Pharmacology – HLS

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Drugs used in Thromboembolic Disease II

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Oral Anticoagulant Drugs

- **Spoiled sweet clover caused hemorrhage in cattle(1930s).**
- **Substance identified as bishydroxycoumarin.**
- **Initially used as rodenticides, still used and is very effective, more than strychnine.** Check next slide for further explanation.
- **Warfarin was introduced as an antithrombotic agent in the 1950s.**

At these times, the only known drug was Heparin and it was given parenterally and intravenously; so, when Warfarin came and it was allowed to be administered orally, it was shown to be more practical to give it instead, and the idea of oral antithrombotic drugs started.

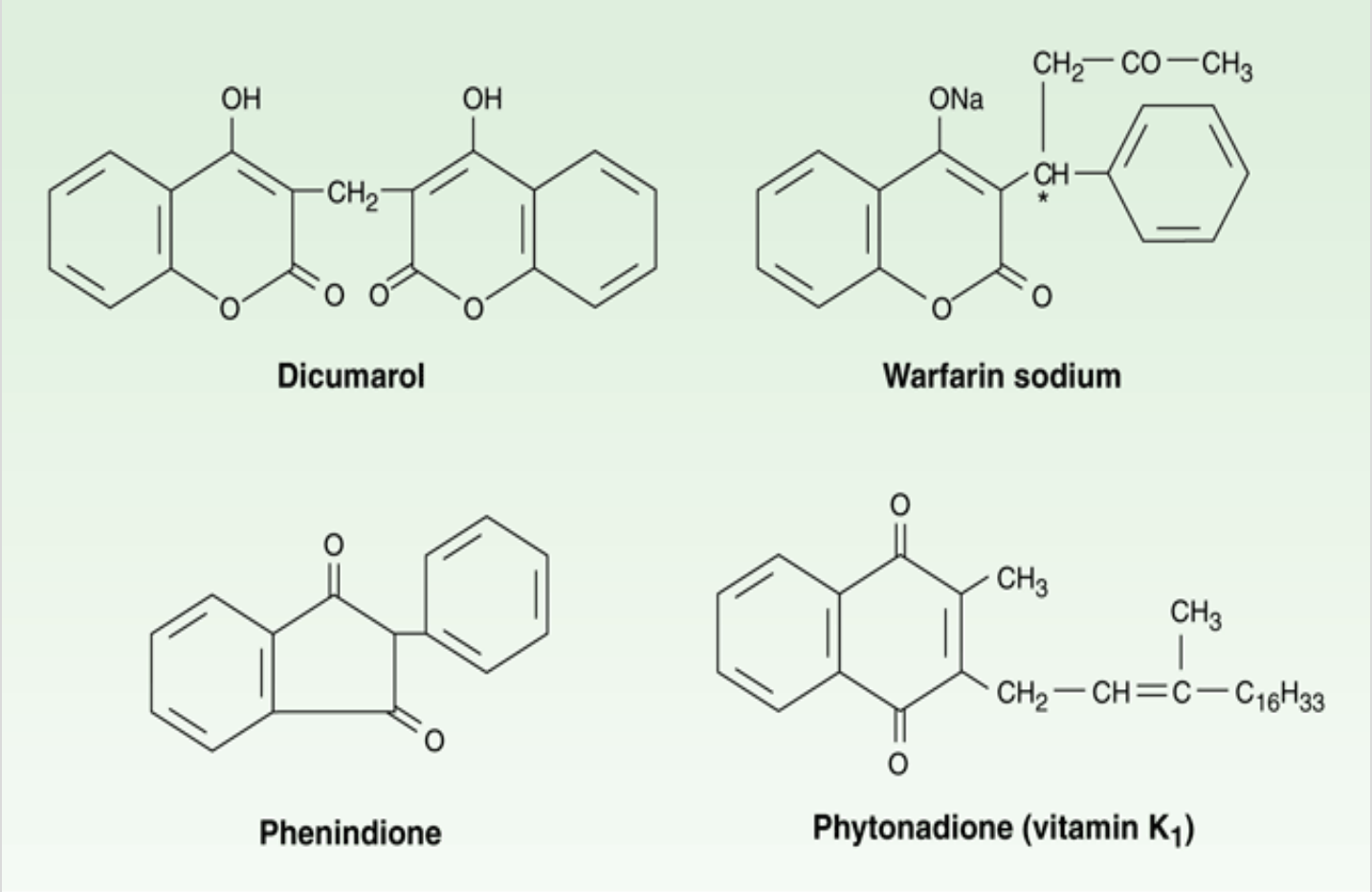
Nowadays thrombin Inhibitors and Factor 10 inhibitors are also anticoagulants drugs, and they can be given orally so the name oral anticoagulant drugs is a misnomer.

More explanation on the rodent poisoning point:

Strychnine was previously used to kill rodents by giving them epileptic attacks and convulsions, but rodents were very smart, they sacrificed a few of the herd to test the strychnine, and when they saw that it was toxic, they avoided it; so, despite being effective, it couldn't outsmart the rodents; that's why we use bishydroxycoumarin instead.

Bishydroxycoumarin doesn't have an immediate effect, it needs 48 hours to work, this way it outsmarted the rodents since they can't see their groupmates dying immediately of the drug, and they won't think that it was toxic, so they all have it.

These are some of the derivatives of the bishydroxycoumarin.. note that these drugs have an effect that opposes the effect of vitamin K1 because they are anticoagulants



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Note that vitamin K1 (fat-soluble vitamin) is not an anticoagulant drug and is not a derivative of the bishydroxycoumarin; on the opposite it is a procoagulant drugs and it is essential for the mechanism of coagulation in the blood.

Oral Anticoagulant Drugs

- **Warfarin:**
- **Is one of the most commonly prescribed drugs, actually it is *under prescribed*.** (this is mainly because of two reasons:
- 1. doctors are hesitant and conservative about prescribing warfarin to patients because it is a difficult drug to use and monitor, and it may cause excessive bleeding.
- 2. because patients are hesitant to take Warfarin and they miss their doses either intentionally or unintentionally).
- **100% bioavailability** (this means that the whole administered dose is absorbed, and it doesn't go through the first-pass metabolism) **, peaks after one hour** (The peak of Warfarin and concentration in the blood).

Warfarin cont'd:

- Immediately after absorption, **99% bound to plasma proteins, leading to small volume of distribution and long half-life(36hr).**
- Longer Half-Life is because there is a 1% remaining warfarin that is not bound to plasma proteins which is the active drug, and when this percentage of the drug is consumed, another 1% is freed from plasma proteins to be active again and so on, so it takes much longer time to consume 50% of the dose of Warfarin, giving it a longer half life.
- Small volume of distribution occurs when the drug is bound to a plasma protein, this limits the compartments of the body that it can reach, compelling it to stay in the circulation, and this is an advantage that helps it perform its action when activated (because it will always be nearby).
- **Does not cross BBB** (because it's bound to a large plasma protein) **but crosses the placenta** (that's why it is contraindicated in pregnant ladies).
- **After circulating in the blood, it is Hydroxylated in the liver.**
- **Present in two enantiomorphs.**

Oral Anticoagulant Drugs

Mechanism of Action:

Act in the liver, not in the circulation. It works on the synthesis of coagulation factors in the liver..

Structure is similar to vitamin K.

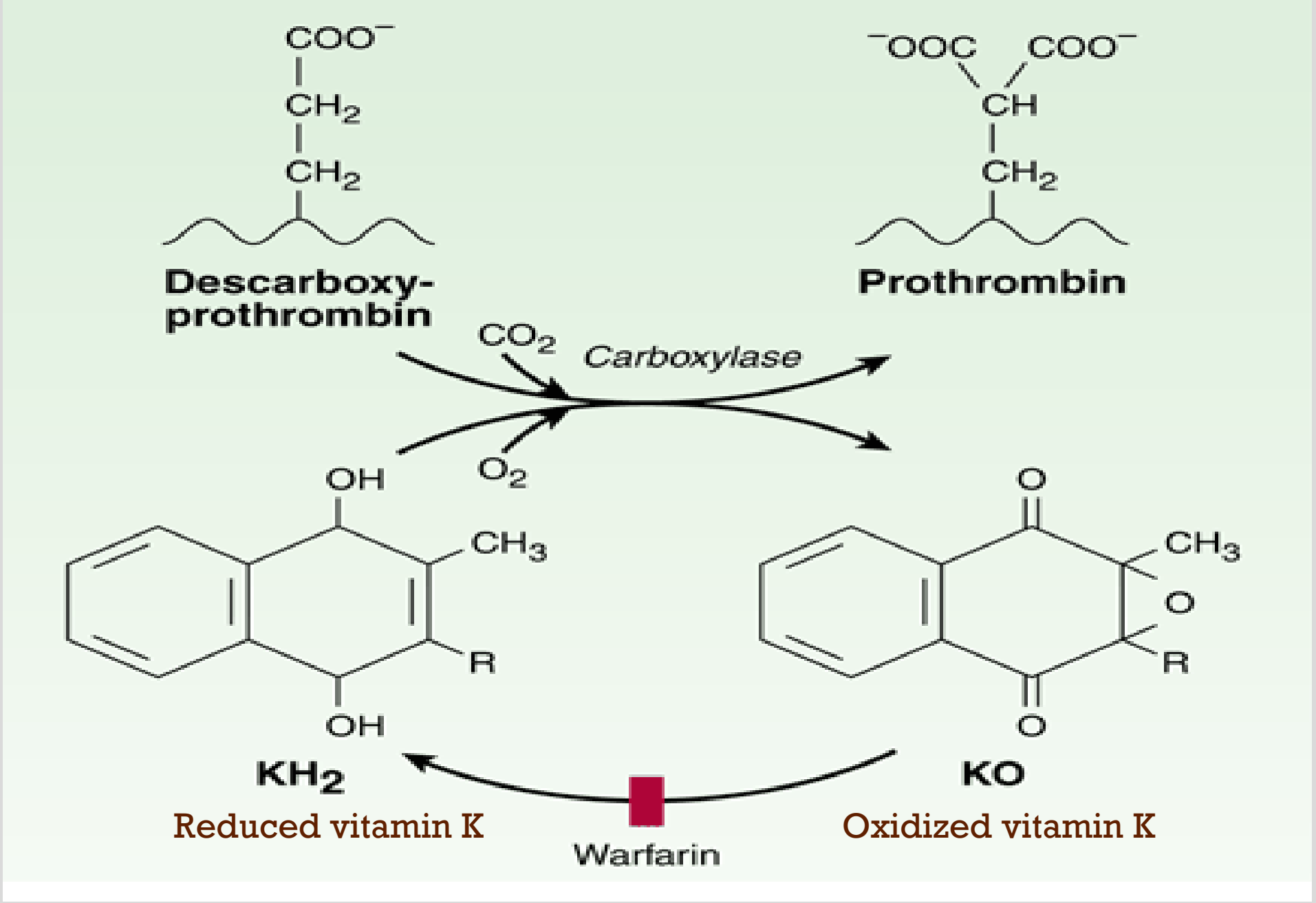
- **Block the ɣ-carboxylation which is a final synthetic step that transforms a common precursor into various factors: prothrombin, VII, IX, and X as well as the endogenous anticoagulant proteins C and S.** And consequently, this will affect the synthesis of all of these factors.
- **This blockage results in incomplete coagulation factor molecules that are biologically inactive.** That's why we can call these drugs as **"coagulation factors synthesis inhibitors"**

Oral Anticoagulant Drugs

Mechanism of Action:

The protein carboxylation reaction is coupled to the oxidation of vitamin K. This means that the reduced form of vitamin K is a stimulant of carboxylation reaction so:

- **The vitamin must then be reduced to reactivate it.**
- **Therefore, warfarin prevents reductive metabolism of the inactive vitamin K epoxide back to its active hydroquinone form.** Inhibiting vitamin K reduction prevents it from stimulating the carboxylation reaction.. As shown in the next slide:


Descarboxy-prothrombin
Prothrombin
CO_2
Carboxylase
O_2
OH
CH_3
R
OH
KH_2
O
CH_3
O
R
O
KO
Reduced vitamin K
Warfarin
Oxidized vitamin K

Warfarin

Onset of Action: The onset of action depends on the remaining amount of coagulation factors remaining in the circulation after the warfarin did its job

- **Time to maximal effect depends on factor degradation half-lives in the circulation.** And coagulation factors differ in their half-lives: **VII=6, IX=24, X= 40 and II=60 hrs.**

- **Action starts after about 48 hrs., i.e. after elimination of most of the factors in the circulation. So, do not increase the dose.**

Many patients and sometimes doctors do not notice the effects of Warfarin in the first 48 hours, so they decide to increase the dose; which is very dangerous, they must wait until these 48 Hours are done and then they can see the desired effect.

In some cases, we also give Heparin for the first 48 hours and then after the 48 hours we can see the effects of Warfarin, so we stop giving Heparin.

- After some time, a few days maybe, **Effect results from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K dependent clotting factors.**

Warfarin

- **Administration and Dosage:**
- **Treatment is initiated with small doses of 5-10mg, not large loading doses.** (Keep in mind that we don't see the effects of Warfarin until 48 hours after administration).
- **Warfarin resistance is seen in cancer patients.**
- **Response monitored by Prothrombin Time.**
- **International Normalized Ratio (INR)=**
  - **Patient PT/ Mean of normal PT for the lab.**
  - PT: prothrombin time

Warfarin

Toxicity:

- **Bleeding** (Excessive).
- **Teratogenicity.** Because it crosses the Placenta, so it can induce hemorrhage in the fetus, and giving it in early stages of pregnancy can cause congenital malformations for the fetus.
- **Cutaneous necrosis, infarction of breast, fatty tissues, intestine and extremities. This is due to inhibition of Protein C and S, especially in patients genetically deficient in them.**

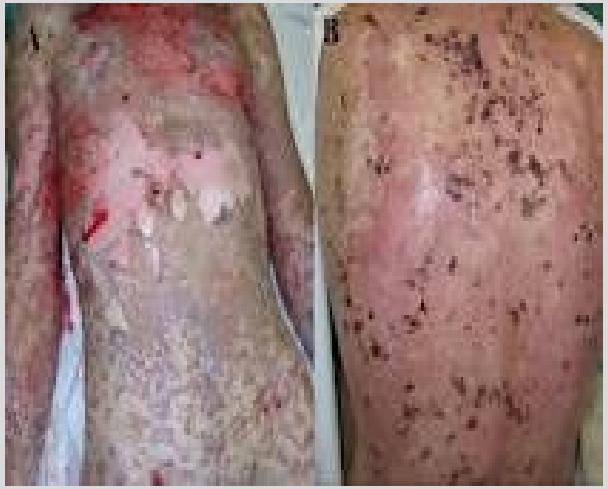


TABLE 34-2 Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	*Pharmacodynamic*	*Pharmacokinetic*	*Pharmacodynamic*
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K
Metronidazole[1]	Heparin		**Body factors**
Fluconazole[1]	**Body factors**		Hereditary resistance
Phenylbutazone[1]	Hepatic disease		Hypothyroidism
Sulfinpyrazone[1]	Hyperthyroidism		
Trimethoprim-sulfamethoxazole			

طبعا هتقولي أحفظ كل دا ازاي يا دكتور؟
هقولك أي نعم خلقت بلسما بس الجدول دا مش حفظ يا برنس

Warfarin

- **Reversal of Action:** If we needed to reverse the action because of severe bleeding, high PT or high INR.. we use:
  - **Vitamin K.**
  - **Fresh-frozen plasma,** it must be fresh because we want it to have fresh coagulation factors.
  - **Prothrombin complex concentrates.**
  - **Recombinant factor VII.**

Fibrinolytic Agents

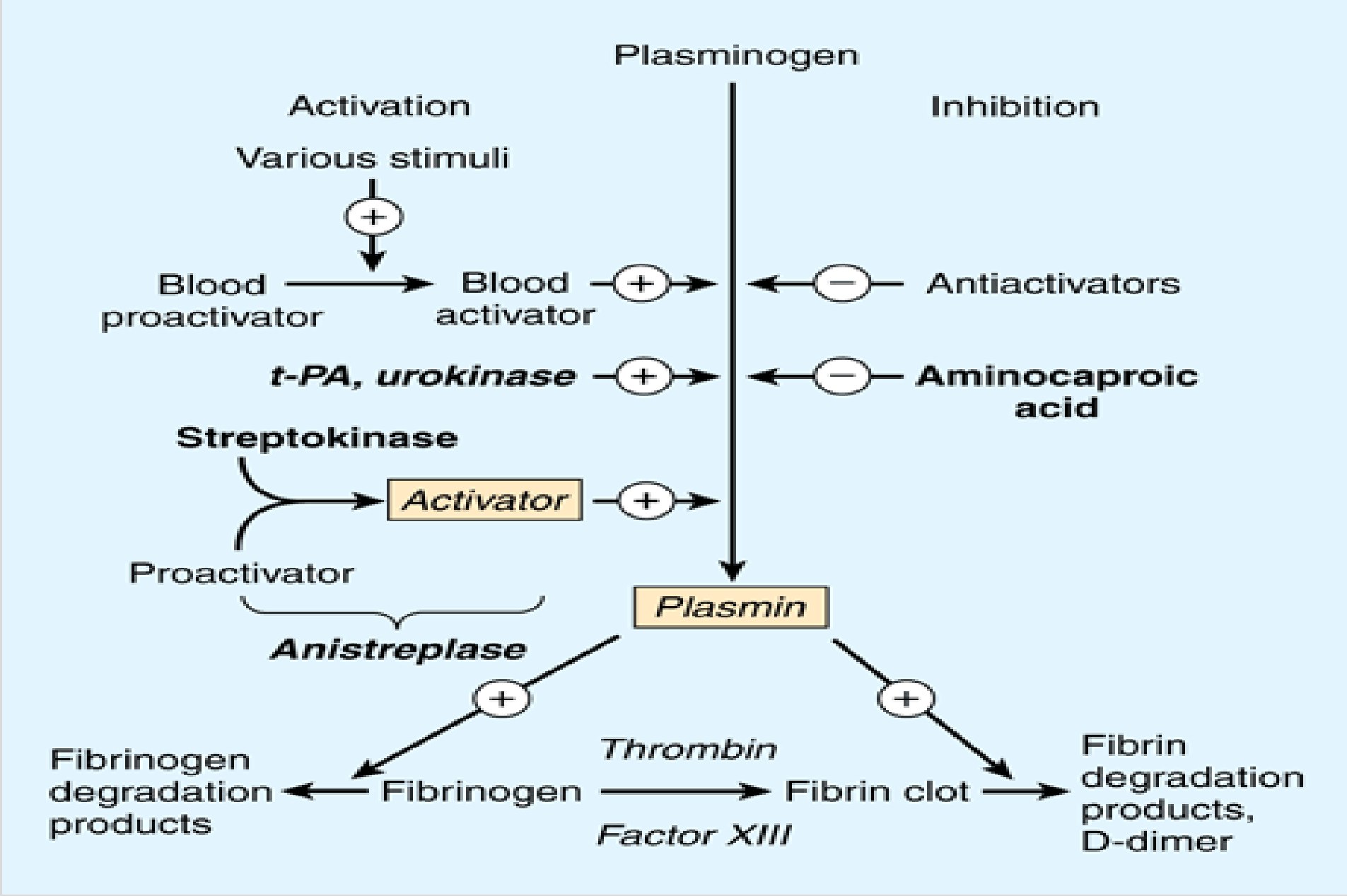
أخيرا اشي مش ورفرين ..يا دين النبي !!

- **These drugs rapidly lyse thrombi by catalyzing the formation of the serine protease Plasmin from its precursor zymogen, Plasminogen.**

So, their job is basically catalyzing plasminogen turning into plasmin, and plasmin can then dissolve the fibrous clot.

- **They create a generalized lytic state.**
- **Aspirin** (An antiplatelet drug) **will be still required.**

This diagram shows the conversion of plasminogen into plasmin and how plasmin degrades both fibrinogen and fibrin in order to lyse the clot.



Fibrinolytic Agents

Streptokinase:

- **Protein synthesized by *Streptococcus*.** They discovered that streptococcus invades tissues like blood by secreting streptokinase that prevents blood coagulation, and this helps it invade the blood and spread in it.
- **Binds with the proactivator plasminogen in plasma to activate it.**
- **Not fibrin - specific → Bleeding.** (Does not bind specifically to fibrin, so it can cause bleeding everywhere)
- **Highly antigenic** (Because it's derived from Streptococcus bacteria) :
  - **Can cause allergic reactions .**
- **This can result in inactivation of the drug** (If the patient was previously exposed to streptococcus bacteria and has antibodies towards it, it can result in inactivation of the drug when it is used as a fibrinolytic agent).
- **Early administration** After the diagnosis of the thrombotic problem **is important**, it's not very practical but it is cheap, and it is rarely used nowadays.

Fibrinolytic Agents

Urokinase:

- Is a human enzyme synthesized by the kidneys (Extracted from human urine).
- Directly converts plasminogen into plasmin.
- Not antigenic.
- Expensive and not practical.

Fibrinolytic Agents

Anistreplase (Anisoylated Plasminogen Streptokinase Activator Complex,ASPAC):

- More active and selective.
- Deacylated at fibrin surface → Active complex released.
- Long action, t½ → 6h

Fibrinolytic Agents

- **Tissue-type Plasminogen Activators (t-PA):**
  - **Ateplase**
  - **Reteplase.**
  - **Tenecteplase**
- **Normally synthesized by the endothelial cells, also recombinant** (commercial preparation is available using recombinant DNA technology).
- **Bind to fibrin and activate plasminogen at the fibrin surface.**
- **Action less affected by age of thrombus.**
- **Specific action — within the thrombus, avoids systemic activation.**
- **Short action t½ = 8 min.**
- **Given by infusion over 1-3 hours.**
- **Very Expensive.**

Fibrinolytic Agents

Indications: May be the same as anticoagulants but they're more effective and less toxic than them

- **Pulmonary embolism with hemodynamic instability.**
- **Deep venous thrombosis.**
- **Ascending thrombophlebitis.**
- **Acute myocardial infarction.**

Antiplatelet Drugs

They work on platelets rather than coagulation cascade.. so, they have no business with coagulation factors..

Types of Platelet Regulators:

- **Agents generated outside platelets which interact with membrane receptors,** these are available in the systemic circulation, cause vasoconstriction and platelet aggregation:

  Catecholamines, collagen, thrombin, and prostacyclin.

- **Agents generated inside and interact with membrane receptors: ADP, PGD2, PGE2 and serotonin** (5-hydroxytryptamine)**.**
- **Agents generated within and interact within platelets: TXA_2, cAMP, cGMP and calcium.**

Platelet adhesion and aggregation

- **GPIa/IIa and GPIb** are platelet receptors that bind to collagen and von Willebrand factor (vWF), causing platelets to adhere to the subendothelium of a damaged blood vessel.

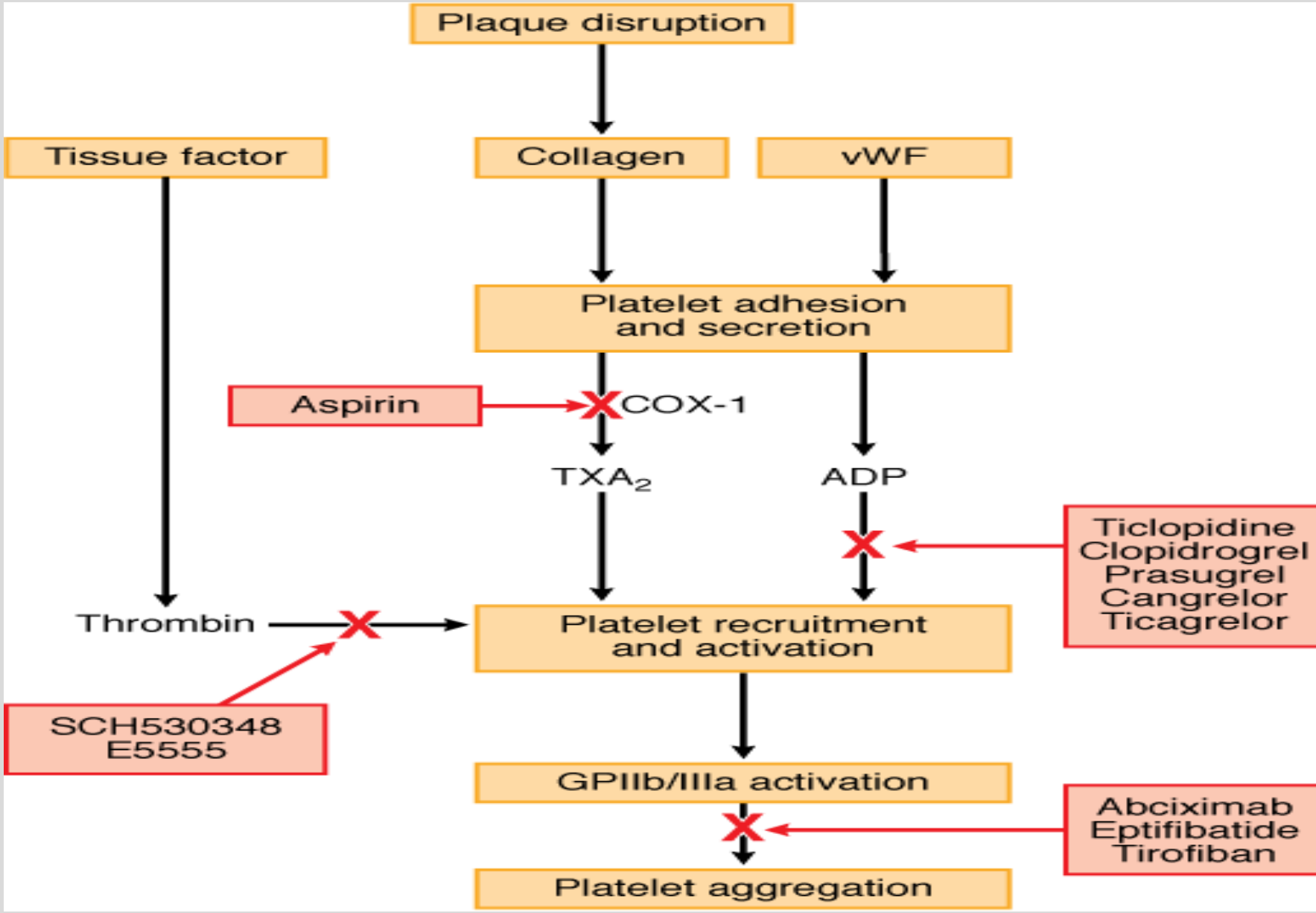
- **P2Y1 and P2Y12** are receptors for ADP. When stimulated by agonists, these receptors activate the fibrinogen-binding protein GPIIb/IIIa and cyclooxygenase-1 (COX-1) to promote platelet aggregation and secretion.

Platelet adhesion and aggregation

- **PAR1 and PAR4 are protease-activated receptors that respond to thrombin (IIa).**
- **Thromboxane A2 (TxA2) is the major product of COX-1 involved in platelet activation.**
- **Prostaglandin I2(prostacyclin, PGI2), synthesized** by **endothelial cells, inhibits platelet activation,** can also cause vasodilation

This graph shows the interaction of the factors mentioned previously and explains the activity of each drug on their pathways and the action it performs on platelets

And stuff…



Sites of action of antiplatelet drugs.

- **Aspirin inhibits thromboxane A2(TXA2) synthesis by irreversibly acetylating cyclooxygenase-1 (COX-1). Reduced TXA2 release attenuates platelet activation and recruitment to the site of vascular injury.**
- Side note: Aspirin is also a prostaglandin inhibitor as well.
- **Ticlopidine, clopidogrel, and prasugrel irreversibly block P2Y12, a key ADP receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of P2Y12.**

Sites of action of antiplatelet drugs.

- **Abciximab, eptifibatide, and tirofiban** Block fibrinogen and von Willebrand factor (vWF) from binding to activated glycoprotein (GP) IIb/IIIa.

- **Zontivity** inhibit thrombin-mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on platelets.

Antiplatelet Drugs

- **Aspirin = Acetyl Salicylic Acid**
  - **Causes irreversible acetylation of COX in platelets.**

Platelets do not have DNA or RNA, so aspirin causes permanent inhibition of platelets' COX (half-life 7-10 days).

Endothelium can synthesize new COX, so PGI2 production is not affected.

  - **Dose: 80 — 325 mg.**

- والنبي يا بلسم تلحقني عال **next slide** عشان أقولك كلمتين حلوين يستروك في الامتحان والسلايد هاي ما يعلم بيها الا ربنا..

The story of Aspirin..

Aspirin was originally a non-steroidal anti-inflammatory drug (NSAID) known to be a good agent in lowering high body temperature and is known to be a good analgesic all by inhibiting prostaglandin synthesis..

Aspirin irreversibly damages the platelets, so damaged platelets cannot aggregate throughout their lives; and since aspirin is a prostaglandin synthesis inhibitor, it also inhibits the synthesis of PGI2 in endothelium, but endothelium –unlike the platelets- can synthesize new COX, so PGI2 production will not be affected..

And since PGI2 causes vasodilation, it opposes the effect of TXA2, and inhibit platelet activation and aggregation, further delaying the coagulation mechanism..

So, one dose of Aspirin inhibits the coagulation n 2 ways, that's why very small amount of aspirin is needed to inhibit the action of cyclooxygenase enzyme so it can be given once every two or three days, but it's usually given once daily.

كمان مرة عال next slide وخليك صاحي للكلام..

The story of Aspirin pt. 2..

Aspirin used to be taken in high doses in the past, like 325mg 10 times a day to suppress inflammatory processes like in Rheumatoid arthritis..
But here we need about 80mg a day only.

Baby aspirin is not for children, it's only for adults. يا دكتور يا متعلم

Aspirin is only used for its antiplatelet activity, not its anti-inflammatory or analgesic features nowadays, and it’s very very cheap.

يلا يا ماما كمل المحاضرة بقى..

Antiplatelet Drugs

- **Clopidogrel (Plavix).**
- **Ticlopidine (Ticlid).**
  - **Irreversibly block ADP receptors on platelets.**
  - **Useful in TIAs** (Transient ischemic attacks), **completed stroke, unstable angina and after placement of coronary stents.** Coronary stent patients receive ticlid. for a whole year and afterwards continue with aspirin since aspirin is cheaper.
  - **Useful for patients who cannot tolerate aspirin.**
  - **Can cause leukopenia, GI irritation** (but much less than aspirin does) **and skin rash.**

Antiplatelet Drugs

Abciximab.

- Monoclonal antibody

Eptifibatide.

- Synthetic peptide.

Tirofiban.

- All inhibit the platelet glycoprotein IIb/IIIa complex, which works as a receptor mainly for fibrinogen and vitronectin as well as for fibronectin and von Willebrand factor.

Antiplatelet Drugs

Dipyridamole

Cilostazole

Also work as vasodilators.

- **Work by inhibiting adenosine uptake and phosphodiesterase enzyme $\rightarrow\uparrow$c AMP in platelets and elsewhere.**

Antiplatelet Drugs

Dazoxiben:

Inhibits TX synthetase enzyme.

Sulotroban:

Inhibits TXA2 receptor.

Anagrelide:

Reduces platelet production by decreasing megakaryocyte maturation.

Lipid Lowering Agents

Reduced lipids in the plasma and reduced viscosity will reduce activity of platelets

Hemostatic Agents

(drugs to increase coagulativity of the blood)

- **Whole Blood:** a Primitive way of supplying extra fresh RBCs as well as platelets and coagulation factors.
- **Fresh Frozen Plasma:** If it's not fresh then the platelets and coagulation factors will be deficient.
- **Plasma fractions:** Isolated coagulation factors that are available commercially, not all of them are widely used, but hemophiliac Factor (hemophilia A) is widely used because there are many hemophiliac patients especially in the Western world, Vitamin K is also widely used and beneficial because it enhances the coagulation factors synthesis.
- **Vitamin K.**

This table shows the coagulation factors and their indications. The most important of them is factor 8 (hemophiliac factor), it used to be isolated from fresh frozen plasma of the blood donors (cryoprecipitate) in the past, now the recombinant form of factor 8 is available commercially for patients with hemophilia A

In the past factors used to be transfused to patients from blood donors & this helped in spreading the AIDS virus among people in the early 80s

Nov-21

TABLE 34–3 Therapeutic products for the treatment of coagulation disorders.

Factor	Deficiency State	Hemostatic Levels	Half-Life of Infused Factor	Replacement Source
I	Hypofibrinogenemia	1 g/dL	4 days	Cryoprecipitate FFP
II	Prothrombin deficiency	30–40%	3 days	Prothrombin complex concentrates (intermediate purity factor IX concentrates)
V	Factor V deficiency	20%	1 day	FFP
VII	Factor VII deficiency	30%	4–6 hours	FFP Prothrombin complex concentrates (intermediate purity factor IX concentrates) Recombinant factor VIIa
VIII	Hemophilia A	30–50% 100% for major bleeding or trauma	12 hours	Recombinant factor VIII products Plasma-derived high purity concentrates Cryoprecipitate[1] Some patients with mild deficiency will respond to DDAVP
IX	Hemophilia B Christmas disease	30–50% 100% for major bleeding or trauma	24 hours	Recombinant factor IX products Plasma-derived high purity concentrates
X	Stuart-Prower defect	25%	36 hours	FFP Prothrombin complex concentrates
XI	Hemophilia C	30–50%	3 days	FFP
XII	Hageman defect	Not required		Treatment not necessary
von Willebrand	von Willebrand disease	30%	Approximately 10 hours	Intermediate purity factor VIII concentrates that contain von Willebrand factor Some patients respond to DDAVP Cryoprecipitate[1]
XIII	Factor XIII deficiency	5%	6 days	FFP Cryoprecipitate

Hemostatic Agents

Not drugs but physical procedures to reduce the bleeding, like:

- **Absorbable Gelatin Foam:** Sprinkling it on open wounds
- **Absorbable Gelatin Film:** Especially in plastic surgeries to close the wound
- **Oxidized Cellulose**
- **Thrombin:** Available as a powder and can be sprinkled over these wounds

Plasmin Inhibitors

- α2 Antiplasmin
  - Physiological.
- Aprotinin:
  - Bovine parotid gland.
- Aminocaproic Acid
- Tranexamic Acid

يعطيك العافية يا دكترة، بتقدر تروح عالمحاضرة الي بعدها يا سيد الملحوقين🔥🔥🔥