ENOXAPARIN IN THROMBO-EMBOLIC EVENTS

NSADHU EMMANUEL

Busoga
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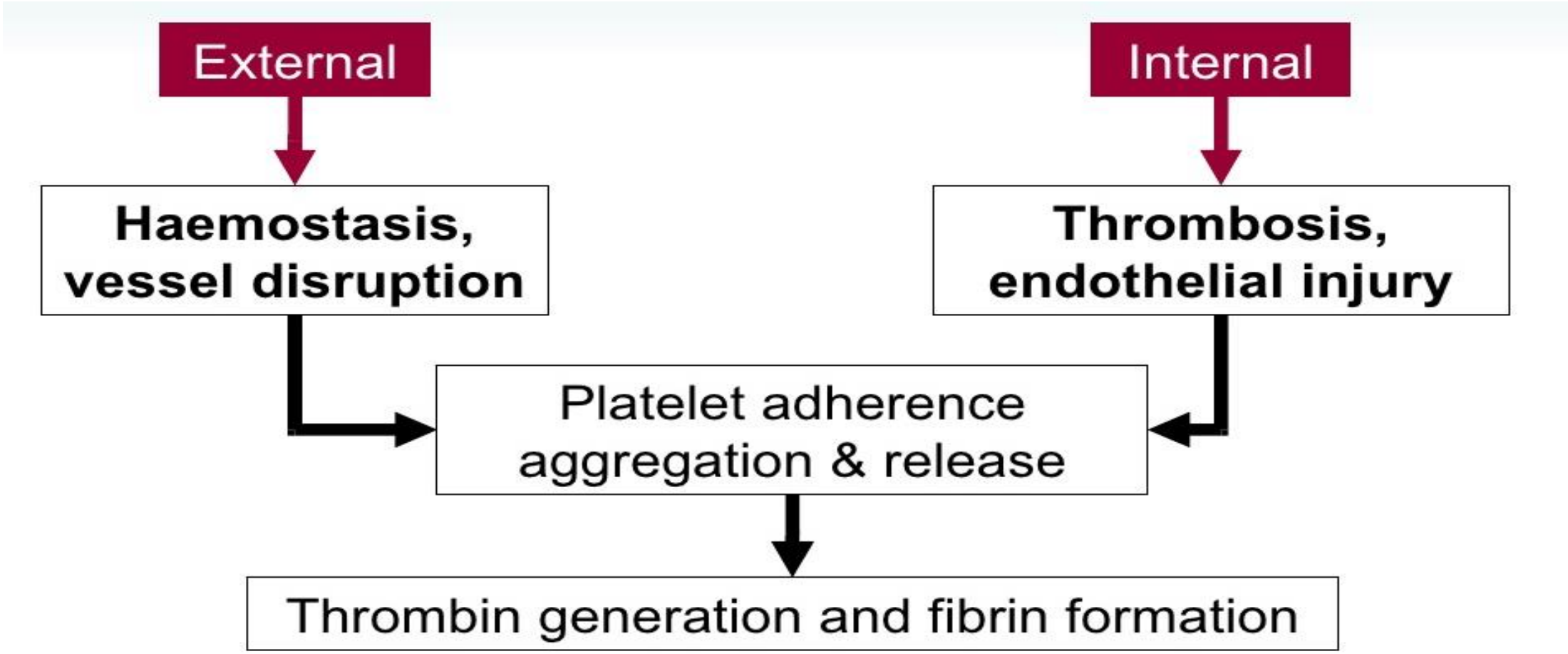
Thrombosis

- Thrombosis is the process of formation of a fibrin blood clot.
- Platelets and a series of coagulant proteins (clotting factors) contribute to clot formation.
- An embolus is a small part of a clot that breaks and carried by blood flow to another part of the vascular system.
- Damage caused when the embolus becomes trapped in a small vessel, causing occlusion leading to ischemia or infarction of the surrounding tissue.
- Normal clot formation maintains the integrity of the vasculature in response to injury, but pathologic clotting can occur in many clinical settings.
- Abnormal thrombotic events include venous thromboembolism [DVT] , its primary complication, pulmonary embolism [PE]), as well as stroke and other systemic manifestations of embolization of clots that form within the heart.

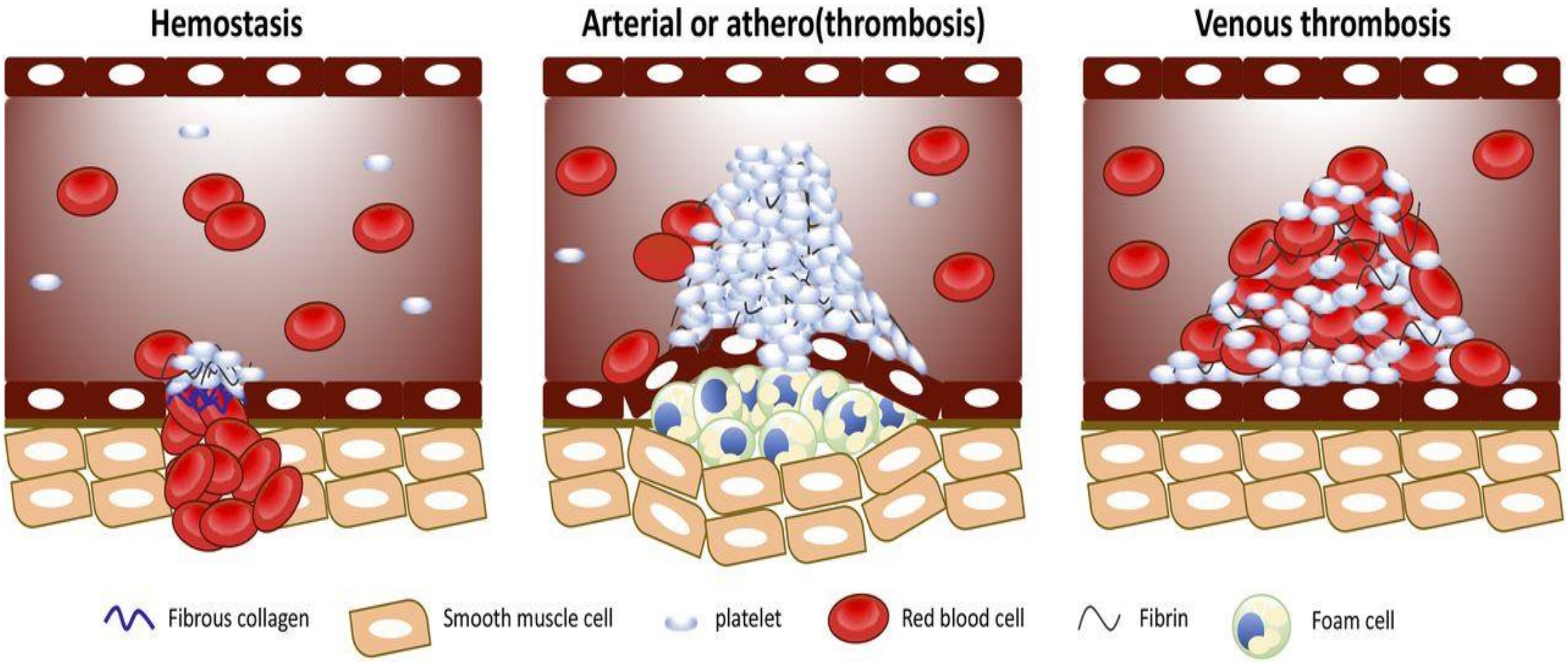
Thrombosis


External
Internal
Haemostasis, vessel disruption
Thrombosis, endothelial injury
Platelet adherence aggregation & release
Thrombin generation and fibrin formation

PATHOLOGIC THROMBI

- Pathologic thrombi are sometimes classified according to location and composition.
- Arterial thrombi are composed primarily of platelets, although they also contain fibrin and occasional leukocytes. Arterial thrombi generally occur in areas of rapid blood flow (i.e., arteries) and are typically initiated by spontaneous or mechanical rupture of atherosclerotic plaques followed by aggregation of platelets.
- Venous thrombi are found primarily in the venous circulation and are composed almost entirely of fibrin and erythrocytes. Venous thrombi have a small platelet head and generally form in response to either venous stasis or vascular injury after surgery or trauma. The areas of stasis prevent dilution of activated coagulation factors by normal blood flow.

Hemostasis , Arterial and venous thrombus



Thrombo-embolic events

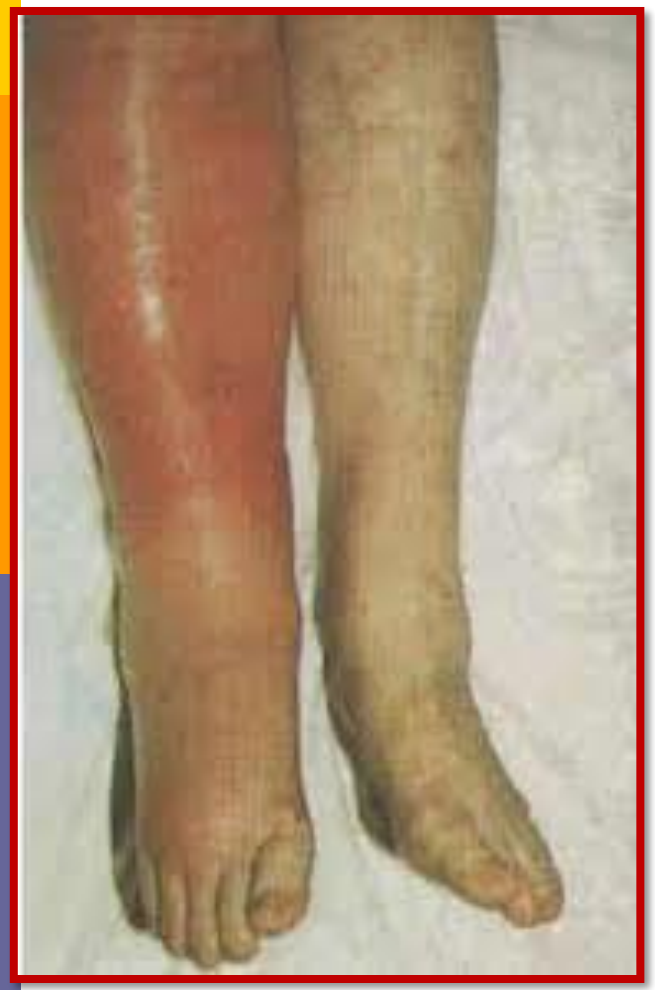
- Venous thrombo embolism VTE
  - DVT
  - PE
- Acute Coronary syndrome
  - STEMI
  - UA/NSTEMI

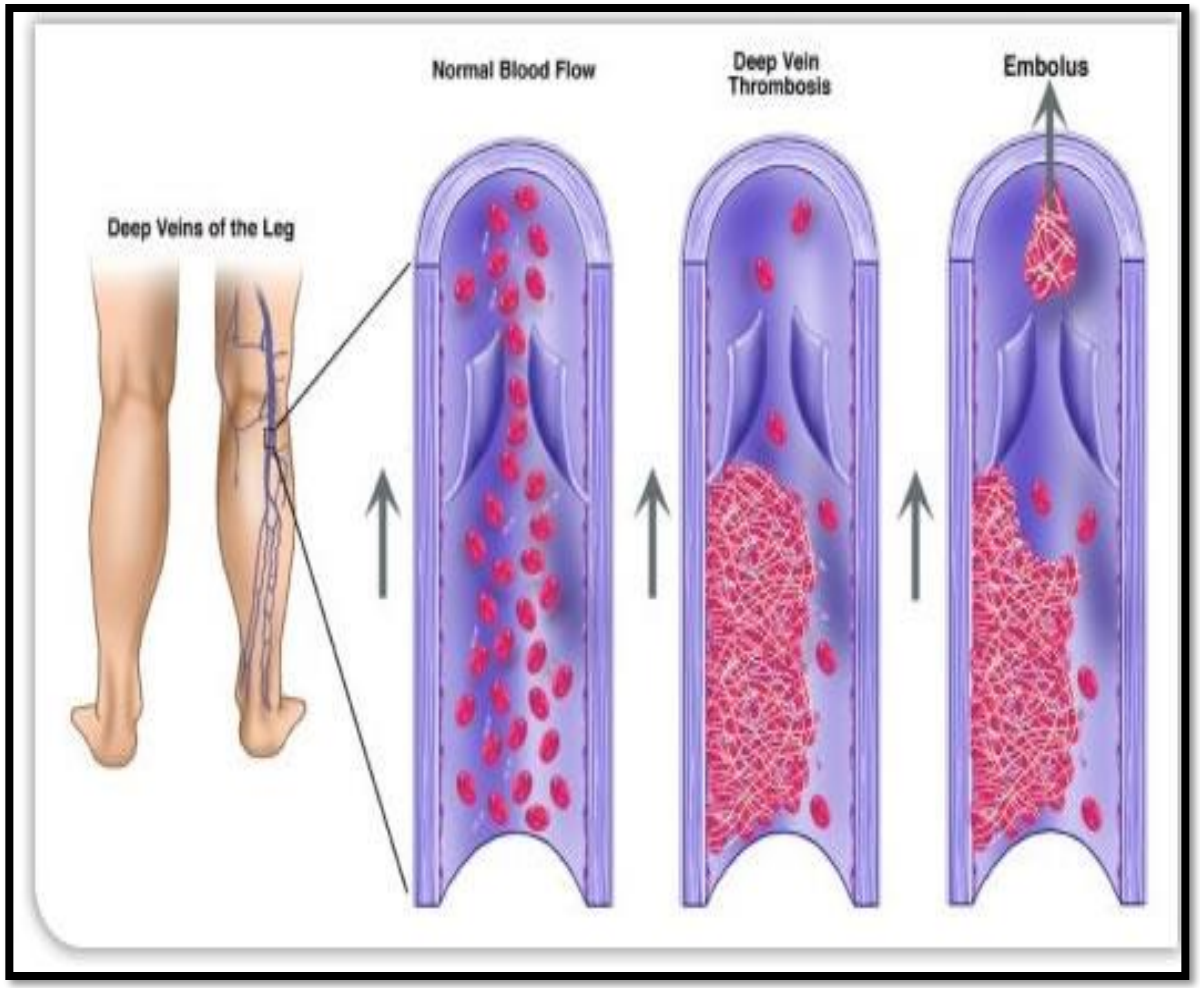
VTE

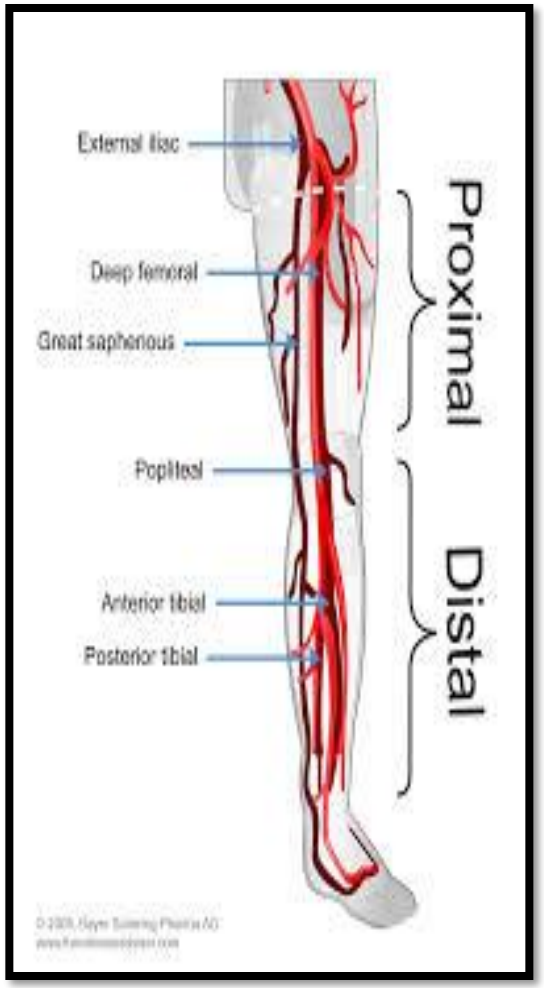
- VTE is one of the most common cardiovascular disorders.

- VTE is manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE) resulting from thrombus formation in the venous circulation.

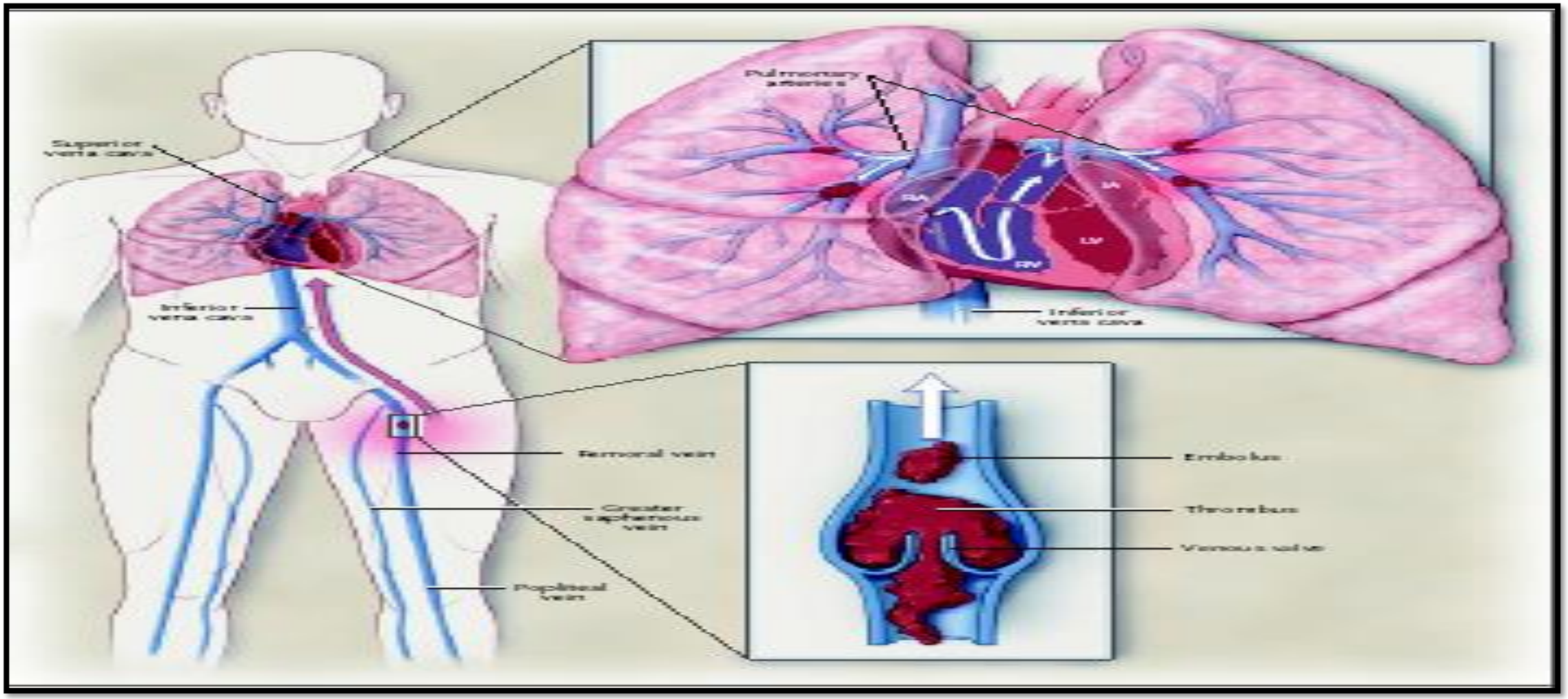
DVT:



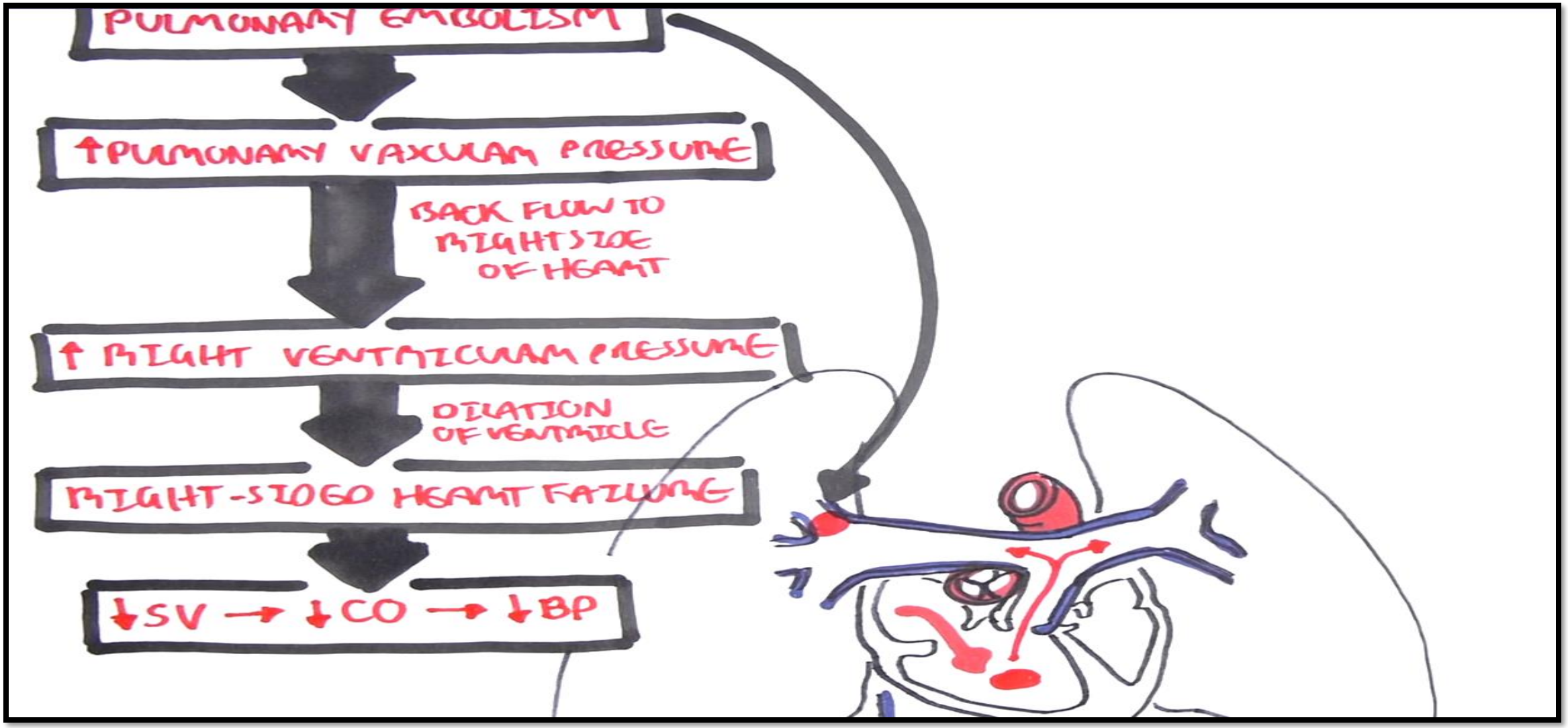

Normal Blood Flow
Deep Vein Thrombosis
Embolus
Deep Veins of the Leg


External iliac
Deep femoral
Great saphenous
Popliteal
Anterior tibial
Posterior tibial
Proximal
Distal

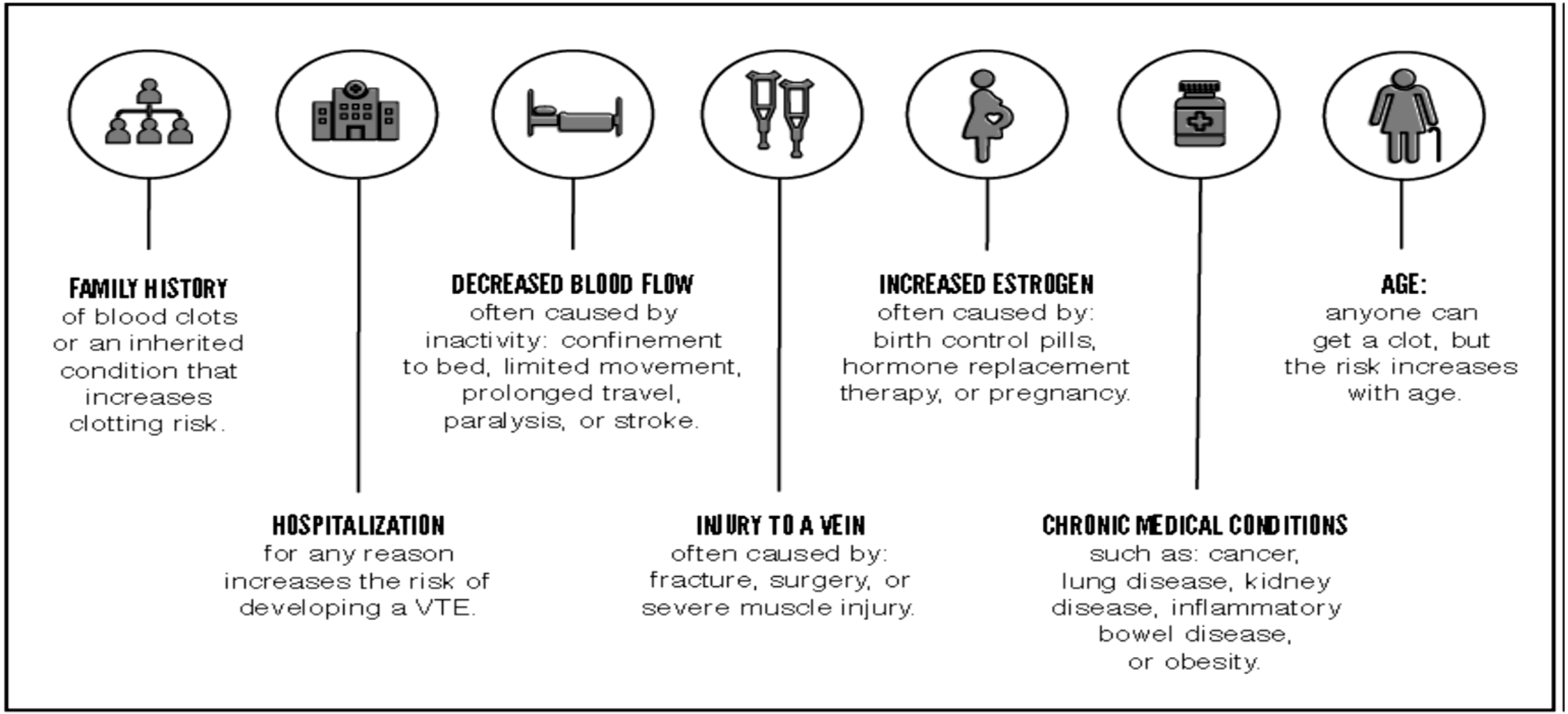
PE


Pulmonary artery
Superior vena cava
Inferior vena cava
RA
LA
RV
LV
Inferior vena cava
Femoral vein
Greater saphenous vein
Popliteal vein
Embolus
Thrombus
Venous valve

PE

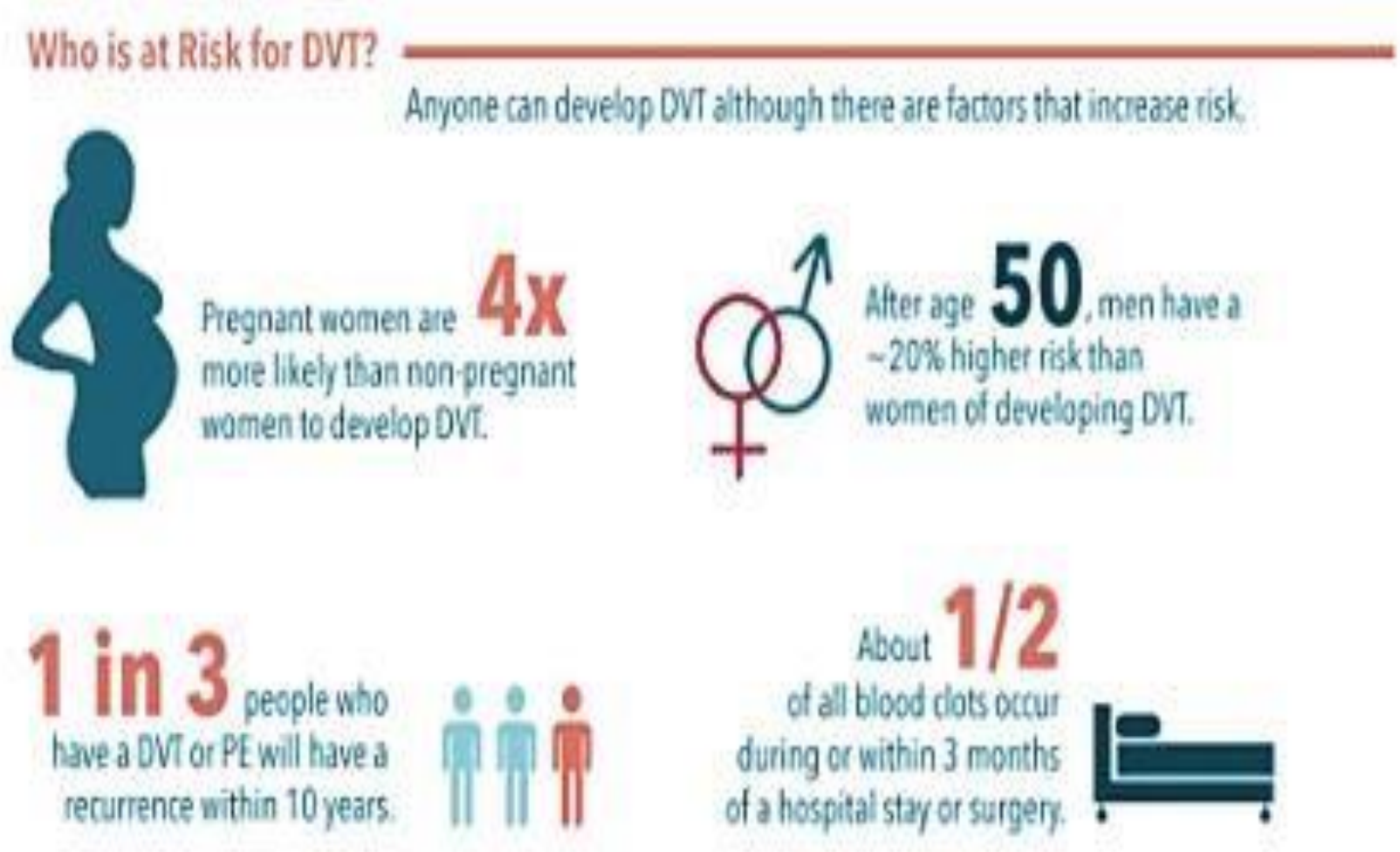

PULMONARY EMBOLISM
↑PULMONARY VASCULAR PRESSURE
BACK FLOW TO RIGHT SIDE OF HEART
↑ RIGHT VENTRICULAR PRESSURE
DILATION OF VENTRICLE
RIGHT-SIDED HEART FAILURE
↓SV → ↓CO → ↓BP

Risk factors for VTE



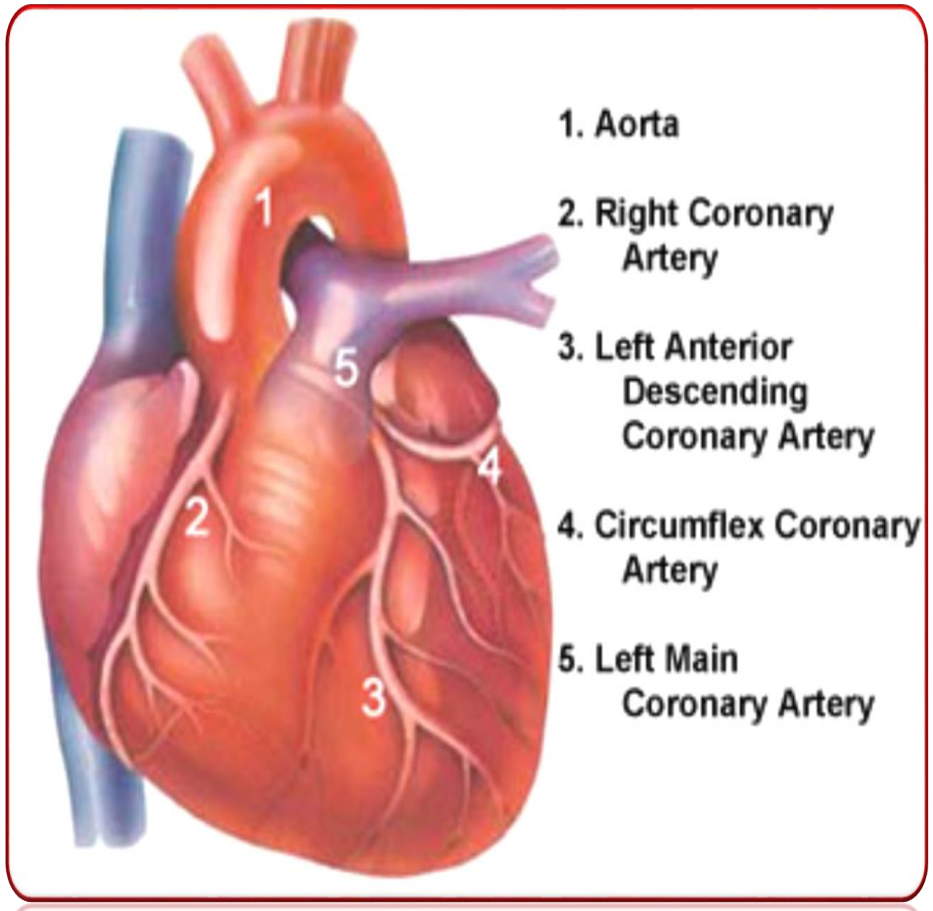
Risk factors

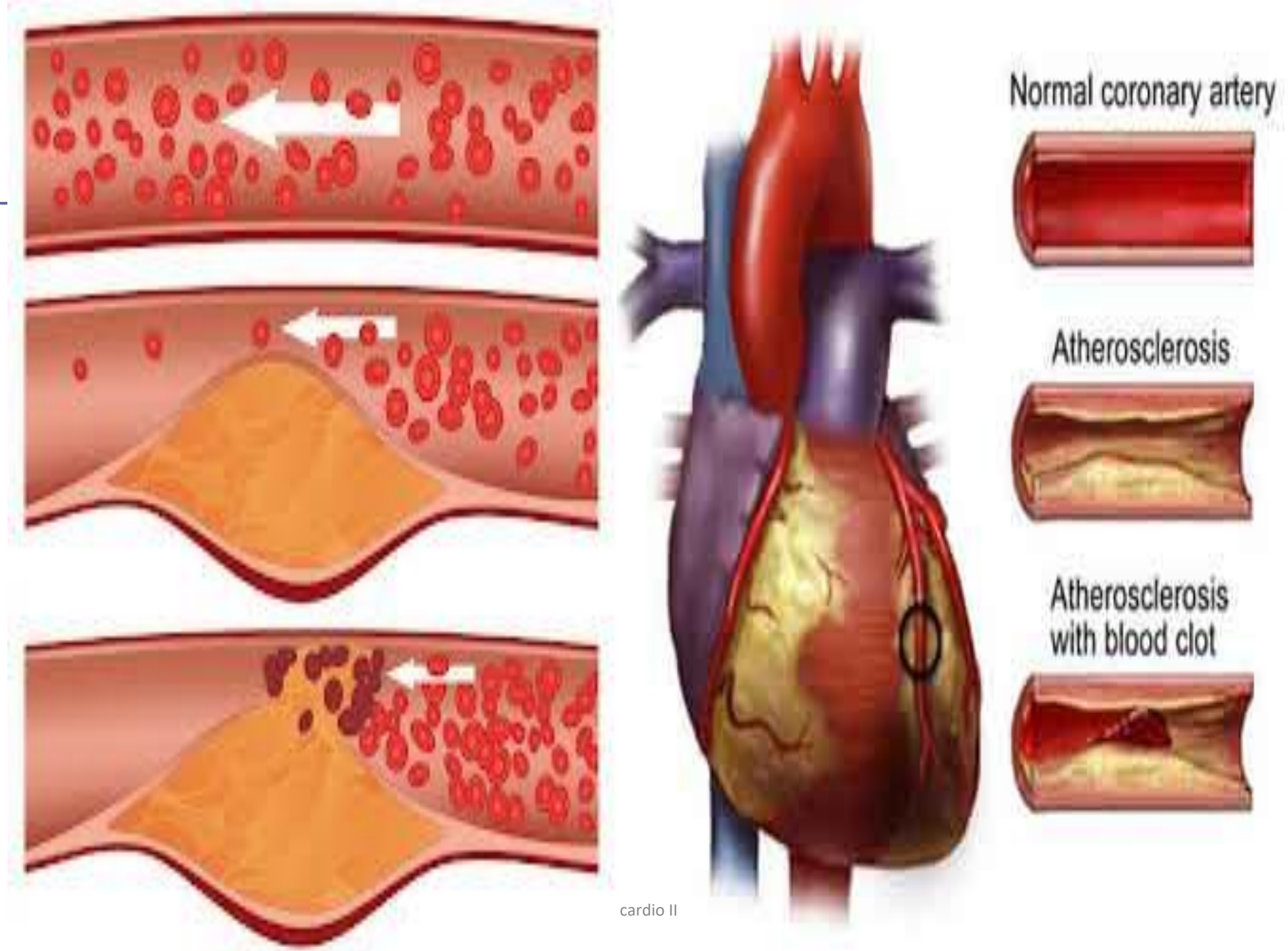
Risk factors



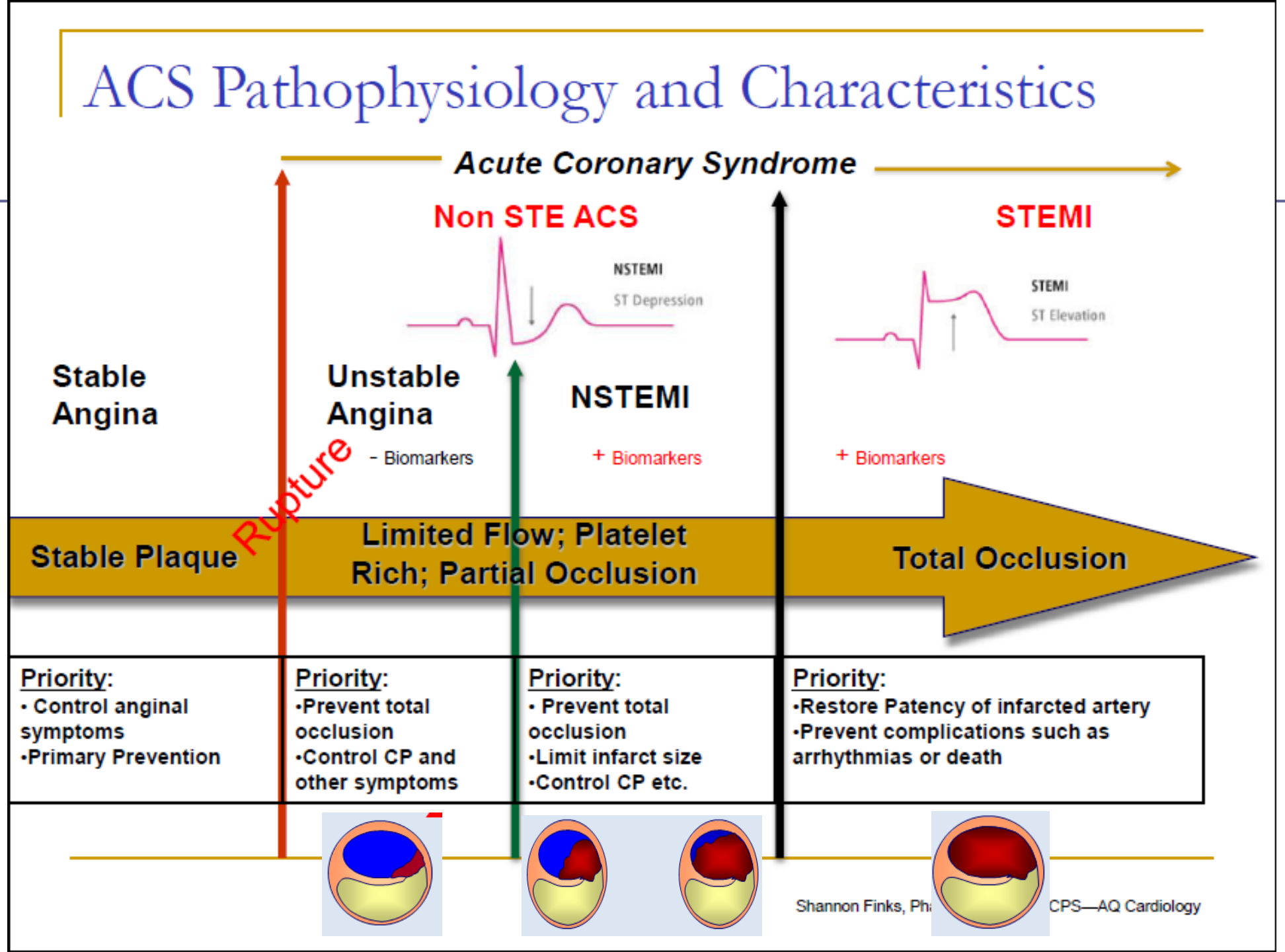
Acute Coronary Syndrome

- Acute coronary syndrome (ACS) are a spectrum of conditions compatible with acute myocardial ischemia or infarction due to an abrupt reduction in coronary blood flow.

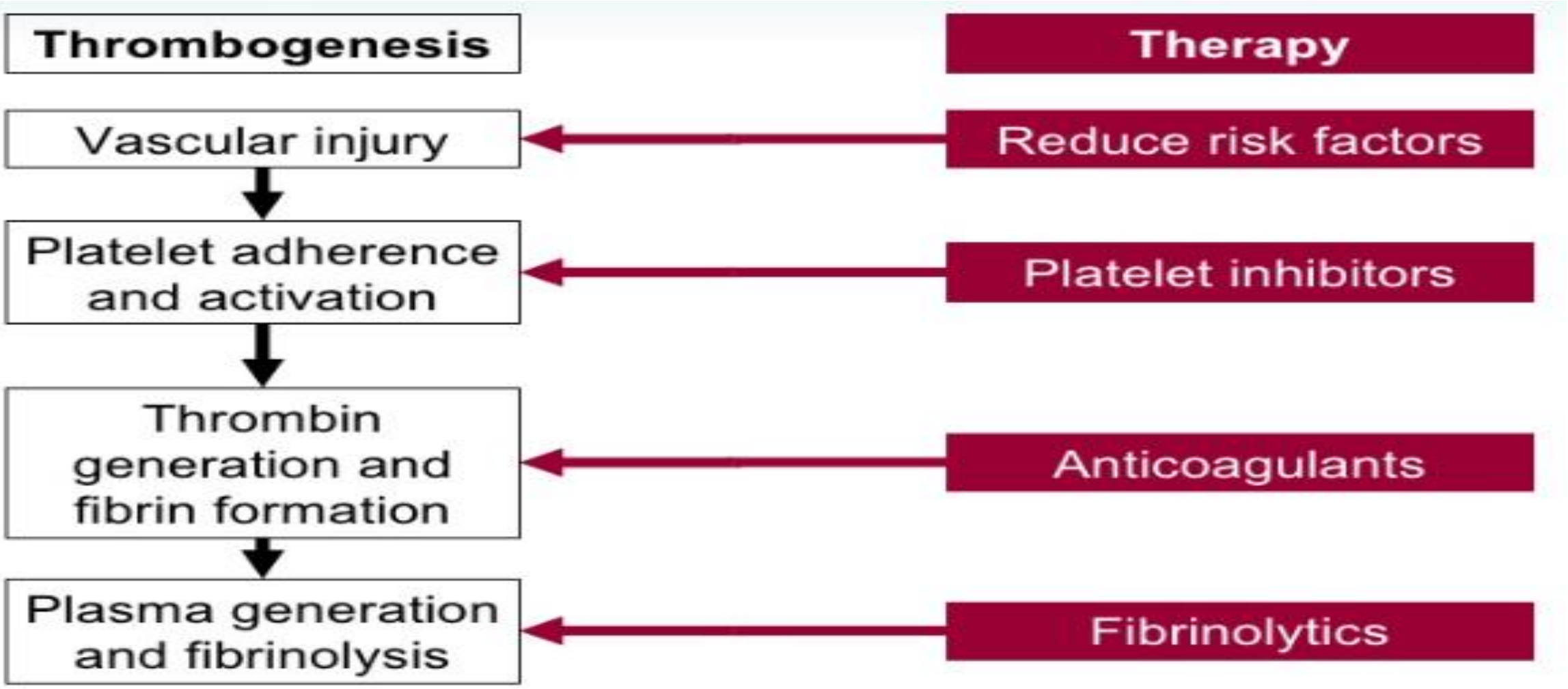



Normal coronary artery
Atherosclerosis
Atherosclerosis with blood clot

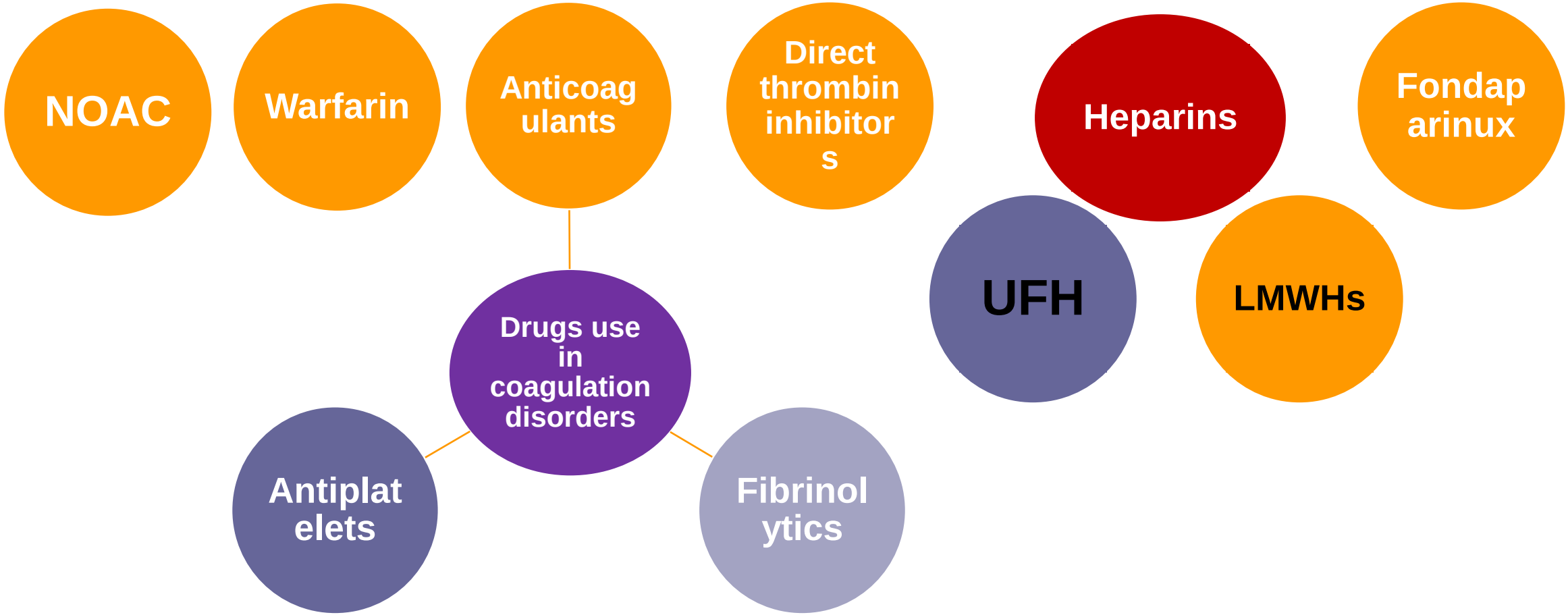
ACS Pathophysiology and Characteristics



Antithrombotic



Drugs use in coagulation disorders

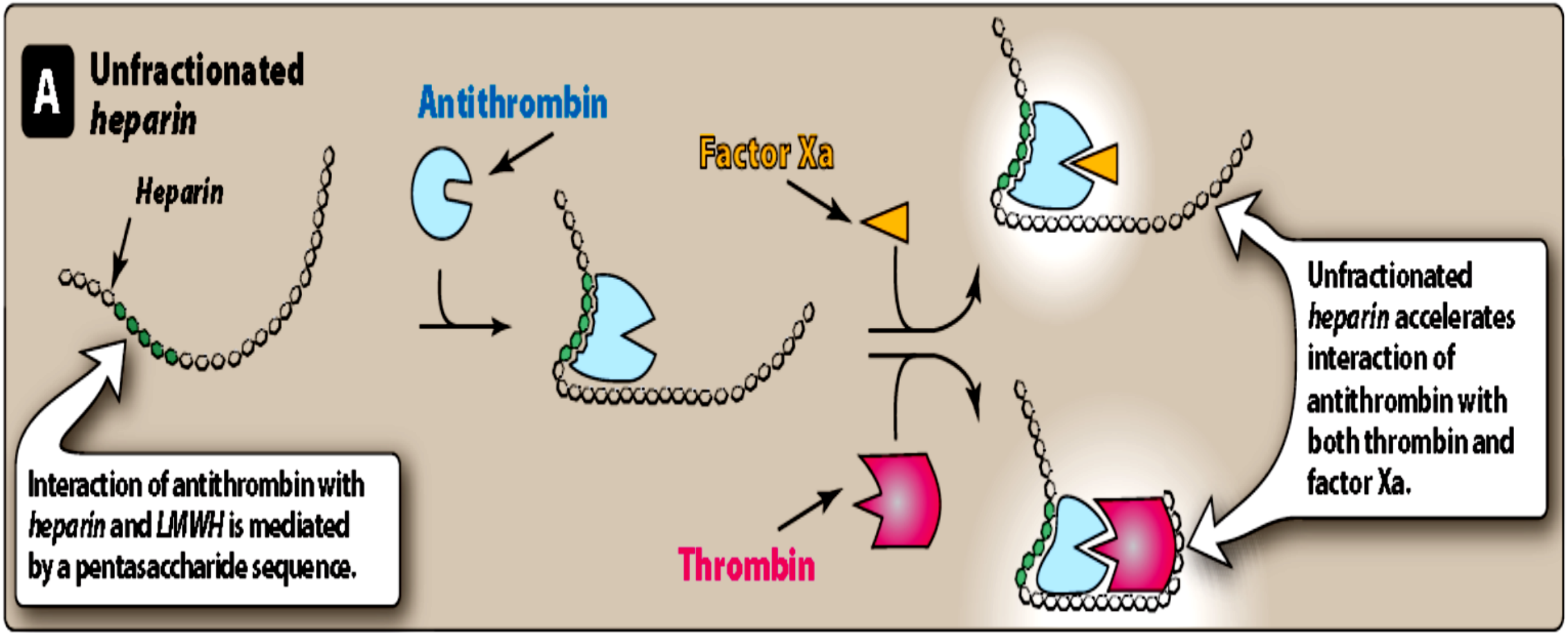


Heparin

- Heparin is a rapid-acting anticoagulant that is administered parenterally. Standard heparin (unfractionated heparin [UFH]) is a heterogeneous mixture of glycosaminoglycans of varying molecular weights obtained from bovine lung or porcine intestinal mucosa

- The action of heparin is facilitated by its binding to the naturally circulating anticoagulant ant thrombin (AT), a serine protease also referred to as heparin cofactor. Binding of heparin to AT accelerates the anticoagulant effect of AT. The heparin–AT complex attaches to and irreversibly inactivates factor IIa (thrombin) and factor Xa, as well as activated factors IX, XI, and XII.3 Approximately one-third of the molecules present in UFH bind to AT and provide the anticoagulant properties of heparin.

Heparin Mode of action



Heparin

- The remaining two-thirds of the heparin molecules bind to plasma proteins and to endothelial cells. In addition to its anticoagulant effects, heparin inhibits platelet function and increases vascular permeability; these properties contribute to the hemorrhagic effects of heparin.

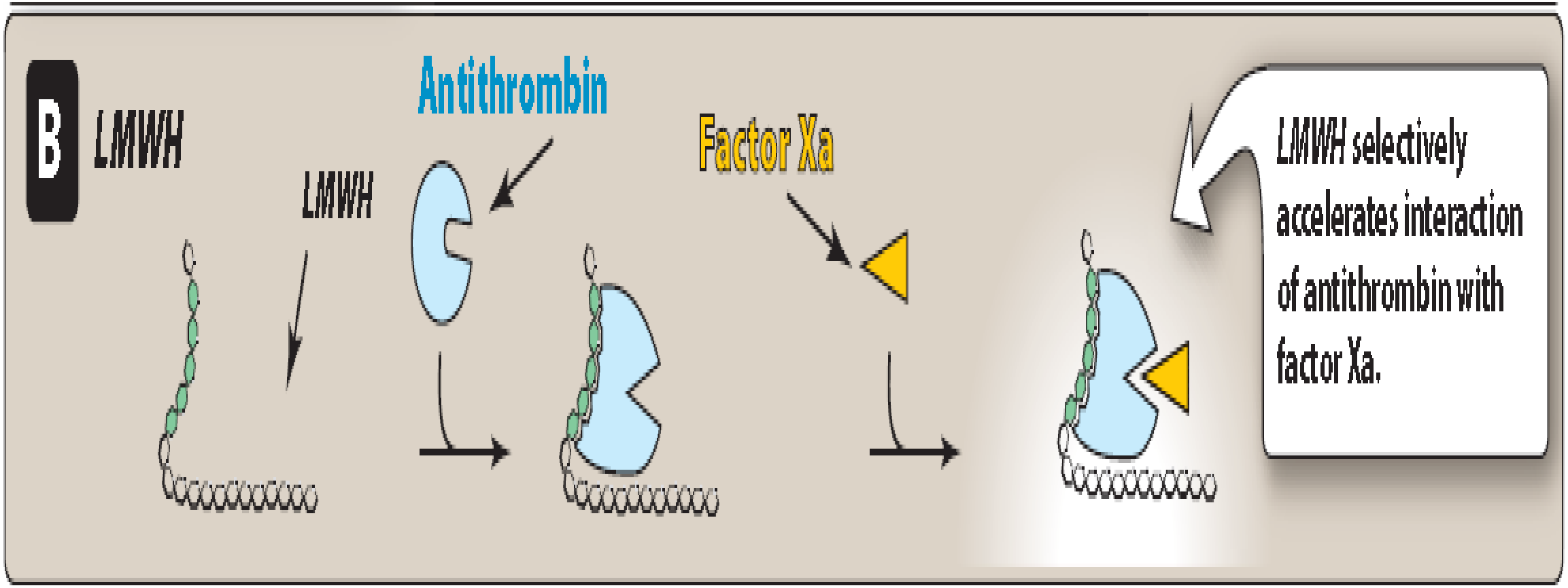
- Heparin may be administered intravenously (IV) by continuous infusion, or subcutaneously (SC), although its bioavailability is significantly reduced by SC administration. Intramuscular administration of heparin (as well as intramuscular administration of other drugs in patients who are anticoagulated) should be avoided because of the potential for hematoma formation.

Low molecular weigh heparin

- By using chemical or enzymatic depolymerization techniques, unfractured weight heparin can be separated into fragments based on molecular weight.

- Several low molecular weight heparin molecules have been isolated and commercially marketed as anticoagulants

Mode of action of low molecular weight heparins



UFH vs LMWH

Property	UFH	LMWH
Molecular weight range[a]	3,000–30,000	1,000–10,000
Average molecular weight[a]	12,000–15,000	4,000–5,000
Anti-Xa: anti-IIa activity	1:1	2:1–4:1
aPTT monitoring required	Yes	No
Inactivation by platelet factor 4	Yes	No
Capable of inactivation of platelet-bound factor Xa	No	Yes
Inhibition of platelet function	++++	++
Increases vascular permeability	Yes	No
Protein binding	++++	+
Endothelial cell binding	+++	+
Dose-dependent clearance	Yes	No
Primary route of elimination	Saturable binding processes Renal	Renal
Elimination half-life	30–150 minutes	2–6 hours

THE BIG QUESTION: Why Use LMWH vs. UFH?

- NO monitoring in majority of patients - when given on a weight-adjusted basis, the LMWH anticoagulant response is predictable and reproducible
- Higher bioavailability - 90% vs 30%
- Subcutaneous vs. IV
- Outpatient vs. inpatient
- Lower incidence of HIT

THE BIG QUESTION: Why Use LMWH vs. UFH?

- More predictable anticoagulant response needing little or no laboratory monitoring
- Unfractionated heparin is mixture of large and small heparin fractions
- Unfractionated heparin metabolism
  - Removes larger biologically inactive fractions quickly
  - Leaves behind smaller active fractions removed more slowly
- LMWH = uniform size
- LMWH = metabolized at a slower rate
  - Longer half-life - 4 to 6 hours vs 0.5 to 1 hour and renal (slower) vs hepatic clearance .

THE BIG QUESTION: Why Use LMWH vs. UFH?

- Pharmacokinetics of UH are influenced by its bindings to plasma protein, endothelial cell surfaces, macrophages, and other acute phase reactants
- Less inhibition of platelet function potentially less bleeding risk, but not shown in clinical use
- Lower incidence of thrombocytopenia(low blood platelet count)
- More practice for out patient use

LMWH Monitoring

- Anti Xa
- Unnecessary in majority of patients
- Samples should be drawn 4 hours after dosing
- May be useful in specific instances and patients that need monitoring are:
  - Pregnant
  - Pediatric
  - Renal insufficiency
  - Prolonged therapy
  - Those at risk for bleeding
  - Obese patients with altered drug pK .

Anti Xa assay

- Therapeutic ranges of heparin are as follows:
  - LMWH: 0.5-1.2 IU/mL
  - UH: 0.3-0.7 IU/mL

- Prophylactic ranges of heparin are as follows:
  - LMWH: 0.2-0.5 IU/mL
  - UH: 0.1-0.4 IU/mL

Enoxaparin

Enoxaparin

- Enoxaparin is a low molecular weight heparin (LMWH) with anti-thrombotic properties
- FDA Approval – December, 1998
- Enoxaparin acts primarily on the coagulation factor Xa, and also, but to a lesser degree, on thrombin (factor IIa).

Enoxaparin Indications

- Prophylaxis/Treatment of DVT
  - Presurgical / Postsurgical
- Inpatient TX./ Outpatient Tx.
- Therapy of ACS

FDA Approved Indications for LMWH

Indication	Enoxaparin	Dalteparin	Tinzaparin
Abdominal surgery prophylaxis	X	X	
THR (inpatient) prophylaxis	X	X	
THR (extended prophylaxis)	X		
TKR prophylaxis	X		
DVT ± PE inpatient	X		X
DVT outpatient	X		
NSTE ACS	X	X	
STEMI	X		
Medically ill prophylaxis	X	X	
Extended treatment in cancer patients		X	

Brands of Enoxaparin in Uganda

- Clexane –originator brand
- Lomoh
- Parin-E
- Noxa
- Enoxamed –Newest
- Many more

Observations and challenges

- The originator brand despite its cost remains the most trusted and stocked brand in Ugandan hospitals
- Complaints of quality issues by the doctors of other brands
- Despite the trust, their has been challenges of scarcity of the originator brand time after time
- The newest brand (Enoxamed) seems to be the solution to issues of quality, cost and availability

Why Enoxamed

- Manufactured by one of the oldest laboratories in Tunisia .(UNIMED) has over 30 years of expertise and leadership in sterile injectable medicines production .
- Enoxamed(enoxaparin) is produced from natural heparin
- Enoxaparin is the market leader of the five currently marketed low molecular weight heparins
- Assured of the same potency and efficacy like that of the originator
- By 30% cheaper than the originator

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Research Article
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Comparability of "Enoxamed" a Tunisian Generic Enoxaparin with the Originator Product: Non-clinical and Clinical Studies

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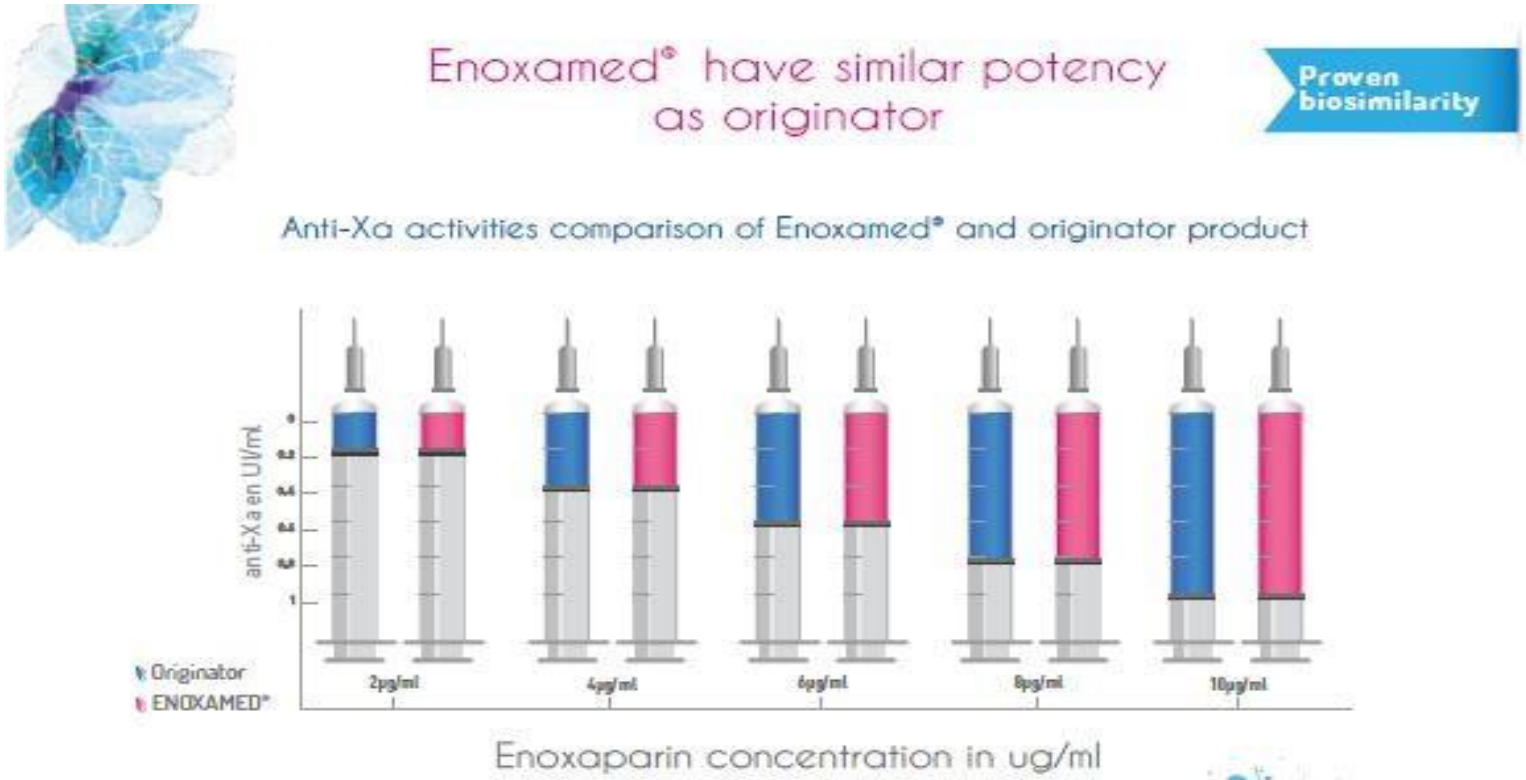
Fact 1


Enoxamed® have similar potency as originator
Proven biosimilarity
Anti-Xa activities comparison of Enoxamed® and originator product
anti-Xa en UI/mL
Originator
ENOXAMED®
2µg/ml
4µg/ml
6µg/ml
8µg/ml
10µg/ml
Enoxaparin concentration in ug/ml
In Vitro study* Comparative study of the anticoagulant activity of Enoxamed® and originator product.
Study carried out in the hematology laboratory of Tenon Hospital, Paris.

Considering the Non-clinical in vitro study

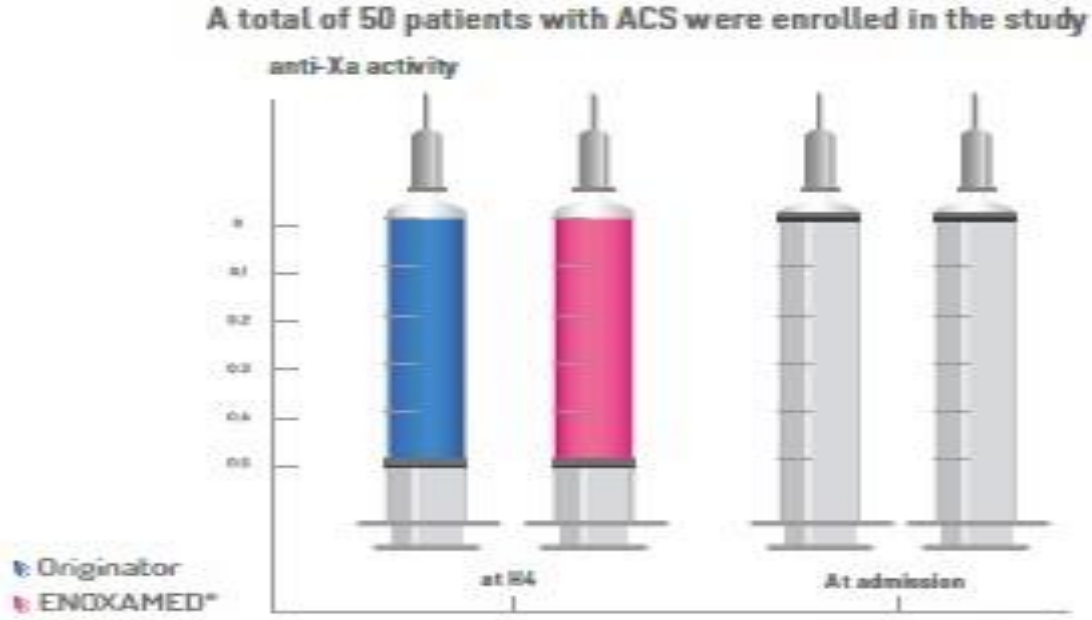
There were no statistical differences between Enoxamed and the original brand . Enoxamed has similar potency as originator

Fact 2

Proven biosimilarity

Enoxamed® is as effective and well tolerated as the originator

Anti-Xa activities comparison of Enoxamed® and originator product



Clinical study* comparing the anti-Xa activity of Enoxamed® and the originator product

Considering the phase III clinical study result

- There were no significant differences between Enoxamed and the originator groups with regard to the demographic characteristics .
- No significant difference with regard to death and major adverse cardiovascular events(MACE)t 30 days after initial admission between the two groups
- No significant hemorrhagic complications in both groups during follow up
- Enoxamed is as effective and well tolerated as the originator .

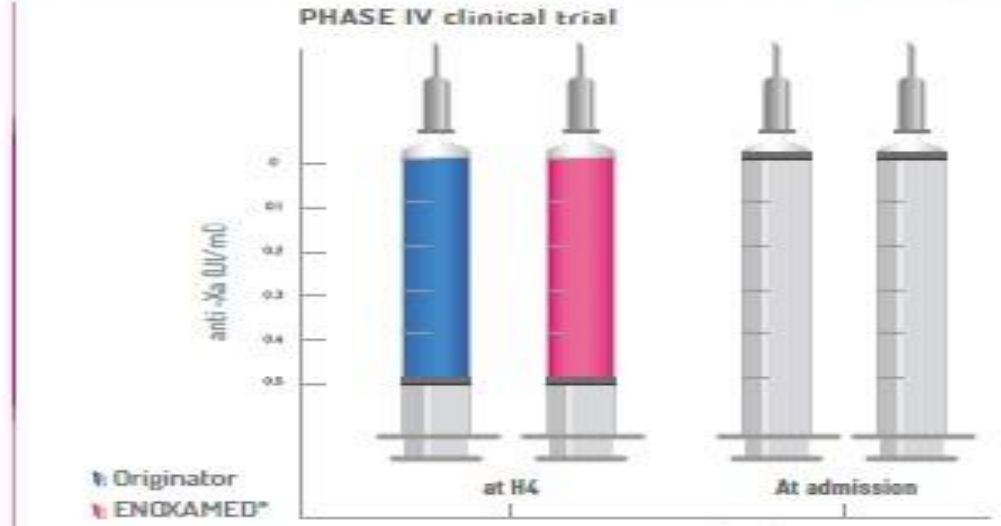
Fact 3

Enoxamed® is **similar** to the originator in terms of **efficacy** and **tolerance**

Proven biosimilarity

100%
of the patients
tolerated well
the treatment

Anti-Xa activities comparison of Enoxamed® and originator product



Post Marketing Authorization P.R.O.B.E Clinical Study **
About 238 patients Multicentric study

Discussion

- There was no significant differences between enoxamed and the originator groups with regard to the demographic characteristics .
- No significant haemorrghic complications in both groups during follow up.
- No significant difference with regard to death and MACE at 30 days after the initial admission between the two groups .
- Enoxamed prove comparability and then the main regulatory criteria and bioequivalence with the originator product .

Indications and posology

- A- prophylaxis of VTE in surgery
- In the event of a moderated risk surgery and when patients do not present a high risk of thromboembolism, effective prevention is by daily injection of a dose of 4000IU .The treatment regimen includes two hours before surgery .
- For cases of high thrombogenic risk , the treatment regimen includes an initial injection of 4000IU anti Xa performed 12 hours before the procedure and an injection of 2000IU anti Xa 2 hours before the injection .

Duration of treatment

- Treatment with LMWH , with the usual techniques of elastic compression of the lower limbs must be maintained at full and active ambulation of the patient .
- General surgery, duration of LMWH treatment must be less than 10 days out of a particular risk of venous thrombo embolism .
- The benefit of prophylaxis in hip orthopedic surgery was established by Enoxaparin injection at a dose of 4000IU ant Xa per day for 4-5 weeks was established .

Duration of treatment ctd

- If the venous thrombo embolic risk persists beyond the recommended treatment period, its necessary to consider further prophylaxis , including oral anticoagulants .
- However, the clinical benefit of a long term treatment with LMWH or ant-vitamin k is not evaluated at present .

Prophylactic treatment in medical setting

- The dosage is 4000IU for a period of 6-14 days.

Curative treatment of DVT , with or without PE

- Any suspicion of DVT must be quickly confirmed by appropriate examinations .
- Frequency of administration : 2 injections per day, 12 hours apart.
- Dose administered : The dose per injection is 100IU ant –Xa per kg.
- The dosage of LMWH has not been evaluated by body weight in patients weighing more than 100kg or less than 40kg.

- LMWH may appear less effective for patients weighing more than 100kg or an increased bleeding risk for patients weighing less than 40kg.
- Specific clinical monitoring is required .
- Duration should not exceed 10 days .

Curative treatment of unstable angina

- Enoxaparin is administered in two subcutaneous injections per day(12 hours apart), 100 anti-Xa IU/kg each, in combination with aspirin (recommended dose: 75 to 325 mg orally , after minimum loading dose of 160mg).
- The recommended duration of treatment is 2 to 8 days , until clinical stabilization .

References

Applied therapeutic 11th ED

Lippincott pharmacology

ACCCP cardiology

ESC cardiology 2018

ASH 2019 VTE guidelines