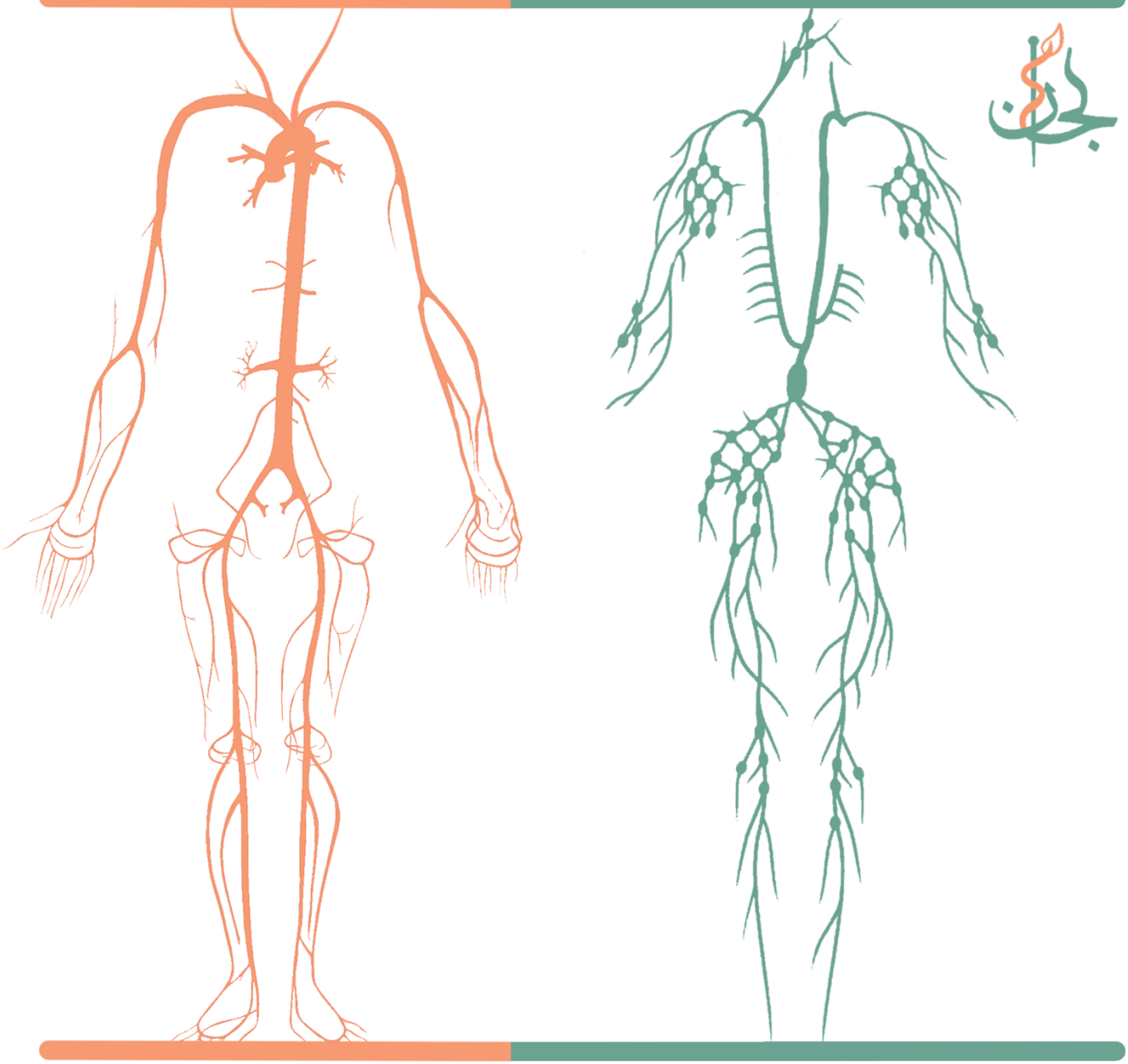
Pharmacology

HematoLymphatic



Title: Sheet 4 – Drugs of thromboembolic diseases II

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Anything mentioned in boxes is only for further clarification and it's not required

RECAP:

Thromboembolism: obstruction of a blood vessel by a blood clot.

Drugs used in Thromboembolic Disorders

I. Anticoagulants:
- Factor inhibitors: Heparin, Rivaroxaban,..
- Factor synthesis inhibitors: Oral anticoagulants.

II. Fibrinolytic Drugs (aka. Thrombolytics):
- Streptokinase (bacterial)
- Urokinase
- Anistreplase/ ASPAC (Anisoylated Plasminogen Streptokinase Activator Complex)
- Tissue-type Plasminogen Activators (t-PA): Alteplase

III. Antiplatelet Drugs
- Aspirin.
- Dipyridamole
- Sulfinpyrazone.

In this sheet we're going to discuss the oral anticoagulants, fibrinolytic drugs, as well as the antiplatelet drugs.

1. Oral Anticoagulant Drugs

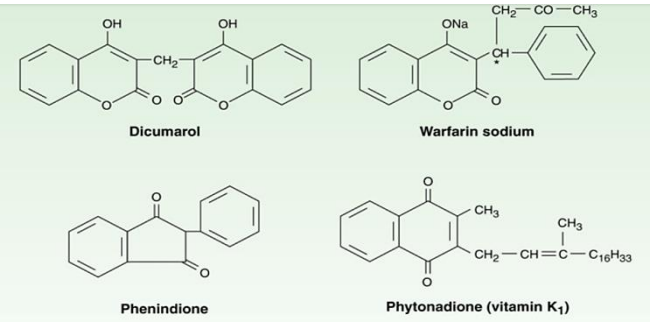
Short -very unimportant- sad story:

In the 1930s, some cattle ingested spoiled sweet clover and developed severe hemorrhage. After investigation, **Bishydroxycoumarin** was identified as the cause of bleeding. So, they used it in rodenticides to kill rodents, it's still used and it proved to be effective even more than Strychnine, which was usedto cause convulsions in these animals.

But why was it more effective? Bishydroxycoumarin has a delayed onset of action that starts 48 hours after ingestion. So, rodents didn't avoid it because they never knew it was the cause of their death.

Derivatives of Bishydroxycoumarin:

All can be used as anticoagulants -since they work as competitive inhibitors for vitamin K- EXCEPT vitamin K1, which is a pro-coagulant that's used as an **antidote** for the others.



Warfarin:

- In the 1950s, when Heparin was the only known anticoagulant, Warfarin was introduced. And as it was given **orally**, it made such a big deal because Heparin was given parenterally.
- Generally, Warfarin is one of the most commonly prescribed drugs, and it's actually underprescribed (we should prescribe it more often). Doctors tend to avoid prescribing Warfarin because – in certain cases- it causes severe bleeding and thus, it requires monitoring.

The life story of a drug:

i. It begins after administration of a specific dose through a specific route.
ii. When it's given orally, the drug concentration is reduced before reaching the systemic circulation (first pass effect) affecting the bioavailability.
iii. Then, the drug is absorbed to the circulation to do its job.
iv. After that, it is metabolized to facilitate excretion.
v. Then it's eliminated from the body.

Let's follow Warfarin as it goes through these steps:

i. It's administered orally.
ii. It has **100% bioavailability** and the concentration peaks after one hour. Meaning that it is rapidly and completely absorbed with no first pass effect.
iii. 99% of the drug is bound to plasma proteins, leading to a small volume of distribution (small proportion is free and active; the distribution is limited to the circulation) and a long half-life of 36 hours. It does not cross the blood-brain barrier (BBB), but crosses the placenta, so it's **contraindicated** in pregnancy.
iv. It's metabolized by **hydroxylation** in the liver. And it consists of a racemic mixture of two active **enantiomers**; R and S forms.

Remember that the free drug is the active drug, and in the case of Warfarin, only 1% of the drug is free. When this 1% is consumed another 1% gets released and so on, and this explains the long half-life.

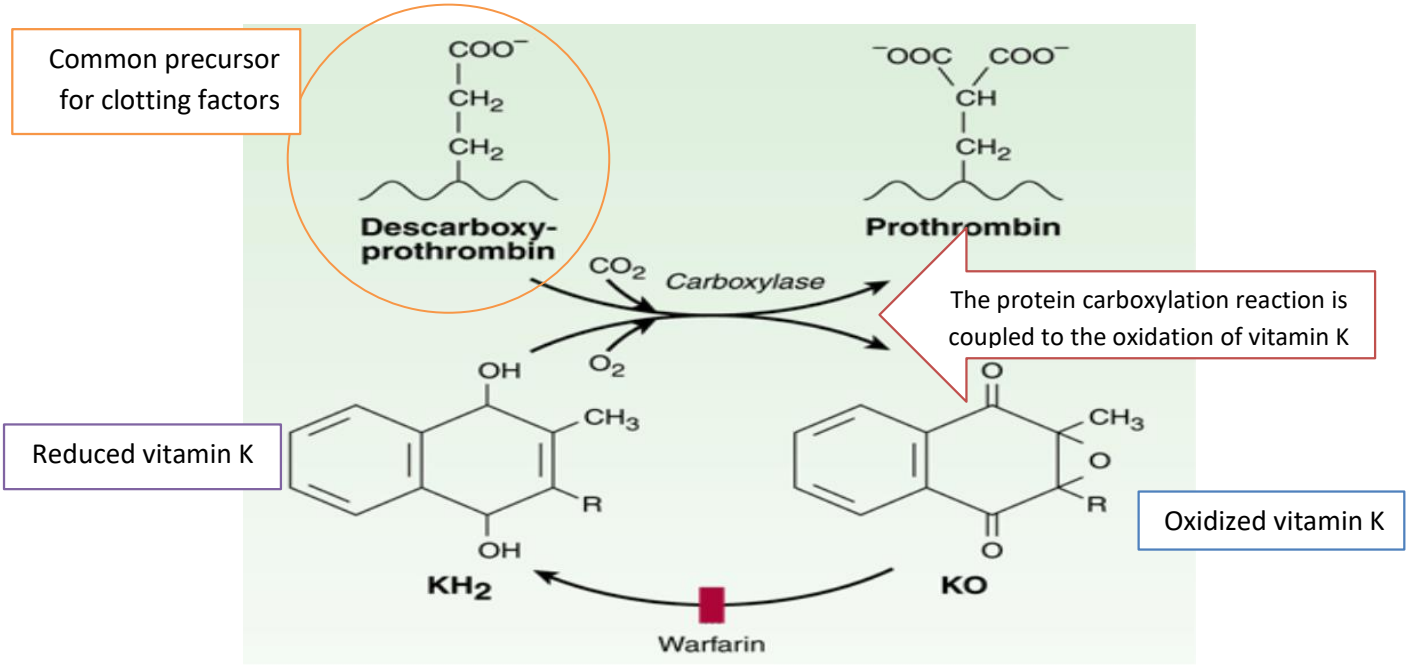
The 36-hour half-life means that the drug needs 36 hours for half of the administered dose to be eliminated BUT this doesn't have to do with the pharmacological effect, as it can persist for a longer period.

Mechanism of Action:

Warfarin acts in the **liver** not in the circulation by inhibiting coagulation factors' synthesis from the liver.

Because of the similarity in structure between Warfarin and vitamin K, Warfarin can competitively inhibit the production of active clotting factors, by blocking the vitamin K dependent ɣ-carboxylation of a common precursor into clotting factors II, VII, IX, and X as well as the endogenous anticoagulant proteins C and S (refer to box in Warfarin toxicity). This blockade results in incomplete coagulation factor molecules that are biologically inactive.

For further explanation:



The vitamin then must be reduced to reactivate the carboxylase, and when Warfarin prevents the reduction of the inactive vitamin K epoxide back to its active hydroquinone form, synthesis of several clotting factors is inhibited.

Warfarin Onset of Action:

The time to produce the maximal effect depends on the clotting factor half-life.

**To see the effects of the anticoagulant drug, we have to wait for the already synthesized and activated clotting factors to be eliminated, and that is dependent on their half-lives.

The half-lives of some clotting factors are as follows: VII=6, IX=24, X= 40 and II=60 **hrs**. So, on average, the action starts after about **48 hrs**, i.e. after elimination of most of the factors in the circulation. So, DO NOT increase the dose if you don't see an immediate effect. But, that doesn't mean that we have to wait this long, one solution is to give **Heparin** for the first 48 hours and then continue with the oral anticoagulant.

➔ Therefore, the final effect results from a balance between:

a. Partially inhibited synthesis (due to drug).
b. Unaltered degradation of the four vitamin K dependent clotting factors. (II, VII, IX, X)

Warfarin Administration and Dosage:

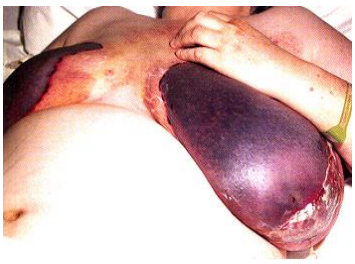
A loading dose: an initial higher dose of a drug that may be given at the beginning of a course of treatment before dropping down to a lower maintenance dose.

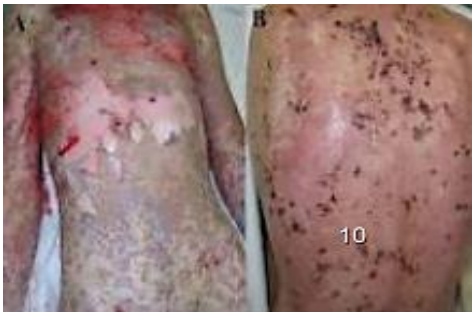
- Treatment is initiated with small doses of 5-10mg, **not large loading doses**.
- Warfarin resistance is seen in cancer patients.
- Response is monitored by:
  a. Prothrombin Time (PT), to measure how quickly your blood clots. (clinically variable)
  b. International Normalized Ratio (INR)= Patient PT/ Mean of normal PT for the lab. (standardized)

Warfarin Toxicity leads to:

- Bleeding.
- Teratogenicity and congenital malformations; as it crosses the placenta and can cause hemorrhage in the fetal tissue.
- Cutaneous necrosis, infarction of breasts, fatty tissues, intestines and extremities. This is due to inhibition of **Protein C and S,** especially in patients with genetic deficiency. (Remember, Proteins C and S are endogenous anticoagulant proteins).

This may sound contradictory, but since Warfarin initially decreases protein C levels, it can paradoxically increase the coagulation tendency when treatment is first begun, leading to massive thrombosis with skin necrosis and gangrene of limbs.





✓ Factors increasing/decreasing PT

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			

Drugs that increase the PT; ↑ effect of oral anticoagulants	Drugs that decrease PT; ↓ effect of oral anticoagulants

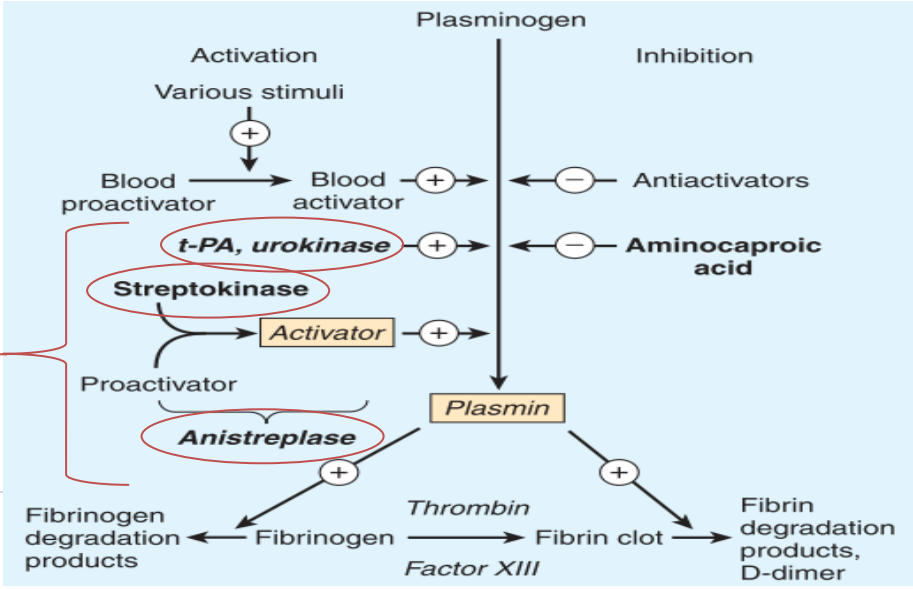
Remember: increased prothrombin time means the blood takes longer time to clot, and vice versa.

Reversal of Action: When there is increased PT or increased INR (i.e. drug toxicity), we can reverse the drug action by:

- Administration of Vitamin K.
- Fresh-frozen plasma (contains the coagulation factors).
- Prothrombin complex concentrates.
- Recombinant factor VII.

2. Fibrinolytic Agents

These drugs rapidly lyse thrombi by catalyzing the formation of the serine protease **Plasmin** from its precursor zymogen, Plasminogen. They create a generalized lytic state. **However, Aspirin will be still required.**



a. Streptokinase:

- It's a protein synthesized by Streptococcus bacteria to help it invade tissues.
- It binds to the proactivator plasminogen in plasma to activate it.
- **It's not specific to fibrin so it may cause bleeding.**
- It's highly antigenic:
  - Can cause allergic reactions.
  - Can result in inactivation of the drug, if the patient was previously infected and had antibodies for streptococcus.
- Early administration is important: We must use it instantly after the diagnosis of thrombotic incident, so it's not practical.
- Very cheap.

b. Urokinase:

- It's a **human enzyme** synthesized by the kidneys.
- It directly converts plasminogen into plasmin.
- It's not antigenic.
- It's expensive, as it's not practical to extract it from humans.

c. Anistreplase (Anisoylated Plasminogen Streptokinase Activator Complex, ASPAC):

- It's deacetylated at the **fibrin** surface to release the active complex.
- It's more active and **selective**.
- **Prolonged** action since the t½ is 6 hours.

d. Tissue-type Plasminogen Activators (t-PA):

Alteplase, Reteplase, Tenecteplase

- They're normally synthesized by the endothelial cells, but commercial preparations using recombinant DNA technology are available.
- They bind to **fibrin** and activate **plasminogen** at the **fibrin** surface.
- Their action is less affected by age of thrombus.
- Specific action (they act within the thrombus, and avoid systemic activation).
- **Short** action; t½ = 8 min.
- Given by infusion over 1-3 hours.
- Very expensive.

Fibrinolytic Agents Indications:

- Pulmonary embolism with hemodynamic instability.
- Deep venous thrombosis (DVT).
- Ascending thrombophlebitis.
- Acute myocardial infarction.

They're the same indications as the anticoagulants', however, these drugs are more effective and less toxic.

3. Antiplatelet drugs

They work on platelets rather on the coagulation cascade or factors.

Types of Platelet Regulators:

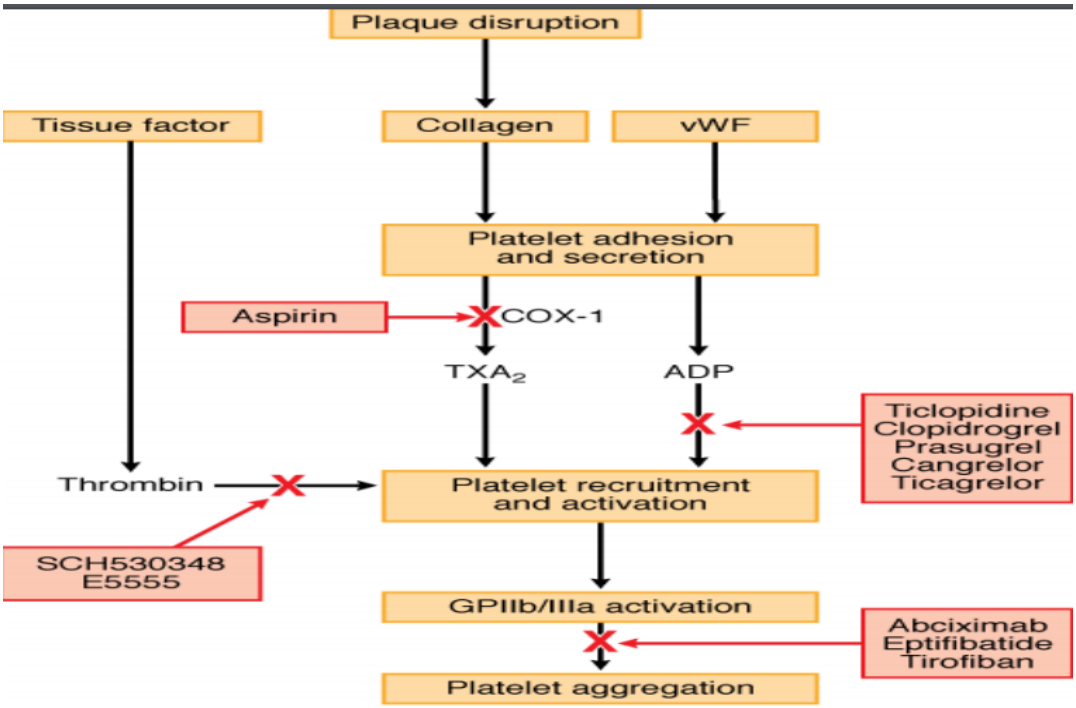
a. Agents generated **outside** platelets, interact with membrane receptors. E.g. Catecholamines (cause vasoconstriction and platelet aggregation), collagen, thrombin, and prostacyclin.
b. Agents generated **inside** platelets but interact with membrane receptors: ADP, PGD2, PGE2 and serotonin (5-hT).
c. Agents generated **within** and **interact** within platelets: TXA2 , 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.**
- 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 and causes vasodilation.

Sites of action of antiplatelet drugs:

a. **Aspirin (prostaglandin synthesis inhibitor)**
   It inhibits thromboxane A2 (TXA2) synthesis by **irreversibly** acetylating cyclooxygenase-1 (COX-1). Reduced TXA2 decreases platelet activation and recruitment to the site of vascular injury.
b. **Ticlopidine, Clopidogrel, and Prasugrel**
   They irreversibly block P2Y12, a key ADP receptor on the platelet surface. cangrelor and ticagrelor are reversible inhibitors of P2Y12.
c. **Abciximab, Eptifibatide, and Tirofiban**
   They inhibit the final common pathway of platelet **aggregation** by blocking fibrinogen and Von Willebrand factor (vWF) from binding to activated glycoproteins IIb/IIIa.
d. **Zontivity (SCH530348 and E5555)**
   Inhibit thrombin mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on platelets.



Antiplatelet Drugs:

a. Aspirin = Acetyl Salicylic Acid

- Causes **irreversible** acetylation of COX in platelets. And because platelets do not have DNA or RNA, aspirin causes permanent inhibition of platelets' COX.
- Platelets life span is about **7-10 days**, so a single dose of aspirin can produce effects for about a **week**.
- Endothelium can still synthesize new COX, so PGI2 production is not affected. (PGI2 works against TXA2; it inhibits platelet aggregations and it's a vasodilator).
- Adult Pill Dose: 80 – 325 mg. (A pill of baby aspirin contains 80-100 milligrams of aspirin. That's about a quarter of the dose in an adult aspirin pill). Both adult and baby aspirin pills are contraindicated in children.
- Very effective in lowering body temperature, and it acts as an analgesic. (not used nowadays for these purposes).
- It doesn't work on the central nervous system.
- Very cheap.

b. Clopidogrel (Plavix), Ticlopidine (Ticlid).

- Irreversibly block ADP receptors (P2Y12) on platelets.
- Useful in transient ischemic attacks, completed stroke, unstable angina and after placement of coronary stents.
- Useful for patients who cannot tolerate aspirin.
- Can cause leukopenia, GI irritation and skin rash, **but much less than aspirin.**

c. **Abciximab** (monoclonal antibody), **Eptifibatide** (synthetic peptide) and **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.

d. **Dipyridamole** and **Cilostazole**

They work by inhibiting adenosine uptake and **phosphodiesterase** enzyme (which hydrolyses down cAMP) leading to increased cAMP in platelets and elsewhere. They also work as **vasodilators**.

e. **Dazoxiben**:

Inhibits TXA2 synthetase enzyme.

f. **Sulotroban**:

It inhibits TXA2 **receptor**.

g. **Anagrelide:**

It reduces platelet production by decreasing megakaryocyte maturation in the **bone marrow**.

h. **Lipid Lowering Agents**

Reduce platelet activity indirectly, by reducing viscosity of plasma.

4. Hemostatic Agents: Agents that promote blood coagulation to **stop** bleeding.

- Whole Blood → extra RBCs, coagulation factors and platelets.
- FRESH Frozen Plasma.
- Plasma fractions (e.g. hemophilic factors (FVIII, and FIX)).
- Vitamin K.
- Physically-working hemostatic agents: (applied over open wounds)
  1. Absorbable Gelatin Foam
  2. Absorbable Gelatin Film
  3. Oxidized Cellulose
  4. Thrombin (powder form)
- Plasmin Inhibitors:
  1. α2 Antiplasmin (physiological, might not be available commercially).
  2. Aprotinin (isolated from bovine parotid gland).
  3. Aminocaproic Acid (synthetic).
  4. Tranexamic Acid (synthetic).

Therapeutic products for the treatment of coagulation disorders:

Notice that deficiency in any of the factors can be compensated for by a replacement source.

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

Good Luck

Test your understanding ☺

1) Which of the following compounds is mostly likely to block ADP receptors and prevent platelet aggregation?

   A. Clopidogrel.
   B. Aspirin.
   C. Prostacyclin.
   D. Abciximab.
   E. Streptokinase.

2) A woman who has a mechanical heart valve and who is taking warfarin informs you that she hopes to get pregnant in the near future. What advice should she receive regarding her anti-thrombotic medication do you think the anticipated pregnancy?

A. Warfarin should be continued until the third trimester.
B. Warfarin should be replaced with aspirin at analgesic (high) doses.
C. All medications that affect the blood should be discontinued.
D. Warfarin should be replaced with heparin.
E. Warfarin should be discontinued and supplementary vitamin K taken throughout the pregnancy.

✓ Remember that heparin is a low molecular weight compound and is advised to be used during pregnancy (actually it's the anticoagulant of choice in pregnant women who need continued protection against thrombus formation).

3) Which of the following statements regarding warfarin is true?
A. It is a prodrug, converted to its active metabolite spontaneously in the blood.
B. It has low lipophilicity and does not cross the placental barrier.
C. It causes a depletion in protein C before it decreases prothrombin.
D. It inhibits the release of vitamin K dependent clotting factors from hepatocytes.
E. It is an activated by Protamine.

4) Which of the following statements is true regarding the parental administration of Alteplase?
A. It increases the formation of plasminogen.
B. It is less effective than streptokinase when given after a myocardial infarction.
C. It causes a high incidence of thrombocytopenia.
D. It may cause bleeding reversible by Aminocaproic acid.
E. It activates **free** plasminogen.

✓ Recall that Aminocarpoic acid is a plasmin INHIBITOR, meaning that it counteracts the effect of fibrinolytics.

5) Following a myocardial infarction, a patient is stabilized on warfarin, the dose being adjusted to give a prothrombin time of 22 seconds. Which of the following statements regarding potential drug interactions in this patient is accurate?
A. Cholestyramine will increase the prothrombin time.
B. Cimetidine is likely to decrease prothrombin time.
C. Antibacterial sulfamethoxazole-trimethoprim may enhance the effects of warfarin.
D. Vitamin K would restore prothrombin time to normal within 30 minutes.
E. If this patient takes half an aspirin tablet daily, the dose of warfarin will need to be increased.

1. A	2. D	3. C	4. D	5. C