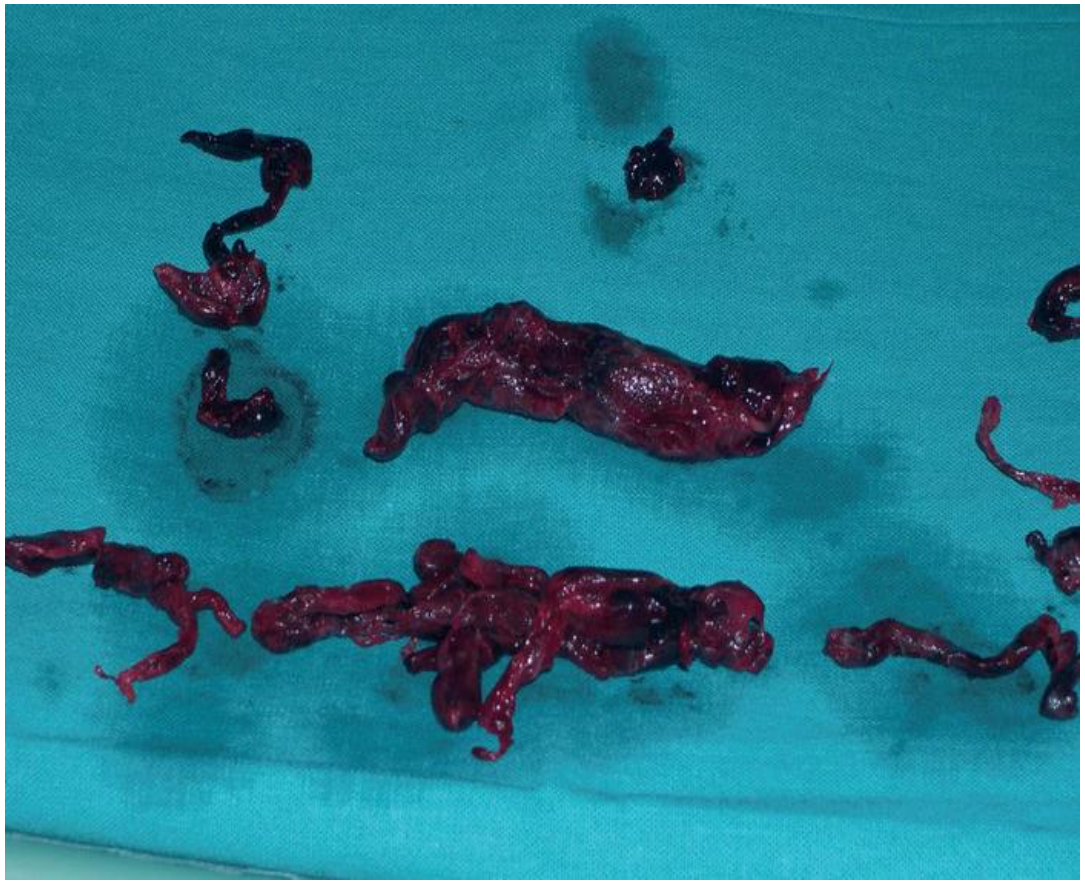
In general:

1. **Allow normal circulation in the limbs and to prevent damage to the veins.**

2. **Prevent associated PE and also recurrence of either venous thrombosis or PE.**

AIM OF TREATMENT

- **In acute massive PE**, the initial priority is to
  - **correct the circulatory defect that has caused the hemodynamic upset.**
  - **rapid removal of the obstruction using**
    - **thrombolytic drugs**
    - **surgical removal of the embolus**



AIM OF TREATMENT

- The treatment of VTE consists of the use of **anticoagulants** and, in severe cases, **thrombolytic** drugs.

- Anticoagulant therapy involves the use **heparin** and oral anticoagulants, the commonest of which is **warfarin**.

- These medications are used
  - **to treat the acute event**
  - **to prevent recurrent thromboembolism**

HEPARINS

- **Conventional** or **unfractionated heparin (UFH)** is a heterogeneous mixture of large molecules ranging widely in molecular weight between 3000 and 30,000, with immediate anticoagulant properties.

- It acts by increasing the rate of the interaction of thrombin with antithrombin III, thus, **prevents the production of fibrin from fibrinogen**.

- Heparin also has effects on the inhibition of production of activated clotting factors IX, X, XI and XII.

HEPARINS

- **UFH** is a rapid acting anticoagulant. It has a transient action **(short half life 60 minutes**, but is shorter in patients with **PE**).
- It is highly protein bound, its bioavailability is reduced by subcutaneous route.
- t does **not cross the placenta** and does **not appear in breast milk**.
- It is removed from the body by metabolism in the liver, and by renal excretion.

HEPARINS

- Unlike UFH, **low molecular weight heparins (LMWHs)** contain plosaccharide with a molecular weight ranging between 4000 and 6000.
- LMWHs predominantly inactivate only **factor Xa**.
- LMWH have reduce binding affinity for plasma protein.
- Bemiparin, dalteparin, enoxaparin, reviparin and tinzaparin are LMWHs with similar efficacy and adverse effects.
- **UFH** and **LMWHs** are not absorbed via the gastro-intestinal tract and must be given by intravenous infusion or deep subcutaneous injection.
- **Never intramuscular** because of the danger of **haematoma** formation

HEPARINS

- **LMWHs** have a number of **potentially desirable pharmacokinetic** features compared with UFH.
- They are mainly excreted **renally**.
- They have **longer** and **more predictable half-lives** than UFH and so have a more predictable dose than UFH.
- They can, therefore, be given once or twice daily in a fixed dose, sometimes based on the patient's body weight, without the need for laboratory monitoring, except for patients given treatment doses and at high risk of bleeding.

HEPARINS

- Heparin can be given during **pregnancy** but should be completely stopped during delivery.
- Patient can returned to treatment as soon as bleeding from **delivery was controlled**.
- **Menstruation** is not a contraindication to heparin use unless if it is excessive.

HEPARINS

- The major adverse effect of all heparins is **hemorrhage**, which is common in patients with
  - **severe heart disease**
  - **severe liver disease**
  - **renal disease**
  - **general debility**
  - **women aged over 60 years.**
  - **patients with prolonged clotting times**
  - **patients given heparin by intermittent intravenous bolus rather than by continuous intravenous administration**

GENERAL GUIDELINES FOR HEPARIN THERAPY

- Heparin monitoring is very important owing to its significant adverse effect (i.e., **hemorrhage**), however, this monitoring is mainly
  - **looking for the response to a given dose of heparin**
  - **avoiding any hemorrhage or recurrent embolism**

GENERAL GUIDELINES FOR HEPARIN THERAPY

- Before starting **antithrombotic therapy**, a clinician should obtain a base line
  - **Platelet count**
  - **Hematocrit values** is the ratio of the volume occupied by red cells to the total volume of blood.
  - **Prothrombin Time (PT)** is a blood test that measures how long it takes blood to clot.
  - **activated Partial Thromboplastin Time (APTT)** is a medical test that describes blood coagulation.
  - **Activated clotting time (ACT)** test can be used to monitor anticoagulation effects. It is usually ordered in situations where the aPTT test may take an excessive amount of time to process. Prolongation of the ACT may indicate a **deficixency in coagulation factors, thrombocytopenia or platelet dysfunction.**
  - **The coagulation time (CT)** is a measurement of the intrinsic power of the blood to convert fibrinogen to fibrin.

GENERAL GUIDELINES FOR HEPARIN THERAPY

- **UFH** is primarily monitored by the activated partial thromboplastin time (APTT).
- For example; in those patients with a **APTT** three times greater than control, there is an eightfold increase in the risk of hemorrhage.
- The therapeutic range for the APTT during UFH therapy appears to be between **1.5 and 2.5 times the control values**.
- The reference range of the aPTT is **30-40 seconds**.
- APTT: More than 70 seconds (**signifies spontaneous bleeding**).

GENERAL GUIDELINES FOR HEPARIN THERAPY

- Rapid reversal of the effect of heparin can be achieved using **protamine sulphate**, but this is rarely necessary because of the short duration of action of heparin.

- **LMWHs** may produce **fewer hemorrhagic complications.** At doses normally used for treatment, **routine monitoring is not necessary**.

GENERAL GUIDELINES FOR HEPARIN THERAPY

- Heparins, particularly UFH, may also cause **thrombocytopenia** (low platelet count).

- This may occur in **two forms**. **The first occurs 3–5 days** after treatment and does not normally result in complications.

- **The second type** of thrombocytopenia occurs after **about 6 days** of treatment and often results in much more profound decreases in platelet count and an **increased risk of thromboembolism**.

- **LMWHs** are thought to be less likely to cause thrombocytopenia.

Guidelines to control unfractionated heparin (UFH) treatment

A historic name for APTT measure is the Kaolin cephalin clotting time (KCCT)

Loading dose
5000 iu over 5 min

Infusion
Start at 1400 iu/h (e.g. 8400 iu in 100 mL of normal saline over 6 h). Check after 6 h. Adjust dose according to ratio of the KCCT to the control value using the values below

KCCT ratio	*Infusion rate change*
>7.0	Discontinue for 30 min to 1 h and reduce by >500 iu/h
>5.0	Reduce by 500 iu/h
4.1–5.0	Reduce by 300 iu/h
3.1–4.0	Reduce by 100 iu/h
2.6–3.0	Reduce by 50 iu/h
1.5–2.5	No change
1.2–1.4	Increase by 200 iu/h
<1.2	Increase by 400 iu/h

After each dose change, wait 10 h before next KCCT estimation unless KCCT >5, when more frequent (e.g. 4-hourly) estimation is advisable. Developed using Diogen (Bell and Alton); local validation may be necessary.

GENERAL GUIDELINES FOR HEPARIN THERAPY

- Since the half-life of **UFH is 1 h**, it would take **5 h** (five half-lives of the drug) to reach a steady state.
- A **loading dose** is, therefore, administered to reduce the time to **achieve adequate anticoagulation.**
- **UFH** in full dose can also be given by **repeated subcutaneous** injection.
- The **subcutaneous route** may take **longer** to reach effective plasma heparin concentrations but **avoids the need for infusion devices**.

GENERAL GUIDELINES FOR HEPARIN THERAPY

- **Heparin** is normally used in the **immediate stages** of venous thrombosis and PE **until** the effects of **warfarin become apparent**.

- **In the past**, it has been continued **for 7–10 days**, but recent evidence indicates that around **5 days of therapy** may be sufficient in many instances.

- This shorter treatment may also reduce the risk of very serious complications of severe **Heparin-Induced Thrombocytopenia** (HIT), which **normally occurs after the sixth day**.

GENERAL GUIDELINES FOR HEPARIN THERAPY

- **LMWH** should be administered for **at least 5 days** or **until the INR** has been in the therapeutic range for **two successive days**.

- They have largely replaced UFH, since they can be given **subcutaneously** (without a loading dose), and **without routine monitoring**.

- A **full blood count** should be ordered after 5 days on LMWH and throughout the duration of LMWH treatment to monitor for **heparin-related thrombocytopenia**.

ORAL ANTICOAGULANTS

- **Warfarin**, an oral anticoagulant that it is completely and rapidly absorbed; highly plasma protein bound (99%), therefore has a small volume of distribution.

- **Warfarin** provides
  - **less rapid anticoagulant therapy than heparin**
  - **more convenient for long term treatment for out patient**

ORAL ANTICOAGULANTS

- **Vitamin K** normally helps blood clot so wounds don't bleed too much.
- **Warfarin** works against vitamin K, making your blood clot more slowly.
- So warfarin and vitamin K work against each other in your body.

ORAL ANTICOAGULANTS

- **Warfarin** has a delayed onset of action. The mean half-life is about 40 hours. Therefore, it takes around **5-7 day to reach steady state**.

- That is why in emergency, clinicians start therapy with heparin and then continue with warfarin.

ORAL ANTICOAGULANTS

- The effect of warfarin is monitored using the **international normalized ratio** (**INR**), which is equal to:

$$\mathrm{INR} = \left(\frac{\mathrm{PT}_{\mathrm{test}}}{\mathrm{PT}_{\mathrm{normal}}} \right)^{\mathrm{ISI}}$$

INR - International Normalised Ratio
PT - Prothrombin time
ISI - International Sensitivity Index

- The INR is the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system being used.

ORAL ANTICOAGULANTS

- The dose of warfarin should maintain to reach a goal **INR of 2.5 times** the control value.

- Checking INR first **daily** then **every other day** then less frequently and once a steady state reached, check **every two weeks**.

DOSE & MONITORING OF WARFARIN

- Initiate **warfarin** on day 1 or 2 of **parenteral anticoagulant therapy** (LMWH or UFH).
- Overlap warfarin and parenteral anticoagulant for **at least 5 days** until desired INR (2-3) maintained for 24hr, then discontinue parenteral therapy.
- Initial dose: 2-5mg daily for 2 days then check the INR and adjust the dose accordingly.
- Typical maintenance dose ranges between 2 and 10mg/day.

DOSE & MONITORING OF WARFARIN

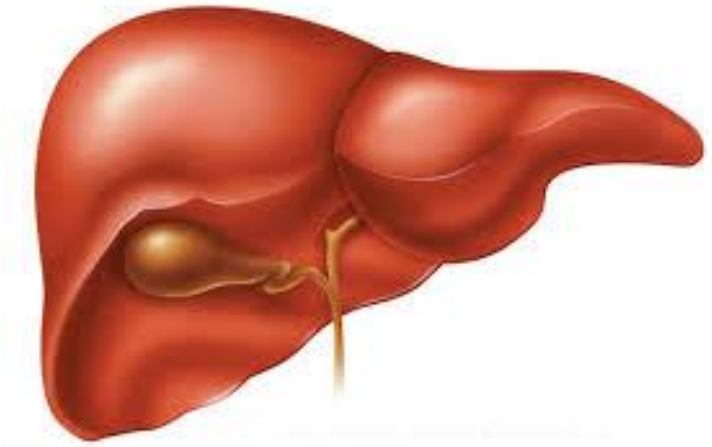
- Warfarin therapy may continue to **6 months after the 1st onset of DVT or PE**, because the risk of recurrence is great during the 1st month, then reduce gradually after the next 5 months.

- Warfarin is **teratogenic**, not given during pregnancy, for **safety use heparin**.

WARFARIN METABOLISM

- Warfarin is metabolized by the liver (Cytochrome P450).

- Warfarin half life range from 20-60hr with a mean of 40hr. It should be not discontinued suddenly, it should taper off.



WARFARIN ADVERSE EFFECT

- The major adverse effect is **hemorrhage**, so stop using the drug once hemorrhage occurs, **vitamin K** should be given by **I.V route (slowly)** or by **infusion over 30-60 min** to prevent flushing, hypotension and cardiovascular collapse.

- It can return **PT** to normal value within **6-12 hr**.

- Vitamin K can also given by S.C. or oral route, but avoid **I.M route because of a risk of hematoma**.

DRUGS ENHANCING ANTICOAGULANT EFFECT OF WARFARIN

- **Antibiotic** may suppresses intestinal synthesis of vitamin K by intestinal normal flora leading hypoprothrombinemia.
- **Enzyme inhibitors** like Cimetidine, Ciprofloxacin, Chloramphenicol and co-trimoxazole.
- **NSAIDs** (including **aspirin**) and antiplatelet (**Clopidogrel**), increase risk of bleeding.
- **Salicylate** also increase level of free drug through competition for plasma protein binding site.
- **Liquid paraffin**, a prolong use for constipation may cause reduction of vitamin K absorption which is fat soluble vitamin.
- Other medications like **Clofibrate**, **Thyroxin**, **Metronidazole** may increase the anticoagulant effect of heparin.

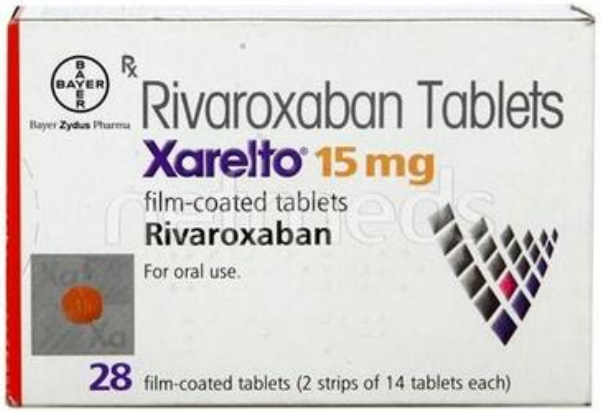
DRUGS REDUCING ANTICOAGULANT EFFECT OF WARFARIN

- **Enzyme inducers** like Barbiturate, Carbamazepine, Griseofulvin, and Rifampicin that increase metabolism of warfarin and reduce its anticoagulant effect.
- **Cholestyramine** and **Colestipol** impair absorption of warfarin.
- Increase dietary intake of **vitamin K** in certain food including **beef liver** and **green leafy vegetable**s, may be associated with **acquired warfarin resistance**.
- **Alcohol ingestion**; a chronic use of alcohol is associated with induction of hepatic enzyme that metabolize warfarin.
- **Oral contraceptive**, **estrogen**, **progesterone**, and **anabolic steroid** antagonize warfarin and reduce anticoagulation.

DIRECT ACTING ORAL ANTICOAGULANTS (DOACS)

- These agents are highly effective, but like all anticoagulants, they can cause potentially life threatening bleeding in some patients.

- ***Apixaban***
- ***Dabigatran***
- ***rivaroxaban***



DIRECT ACTING ORAL ANTICOAGULANTS (DOACS)

- Although DOACs interact with fewer drugs than warfarin, some significant interactions do occur.

- All of the available agents appear to be **substrates** for **p-glycoprotein**, and so various inhibitors or inducers of this system will respectively increase or decrease the effect of the DOACs to different extents.

DIRECT ACTING ORAL ANTICOAGULANTS (DOACS)

- The relatively **short half-lives** of the **DOACs** means adherence to treatment is essential for them to be optimally effective.

- They are not, therefore, an option for a patient who is non-adherent to warfarin or other medicines.

DIRECT ACTING ORAL ANTICOAGULANTS (DAOCS)

- The **DOACs** have been shown in clinical trials to be generally **safe** for use **without routine** anticoagulant monitoring.

- The absence of such monitoring may be a **disadvantage** in some cases, as it is not possible to identify signs of **sub-therapeutic** or **supra-therapeutic plasma levels** until a **thromboembolism** or **hemorrhage** occurs.

DIRECT ACTING ORAL ANTICOAGULANTS (DAOCS)

- It is advised that the **Cockroft–Gault formula** is used to calculate an accurate creatinine clearance before initiation of **DOAC**.

- Dose reductions are advised with DOACs at different levels of renal impairment, and they are also contraindicated at different levels of impairment.

DIRECT ACTING ORAL ANTICOAGULANTS (DAOCS)

- **Hemorrhage** is the major adverse effect of the **DOACs**, and patients should be advised to seek urgent medical attention if they notice signs of bleeding.

- **Idarucizumab**, a monoclonal antibody fragment, is used for reversal of the anticoagulant effect of **dabigatran**. It reversing the anticoagulant effect within minutes.

- **Andexanet alfa**, which is a recombinant modified human factor Xa protein, has been shown to reverse the anticoagulant effects of **apixaban** and **rivaroxaban**, It does not yet have a marketing authorisation in the UK.

FIBRINOLYTIC DRUGS

- **Thrombolytic therapy** is used in life-threatening **acute massive pulmonary embolus**.

- It has been used in **deep vein thrombosis**, particularly in those patients where **a large amount of clot exists** and **venous valvular damage is likely**.

- However, **fibrinolytic drugs** are potentially **more dangerous** than **anticoagulant drugs**, and evidence is not available in situations other than **acute massive embolism** to show a sustained benefit from their use.

STREPTOKINASE

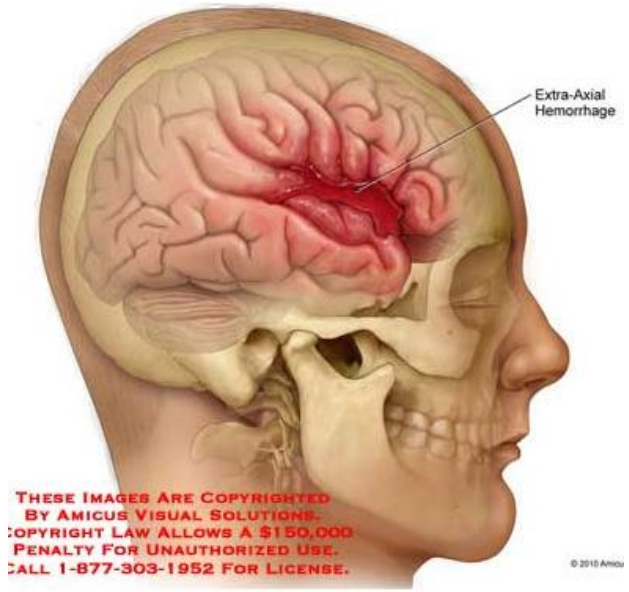
- **Streptokinase** was the first agent available in this class. It binds to and activates plasminogen, thus encouraging the breakdown of formed fibrin to fibrinogen degradation products.

- it **cannot** be administered **orally** and has to be **given by intravenous infusion**. The **half-life** of removal from the body is **30 min**. It is cleared chiefly by the reticuloendothelial system in the liver.

STREPTOKINASE

- Its major adverse effect is to
  - increase the risk of **hemorrhage**
  - might be **antigenic** and produce an **anaphylactic reaction**
  - It may also cause **hypotension during infusion**

- In some patients, mainly those who have been administered the drug within the previous 12 months, a relative **resistance to the drug may occur**.



STREPTOKINASE

- Thrombolytic therapy is contraindicated in patients
  - **major surgery**
  - **gastro-intestinal bleeding**
  - **genitourinary tract bleeding**
  - **history of stroke**
  - **renal or liver disease**
  - **hypertension**

- It should also be **avoided** during **pregnancy** and the **postpartum period**.

ALTEPLASE

- **Tissue plasminogen activator (rt-PA)** or **Alteplase** was developed using recombinant DNA technology.

- Although this agent is much more expensive than streptokinase, it can be used in those situations where streptokinase may be less effective for example
  - ***within 1 year of previous streptokinase use***
  - ***allergy to streptokinase.***

- Immediate use of **heparin** subsequently is necessary to prevent recurrence of **thrombosis**.

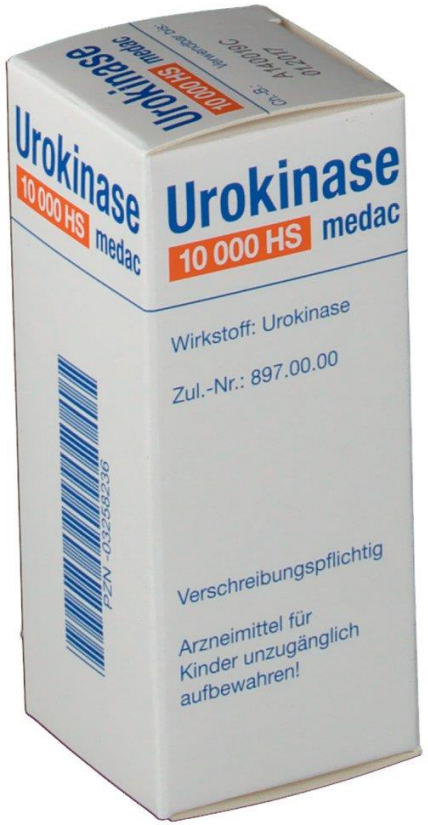
RETEPLASE AND TENECTAPLASE

- **Reteplase**, and more recently **tenectaplase**, are also fibrin-specific agents and so **heparin** is required to prevent rebound thrombosis.

- They are indicated for the treatment of **acute myocardial infarction**.

UROKINASE

- **Urokinase**, like **alteplase** and **streptokinase**, can be used for the treatment of deep vein thrombosis and PE.



PATIENT CARE

- The patient on **oral anticoagulants** should be given full information on what to do in case of problems and what circumstances and drugs to avoid.

- An anticoagulant card with previous INR values and doses should also be provided.

- The patient should be told of the color code for the different strengths of warfarin tablet and advised to carry their treatment card at all times.

PATIENT CARE

- The likely duration of anticoagulant therapy should be made clear to the patient to avoid unnecessary and potentially dangerous prolongations of treatment.

- Patients who have received a fibrinolytic agent should also carry a card identifying the drug given and the date of administration.

Good Luck !