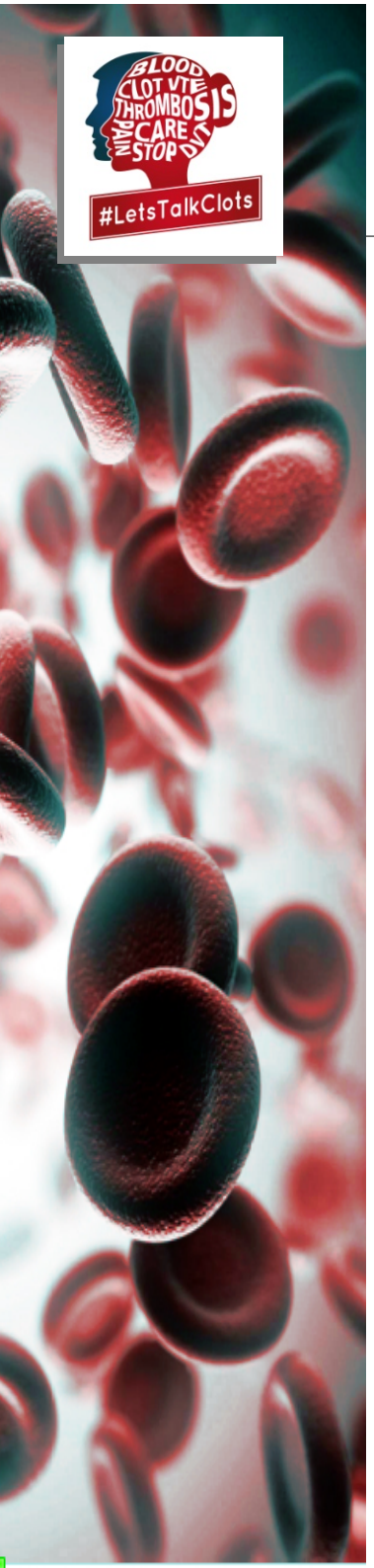
Blood clots? What are they?



Learning outcomes

- Some **simple** physiology/anatomy
- A few **definitions** 
- The **blood-coagulation** process
  - When it is helpful
  - When it is harmful
- Anti-platelets vs Anticoagulants
- Some history and drug design

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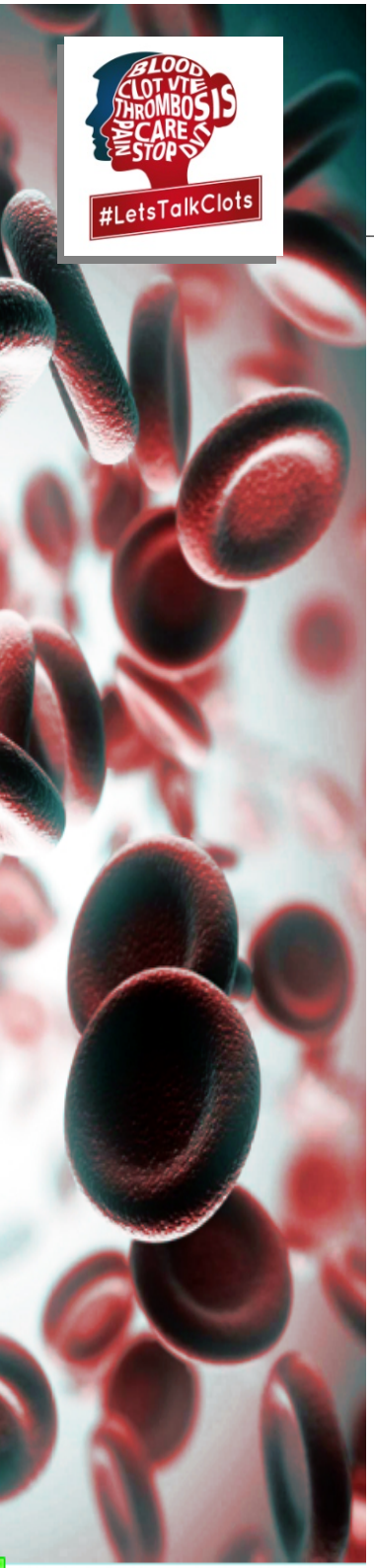

Blood circulation

The blood

- A liquid (plasma)
- Cells (Red/white/platelets)
- Molecules
  - Small (Glucose, amino-acids,ions...)
  - Big molecules (Albumin, haemoglobin…)
- Gas (Oxygen, carbon dioxide)

Transport system

- **Veins** (TO the heart)
- **Arteries** (Away from heart)

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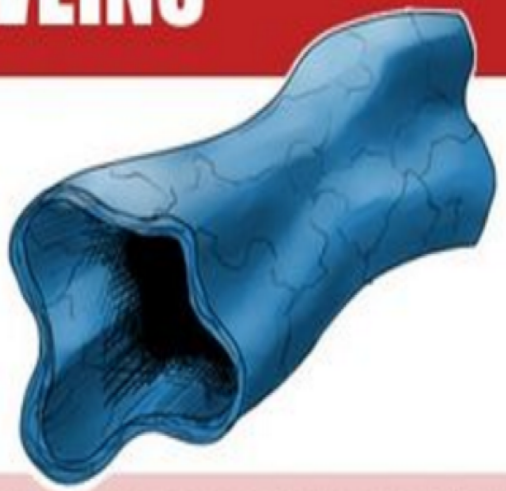
Veins and arteries

ARTERIES VS. VEINS

THIS IS AN ARTERY. IT IS A THICK WALLED VESSEL THAT CARRIES BLOOD AWAY FROM THE HEART UNDER HIGH PRESSURES. ITS WALLS ARE MADE OF SEVERAL LAYERS OF MUSCLE AND ELASTIC TISSUE, WHICH HELP IT MAINTAIN BLOOD PRESSURE TO FACILITATE THE CONTINUED MOVEMENT OF BLOOD.



THIS IS A VEIN. NOTICE HOW THE LUMEN (INSIDE SPACE) OF THE VEIN IS LARGER THAN THE LUMEN OF THE ARTERY. THE WALL OF THE VEIN IS ALSO THINNER THAN THE ARTERY'S AND HAS LITTLE TO NO ELASTIC TISSUE AND MUCH LESS MUSCLE. VEINS ARE LOW PRESSURE, HIGH CAPACITANCE VESSELS. THEY CONTAIN ABOUT 70% OF THE BLOOD IN THE BODY AT REST.

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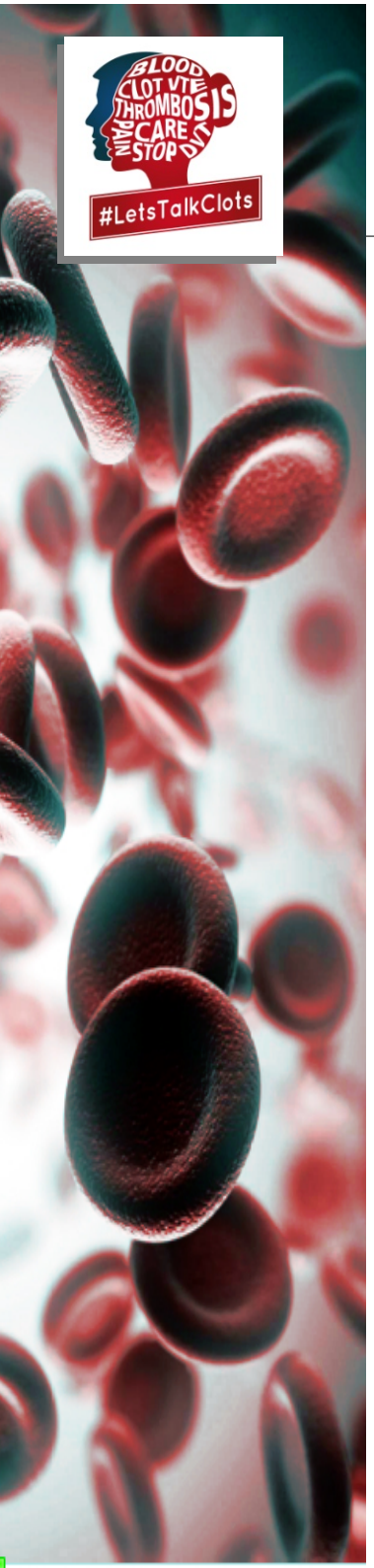


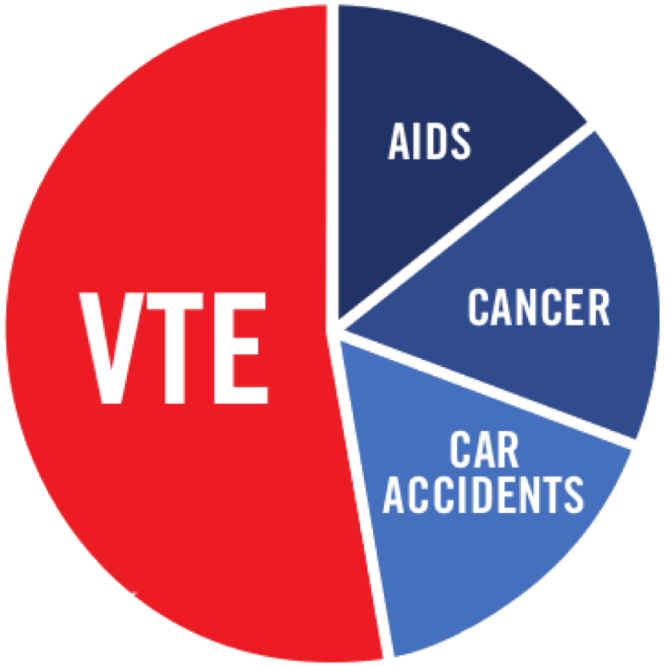
TWO processes → CLOT

Healthy process:

Hemostasis

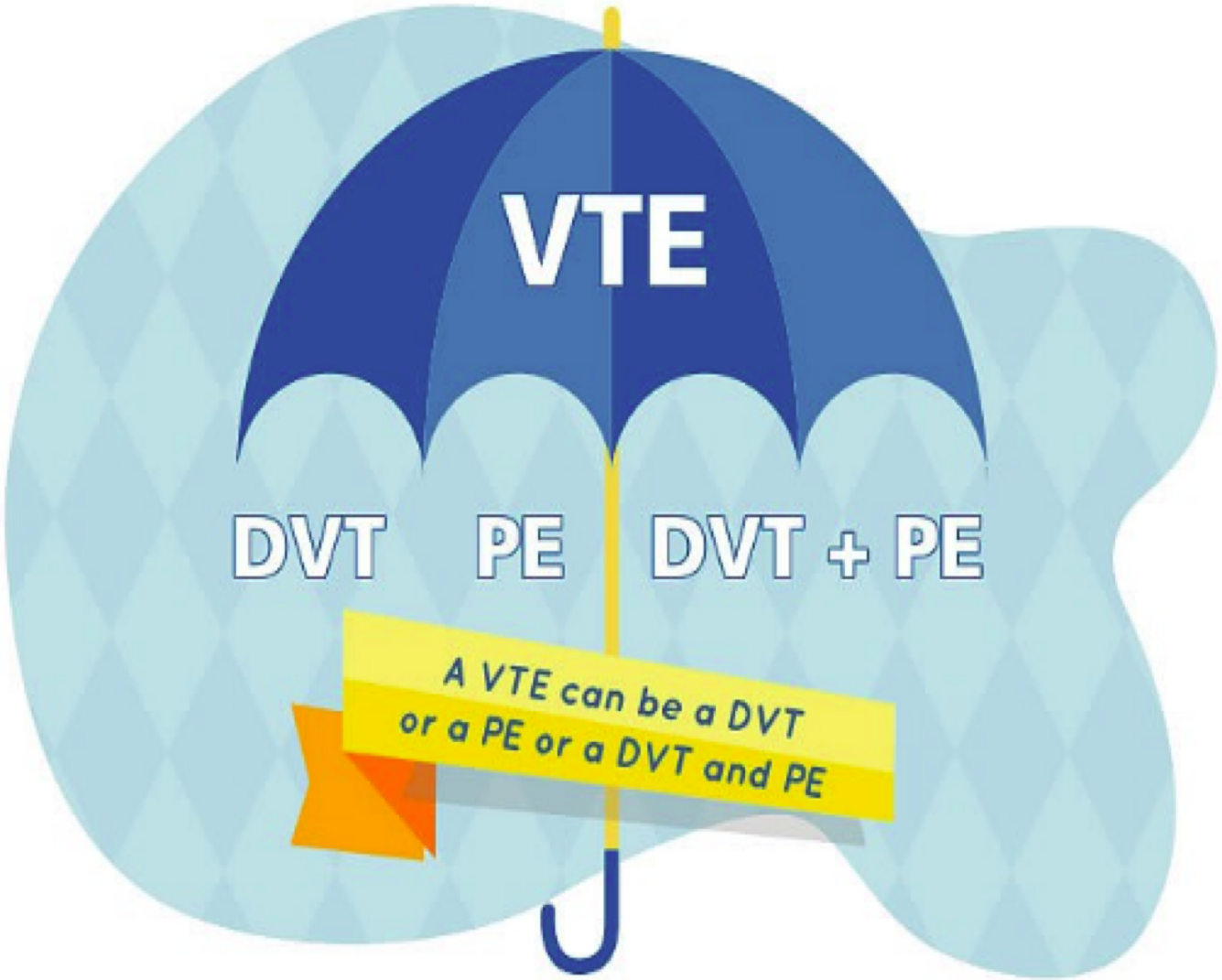
Unhealthy process:

Thrombosis



Thrombosis UK

Some terminology (Jargon)



Thrombosis UK

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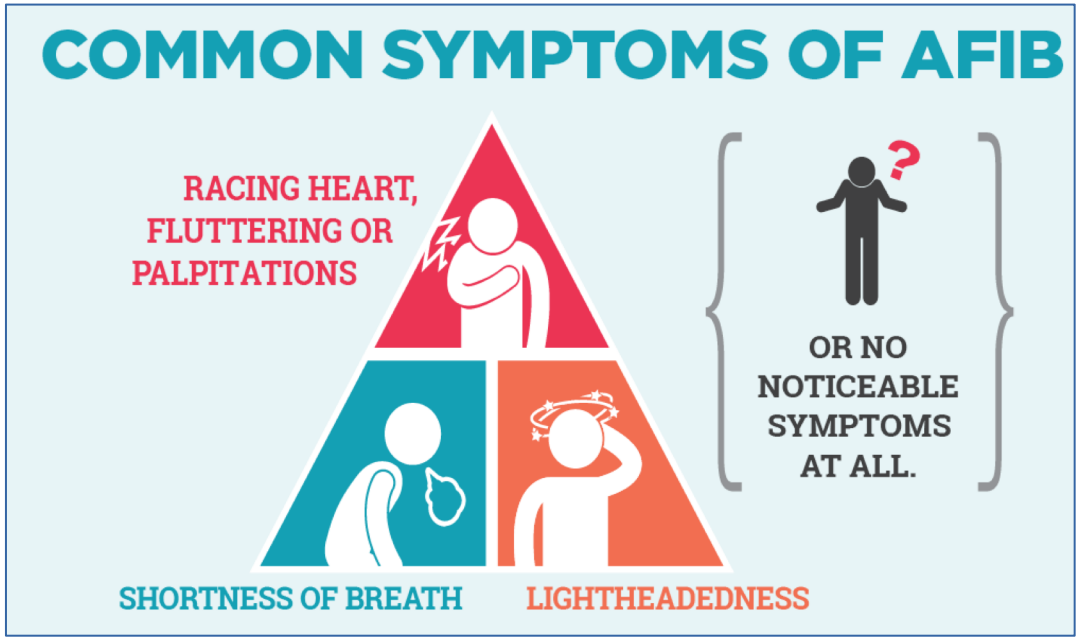
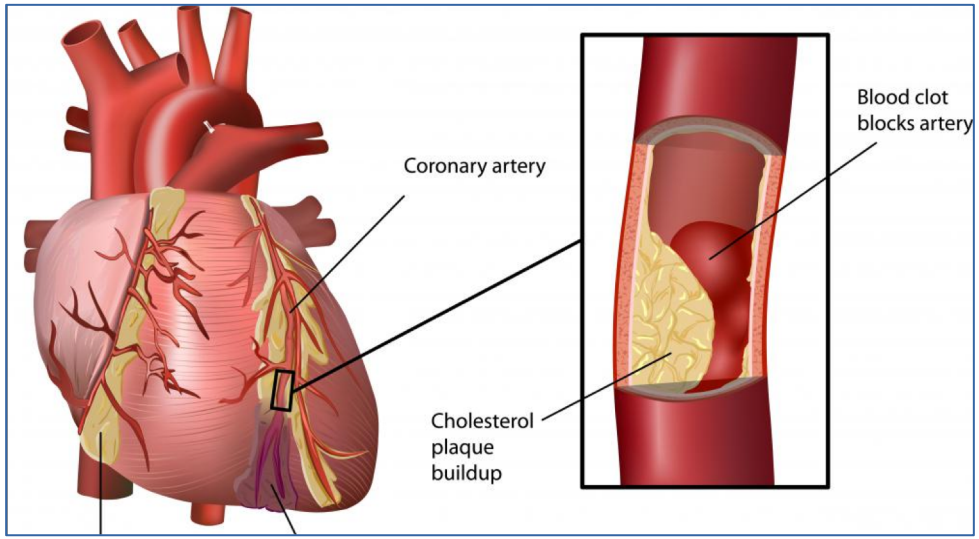


Atrial Fibrillation (AF / AFib)

Heart attack (MI, Myocardial Infarction)



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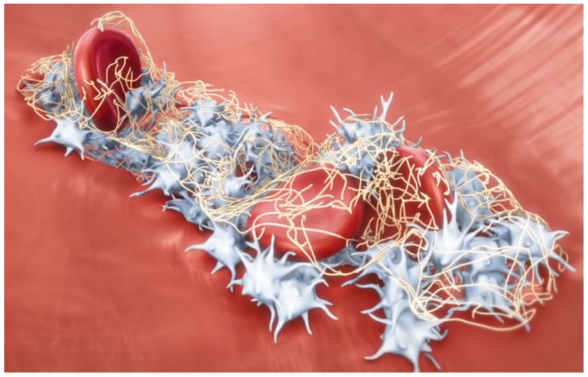
The healthy process (1/2)

- **Hemostasis (Haemostasis):**

Main actors:

- Endothelial cells (Inside the vessels/tubes)
- Muscles in vessel's wall (smooth muscles)
- Platelets (the **"plug"**) and the "**mesh**" (fibrin)

- A lot of molecules
  - ADP, TXa2, serotonin,Vit-K, Ca^{++}
  - Clot. Factors (thrombin IIa, Xa)
    - Fibrinogen, fibrin,



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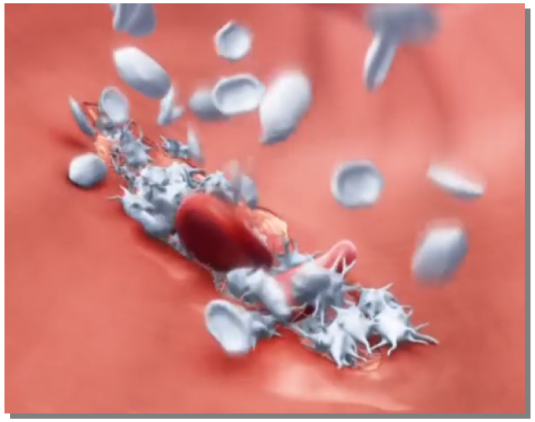
The healthy process (2/2)

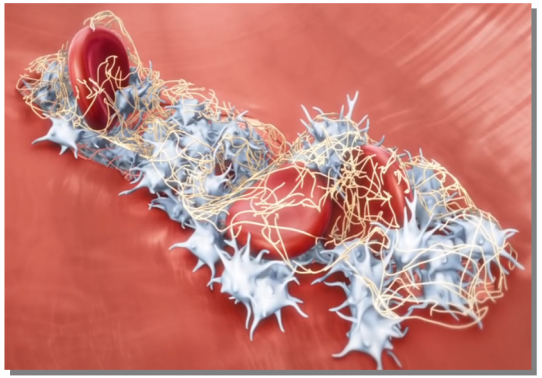
Primary hemostasis:

- Vasoconstriction
- Platelet plug formation



Secondary hemostasis:

- Coagulation
- formation of fibrin mesh



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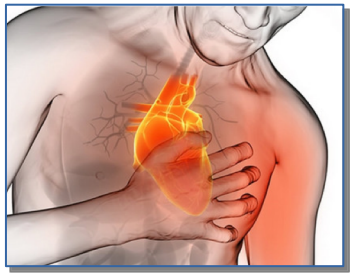
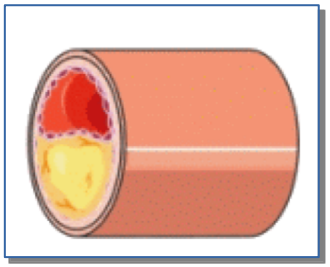
Thrombosis: The not so healthy process

- *Location, location, location*:
  - Leg (DVT: calf, thigh..)→ lung (PE), head (CVA), heart (heart attack, "coronary thrombosis")
- Arterial ("**white clot**")
  - Clot mainly made of **platelets**
- Venous ("**red clot**")
  - Clot mainly made of **fibrin**





Kiat T. Tan, MRCP; Gregory Y. H. Lip, MD Arch Intern Med. 2003;163(20):2534-2535. doi:10.1001/archinte.163.20.2534-a

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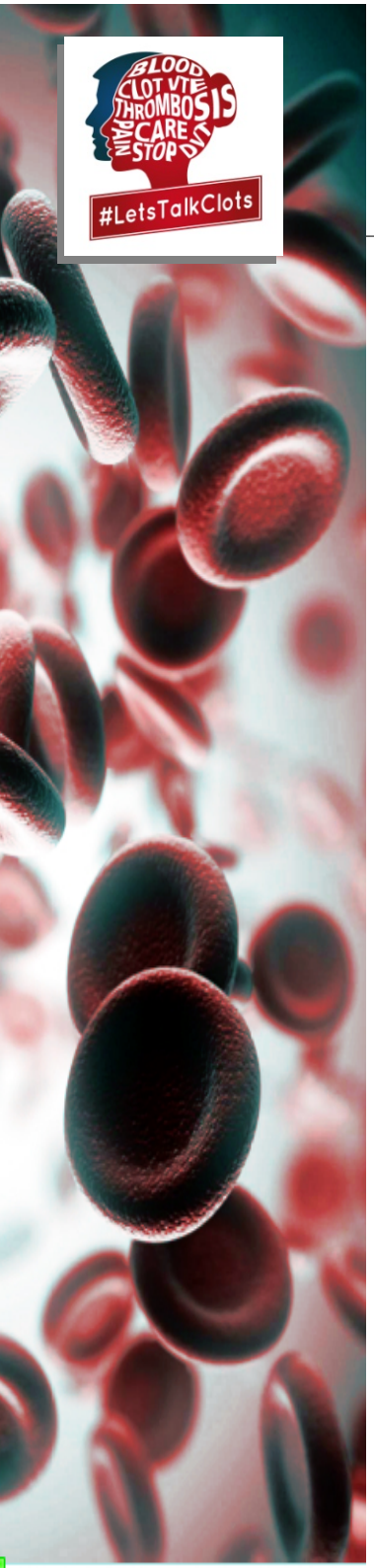

Main risk factors

STRONG RISK

- Being in the hospital for an extended time
- Having surgery *(especially hip, knee and cancer-related surgery)*
- Not moving for long periods of time *(e.g., due to bedrest or long travel)*

MODERATE RISK

- Age (60+)
- Personal or family history of blood clots
- Cancer/chemotherapy
- Using estrogen-based medication *(e.g., oral contraceptives or hormone replacement therapy)*

OTHER FACTORS

- Obesity
- Pregnancy or recent birth
- Smoking
- Alcohol consumption

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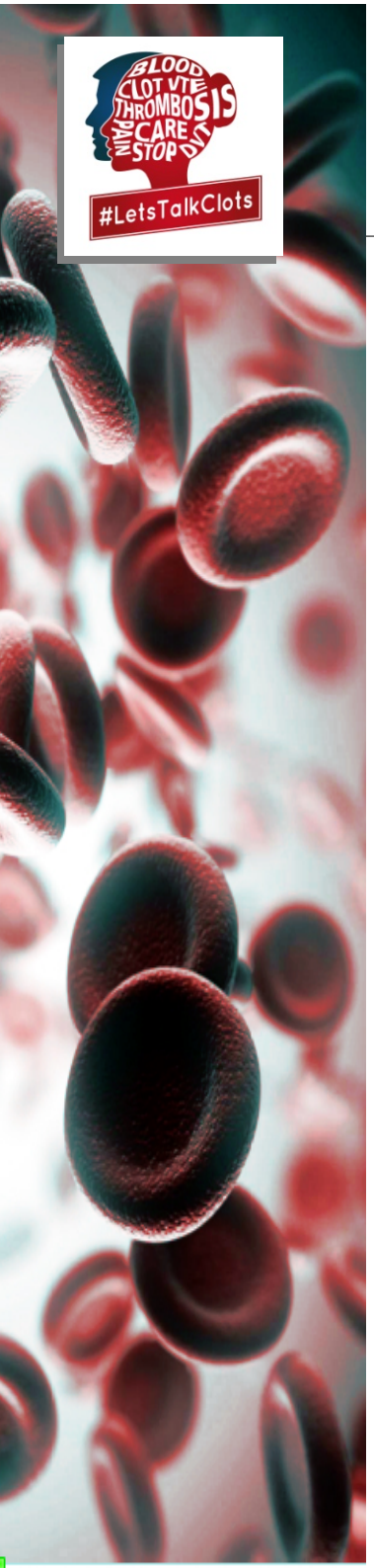

Anti-thrombotic drugs

- **Weapon varies according to the type of clot targeted**

  - **A**rterial (**"white clot"**)
    Clot mainly made of **platelets**
    - ANTIPLATELETS
      - Aspirin, clopidogrel etc...
  - **V**enous ("**red clot**")
    Clot mainly made of **fibrin**
    - ANTICOAGULANTS
      - Warfarin, Edoxaban, Dabigatran etc

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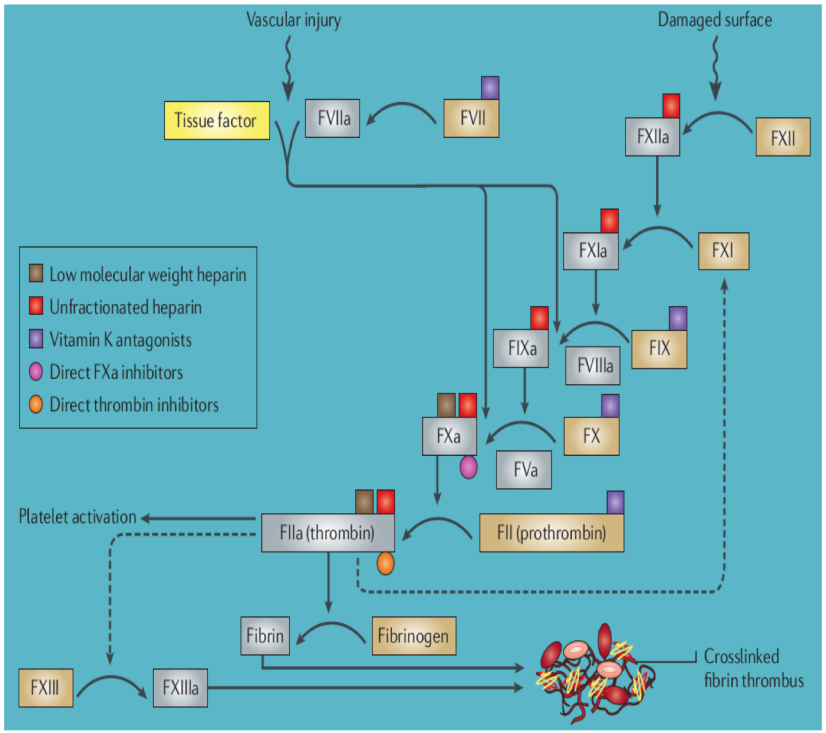
Anticoagulants: Really??

- **Anticoagulants**
  - **PARENTERAL ANTICOAGULANTS**
    - Heparin (UFH= Unfractionated Heparin)
    - Low Molecular Heparins
    - Heparinoids
    - Fondaparinux (Arixtra®)
    - Argatroban (Exembol®)
  - **ORAL ANTICOAGULANTS**
    - AVK (Anti Vitamin K)
    - Direct Oral Anticoagulants



Sabir, I. *et al.* (2014) *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2014.22

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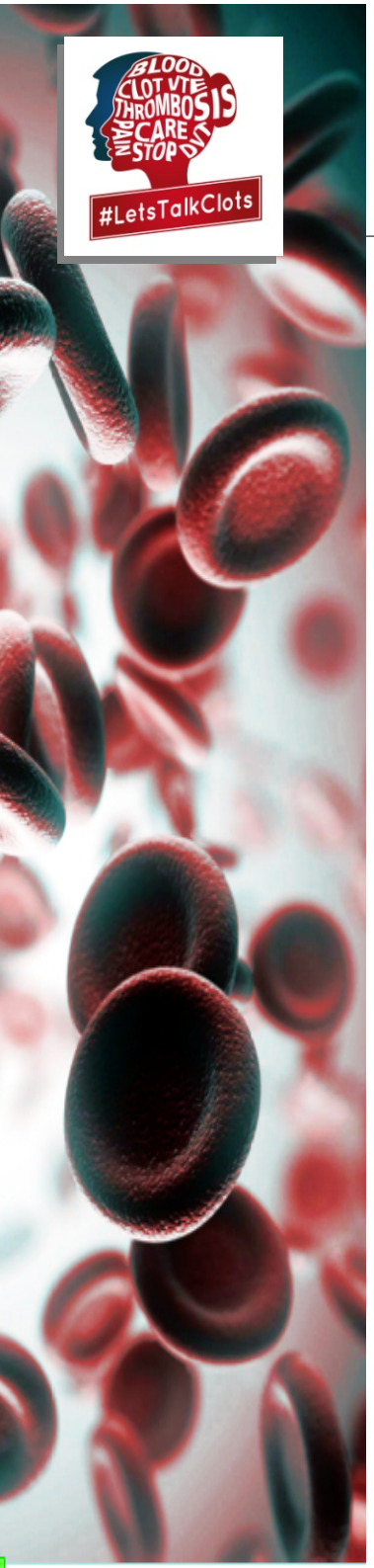
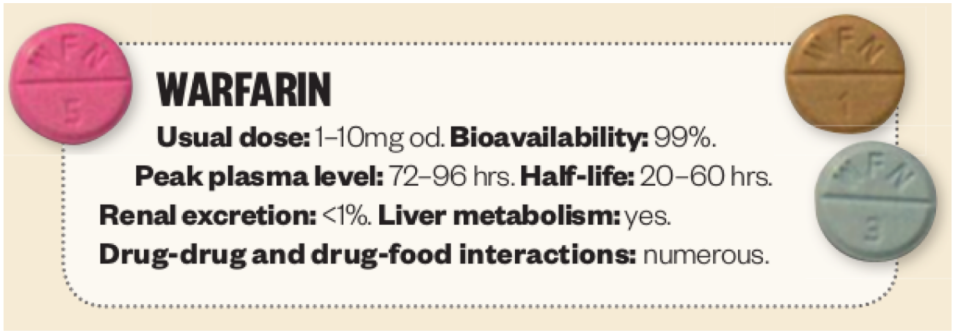


Warfarin: Drug of the past?

- **1920's** Canada and Wisconsin: "Sweet clover disease"
  - 1929 → Ingredient => death of animals (prothrombin)
    - 1939 Active ingredient isolated from clover (rot)
- **W**isconsin **A**lumni **R**esearch **F**oundation (WARF)
  - Named & licensed as rat poison
  - **1951** Man survived a suicide attempt with rat poison → 1954 → licensed for human use
  - 1955 Dwight Eisenhower = "early adopter"
  - Safety established → used for humans **for 65 years** after



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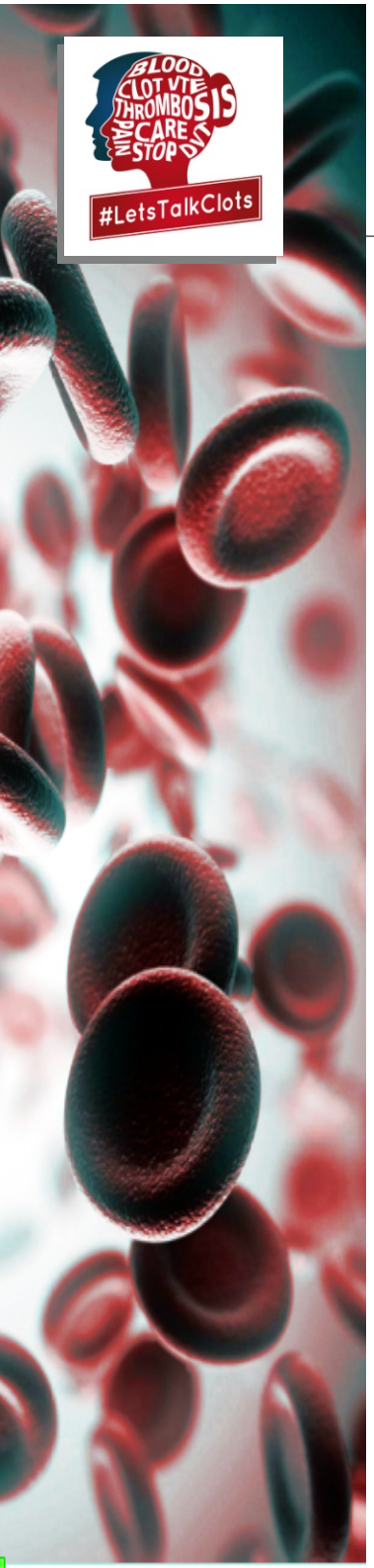
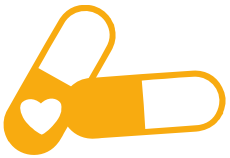
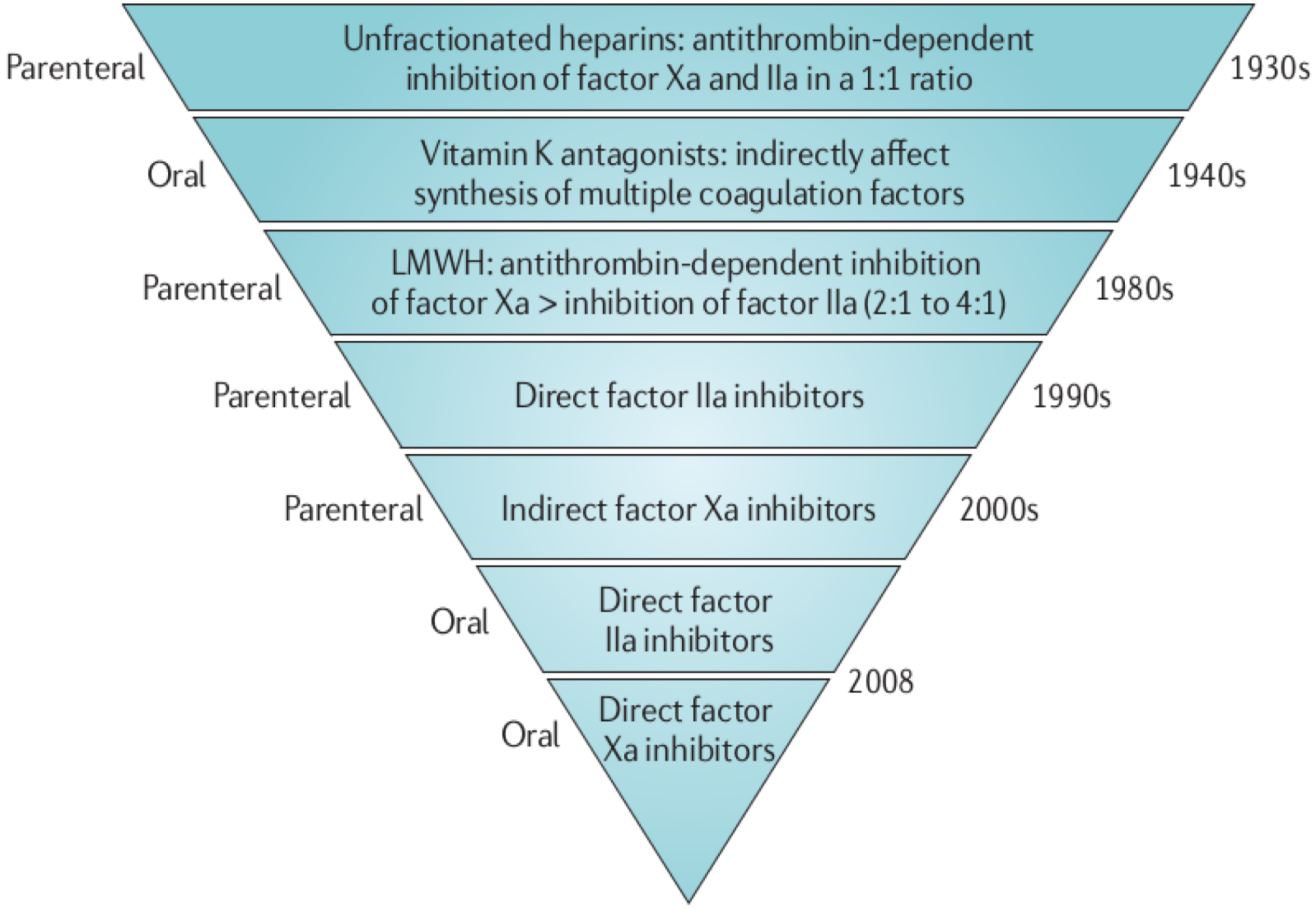


Anticoagulants





Nature review, drug discovery 2011- Vol. 10-61:75

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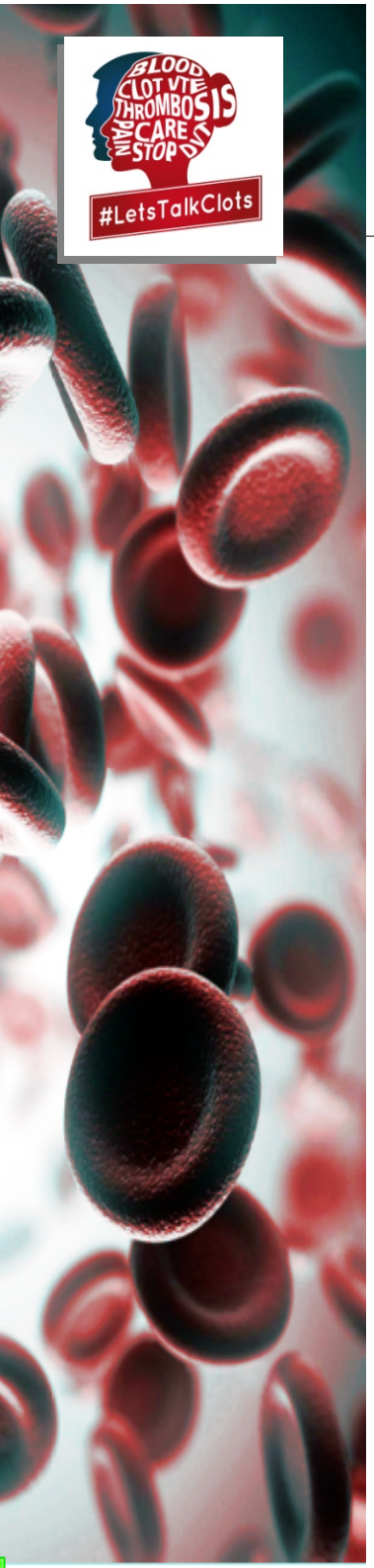

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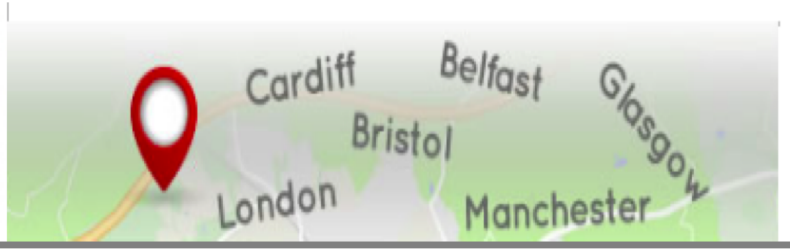
LET'S TALK CLOTS NATIONAL CONFERENCES



Thrombosis UK
Awareness • Research • Care

Thrombosis Committee (since 2016)

@sjaglin

Team Pharma!