بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

Final | Lecture 1

Antiplatelets

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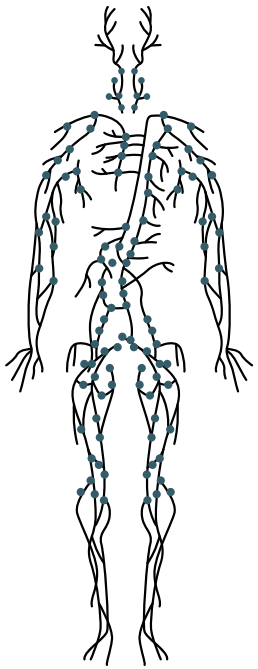


To orient you

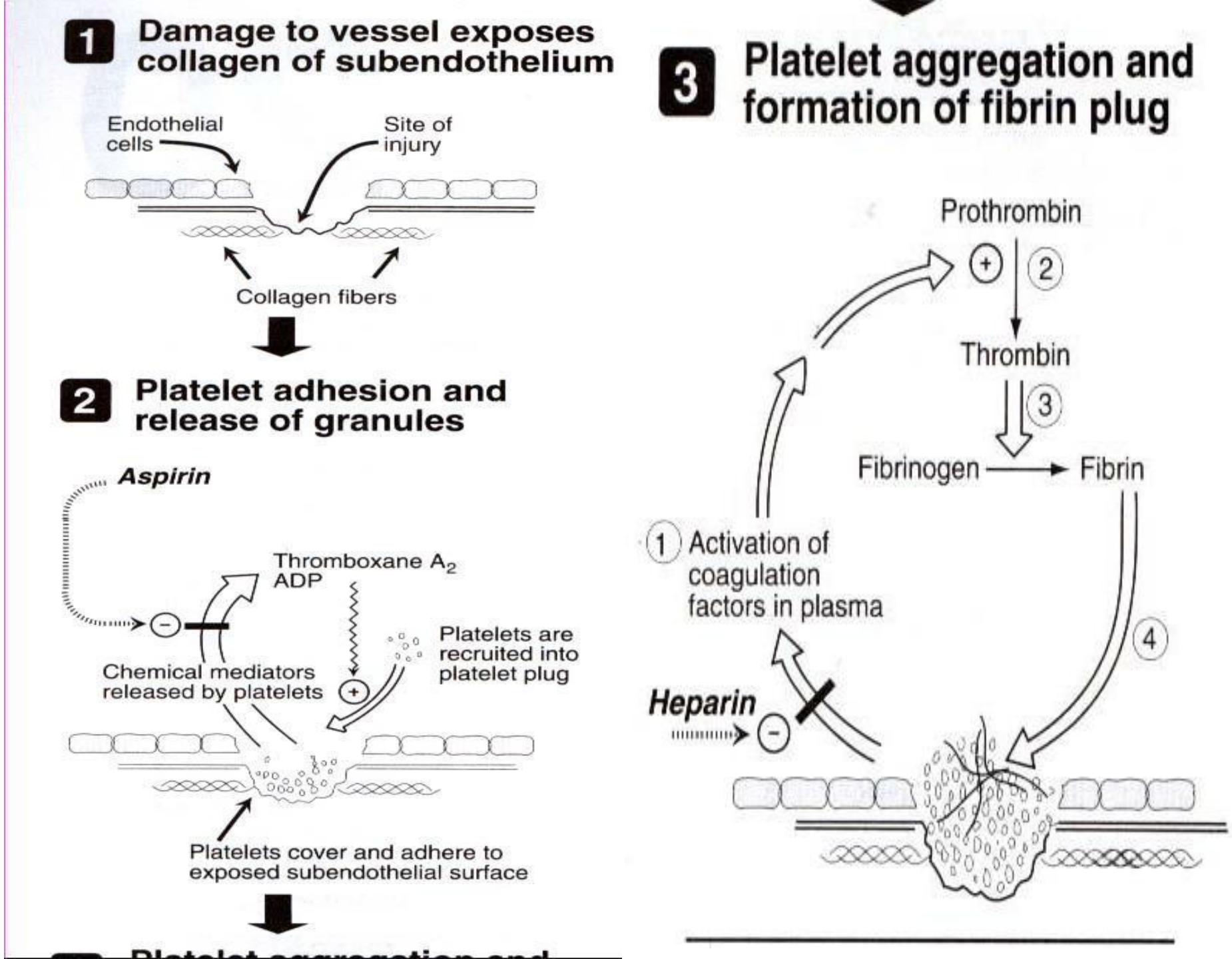
- The body maintains **homeostasis** through balanced opposing systems, like the **sympathetic and parasympathetic**. Similarly, in **hemostasis**, there's a balance between **coagulation factors** and **natural anticoagulants** such as **antithrombin III, protein C, and protein S**.
- During injury, the body shifts toward **coagulation** to stop bleeding, then back to **anticoagulation** to prevent unwanted clots. This balance between **thrombosis and bleeding** is crucial and is often targeted in treating **MI, stroke, DVT, PAD**, and other occlusive diseases, which are common in our region due to **hypertension, diabetes, and smoking** affecting coagulation.

MI: myocardial infarction PAD: peripheral artery disease DVT: deep vein thrombosis

Drugs Used in Clotting Disorders

- **Reduce clotting**
  - **Antiplatelets (5 drugs)**
    - Antiplatelets are a **prophylactic drugs** that **prevent** the **segregation** of the **platelets**.
  - **Anticoagulants (10 drugs)**
    - Anticoagulant **dissolve clots physiologically** by targeting the antithrombotic response to the site of thrombosis in a certain way.
  - **Thrombolytics (2 drugs)**
    - Such as life-saving injections (ابرة الحياة) that **dissolve all clots in the body**, but carry a high risk of **bleeding** and are used in **life-threatening** situations such as myocardial infarction.

- **Facilitate clotting (1 drug)**
  - Through drugs that **promote coagulation**, used in **sports injuries, dental procedures**, and to **control menstrual bleeding** (available as oral tablets).



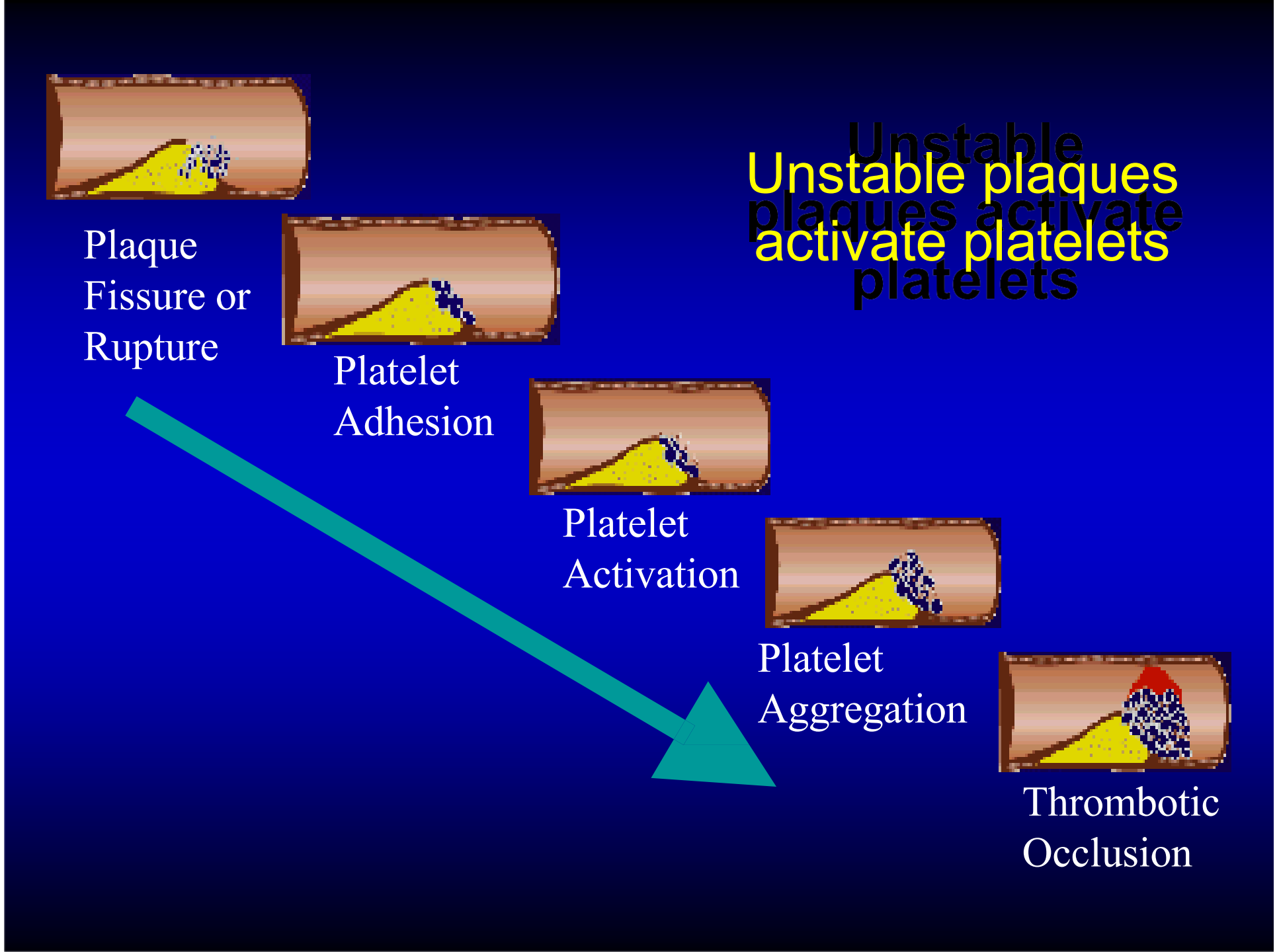
Explanation of the picture in the next slides

Explanation of the previous slide

- To maintain normal blood flow and prevent clot formation on the vessel wall, **endothelial cells** secrete **anticoagulant substances** such as **nitric oxide (NO)** and **prostaglandins**.
- However, when a **blood vessel is damaged or ruptured**—for example, due to **atherosclerosis** (see slide 7)—the **exposed collagen** binds to the **von Willebrand factor (vWF)**. The vWF then links **platelets** to the **collagen** via their **vWF receptors**, initiating **platelet adhesion and aggregation**.
- This platelet–collagen interaction increases **intracellular calcium** levels within platelets, triggering **degranulation** and the release of substances like **ADP** and **thromboxane A2 (TXA_2)**, which promote further platelet activation and aggregation.
- Both **ADP** and **TXA_2** act as **autocrine activators**—they bind to receptors on platelets, reinforcing their activation, secretion, and aggregation, ensuring a rapid and strong platelet response.

Explanation of the previous slide (Cont'd)

- There is an **increase in the number or activation of ADP receptors (P2Y12)** on platelets. Meanwhile, **thromboxane A2 (TXA2)** is produced from **arachidonic acid** in the platelet membrane via the **cyclooxygenase (COX) pathway**.
- This process also promotes the appearance of **fibrinogen receptors** on the platelet surface. **Fibrinogen** then binds platelets together by cross-linking **glycoprotein IIb/IIIa**, forming a **platelet plug**, which is later stabilized by a **fibrin mesh**.
- Several **drugs target this pathway**: for example, **aspirin** inhibits TXA2 production, while other drugs **block P2Y12 receptors** (preventing ADP binding) or **glycoprotein IIb/IIIa** to reduce platelet aggregation.


Unstable plaques activate platelets
Plaque Fissure or Rupture
Platelet Adhesion
Platelet Activation
Platelet Aggregation
Thrombotic Occlusion

Platelet Inhibitors

- **These drugs prevent platelet activation.**

(1) Inhibition of prostaglandin synthesis (aspirin),

(2)Inhibition of ADP-induced platelet aggregation
(*Ticlopidine, Clopidogrel, Prasugrel, Cangrelor, Ticagelor*),

(3)blockade of glycoprotein IIb/IIIa receptors on platelets (abciximab, tirofiban, and eptifibatide).

(4) phosphodiesterase inhibitor (Dipyridamole ?? and cilostazol)

- **cAMP levels in platelets increase**, which **inhibits degranulation** due to the inverse relationship between cAMP and platelet activation.

(5) There are also new drugs in development that block vWF receptors.
(not important for now)

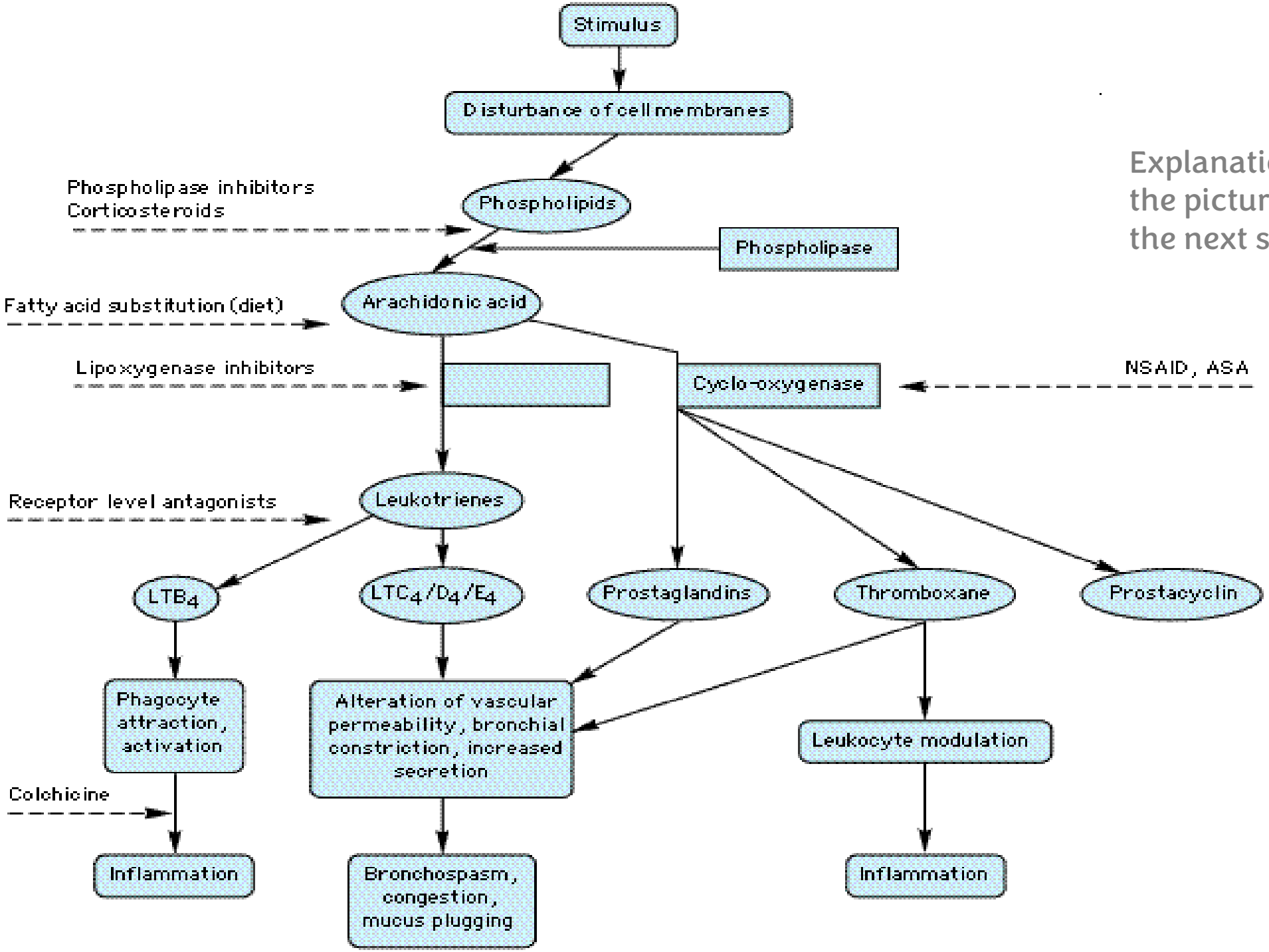
Aspirin

- **MOA: Blocks COX→ inhibits conversion of AA into TXA_2.**
  - The main difference between **aspirin** and other **NSAIDs** is that **aspirin binds irreversibly** to the **COX enzyme**. This gives it **strong effects** (e.g., on platelet inhibition and heat regulation) but also **more side effects**. Because of its irreversible action, **low-dose "baby aspirin"** can be used for **anticoagulation**, unlike other NSAIDs, which bind reversibly.

- **Indications: -prophylactic in transient cerebral ischemia.**
  -to reduce recurrence of MI.
  -in angina.

- **A daily dose of 100 mg** is enough to produce anticoagulation due to irreversible binding COX pathway **.**

- **Adverse effects: hemorrhagic stroke, GIT bleeding.**
  - Aspirin is used usually in **prophylaxis**



Explanation of the picture in the next slide

Explanation of the previous slide

- **Adverse effects of aspirin** occur mainly through **inhibition of prostaglandin synthesis**, which normally protects the stomach lining. This can **worsen peptic ulcers**, so aspirin is **contraindicated** in patients with **ulcer disease**.

- Aspirin blocks the **COX pathway**, but the **lipoxygenase pathway** remains active, producing **leukotrienes** that can cause **inflammation and bronchospasm**. Therefore, it is **contraindicated in asthma patients**.

- In patients **under 19 years old** with **viral infections**, aspirin carries a risk of **Reye's syndrome**.

- Aspirin is used as **prophylaxis** in patients needing **platelet protection**, such as those with **angina or a history of MI or stroke**. However, in **high-risk patients**, aspirin alone is insufficient, and **dual antiplatelet therapy** is recommended (see next slide).

Ticlopidine & Clopidogrel

- **Useful in patients who cannot tolerate aspirin or who failed aspirin.**
- **MOA: block ADP receptors on platelet.**
- **Indications:**
- **-prevent vascular events in patients with transient ischemic attacks (TIA)**
- **-unstable angina.**
- **-prevent thrombotic stroke.**
- **-to prevent thrombosis in patients undergoing placement of a coronary stent.**

Ticlopidine & Clopidogrel

Adverse effects:

Ticlopidine has a higher risk of adverse effects compared to newer alternatives and is therefore rarely prescribed today.

- **Hemorrhage**
- **Leukopenia: should monitoring WBCs during the first 3 months.**
- **Thrombotic thrombocytopenic purpura (TTP)** (See next slide)
  - 3 per 100 patients

Clopidogrel - fewer than with ticlopidine (Safer than Ticlopidine)

- **Neutropenia.**
- **TTP** 4 per 1 million
- Mild bleeding

These rare cases are often due to **genetic differences**, such as **single nucleotide polymorphisms (SNPs)**, which affect individual responses to drugs.

Thrombotic thrombocytopenic purpura (TTP)

(Causes thrombosis) (Low platelets count) (Purple-bluish skin color)

- Ticlopidine's selectivity isn't absolute. In **3% of ticlopidine-treated patients**, it can bind to an enzyme called **ADAMTS13**, inhibiting it. This enzyme normally cuts **von Willebrand Factors (vWF)** to keep them in check. When inhibited, large vWFs accumulate, **exerting their platelet-aggregation effects excessively**, leading to clot formation in various places.

- Early on, it affects **small blood vessels** like those in the arms and legs, later affecting **renal and coronary arteries**, eventually leading to death. This can cause areas of **bluish or purple color** due to blockade. As many clots form, the number of **free platelets** decreases, hence the “thrombocytopenic” part.

Ticlopidine & Clopidogrel

- **Dose:**

-Ticlopidine: 250 mg BID orally.

-Clopidogrel: oral loading dose 300 mg, maintenance dose 75 mg once daily.

- **Because of less side effects & more convenient dosing with clopidogrel, it is preferred over ticlopidine**

the name of the receptor on platelets

($P2Y_{12}$)ADP receptors blockers

The Drug	Adverse effects or some info
• Cangrelor (Kengreal)	IV (not a prodrug)
• Clopidogrel (Plavix)	Prodrug ??????
• Prasugrel (Effient)	bleeding Hypertension (8%), hypotension (4%), atrial fibrillation (3%), bradycardia (3%),
• Ticagrelor (Brilinta)	not a prodrug bleeding shortness of breath (dyspnoea)
• Ticlopidine (Ticlid)	not any more (due to TTP)

(See next slides for more explanation)

($P2Y_{12}$)ADP receptors blockers

- Some of these treatments are **prodrugs** (**clopidogrel**, **prasugrel**). They need **activation** in the **liver**. So they are **contraindicated** for those with **liver failure**. And more specifically for those with **impaired CYP2C19** enzyme (Clopidogrel is especially more sensitive than the other 2 by deficiencies in this enzyme) which could be the result of mutations in the responsible gene.

- In Jordan, approximately **0% of people have a deficiency in both alleles**, making them **"poor metabolizers"** for this drug. About **12% have a deficiency in only one allele**, called **"intermediate metabolizers"**. Those with **both normal alleles** are **"normal metabolizers"**.

- Similarly, **single nucleotide polymorphisms (SNPs)** can produce **"ultra-rapid metabolizers"**. The drug is **contraindicated** for poor metabolizers, the dose is **doubled** for intermediates, and given **normally** for ultra-rapid metabolizers, since clopidogrel generally does **not pose significant risk even with rapid activation**.

($P2Y_{12}$)ADP receptors blockers

- We can assess a patient's **clopidogrel metabolizer type** using either **PCR** (which takes longer) or a **platelet function test** ("anti-plate"). This test uses the patient's blood under conditions that allow coagulation, with the drug added, to evaluate its **potential efficacy**. For example:
  - **Normal metabolizer:** clotting takes longer (drug works)
  - **Poor metabolizer:** blood coagulates normally (drug ineffective)

- The test can also be done by taking a **blood sample after the drug has been administered**, typically **hours before a procedure** requiring **P2Y12 inhibition**, to ensure efficacy. For procedures like **coronary stent placement**, the **metal stent** acts as a **foreign surface** inside the artery. This triggers **platelet activation and aggregation**, which can quickly form a **clot (stent thrombosis)** — a life-threatening event. So patients are "prepared" **hours in advance with loading doses** of **clopidogrel, cangrelor, or prasugrel** until a **steady state** is achieved.

($P2Y_{12}$)ADP receptors blockers

Cangrelor

- Has a **very short half-life (~2.5 minutes)**, so it is given as an **IV drip** rather than a bolus to maintain effect.
- Used in **emergencies** where "preparing" isn't possible, since it **doesn't need preparation**.

Clopidogrel

- The **most used**.
- Requires **preparing hours before procedures** to ensure efficacy.

Prasugrel

- Given for a patient **after stent**, for a patient who is a **poor metabolizer for Clopidogrel**, or when there is **time to prepare for surgery**.
- Has **higher bleeding risk than Clopidogrel**.
- Used for **up to one year**.

Ticagrelor

- Considered **safest**, but also has **high bleeding risk**.
- Causes **dyspnea** and is taken **twice a day**.

Additional note: Both **Cangrelor** and **Prasugrel** are **expensive**.

Doctor didn't comment on this slide, but read it just in case

Warning

- Clopidogrel was issued a black box warning from the FDA on 12 March 2010, as the estimated 2–14% of the US population who have low levels of the CYP2C19 liver enzyme needed to activate clopidogrel may not get the full effect. Tests are available to predict if a patient would be susceptible to this problem or not

Abciximab, eptifibatide, & tirofiban.

Glycoprotein IIb/IIIa inhibitors:

- (GP 2b/3a) is surface receptor (integrin) on platelet cells that binds fibrinogen and υWFs (bridging) enabling platelet aggregation.

- **Abciximab** (was used before clopidogrel) is a humanized monoclonal antibody directed against IIb/IIIa complex.
  - Irreversible binding (impairs function), much higher risk of bleeding even higher than all P2Y12 inhibitors (very strong).
- **Eptifibatide** & **Tirofiban** inhibit ligand binding to IIb/IIIa receptor by their occupancy of the receptor acting as competitive inhibitors.

➔ All Inhibit bridging of platelet by fibrinogen.

- Approved for use in percutaneous coronary intervention (PCTA) & in ACSs.
- The three agents are administered parenterally

PCTA: percutaneous transluminal coronary angioplasty ACS: acute coronary syndrome).

Dipyridamole:

- **MOA: -inhibits phosphodiesterase→ ↑ cAMP→ potentiates effects of prostacyclin→ platelet inhibition.**

-dipyridamole is also a coronary <u>vasodilator</u>.

- cAMP activates PKAs and reduces cytoplasmic Ca++ in platelets and smooth muscles, **inhibiting platelet aggregation and acting as a vasodilator** for smooth muscles—so **two effects, not just one.**
- Dipyridamole inhibition is often complemented with other drugs so that we have desired effect, since its effects alone are not enough. Doctor called such drugs "add-on" drugs; you complement them with other supporting drugs.

- **Indications:-with <u>aspirin</u> for prophylaxis in angina.**

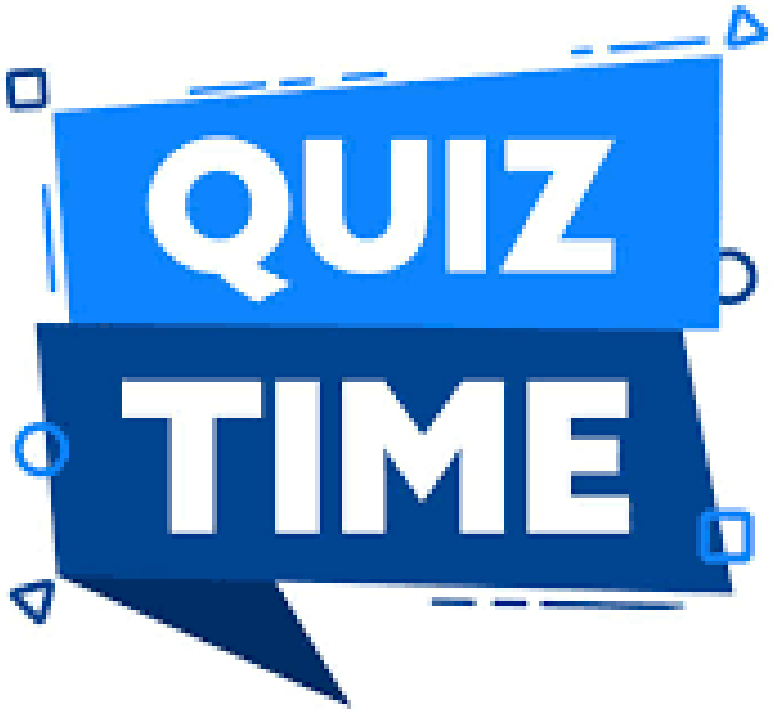
-with <u>warfarin</u> to inhibit embolization from prosthetic heart valves.

Cilostazol **intermittent claudication**

- Another drug that inhibits PDE is **Cilostazol**. **Intermittent claudication**—pain and cramping in the calves due to limited blood flow—is specifically treated with Cilostazol, which acts as both an **antiplatelet and vasodilator**.

(Phosphodiesterase=PDE)

Pharmacology Quiz 1



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