ANTICOAGULANTS

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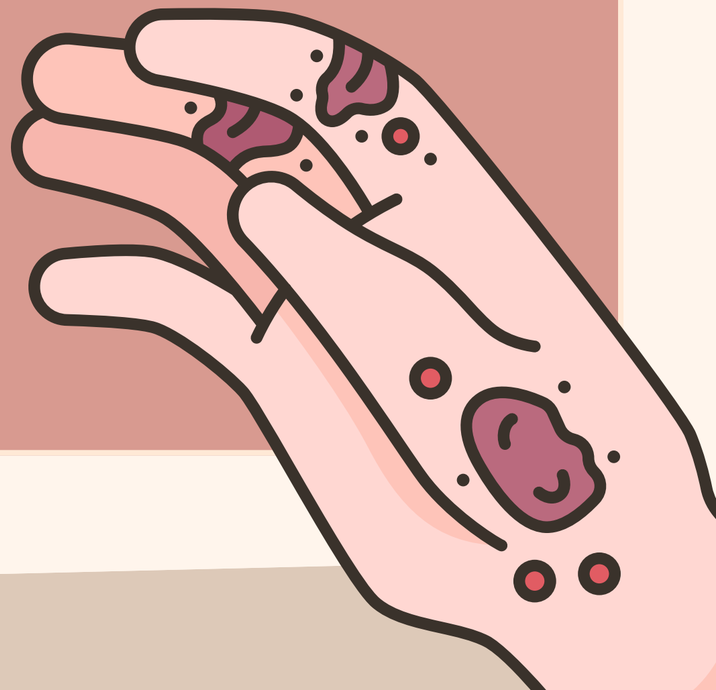
HEMOSTASIS :

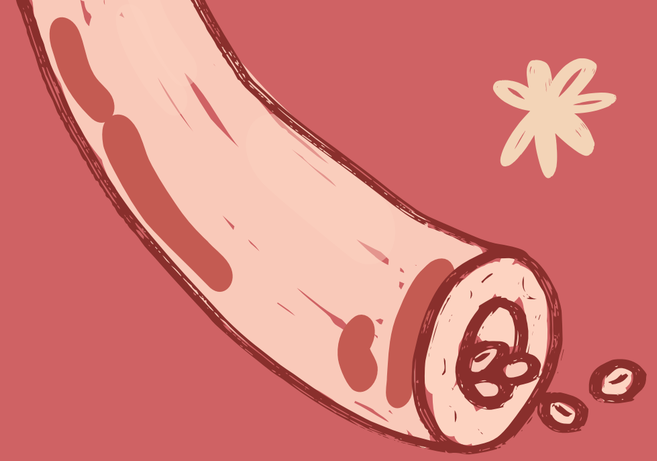
- Is the physiological process by which a bleeding stops after endothelial damage . Its final result is a thrombus (blood clot), which consists of blood cells and fibrin strands.

Hemostasis involves the following mechanisms:

- primary hemostsis
- Secondary hemostasis
- fibrinolysis



1.PRIMARY HEMOSTASIS :



A. Vascular hemostasis:

- Endothelial injury results in:
- Neural stimulation reflexes and endothelin release → transient vasoconstriction, leading to:

1

Reduced blood flow → reduced blood loss.

2

Platelet accumulation at the vessel walls Due to increased shear stress.

3

Exposure of subendothelial collagen → circulating von Willebrand factor binds to the exposed collagen.

VON WILLEBRAND FACTOR (VWF):

plasma protein that is synthesized by and stored in endothelial cells (in Weibel-Palade bodies) and platelets (in α-granules).

- Mediates platelet adhesion and aggregation
- Binds factor VIII (and thereby prevents its degradation)

B. Platele hemostasis:

- **Platelet adhesion:**

platelets bind to vWF via platelet GpIb receptor at the endothelial injury site.

Ristocetin normally activates vWF to bind to GpIb.

- **Platelet activation:**

After binding to vWF, platelets change their shape and release mediators that lead to activation of more platelets (positive feedback).

These mediators include:

• Adenosine diphosphate (ADP): promotes adhesion of platelets to endothelium.

• Thromboxane A2 (TXA2): activates additional platelets and promotes vasoconstriction.

• Calcium: required for secondary hemostasis.

• Platelet-activating factor (PAF): a phospholipid mediator that is produced by platelets and inflammatory cells (e.g: neutrophils, monocytes, macrophages), involved in platelet aggregation and activation and local inflammatory response.

- **Platelet aggregation:**

mediated by GpIIb/IIIa-receptor and fibrinogen → formation of a white thrombus composed of platelets and fibrinogen.

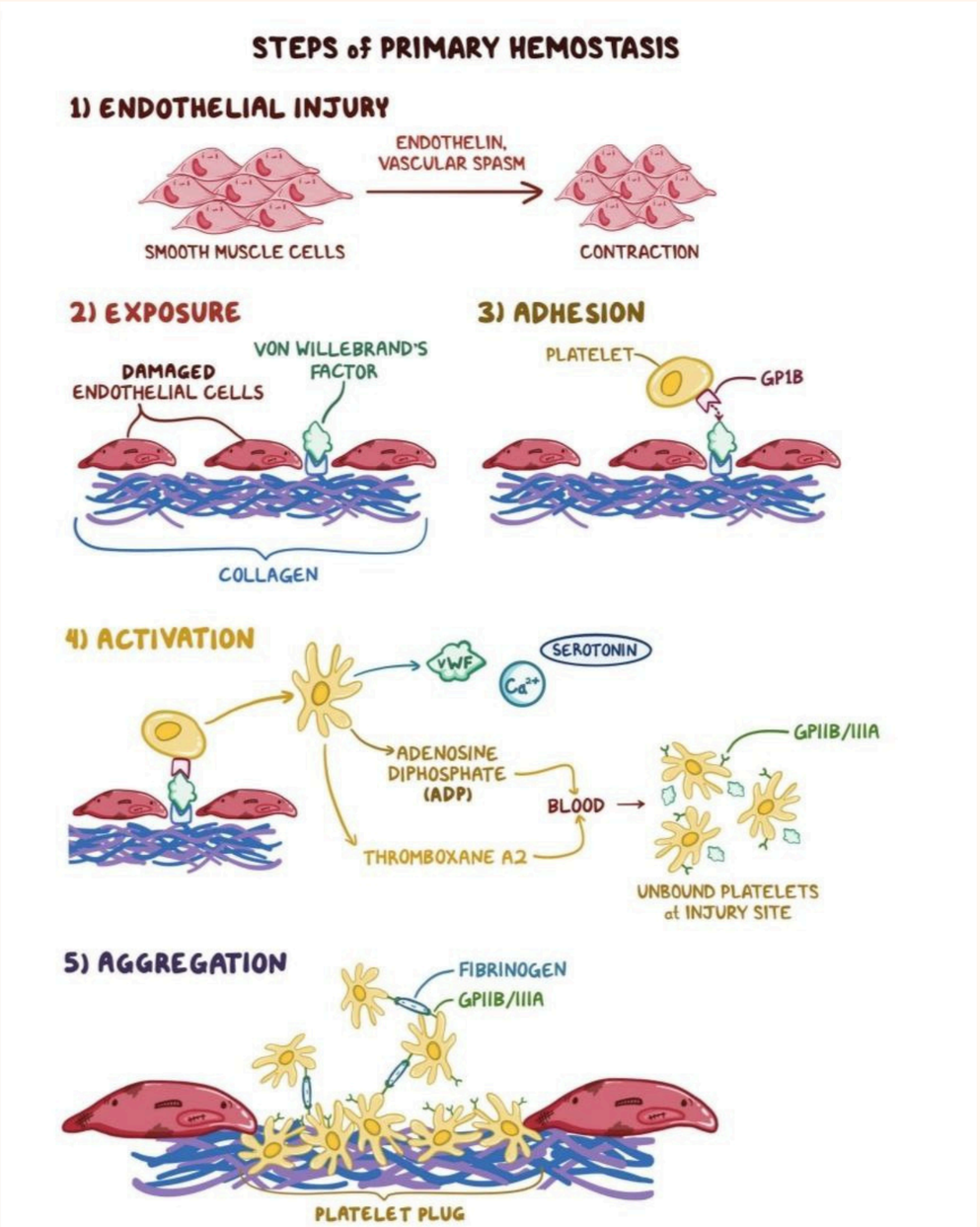
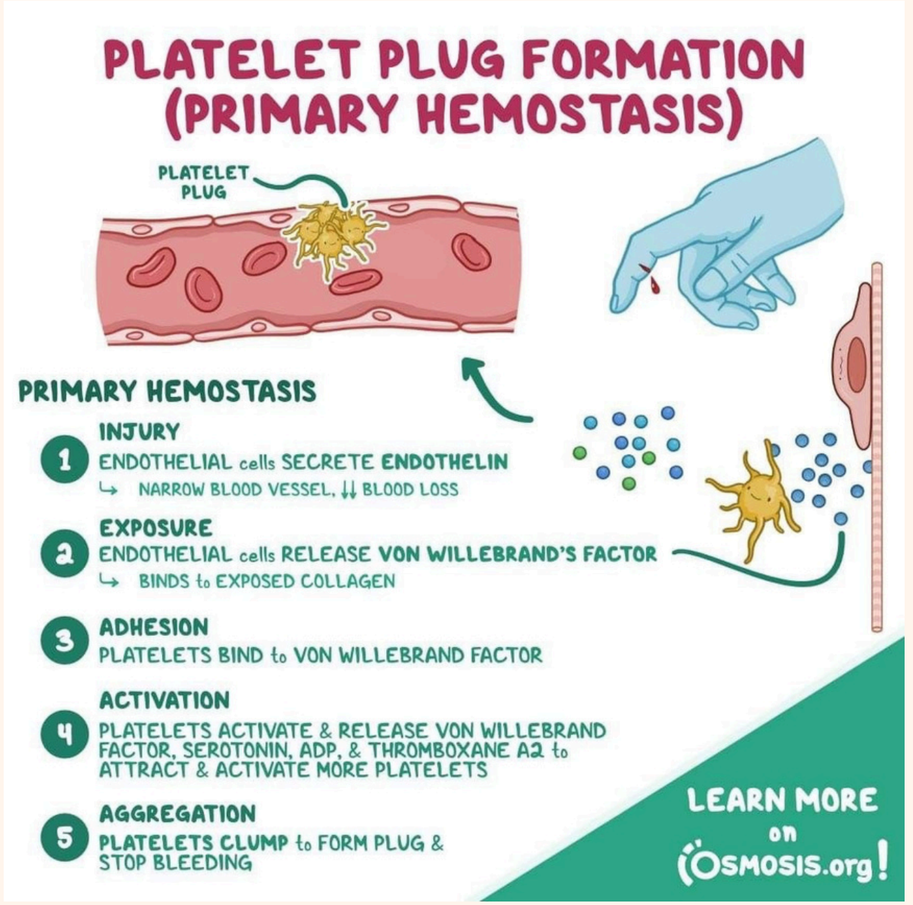


Figure 43.3 Platelet plug formation steps.



2. SECONDARY HEMOSTASIS :

- A processes that lead to stabilization of the platelet plug (white thrombus) by creating a fibrin network .

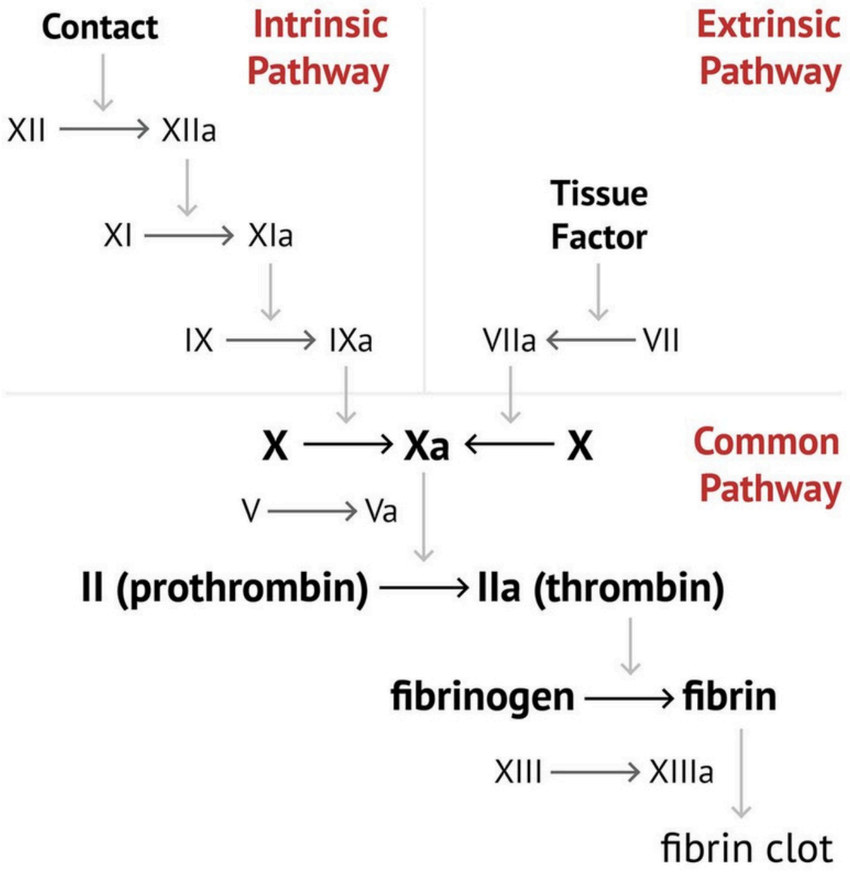
COAGULATION CASCADE

- a sequence of events triggered by the activation of the intrinsic or extrinsic pathway of coagulation that results in the formation of a stable thrombus.

COAGULATION FACTORS

- Substances that interact with each other to promote blood coagulation.

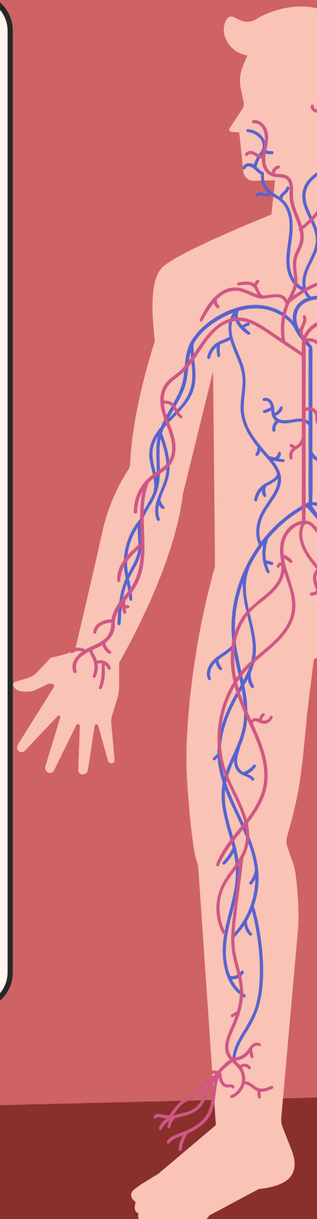
COAGULATION CASCADE



COAGULATION FACTORS

CLOTTING FACTORS

Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue Thromboplastin
Factor IV	Calcium Ions
Factor V	Labile Factor
Factor VII	Stable Factor
Factor VIII	Antihemophilic Factor
Factor IX	Christmas Factor, or Plasma Thromboplastin Component (PTC)
Factor X	Stuart-Prower Factor
Factor XI	Plasma Thromboplastin Antecedent (PTA)
Factor XII	Hageman Factor
Factor XIII	Fibrin Stabilizing Factor



INHIBITION OF HEMOSTASIS

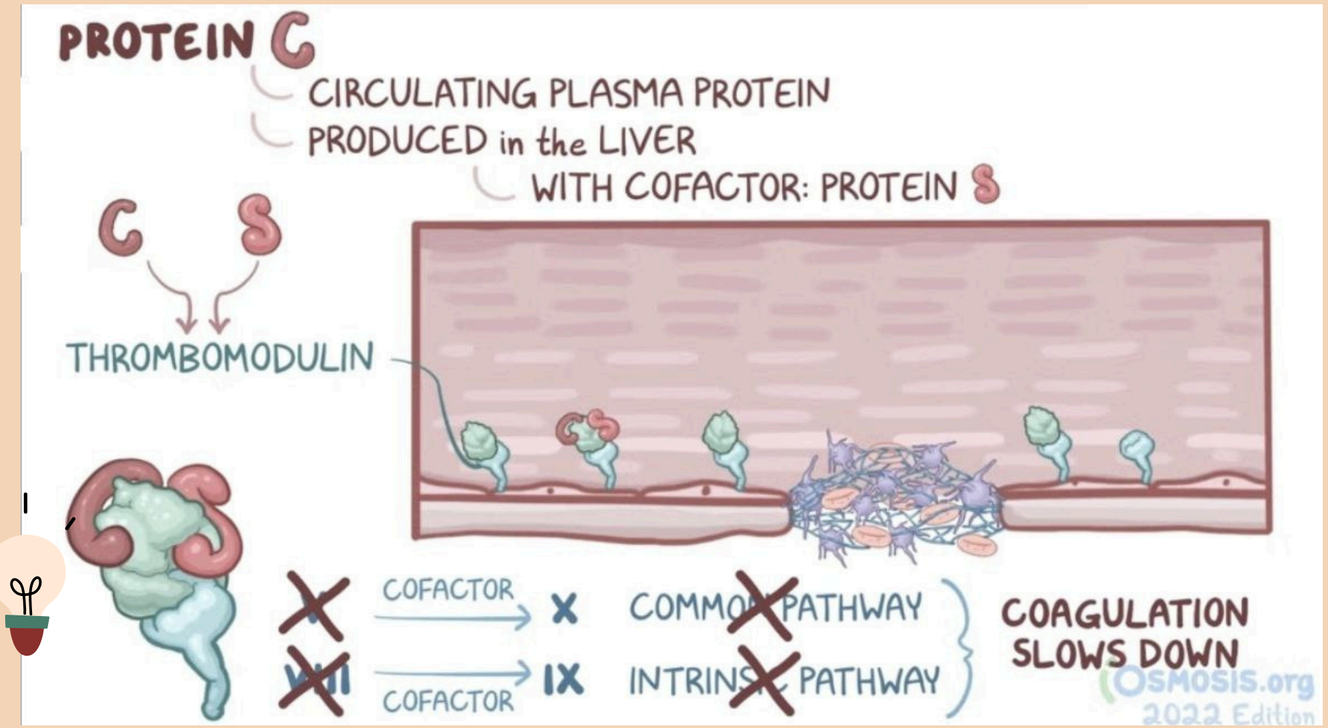
1.Tissue factor pathway inhibitor:

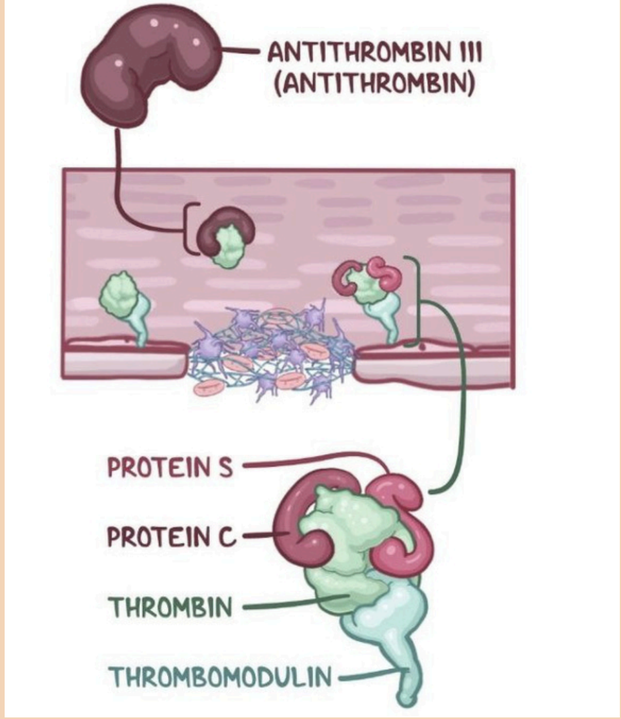
- inhibits tissue factor

2. Protein C and protein S:

- Activated protein C and its cofactor protein S form the activated protein-C complex (APC complex), which inhibits factors Va and VIIIa.
- Vitamin K-dependent synthesis in the liver
- Shorter half-life than vitamin K-dependent coagulation factors (relevant for treatment with vitamin K antagonists, e.g: warfarin)
- Clinical relevance
  - APC resistance.
  - Factor V Leiden.
  - Protein C deficiency, protein S deficiency.

INHIBITION OF HEMOSTASIS





INHIBITION OF HEMOSTASIS

3.Antithrombin :

- Degrades mainly thrombin and factor Xa.
- Activates tissue plasminogen activator (tPA).
- Clinical relevance: antithrombin III deficiency (e.g., due to liver failure or kidney failure)

4.Non specific factors:

- protease inhibitors in plasma (e.g: alpha-1 antitrypsin, alpha-2 macroglobulin).

5.Drug-induced :

- anticoagulant treatment.

6.Others :

- Protein Z (factor X inhibitor).
- Heparin-like glycosaminoglycans (boosts antithrombin).
- Heparin cofactor II (requires heparin for activation).

3. FIBRINOLYSIS :

- Is the degradation of the fibrin network of thrombi by the enzyme plasmin.

MECHANISM

- Tissue injury leads to the release and activation of plasminogen activators, which convert plasminogen to its active form plasmin.

1. Tissue plasminogen activator (tPA)
2. Urokinase (see fibrinolytics)

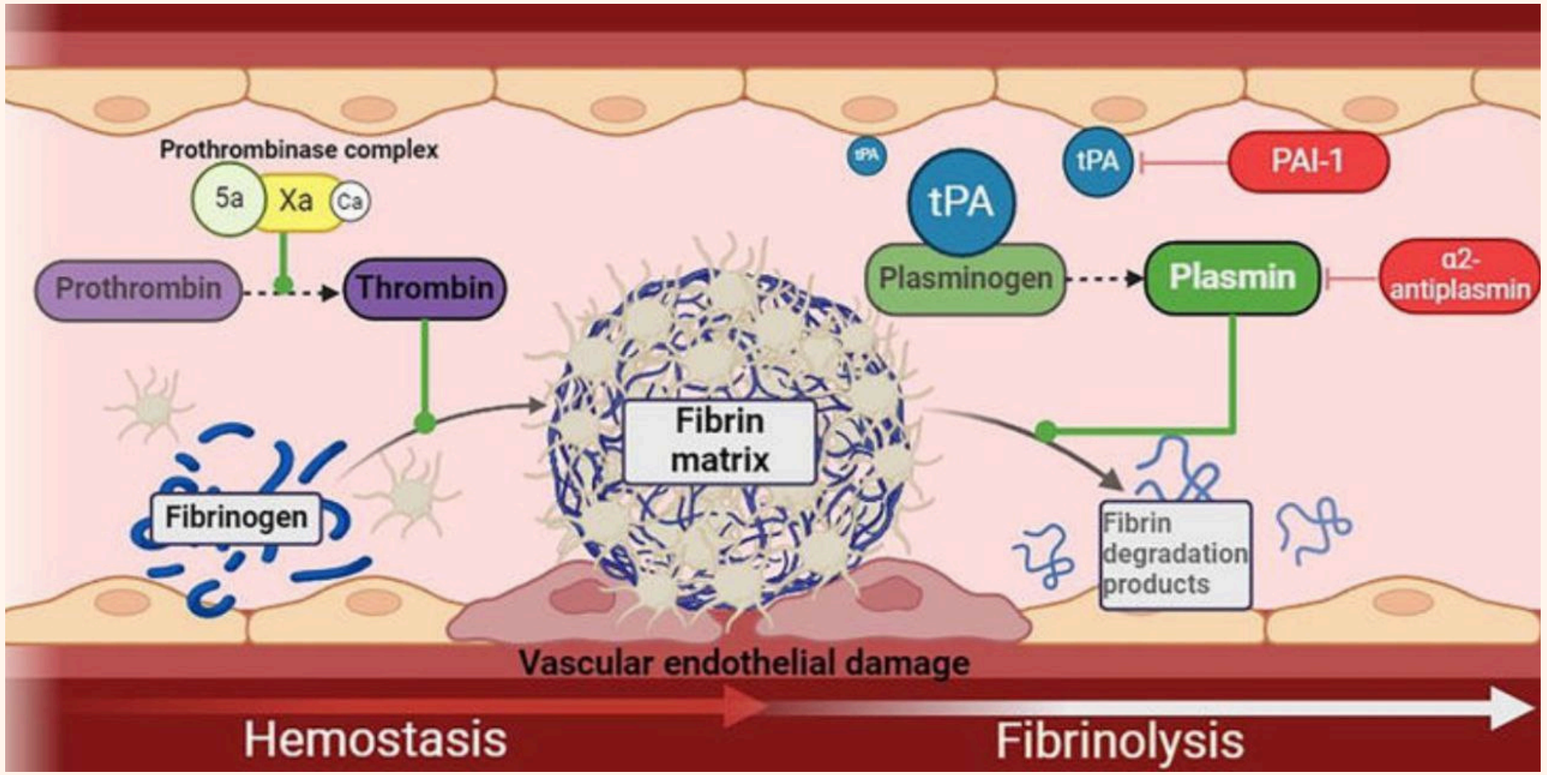
- Plasmin breaks down and deactivates fibrin and fibrinogen → release of fibrin degradation products (e.g:D-dimers)

REGULATION

- Plasminogen activator inhibitors (e.g:PAI-1) inhibit tPA
- Plasmin inhibitors (e.g:PPIC ,alpha2antiplasmin)

3. FIBRINOLYSIS :

- Is the degradation of the fibrin network of thrombi by the enzyme plasmin.



TESTS FOR HEMOSTASIS PATHWAYS:

- The pathway that begins by factor XII is called the intrinsic pathway and the pathway that begins by tissue factor is called the extrinsic pathway. And they are tested separately inside the laboratory.

Intrensic pathway test :

- **The test for the intrinsic pathway is the activated partial thromboplastin time (PTT), to do this test in the lab you take a plasma sample of the patient and add it to a negatively charged substance (silica) and measure the time it takes to form a clot.**
  - PTT normal range: it varies but 25 to 35 seconds is considered normal.

Extrinsic pathway test :

- **The test of the extrinsic pathway is prothrombin time (PT), in this test tissue factor is added to a sample of patient's plasma and you measure the time it takes to form a clot.**

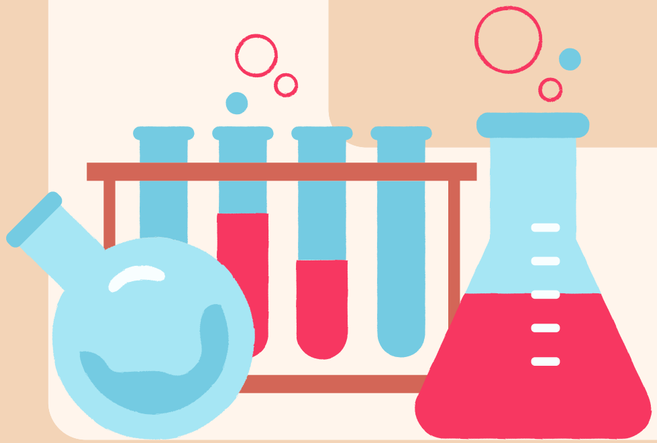
$$INR = \left(\frac{\text{Patient PT}}{\text{Mean Normal PT}} \right)^{ISI}$$

  - PT normal range: 11 to 13.5 seconds.
  - INR normal range: 0.8-1.1

Thrombin time test :

- **the final way to test the coagulation cascade is to measure thrombin time, by adding thrombin to a blood sample and measuring the time to form the clot .**

  - **Thrombin time: less than 20 seconds (15-19 seconds).**



ANTICOAGULATION THERAPY

HEPARIN

1- Unfractionated heparin (UFH)
"Standard heparin "

2- Low Molecular Weight Heparin

3- Synthetic heparin

4- Heparinoid (glycosaminoglycan)

WARFARIN

DIRECT ORAL ANTICOAGULANTS

1.Direct factor Xa inhibitors

2.Direct thrombin (factor II) inhibitors

HEPARIN

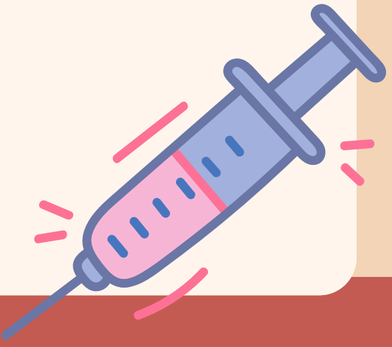
1- Unfractionated heparin (UFH) “Standard heparin “

1.Mechanism of Action:

- Potentiates the action of antithrombin III to primarily inhibit clotting factors IIa and Xa, preventing conversion of fibrinogen to fibrin.
- Half-life of standard heparin is 1 hour.

2.Administration :

- Therapeutic →intravenously as an initial bolus followed by continuous IV infusion.
- Prophylactic → subcutaneously.



HEPARIN

1- Unfractionated heparin (UFH) “Standard heparin “

3.Indications for use :

- Venous thromboembolism (e.g: DVT, PE).
- Atrial fibrillation in acute setting.
- Acute coronary syndromes (e.g: unstable angina, MI)
- DVT prophylaxis in hospitalized patients.

4.Monitoring during therapy :

- PTT or antifactor Xa levels and platelet count.
- therapeutic PTT is usually 60 to 90 seconds, although this varies depending on the clinical situation.

In order to detect heparin induced thrombocytopenia platelets must be continuously monitored during heparin therapy and a baseline should be established before commencing treatment.

HEPARIN

1- Unfractionated heparin (UFH) “Standard heparin “

5.Adverse effects:

- Bleeding.
- heparin-induced thrombocytopenia (HIT)→ skin necrosis may occur as a consequence.
- Osteoporosis with chronic use, lower incidence with LMWHs.
- Transient alopecia.
- Rebound hypercoagulability after discontinuation due to depression of AT III.

6.Contraindications:

- History of HIT.
- Active bleeding (e.g: GI bleeding, intracranial bleeding).
- Severe thrombocytopenia.
- Use with caution in severe HTN or after recent surgery (especially of eyes, spine, brain).

7.Clearance:

- hepatic (preferred agent for patients with renal insufficiency)

8.Reversing effects of heparin :

- Antidote protamine sulfate (a positively-charged protein that can neutralize negatively-charged heparin by forming inactive complexes).
- Administer FFP if severe bleeding occurs .

HEPARIN

2- Low Molecular Weight Heparin.

- **Drugs: enoxaparin,** dalteparin, tinzaparin, nadroparin, certoparin

1.Mechanism of Action:

- **LMWHs primarily inhibit factor Xa (equivalent inhibition of factor Xa as standard heparin, but less inhibition of factor IIa [thrombin])**

2.Administration :

- **subcutaneous**

3.Monitoring during therapy :

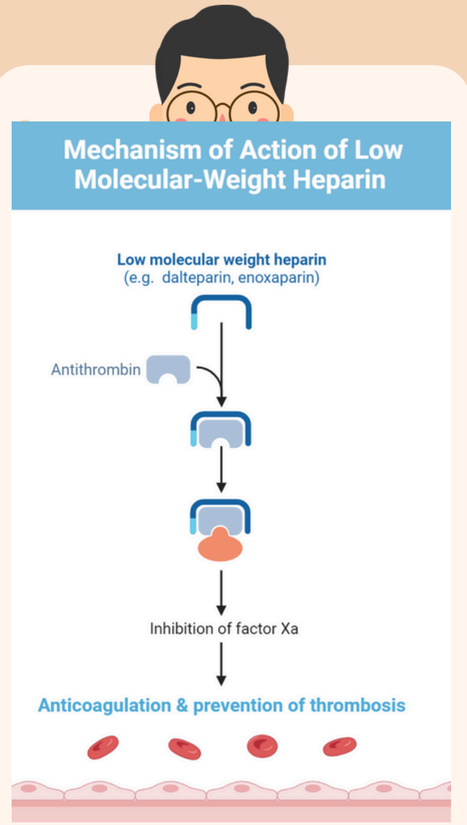
- **anti-factor Xa activity can be assessed in specific cases.**
- **Cannot be monitored by PT or PTT because they do not affect either.**

HEPARIN

2- Low Molecular Weight Heparin.

4.Indications for use :

- Similar to standard heparin (e.g: DVT/PE, ACS, DVT prophylaxis)
- Used with increasing frequency as compared to standard heparin due to greate convenience (e.g:subcutaneous administration, less frequent monitoring) and decreased risk of side effects (e.g., HIT,osteoporosis)
- More expensive than standard heparin, but often more cost-effective in the lon run due to reduced testing, nursing time, and length of hospital stay.
- Preferred anticoagulant in patients with malignancy.



HEPARIN

2- Low Molecular Weight Heparin.

5.Contraindications:

- Similar to standard heparin (e.g: history of HIT, active bleeding, severe thrombocytopenia)
- Use with caution in patients with renal dysfunction (LMWH excreted via Kidneys).

6.Clearance:

- renal (contraindicated for patients with renal insufficiency).

7.Antidote:

- Protamine sulfate

HEPARIN

3- Synthetic heparin

- **Drugs:** fondaparinux

1.Administration :

- subcutaneous

2.Monitoring during therapy :

- Not generally recommended.
- Anti-factor Xa activity can be assessed in specific cases.

3.Antidote:

- possibly activated prothrombin complex concentrates (aPCC)

HEPARIN

4- Heparinoid (glycosaminoglycan)

- **Drugs:** danaparoid

1.Administration :

- **Prophylaxis → subcutaneous**
- **Therapeutic →continuous intravenous infusion**

2.Monitoring during therapy :

- **anti-factor Xa activity**

3.Antidote:

- **protamine sulfate .**

ANTICOAGULATION THERAPY

HEPARIN

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WARFARIN

DIRECT ORAL ANTICOAGULANTS

1.Direct factor Xa inhibitors

2.Direct thrombin (factor II) inhibitors

WARFARIN

Prototype of cumarine anticoagulants (synthetic).

1.Mechanism of Action:

- Inhibits action of vitamin K epoxide reductase, an enzyme required for the hepatic synthesis of vitamin K dependent coagulation factors, leading to a decrease in factors II, VII, IX, X, and proteins C and S .

2.Administration :

- Given orally.
- Requires periprocedural bridging anticoagulation (heparin).
- Once PTT is therapeutic on heparin alone, initiate warfarin.
- Continue heparin for at least 4 days after starting warfarin.
- Once INR is therapeutic on warfarin, stop the heparin .

WARFARIN

Prototype of cumarine anticoagulants (synthetic).

3.Indications for use :

- **Thromboembolism prophylaxis (e.g:DVT/PE, stroke secondary to atrial fibrillation).**
- **Preferred anticoagulant for patients with mechanical heart valves or antiphospholipid antibody syndrome .**

4.Monitoring during therapy :

(routinely monitored)

- **Prothrombin time (PT)/ INR (in most cases, INR of 2 to 3 is therapeutic. In patients with mechanical heart valves have goal INR of 2.5 to 3.5)**
- **no change to PTT or TT.**

WEPT: Warfarin **E**xtrinsic **p**athway **PT**

WARFARIN

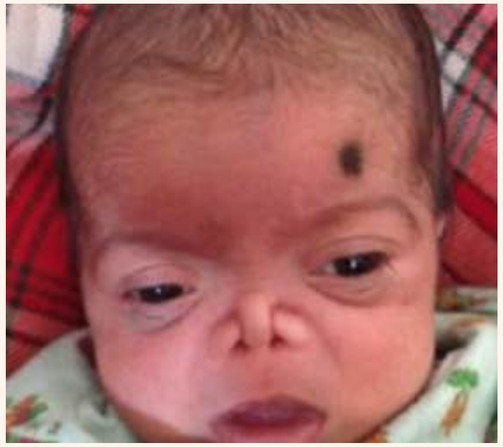
Prototype of cumarine anticoagulants (synthetic).

5.Adverse effects:

- Bleeding
- Skin necrosis–rare but serious complication caused by rapid decrease in protein C (a vitamin K–dependent inhibitor of factors Va and VIIIa).

6.Contraindications:

- Active bleeding.
- Pregnancy: Warfarin is teratogenic, and the main risk is Warfarin fetal syndrome. However, use it in breastfeeding women is not contraindicated.
- Use with caution in alcoholics or any patient prone to frequent falls due to potential for intracranial bleeding.

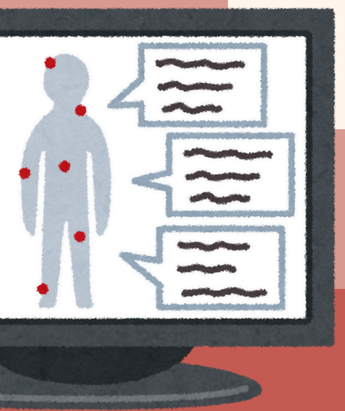


WARFARIN

Prototype of cumarine anticoagulants (synthetic).

7.Reversing effects of warfarin :

- Discontinue warfarin → takes 5 days to correct due to the long half-life of warfarin.
- Administer vitamin K → takes 12 to 24 hours to correct due to the time required for the liver to synthesize new clotting factors.
- Transfuse FFP → may take up to 8 hours to correct due to the time required for transfusion.
- Administer unactivated prothrombin-complex concentrates (PCC) → replaces vitamin K-dependent coagulation factors and corrects within 10 minutes of administration .



DIRECT ORAL ANTICOAGULANTS

1.Direct factor Xa inhibitors :

Rivaroxaban, Apixaban, Edoxaban.

- **Selective and direct inhibition of factor Xa (as opposed to potentiating AT III like heparin).**
- **Prolonged PT and PTT, unchanged thrombin time (not routinely monitored).**
- **Currently approved for treatment of DVT/PE, DVT/PE prophylaxis, and stroke prophylaxis in patients with atrial fibrillation.**

Rivaro**Xa**ban, api**Xa**ban, and edo**Xa**ban are factor **Xa** inhibitors.

DIRECT ORAL ANTICOAGULANTS

2.Direct thrombin (factor II) inhibitors:

Dabigatran ,Lepirudin, Argatroban, .

- **Selective thrombin antagonist inhibit thrombin directly.**
- **Prolonged thrombin time (TT), no change to PTT or PT (not routinely monitored).**
- **Currently approved for treatment of heparin induced thrombocytopenia HIT.**

- **Dabigatran :**

- **Prodrug And Approved For Stroke prevention in patients with Atrial Fibrillation.**
- **More safe And more effective than warfarin .**
- **Antidote : idarucizumab.**

GENERAL NOTES REGARDING ORAL ANTICOAGULATION

Indications for all oral anticoagulants :

- Prophylaxis of thromboembolism following:
  - DVT and/or pulmonary embolism
  - Prolonged immobilization after surgery (e.g: especially in knee or hip surgery)
- Nonvalvular atrial fibrillation.

GENERAL NOTES REGARDING ORAL ANTICOAGULATION

- **Direct factor Xa inhibitors and direct thrombin inhibitors adverse effect:**
  - Dose-dependent increased risk of bleeding
  - Interventional steps to stop the bleeding
  - If life-threatening bleeding occurs, administer PCC
  - General management and specific medication antidotes
    - Antifibrinolytic agents (e.g:tranexamic acid)
    - Oral activated charcoal reduces absorption if anticoagulants were ingested in the past couple of hours.
    - Apixaban and rivaroxaban: andexanet alfa (recombinant modified factor Xa protein)

ANTICOAGULANTS

THANK YOU FOR LISTENING