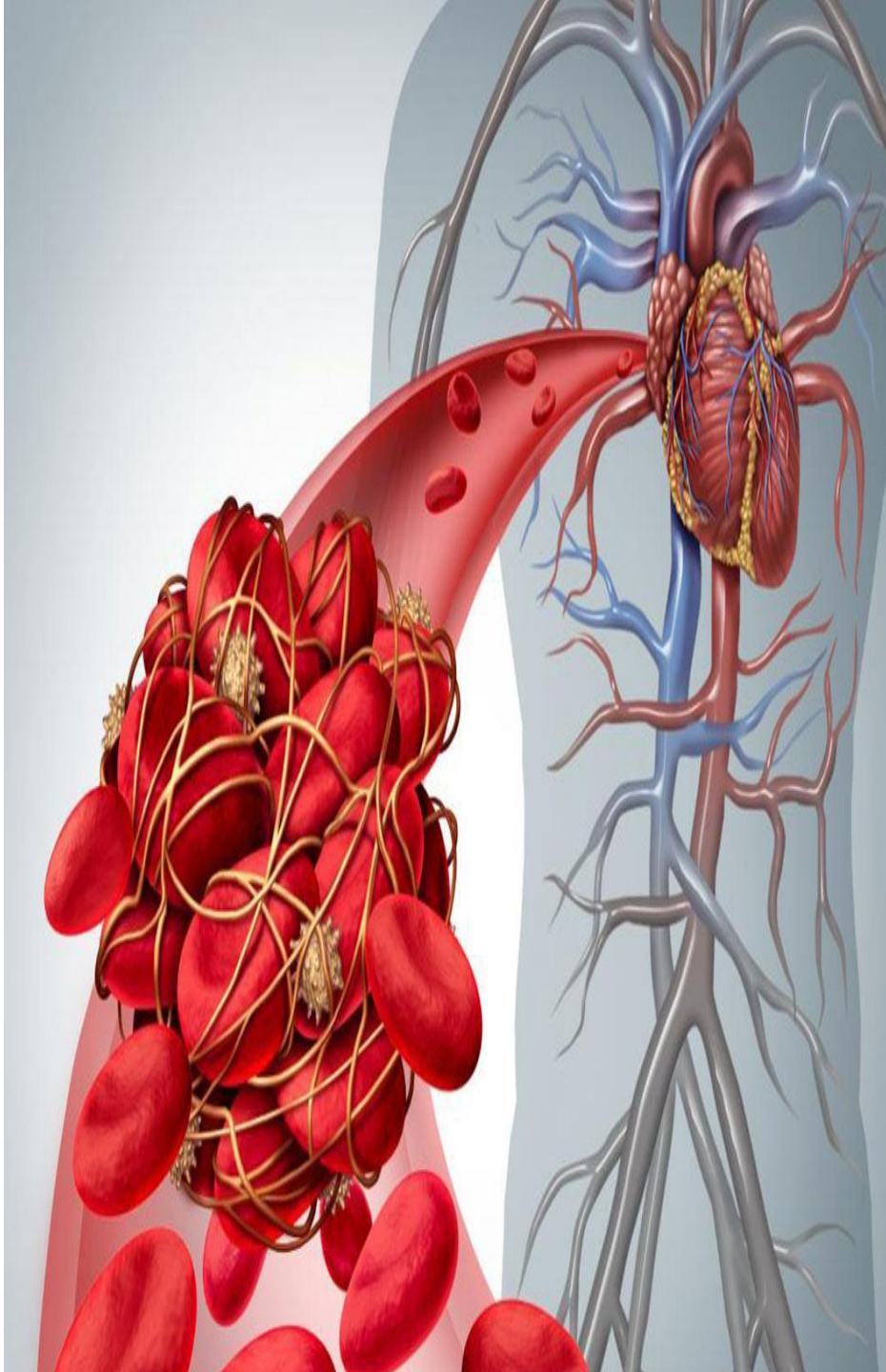
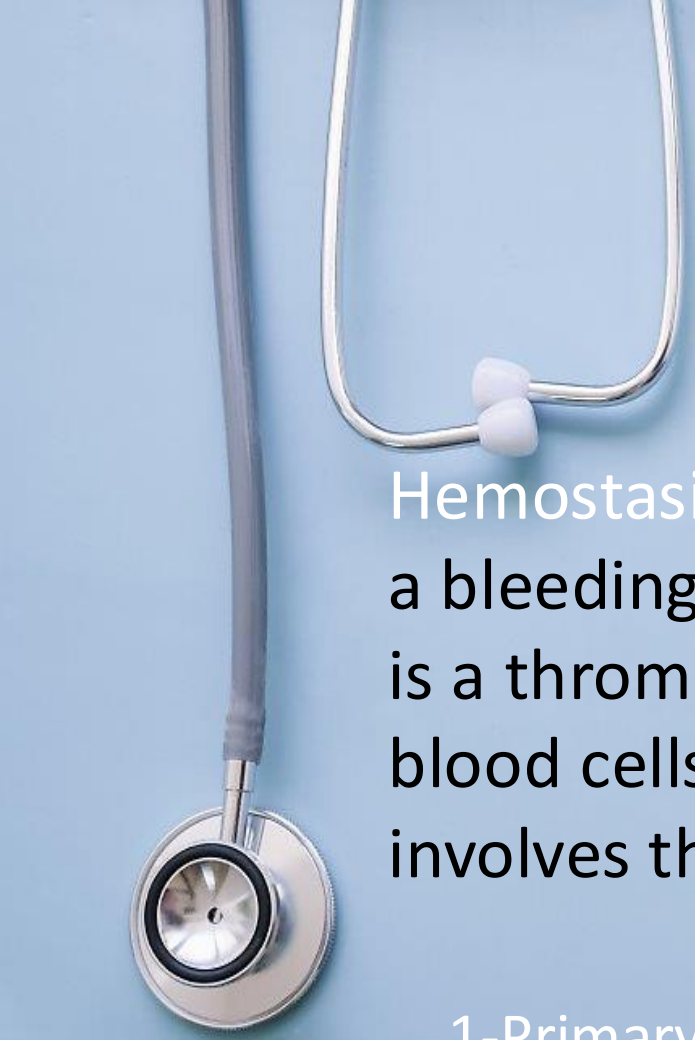
Anticoagulants



presented by :

- Asma'a Jamal Al.bashtawi.
- Amira Almsaeid.
- Islam Abuhamdeah.



Hemostasis is the physiological process by which a bleeding stops after endothelial . Its final result is a thrombus (blood clot), which consists of blood cells and fibrin strands. Hemostasis involves the following mechanisms:

1-Primary hemostasis.
2-Secondary hemostasis .
3-Fibrinolysis .
4-Inhibition of hemostasis .
5-Tests for hemostasis pathways.

Primary hemostasis

1) Vascular hemostasis:

Endothelial injury results in:

□ Neural stimulation reflexes and endothelin release → transient vasoconstriction, leading to:

□ Reduced blood flow → reduced blood loss.

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

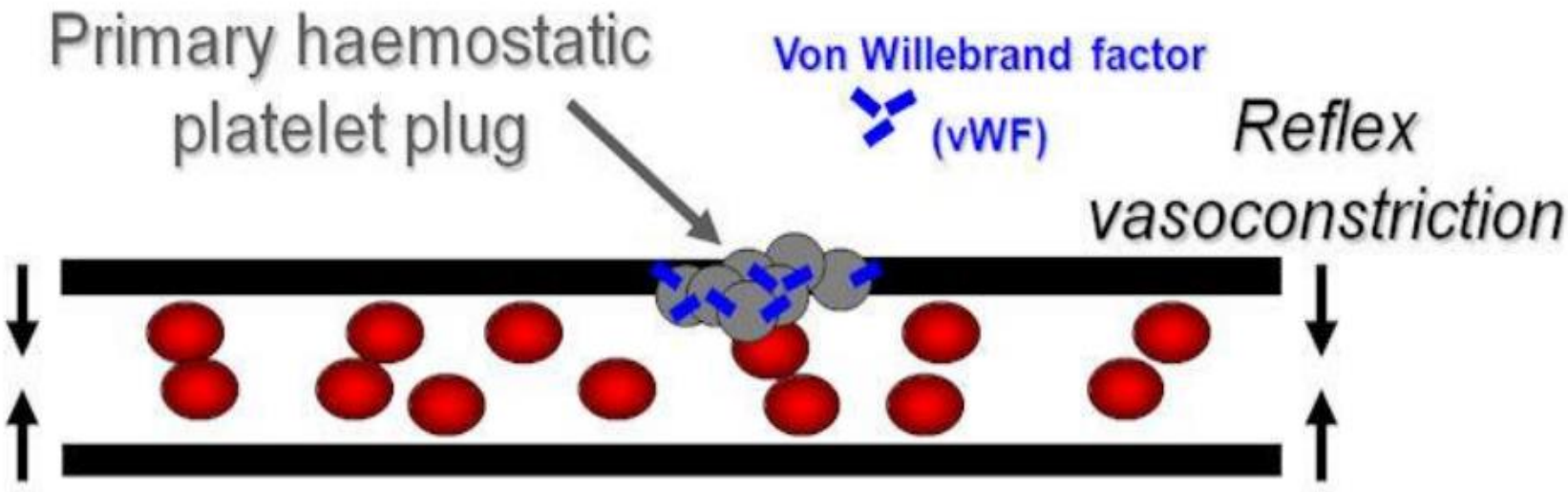
□ Exposure of subendothelial collagen → circulating von Willebrand factor binds to the exposed collagen.

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).

Primary haemostasis



2) Platelet hemostasis :

□ Platelet adhesion: platelets bind to vWF via platelet GpIb receptor at the endothelial injury site Ristocetin normally activates vWF to bind to glycoprotein Ib.

□ 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.

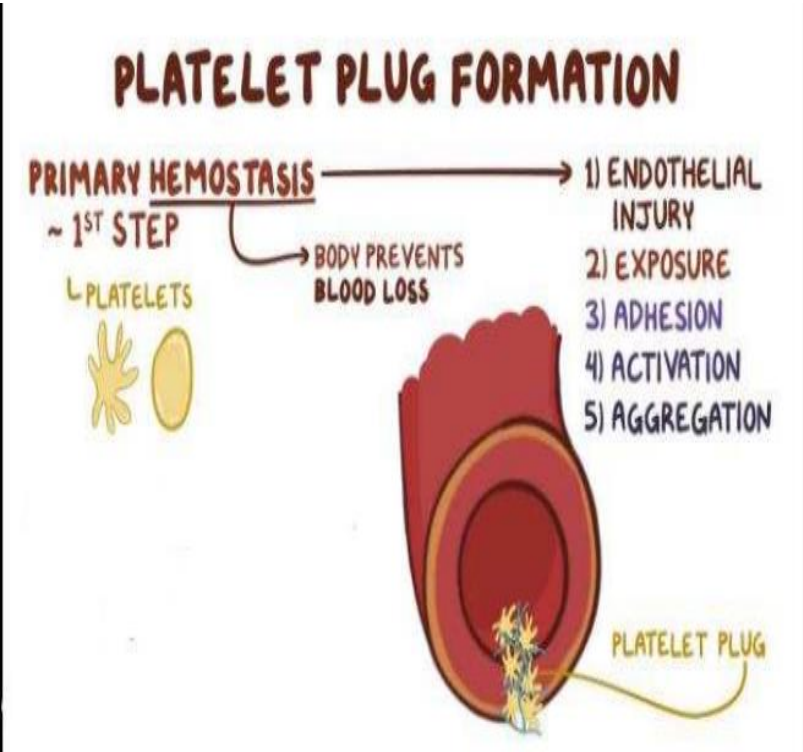
- Thromboxane A2 (TXA2): activates additional platelets and promotes vasoconstriction.

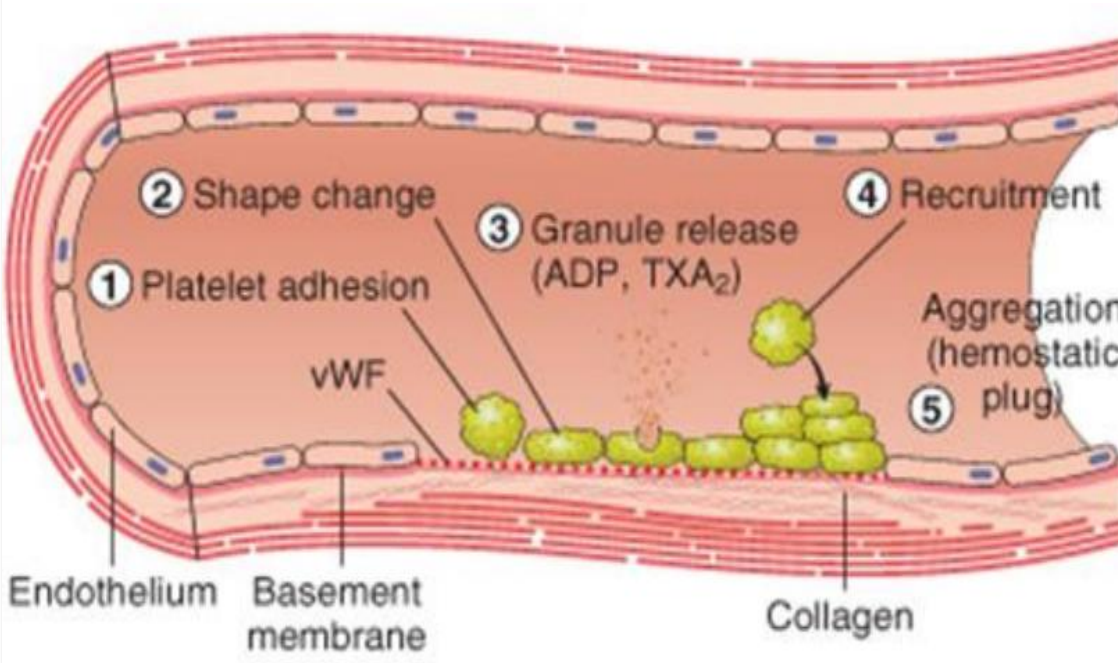
- Calcium: required for secondary hemostasis.

- 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

► A white thrombus is transient, unstable, and easily dislodged. It stabilizes through the process of secondary hemostasis.



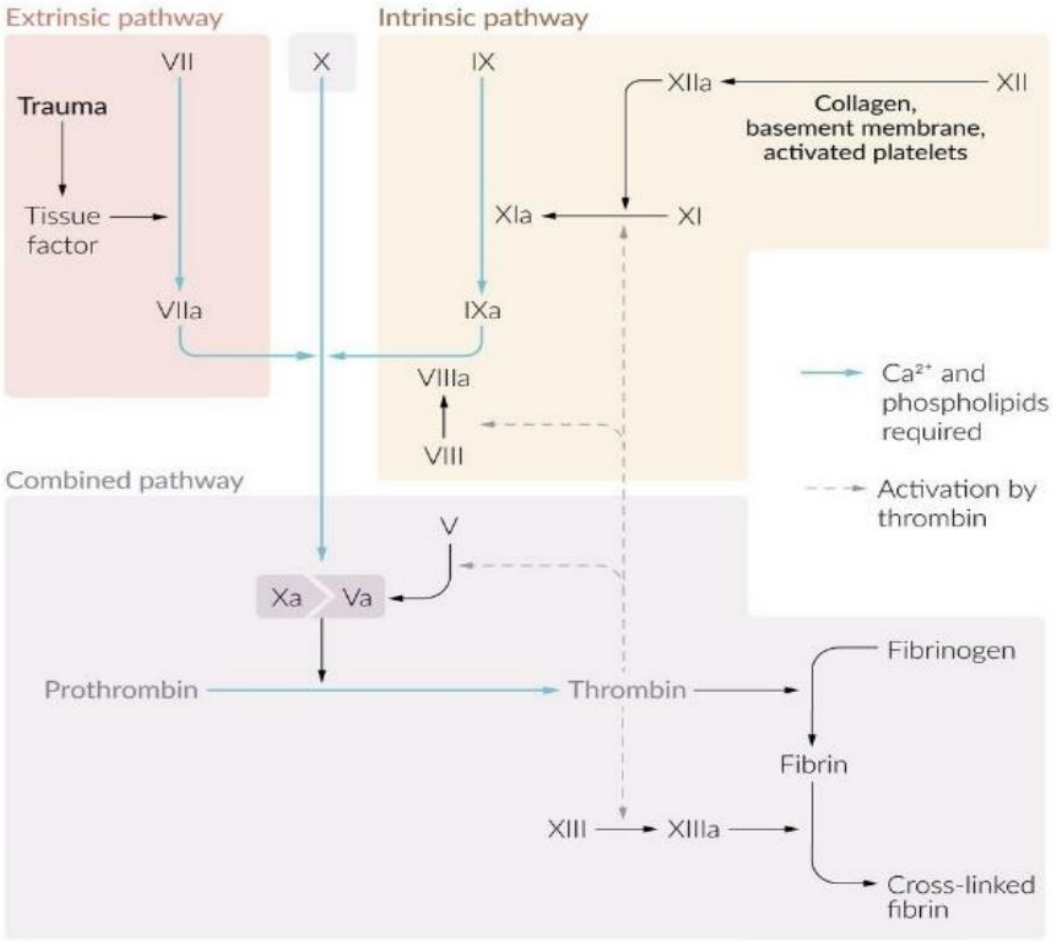


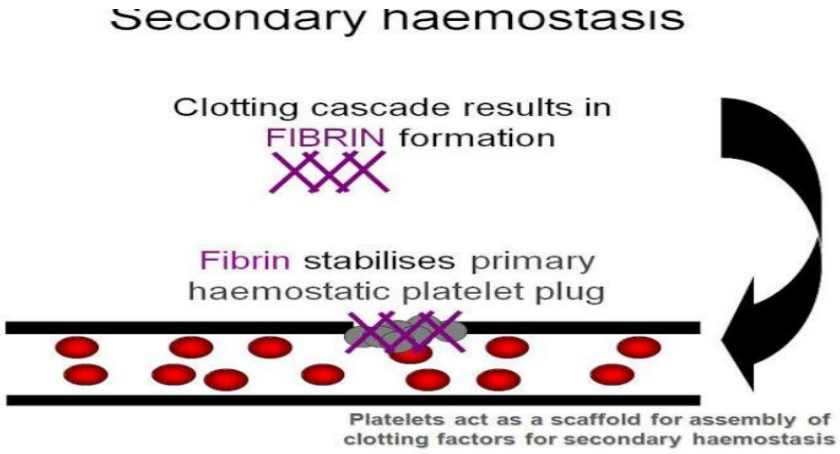
Secondary hemostasis :

► 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.



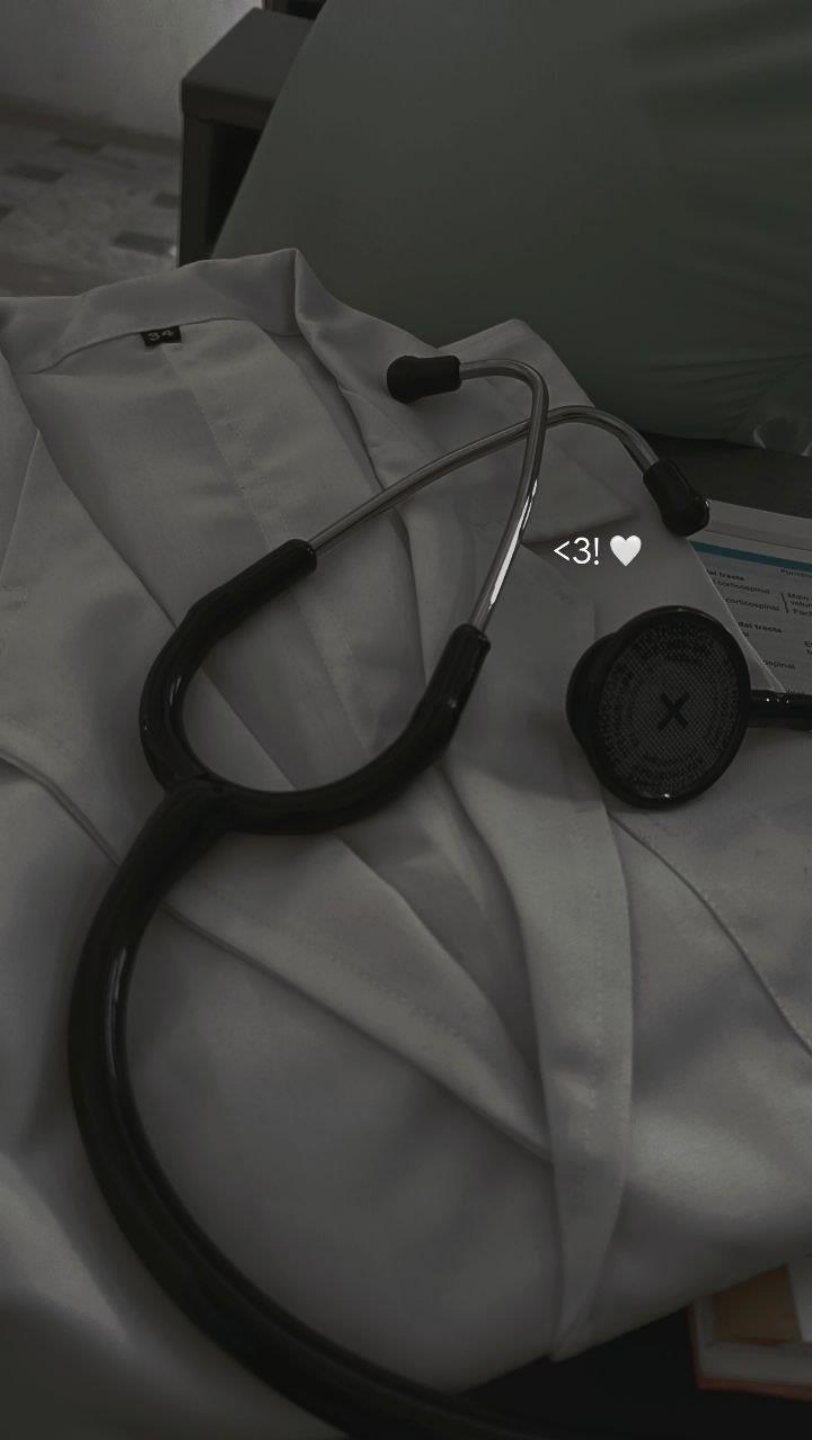


No.	Name	Role
I	Fibrinogen	Clot formation
II	Prothrombin	Activation of factors I, V, VII, VIII, XI, XIII, protein C and platelets
III	Tissue factor	Cofactor VIIa
IV	Calcium	Role in binding of phospholipid coagulation factors
V	Proaccelerin	Cofactor of X – prothrombinase complex
VI		Activated form of V
VII	Proconvertin	Enables factors IX and X
VIII	Antihemophilic factor A	Cofactor of IX complex
IX	Antihemophilic factor B or Christmas factor	Enables factor X, forms the complex tensor with factor VIII
X	Stuart–Prower factor	Forms the prothrombinase complex together with factor V, which will activate factor II
XI	Antecedent of plasma thromboplastin	Activates factor IX
XII	Hageman factor	Enables factors XI, VII and prekallikrein
XIII	Fibrin stabilizing factor	Creating cross-links between fibrin monomers
XIV	Prekallikrein – Fletcher factor	Precursor of kallikrein
XV	HMWK – Fitzgerland factor	Cofactor
XVI	von Willebrand factor	Role in platelet adhesion; it is linked to factor VIII
XVII	Antithrombin III	Inhibits IIa, Xa and other proteases
XVIII	Heparin cofactor II	Inhibits IIa
XIX	Protein C	Inactivates factors Va and VIIIa
XX	Protein S	Cofactor for activated C protein

HMWK: High-molecular-weight kininogen.

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.

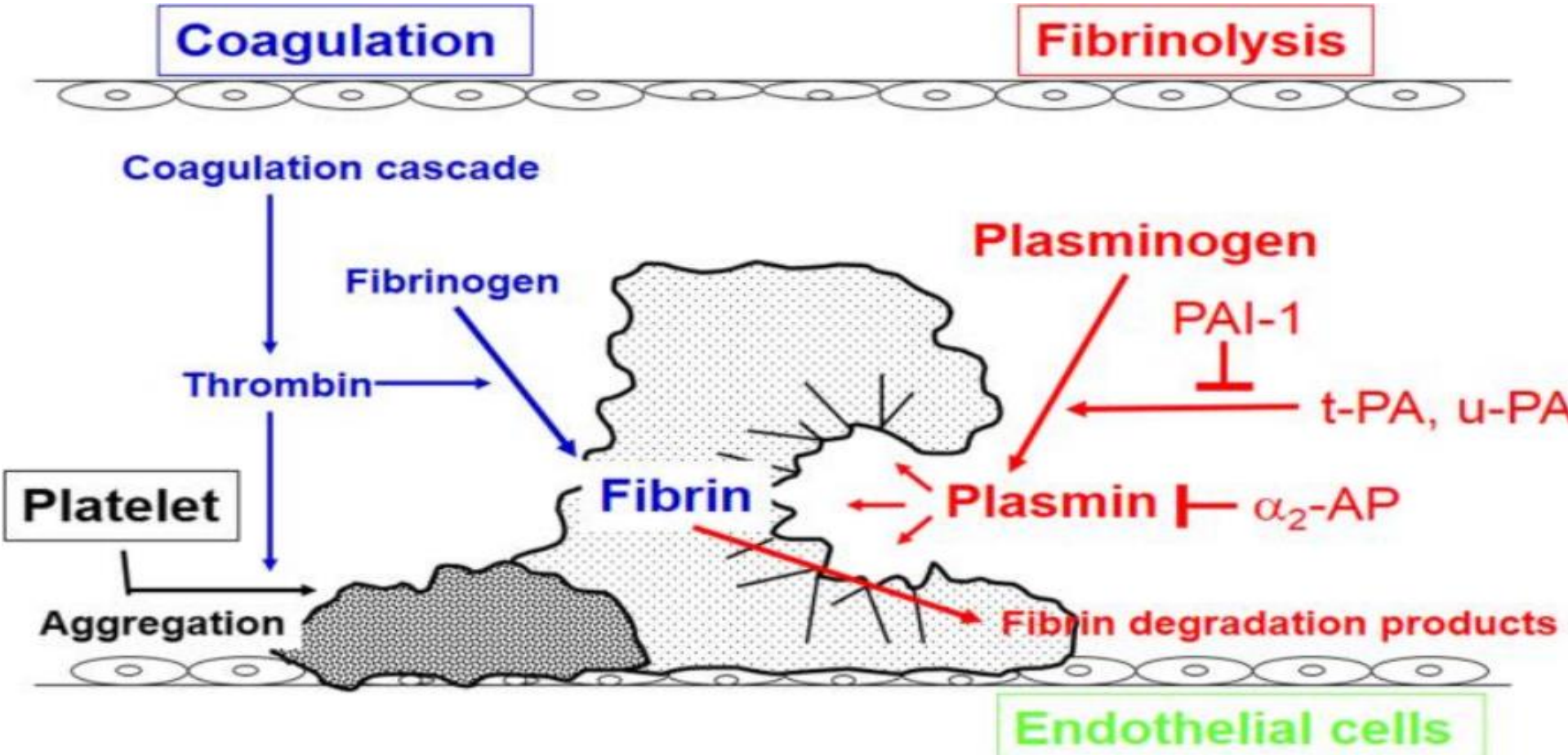
- Tissue plasminogen activator (tPA)

- 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).



Inhibition of hemostasis

- Tissue factor pathway inhibitor: inhibits tissue factor.
- 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

Inhibitor	Target protein
Tissue factor pathway inhibitor (TFPI)	Tissue factor
Antithrombin	Factor II and X
Protein C-protein S	Factor V and VIII
Thrombin activatable fibrinolysis inhibitor (TAFI)	Fibrin

- **Antithrombin**

□ Degrades thrombin and factors IXa and Xa.

□ Activates tissue plasminogen activator (tPA).

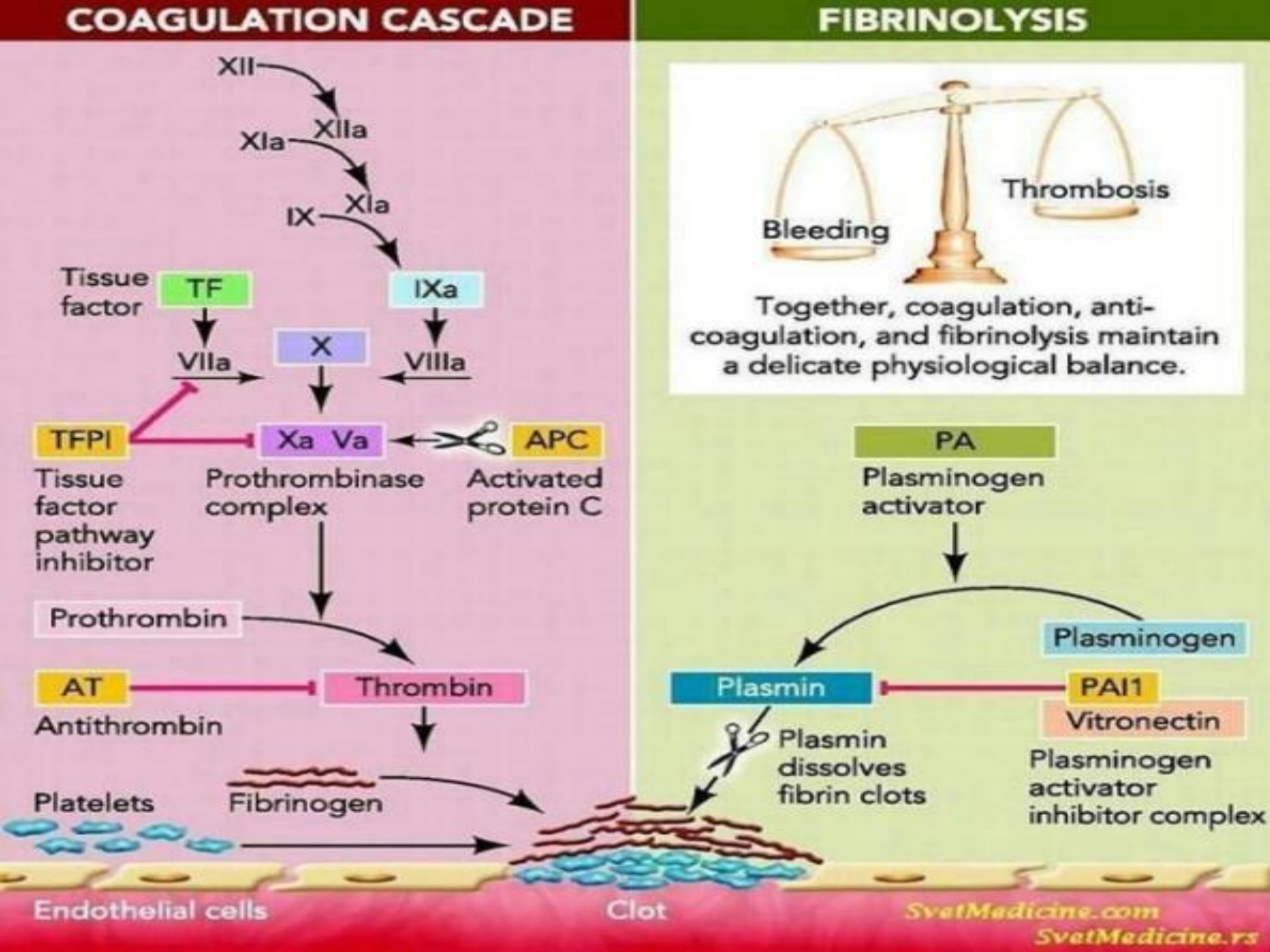
□ Clinical relevance: antithrombin III deficiency (e.g., due to liver failure or kidney failure)

- **Nonspecific inhibitors:** protease inhibitors in plasma (e.g., alpha-1-antitrypsin, alpha-2 macroglobulin).
- **Drug-induced: anticoagulant treatment.**
- **Others**

□ Protein Z (factor X inhibitor).

□ Heparin-like glycosaminoglycans (boosts antithrombin).

□ Heparin cofactor II (requires heparin for activation).


COAGULATION CASCADE
FIBRINOLYSIS
XII
XIIa
XIa
XIa
IX
IXa
Tissue factor
TF
VIIa
X
VIIIa
TFPI
Xa Va
APC
Tissue factor pathway inhibitor
Prothrombinase complex
Activated protein C
Prothrombin
AT
Antithrombin
Thrombin
Platelets
Fibrinogen
Endothelial cells
Clot
Bleeding
Thrombosis
Together, coagulation, anti-coagulation, and fibrinolysis maintain a delicate physiological balance.
PA
Plasminogen activator
Plasminogen
Plasmin
PAI1
Vitronectin
Plasmin dissolves fibrin clots
Plasminogen activator inhibitor complex
SvetMedicine.com
SvetMedicine.rs

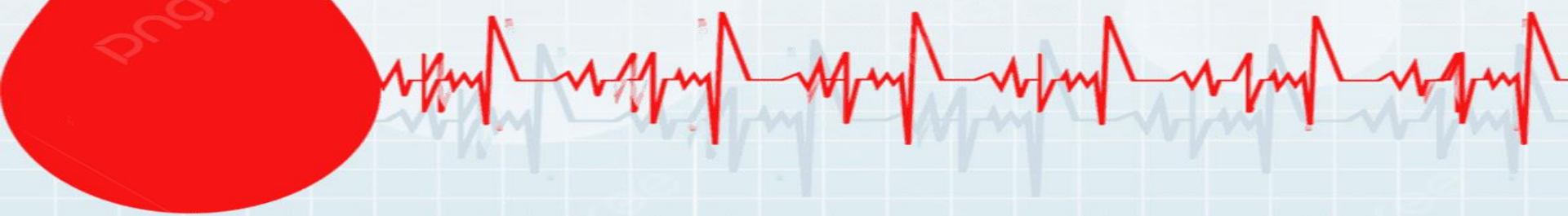
Tests for hemostasis pathways:

► 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.

► 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.

► 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=(pt patient /pt normal) ^ISI).

► 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.



- PTT normal range: it varies but 25 to 35 seconds is considered normal.
- PT normal range: 11 to 13.5 seconds.
- INR normal range: 0.8-1.1
- Thrombin time: less than 20 seconds (15-19 seconds).

Contact activation (intrinsic) pathway

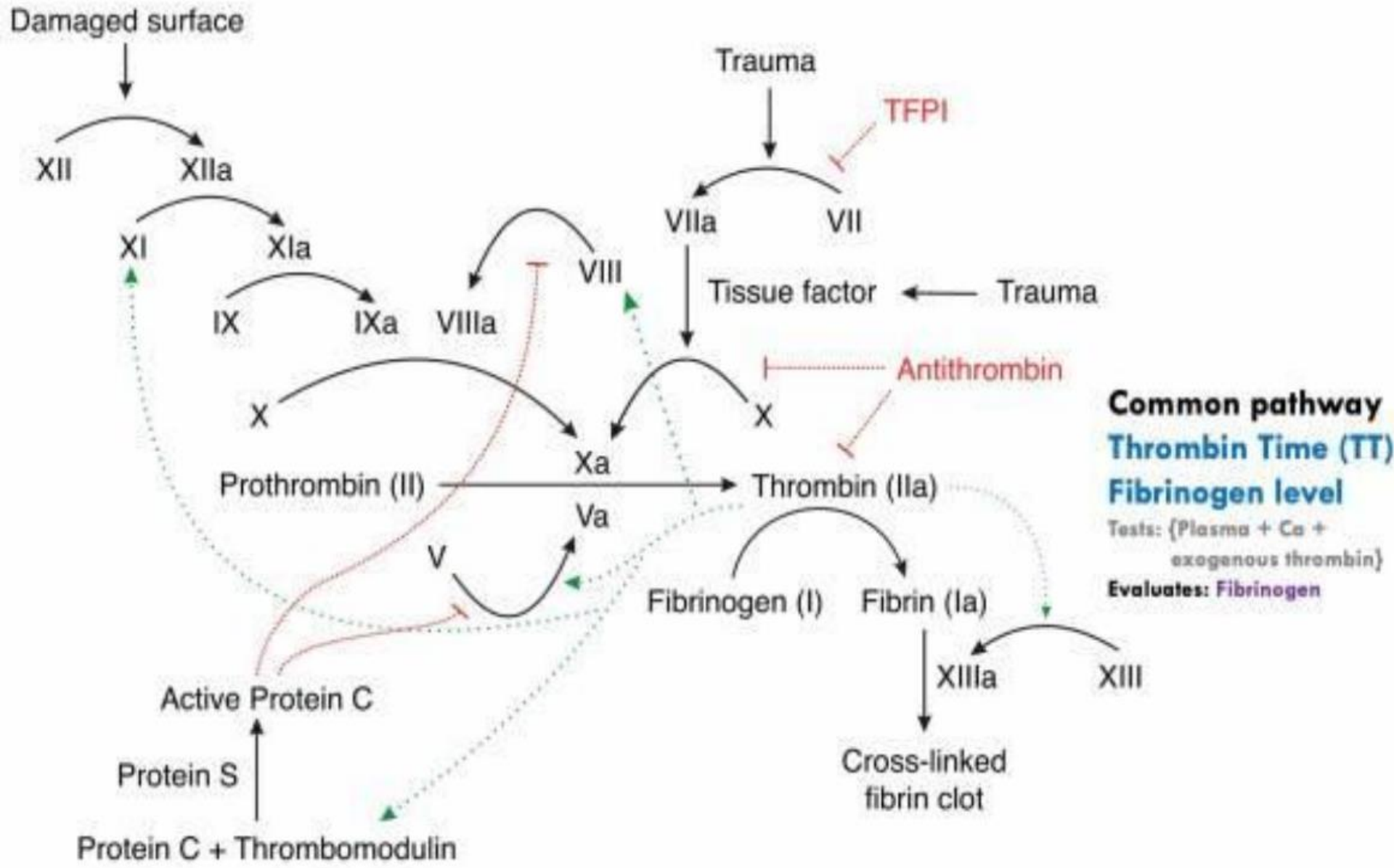
Tests {Plasma + Ca + kaolin + phospholipid}

PTT (evaluates: XII, XI, IX, VIII, X, V, II, fibrinogen)

Tissue factor (extrinsic) pathway

Tests {Plasma + Ca + tissue thrombplastin}

PT / INR (evaluates: VII, X, V, II, fibrinogen)



Common pathway

Thrombin Time (TT)

Fibrinogen level

Tests: {Plasma + Ca + exogenous thrombin}

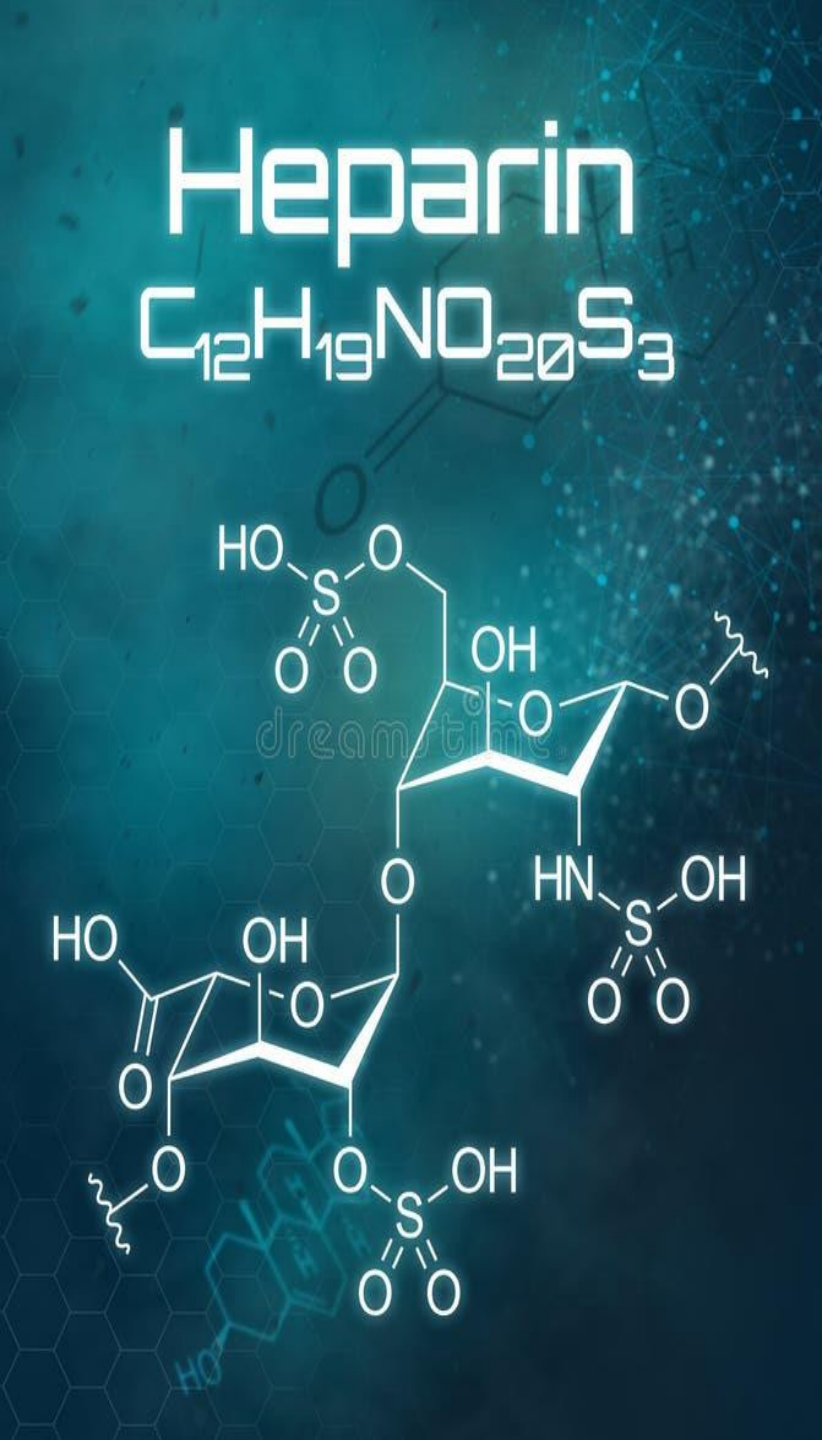
Evaluates: Fibrinogen

Anticoagulants therapy

- Heparin

- Warfarin

- Direct Oral Anticoagulants (DOA)



Heparin

1- Unfractionated heparin (UFH) "Standard heparin .

2- Low–Molecular-Weight Heparin.

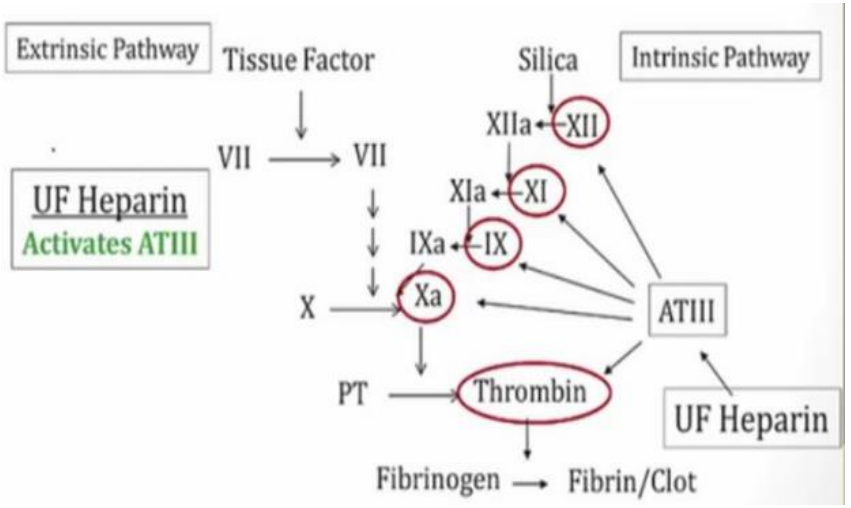
3- Synthetic heparin.

4- Heparinoid (glycosaminoglycan).

1) Unfractionated heparin (UFH) "Standard heparin

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.



Administration

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

Indications for Use

□ Venous thromboembolism (e.g., DVT, PE).
□ Atrial fibrillation in acute setting.
□ Acute coronary syndromes (e.g., unstable angina, myocardial infarction).
□ DVT prophylaxis in hospitalized patients.

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.

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.**

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).

Clearance : Hepatic (preferred agent for patients with renal insufficiency).

Reversing the 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.

2- Low–Molecular-Weight Heparin

Drugs:

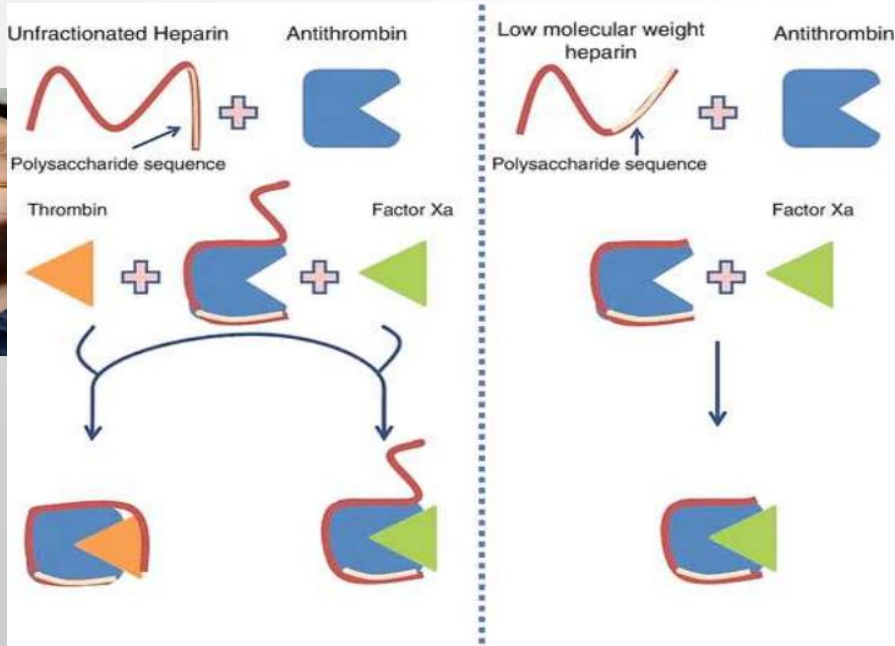
□ enoxaparin, dalteparin, tinzaparin, nadroparin, certoparin .

Administration:

□ subcutaneous

Mechanism of Action:

□ LMWHs primarily inhibit factor Xa (equivalent inhibition of factor Xa asstandard heparin, but less inhibition of factor IIa [thrombin]).



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.

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.

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).

Clearance

□ renal (contraindicated for patients with renal insufficiency).

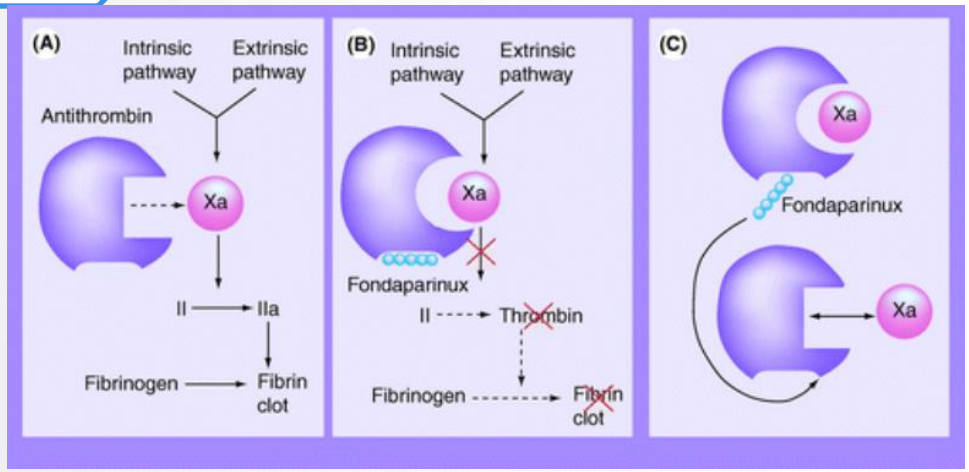
Antidote

□ Protamine sulfate (partial reversal Protamine antagonizes 50% of the effect of LMWH).

Unfractionated Heparin vs LMWH

Unfractionated Heparin		Low Molecular Weight Heparin (LMWH)
Activates anti-thrombin III which forms a complex inhibiting clotting factors IIa and Xa, as well as IX, XI, XII	Mechanism of action	Examples include *enoxaparin, tinzaparin* *Fondaparinux* is a synthetic derivative of LMWH Activates anti-thrombin III which forms a complex inhibiting clotting factor Xa
Intravenous (IV)	Mode of administration	Subcutaneous (SC)
Shorter (~1 hour)	Half-life	Longer (~3-6 hours) Fondaparinux ~17-21 hours
Bleeding, osteoporosis, thrombocytopenia (HIT), hyperkalemia (due to hypoaldosteronism)	Side effects	Bleeding, osteoporosis, thrombocytopenia (HIT), hyperkalemia (due to hypoaldosteronism)
Rapidly reversible by protamine sulphate Useful in situations where rapid reversal required	Reversibility	Partially reversible by protamine sulphate
Useful in renal failure	Use in renal failure	Use with caution/avoid if GFR <30 due to increased risk of bleeding
Higher risk compared to LMWH	Risk of HIT	Lower risk of HIT No risk of HIT when using fondaparinux

3- Synthetic heparin:



Drugs

□ fondaparinux.

Administration

□ subcutaneous

Monitoring during therapy .

□ Not generally recommended.

□ Anti-factor Xa activity can be assessed in specific cases.

Antidote

□ possibly activated prothrombin complex concentrates (aPCC)

4- Heparinoid (glycosaminoglycan)

Drugs:

□ danaparoid

Administration

□ Prophylaxis → subcutaneous

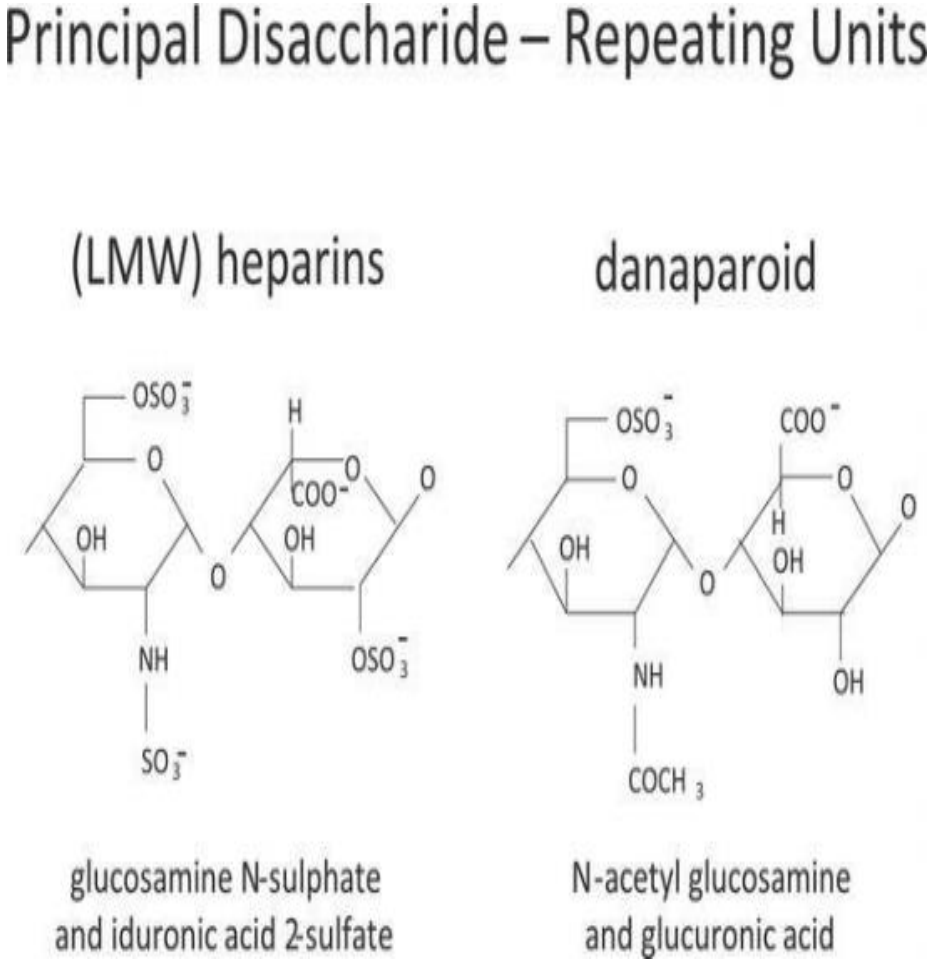
□ Therapeutic → continuous intravenous infusion

Monitoring during therapy

□ anti-factor Xa activity

Antidote

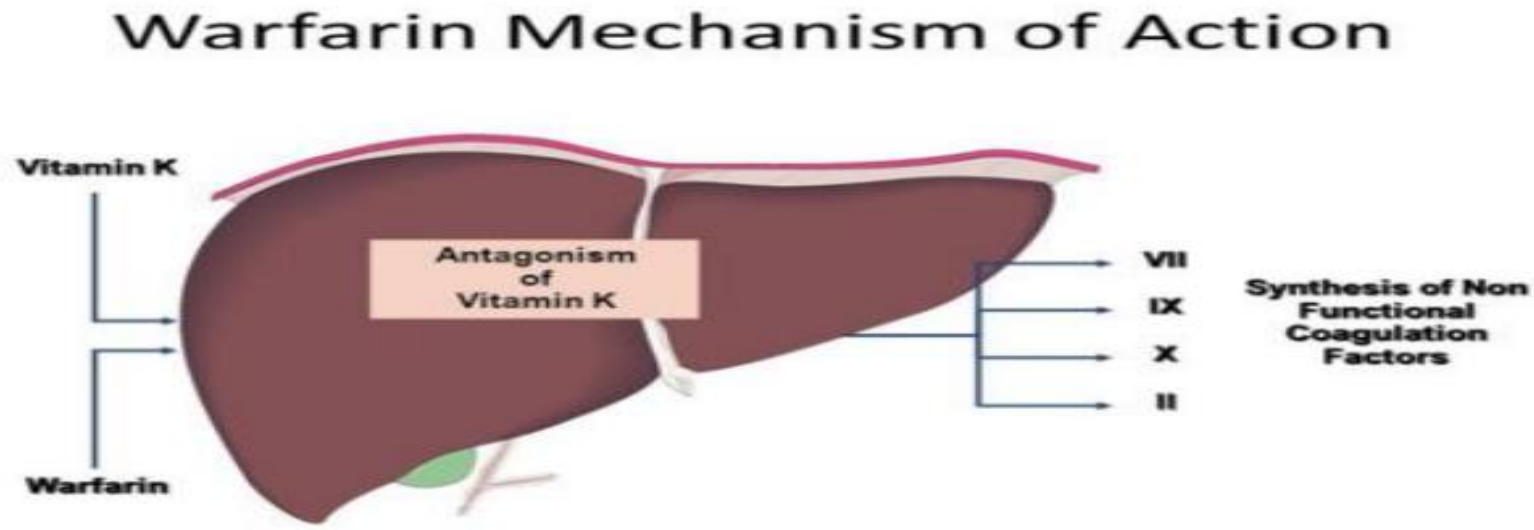
□ protamine sulfate (partial reversal)



Warfarin

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 .



Administration

□ Given orally .
□ Broad range of interactions.

□ 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.

INR Elevation	*INR Depression
Amiodarone (2C9)	Rifampin (2C9)
Ciprofloxacin (1A2/3A4)	Secobarbital (2C9)
TMP/SMX (2C9)	Carbamazepine (2C9)
Metronidazole (2C9/3A4)	Phenytoin (2C9)
Fluconazole (2C9/3A4)	Phenobarbital (2C9)
Fluvastatin (2C9)	Primidone (2C9)
Fluvoxamine (2C9)	St John's wort (2C9)
Isoniazid (2C9)	Cigarette smoking (1A2)
Lovastatin (2C9)	Charbroiled food (1A2)
Phenylbutazone (2C9)	
Sertraline (2C9)	
Gemfibrozil (2C9)	
Ethanol (1A2)	
Clarithromycin (3A4)	
Erythromycin (3A4)	
Voriconazole (3A4)	

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.

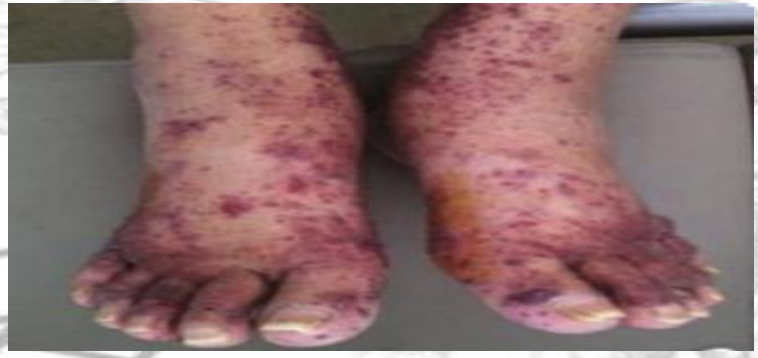
WEPT: Warfarin Extrinsic pathway PT

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.

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) .

Contraindications

□ Active bleeding.

□ Pregnancy (warfarin is a teratogen), use in breastfeeding women is not contraindicated.

□ Use with caution in alcoholics or any patient prone to frequent falls due to potential for intracranial bleeding.

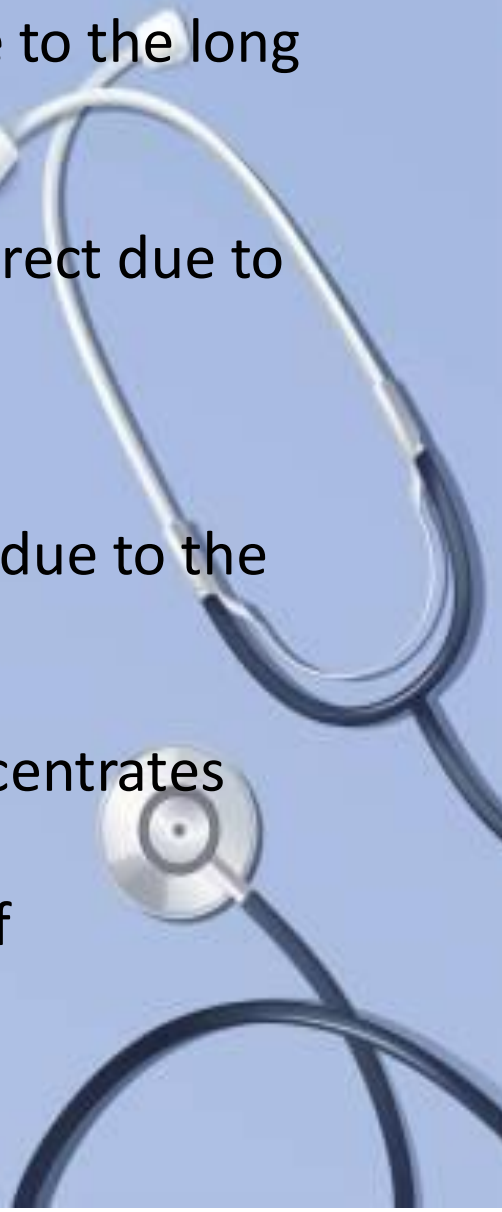
Reversing the Effects of Warfarin

□ 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.

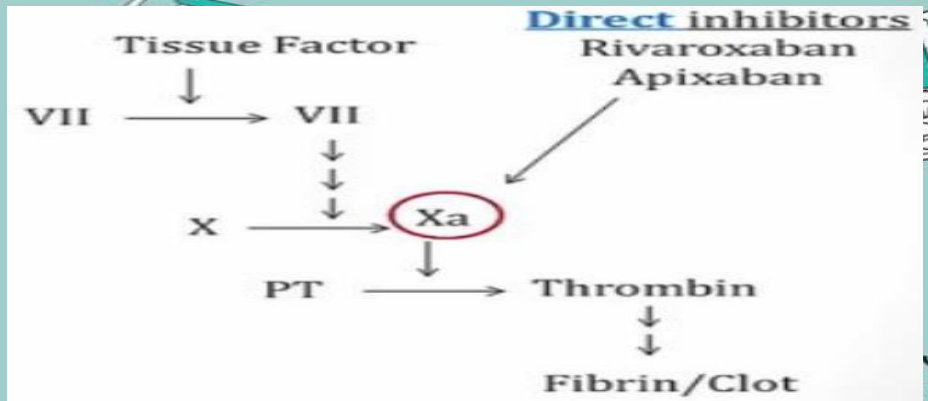


	Heparin	Warfarin
Pathway	Affects the intrinsic pathway	Affects the extrinsic pathway
MOA	Inactivates thrombin and factor Xa	Inhibits synthesis of clotting factors
Route	IV or subQ	PO
Teratogenic	Does not cross placenta or into breast milk	Crosses placenta (**teratogenic**)
Onset	Rapid (minutes)	Slow (hours)
Duration	Brief (hours)	Prolonged (days)
Drug interactions	Few drug interactions	Many drug interactions
Elimination	Eliminated renally	Eliminated hepatically
Monitoring	aPTT	PT
Antidote	Protamine	Phytomenadione (Vitamin K)

3)Direct Oral Anticoagulants (DOA):

1)Direct factor Xa inhibitors :

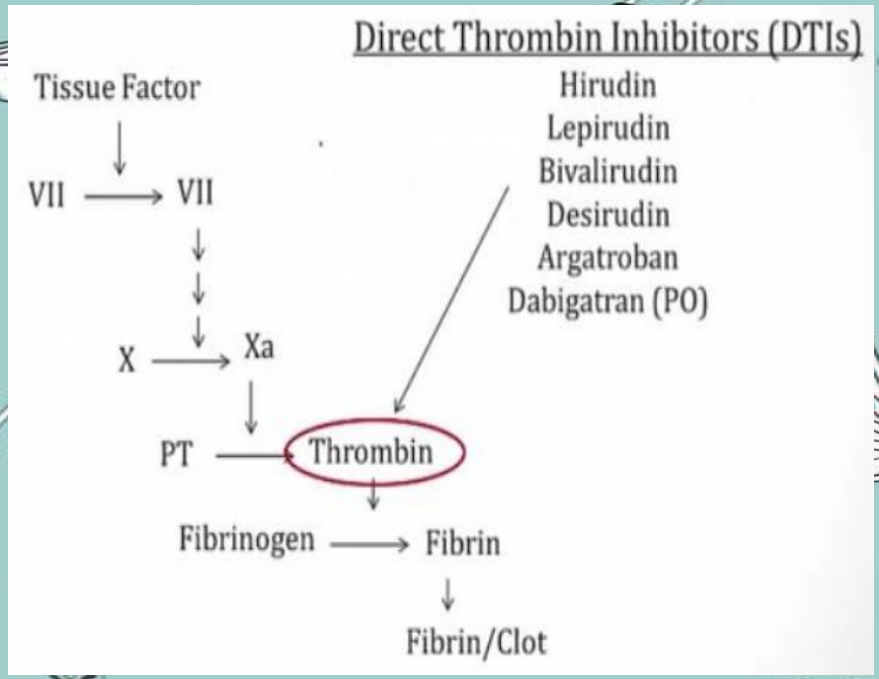
□ Rivaroxaban, Apixaban, Edoxaban.
□ Selective and direct inhibition of factor Xa (as opposed to potentiating AT III like heparin).
□ Prolonged PT and PTT, unchanged thrombin time (not routinely monitored).
□ Currently approved for treatment of DVT/PE, DVT/PE prophylaxis, and stroke prophylaxis in patients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



2)Direct thrombin (factor II) inhibitors :

□ Lepirudin, Argatroban, Dabigatran.
□ 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.

argatroban, bivalirudin, desirudin are direct thrombin inhibitors that administered Intravenous.



3)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.

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

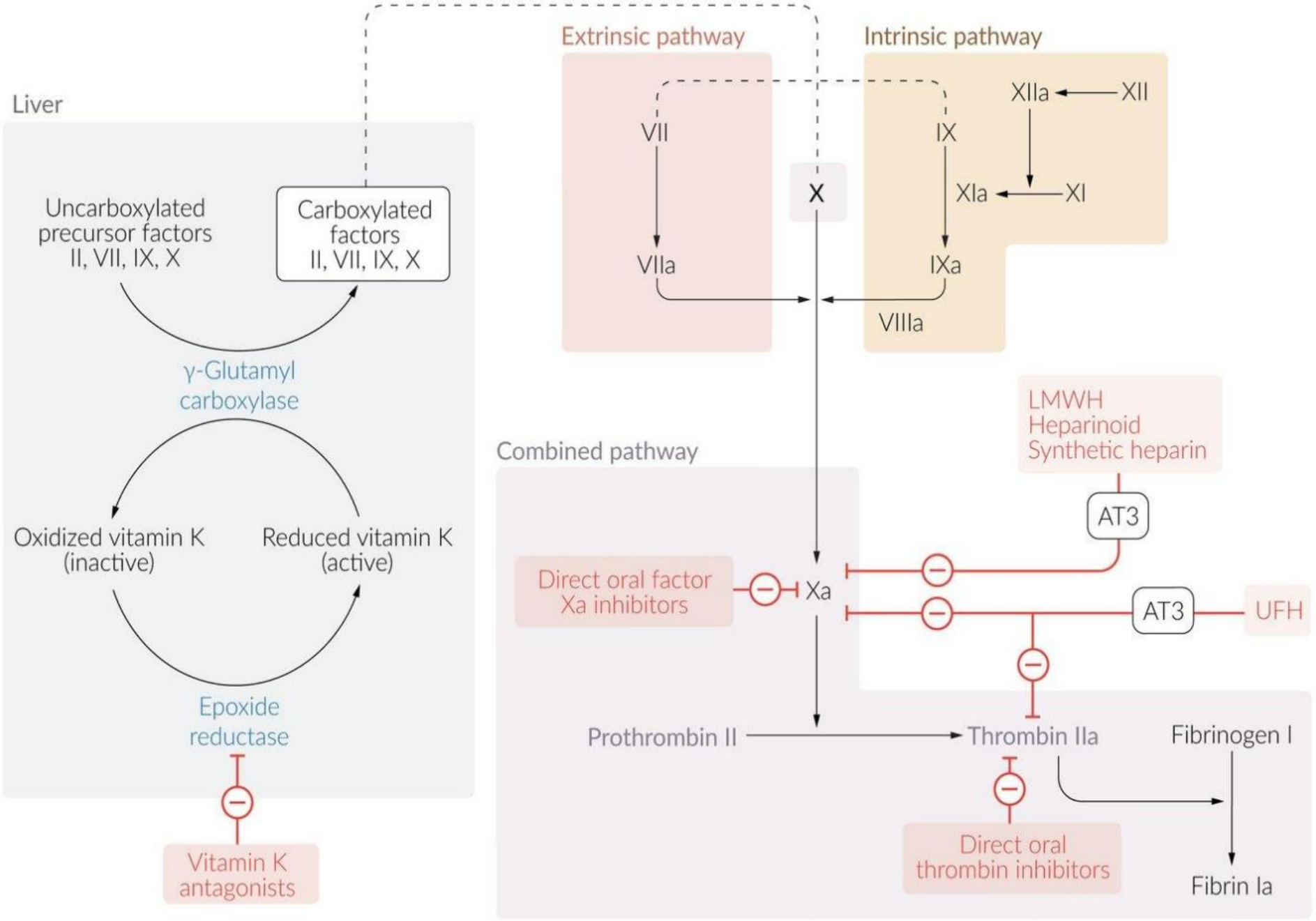
□ General management and specific medication antidotes

• 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)

• Dabigatran: idarucizumab (monoclonal antibody)


Liver
Uncarboxylated precursor factors II, VII, IX, X
Carboxylated factors II, VII, IX, X
γ-Glutamyl carboxylase
Oxidized vitamin K (inactive)
Reduced vitamin K (active)
Epoxide reductase
Vitamin K antagonists
Extrinsic pathway
Intrinsic pathway
VII
VIIa
X
IX
IXa
XIIa
XII
XIa
XI
VIIIa
Combined pathway
LMWH
Heparinoid
Synthetic heparin
AT3
Direct oral factor Xa inhibitors
Xa
AT3
UFH
Prothrombin II
Thrombin IIa
Fibrinogen I
Direct oral thrombin inhibitors
Fibrin Ia

Thank you