# HLS

## MODIFIED NO. 1

# PHARMACOLOGY


**كتابة:** محمود جرادات و حسن النويهي

**تدقيق:** سلطان غيث

**الدكتور:** د. مالك الزحلف


# Drugs Used in Clotting Disorders

| Color code |
| --- |
| Slides |
| Doctor |
| Additional info |
| Important |

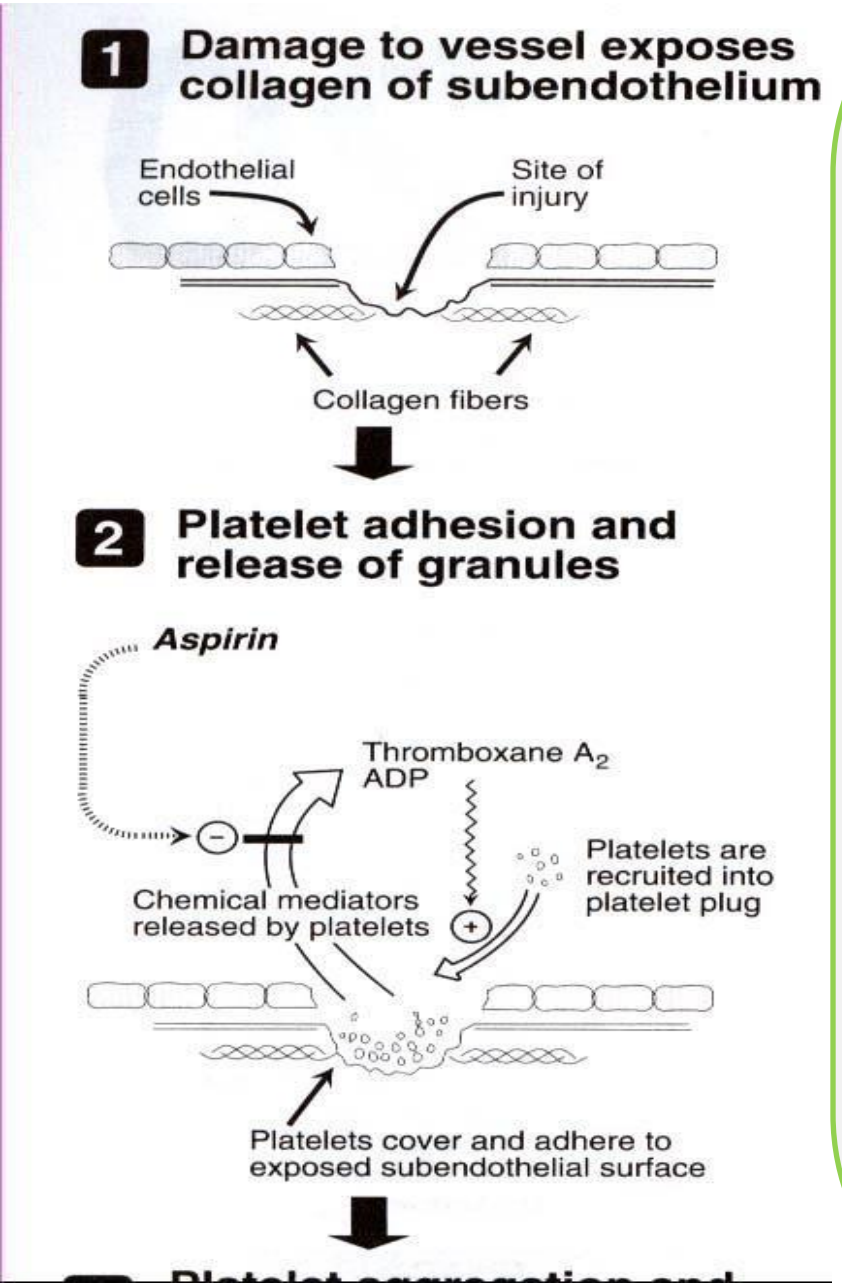
# Drugs Used in Clotting Disorders

- **Reduce clotting**
  - **Antiplatelets**
  - **Anticoagulants**
  - **Thrombolytics**
- **Facilitate clotting**

- Thrombosis is the formation of a blood clot that occurs abnormally in the walls of blood vessels. It consists of a group of platelets and red blood cells (RBCs).

- Key terms:
- Thrombus: The clot that forms in the vessel wall.
- Embolus: A part of the thrombus that detaches and travels through the bloodstream.

- Our body maintains a balance, which includes the presence of specific factors and their opposites. We have coagulation factors, anticoagulation factors, thrombotic factors, and antithrombotic factors. This is the area where we operate; sometimes we increase these factors, and other times we decrease them.

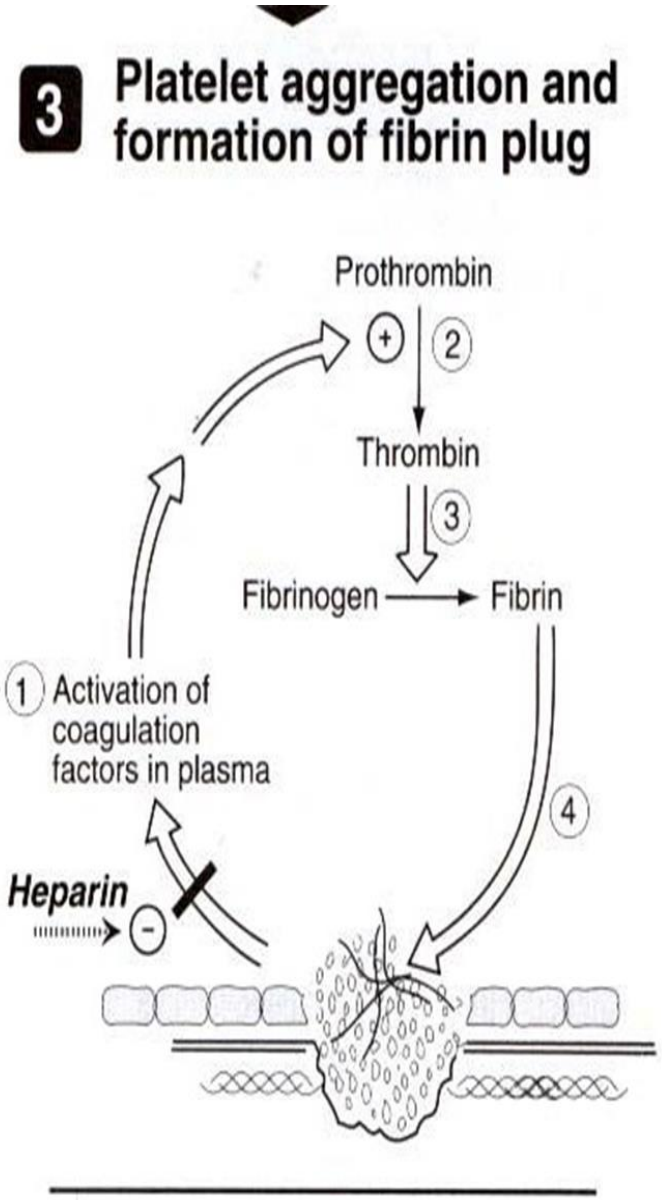



- Platelet Aggregation: When blood vessels are injured, exposed collagen and other substances trigger platelet activation. Activated platelets express receptors, such as glycoprotein IIb/IIIa, which bind to fibrinogen and von Willebrand factor (vWF).
- Glycoprotein IIb/IIIa (GP IIb/IIIa) receptors are crucial for platelet aggregation, allowing platelets to adhere to one another and form a stable clot.

- Activated platelets release signaling molecules (like Adenosine Diphosphate ADP, thromboxane A2 (TXA2), and serotonin) from their granules (degranulation).
- ADP binds to specific receptors on the surface of platelets = P2Y12 Receptor.
- The binding of ADP to its P2Y12 receptors plays a critical role in mobilizing calcium within platelets. Calcium is essential for the release of granules containing ADP, serotonin, and other pro-aggregatory substances. There is a regulator for this process, which is cAMP, an inhibitor of calcium mobilization. Increased levels of cAMP in platelets lead to a decrease in intracellular calcium levels.
- The released ADP and TXA2 enhance platelet activation and aggregation in a positive feedback manner, leading to more platelets becoming activated and aggregating at the site of injury.

- When I need to prevent blockage of blood vessels, such as in the coronary arteries, I will use antiplatelet medications. These drugs do not treat existing clots but serve a prophylactic role to prevent future thrombus formation.

1. ADP receptor blocker drugs, also known as P2Y12 inhibitors, are a class of antiplatelet medications that play a critical role in preventing thrombus formation. They work by inhibiting the P2Y12 receptor on platelets, which is responsible for platelet activation and aggregation in response to ADP.
2. Glycoprotein IIb/IIIa inhibitors are a class of antiplatelet medications that block the glycoprotein IIb/IIIa receptor on platelets, which plays a crucial role in platelet aggregation. By blocking the IIb/IIIa receptor, these drugs prevent the binding of fibrinogen and inhibit platelet aggregation.
3. TXA2 acts on its receptors on platelets, stimulating further platelet activation and aggregation, thus amplifying the clotting process. By acetylating a specific serine residue in the COX-1 enzyme, aspirin effectively blocks the production of TXA2. With decreased levels of TXA2, platelet activation and aggregation are significantly diminished.
4. Increased levels of cAMP in platelets lead to a decrease in intracellular calcium levels. Decreased calcium results in reduced degranulation. We can increase cAMP levels by inhibiting the enzyme phosphodiesterase, which breaks down cAMP. cAMP has functions beyond its role in platelets, including promoting vasodilation. This is particularly important in conditions such as stroke, where blockage of an artery can lead to loss of blood supply, and in myocardial infarction, when a coronary artery is obstructed. In these cases, inhibiting platelet aggregation and promoting vasodilation are crucial for restoring blood flow.



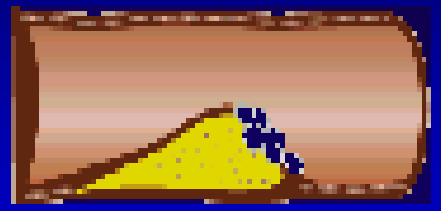

- Factor X is essential for the coagulation cascade, leading to the activation of thrombin, which converts fibrinogen to fibrin. This process results in the formation of a fibrin mesh that stabilizes the platelet plug.

- There is a difference between antiplatelet medications and anticoagulants. Antiplatelet medications are primarily used for prevention, while anticoagulants are used for treatment. For example, in a patient with deep vein thrombosis (DVT), it's important to note that coagulation typically occurs in the veins. Strokes often happen in arteries but can also involve issues in the veins. Antiplatelet medications do not work effectively in cases of deep vein thrombosis. Instead, treatments such as heparin and warfarin are administered.

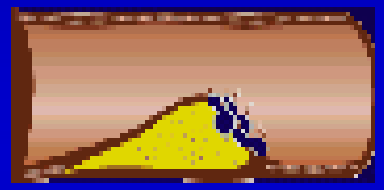
- When a clot forms, it takes a significant amount of time to be dissolved, particularly involving fibrin. In the body, there is a process called fibrinolysis, which is responsible for dissolving the clot. The key player in this process is tissue plasminogen activator (tPA). tPA stimulates the conversion of plasminogen to plasmin, which then breaks down the fibrin mesh and restores blood flow.tPA is often referred to as the "needle of life." It can be administered during a myocardial infarction (heart attack) within six to twelve hours of symptom onset. In the case of a stroke, the patient must receive tPA within three hours; after this time, hypoxia (lack of oxygen) can occur in the brain tissue, leading to irreversible damage.

# Unstable plaques activate platelets

Plaque Fissure or Rupture

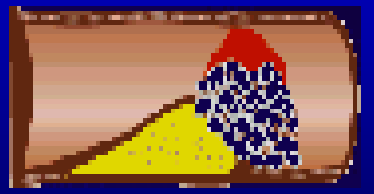


Platelet Adhesion



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).**

# Aspirin

- **MOA: Blocks COX→ inhibits conversion of AA into $TXA_2$.**
- What is the most important difference between aspirin and other drugs? Aspirin has an irreversible effect. So, we don't have baby ibuprofen or baby Voltaren, but we do have baby aspirin.
- **Indications: -prophylactic in transient cerebral ischemia.**
  **-to reduce recurrence of MI.**
  **-in angina.**

**A daily dose of 100 mg.**
**Adverse effects: hemorrhagic stroke, GIT bleeding.**

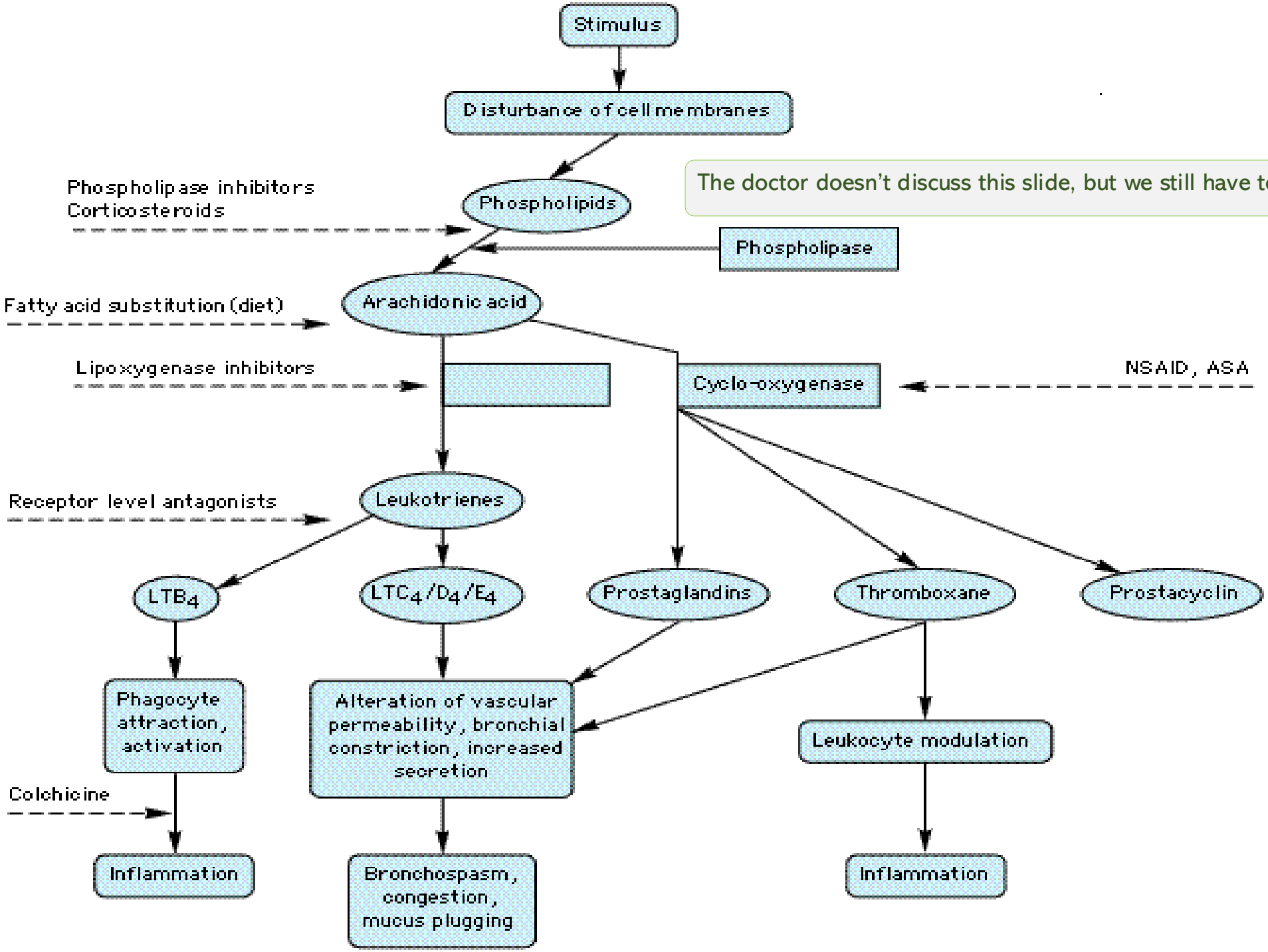
- In the case of major surgery, if a patient has been taking aspirin continuously, we should wait six to seven days before the procedure due to the irreversible effect of aspirin on platelet function. This waiting period allows for the production of new platelets.

- Aspirin is generally not recommended for patients with peptic ulcers.
- The dose of aspirin is typically 325 mg for analgesic purposes, and it is often taken with caffeine for the treatment of migraines.
- For a patient with rheumatoid arthritis, we administer aspirin at a dose of 975 mg three times a day, along with a proton pump inhibitor (PPI) to protect the stomach. We choose aspirin because of its irreversible effect on platelets.
- Aspirin inhibits platelet function, making it less effective in forming clots, but it does not kill the platelets. The platelets remain in circulation for their normal lifespan (about 7-10 days).
- The inhibition caused by aspirin is irreversible for the life of the platelet. New platelets produced after aspirin ingestion will function normally.

- Aspirin is typically dosed at 325 mg for analgesic effects, while the anti-inflammatory dose is often 975 mg, which can be equivalent to three 325 mg tablets. Ibuprofen is used similarly, with a standard dose of 200 mg not being effective for dental pain, but rather for headaches. For dental pain, which often involves inflammation, a higher dose of 400 mg or more may be necessary.

- It's important to note that the effectiveness of these drugs (NSAIDs) is a dose-dependent effect. If you decrease the dose, you may reduce the anti-inflammatory effects. At lower doses, NSAIDs can effectively treat moderate headaches, while increasing the dose can help manage moderate to severe headaches associated with inflammation.
- So, the dose is dependent on the specific disease or condition being treated.

- Aspirin is generally not recommended for children, especially those under the age of 18 unless specifically advised by a healthcare provider. This is primarily due to the risk of Reye's syndrome.




The doctor doesn't discuss this slide, but we still have to memorize it

# 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.**

Clopidogrel is a very famous drug and Plavix is the commercial name

Clopidogrel used to prevent platelet aggregation

Clopidogrel is taken with aspirin because the aggregation depends on ADP and Thrompaxane A2, there is no crossover between the side effects at the bleeding level and there is no peptic ulceration in this dual activity

Dual activity: more mechanisms → better activity

So, Clopidogrel, prasugrel, and ticagrelor are allowed to be taken with aspirin ( the same mechanism of reaction and indication )

Let's remember some concepts from the second year 

- **Loading dose** ( initial large dose ) followed by maintenance dose.
- Steady-state level: The amount of drug given = the amount that is eliminated

- The loading dose is used to reach the steady state level very quickly, so when a patient comes for catheterization ( because of the closure of the coronary artery ) we use the stent to open this artery.

- The stent contains drugs, including cyclosporine to prevent wound healing, so the stent damages the blood vessels so endothelial is damaged and collagen is exposed….go back to slide (4).
- The loading dose should be taken before to prevent platelet aggregation around the wound and this is the only way to prevent it.

- The loading dose is 300mg one day before the operation and 75 mg at the time of the operation or 300 mg before 3 hours of the operation is enough to reach the steady state; the t max (time to peak concentration) is around (1.5- 2.5).

- The t1/2 of Clopidogrel is 7 to 8 hours but in reality, the t1/2 is 2 to 3 days because it is difficult to detach from its receptors ( reversible ) and the inhibition of the platelets (P2Y12) remains 6 days therefore the Clopidogrel and aspirin shouldn't be taken before 6 to 7 days of major surgery.

A stent is a tiny tube placed into a hollow structure in your body. This structure can be an artery, a vein, or another structure, such as the tube that carries urine (ureter). The stent holds the structure open.

# Ticlopidine & Clopidogrel

**Adverse effects:**

**Ticlopidine**

- **Hemorrhage** it depends on the strength of the inhibition
- More drugs → More bleeding
- **Leucopenia: Rare to happen should monitoring WBCs during the first 3 months. in Ticlopidine (this drug is not used anymore)**
- **Thrombotic thrombocytopenic purpura (TTP) common in ticlopidine 1-2%. While other drugs are less than 0.5%**

**Clopidogrel - fewer than with ticlopidine**

- **Neutropenia.**
- **TTP**

TTP (Thrombotic Thrombocytopenic Purpura) occurs more frequently with ticlopidine than with other drugs like Cangrelor, Clopidogrel, Prasugrel, and Ticagrelor. Thrombocytopenia, or low platelet count, results from increased platelet turnover in combination with inhibition of the ADAMTS13 protease, which breaks down von Willebrand factor (vWF). This leads to small platelet aggregations at the junctions of arteries and veins, causing thrombosis. The most dangerous symptom is purpura, characterized by black or dark circles on the body. The thrombocytopenia is caused by thrombosis, but idiopathic thrombocytopenia (an autoimmune disease) can also occur.

Purpura results in red, purple, or brown spots on the skin, which happen when small blood vessels leak blood under the skin's surface.

# 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**

# ( $P2Y_{12}$ )ADP receptors blockers

- 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 (TTP)

- Clopidogrel is a prodrug that requires activation by the CYP2C19 enzyme, a member of the cytochrome P450 family. Due to genetic polymorphisms in this enzyme, patients fall into four categories based on their metabolization rate:
- 1. Ultrafast metabolizers 2. Fast metabolizers. 3. Intermediate metabolizers 4. Poor metabolizers

- If a patient who is a poor metabolizer takes 300 mg of Clopidogrel before stenting, the drug may not work, which could result in severe complications, potentially leading to death.
- Therefore, it is crucial to consider drug warnings and the patient's metabolizer status.

- To address this, two newer drugs are available:

- Ticagrelor (Brilinta is the commercial name): Unlike Clopidogrel, Ticagrelor is not a prodrug and can be given directly, producing a faster effect. However, this rapid action increases the bleeding and can cause dyspnea (shortness of breath) in 6-7% of patients, due to platelet inhibition, similar to the concept behind purpura.

- Prasugrel: This is also a prodrug but is designed to overcome the limitations associated with CYP2C19 polymorphisms.

- Additionally, Cangrelor is a more expensive drug administered intravenously (not orally). It can be used as an alternative to a loading dose because it starts working within half an hour and is important for bridging therapy toward warfarin and heparin.

# 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

| VERSIONS | SLIDE # | BEFORE CORRECTION | AFTER CORRECTION |
|---|---|---|---|
| V1→ V2 | Slide 7 | ..... | Edited figure |
| V2→V3 | | | |

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!