Lecture 9
Anti-platelet

Learning objectives

★ describe different classes of anti-platelet drugs and their mechanism of action

★ understand pharmacological effects, pharmacokinetics, clinical uses and adverse effects of anti-platelet drugs

- Additional Notes
- Explanation –Extra-
- Important

before starting, please check our GIT block correction

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com

Platelets and vessels

In healthy vessels, nitric oxide and prostacyclin (released by endothelial cells lining the blood vessels) inhibit platelets aggregation. (vasodilator)

Damage to the vessel wall leads to interaction between Platelets, Endothelial cells and Coagulation factors which lead to formation of the **CLOT**

Clot

THROMBUS: is the CLOT that adheres to vessel wall.

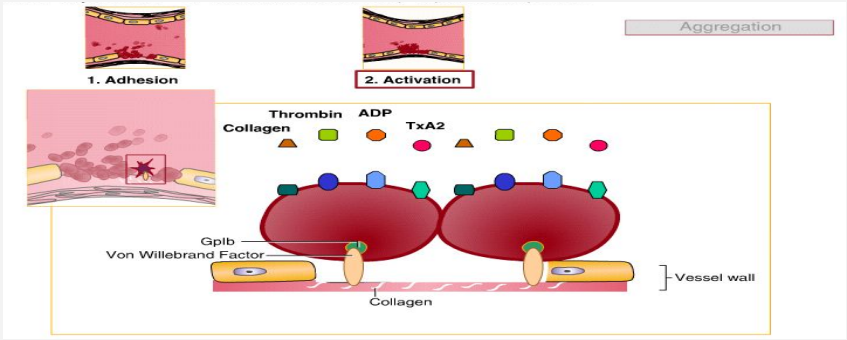
EMBOLUS: is the CLOT that floats in the blood.

THROMBOSIS: is the formation of unwanted clot within the blood vessel, producing life threatening conditions such as:

- Acute myocardial infarction (MI)
- Acute ischemic stroke
- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)

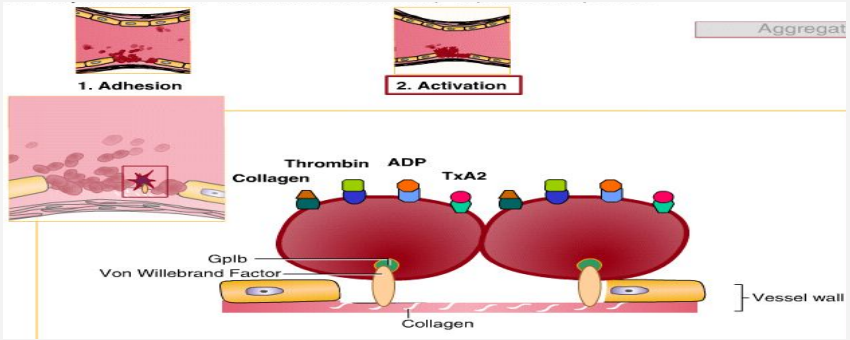
The role of platelets in hemostasis

Adhesion



-Following adhesion, agonists such as collagen, thrombin, adenosine diphosphate (ADP), and thromboxane A_2 activate platelets by binding to their respective platelet receptors.

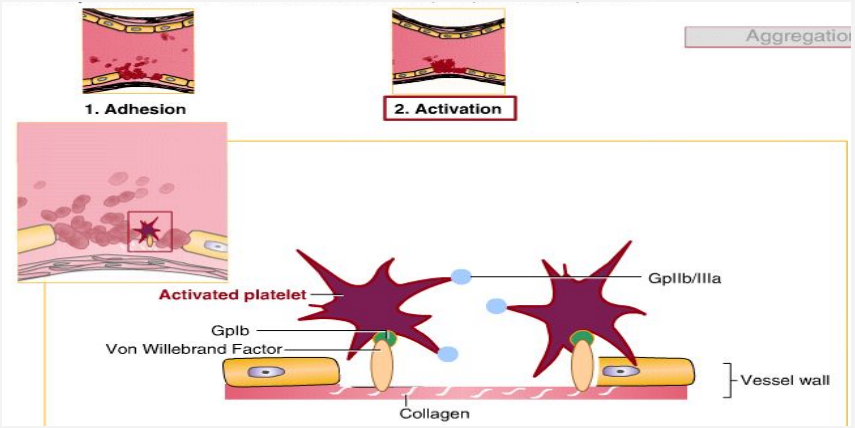
Activation



- Following vascular injury, von Willebrand factor binds to collagen in the exposed subendothelium at the site of injury.
- The other site of the "rod-formed" von Willebrand factor binds to the platelet receptor GPIb and platelets are thereby anchored to the site of the injured endothelium. This is called adhesion.

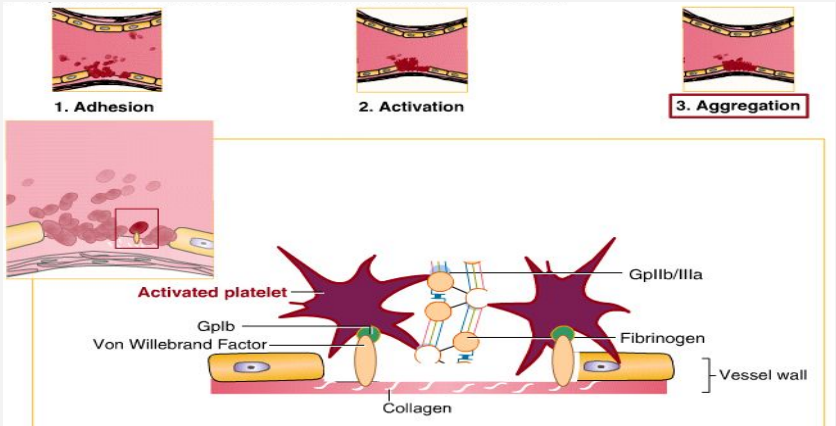
The role of platelets in hemostasis

Activation



The third step of platelet response is aggregation. After activation, binding of fibrinogen to GPIIb/IIIa causes platelets to .adhere to each other into a loose platelet plug

Aggregation



- As a result of agonist binding, platelets undergo a shape change and new structures such as phospholipids and GPIIb/IIIa receptors are exposed on the cell membrane. This is called activation.

Drugs used in thrombosis

Anticoagulants: drugs which prevent clotting by inhibiting **clotting factors** (coagulation process) (used in prevention and treatment of thrombosis).

يمنعوا وصول الجلطة لآخر مرحلة.

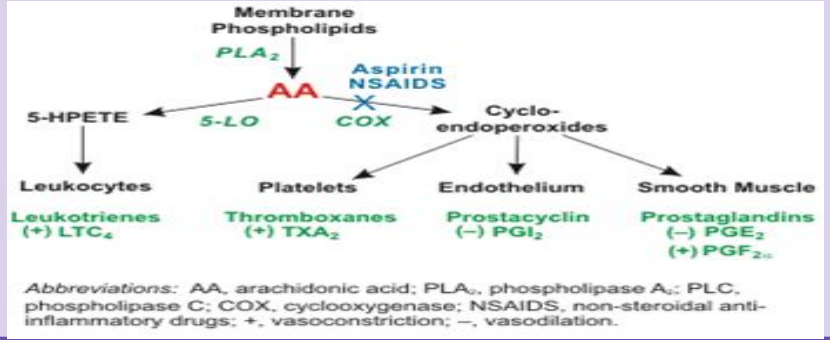
Antiplatelets: drugs which prevent and inhibit **platelet activation and aggression** (used as prophylactic therapy in high risk patients).

Thrombolytics or Fibrinolytics: act by **dissolving existing or already formed thrombi** or emboli and used in the acute treatment of thrombosis.

Classification of antiplatelet drugs:

- **Arachidonic acid pathway inhibitors** — Aspirin
- **Phosphodiesterase inhibitors** — Dipyridamole .
- **ADP inhibitors** — Ticlopidine - Clopidogrel
- **Glycoprotein IIb/IIIa inhibitors** — Abciximab – Eptifibatide -Tirofiban

	Arachidonic acid pathway inhibitors (Aspirin) Acetylsalicylic Acid	ADP pathway inhibitors Ticlopidine & Clopidogrel
Mechanism of action	• **Irreversible** inhibition of cyclooxygenase enzyme (COX-1) via acetylation. • Small dose inhibits thromboxane (TXA2) synthesis in platelets But not prostacyclin (PGI_2) synthesis in endothelium (larger dose).	• These drugs specifically and **irreversibly** inhibit ADP receptor of subtype **P2Y12**, which is required for platelets activation thus prevent platelet aggregation. P2Y12 is purinergic receptor and is a chemoreceptor for adenosine diphosphate (ADP).
Side effects	• Risk of peptic ulcer. • Increased incidence of GIT bleeding (aspirin prolongs bleeding time)	• **Sever neutropenia, (**CBC should be done monthly during treatment.**)** • **Bleeding** (prolong bleeding time). • **G.I.T :** nausea, dyspepsia, diarrhea. • **Allergic reactions.**

	Arachidonic acid pathway inhibitors (Aspirin) Acetylsalicylic Acid	ADP pathway inhibitors Ticlopidine & Clopidogrel
uses	• **Prophylaxis of thromboembolism e.g.** prevention of transient ischemic attack, ischemic stroke and myocardial infarction. • **Prevention of ischemic events** in patients with unstable angina pectoris. • can be combined with other antiplatelet drugs (clopidogrel) or anticoagulants (heparin). • **Dose:** Low-dose aspirin "baby aspirin" (81 mg enteric coated tablet/day) is the most common dose used to prevent a heart attack or a stroke.  *Abbreviations:* AA, arachidonic acid; PLA_2, phospholipase A_2; PLC, phospholipase C; COX, cyclooxygenase; NSAIDS, non-steroidal anti-inflammatory drugs; +, vasoconstriction; –, vasodilation.	• are given orally. • have slow onset of action (3 - 5 days). • pro-drugs, they have to be activated in the liver. • bound to plasma proteins **Clinical Uses of ADP inhibitors** • **Secondary prevention** of ischemic complications after myocardial infarction, ischemic stroke and unstable angina. (**Secondary prevention** : means he had no thrombus, but he could have it). (**Primary prevention** : he had cured from thrombus and this for prevention from another thrombus) .

Clopidogrel

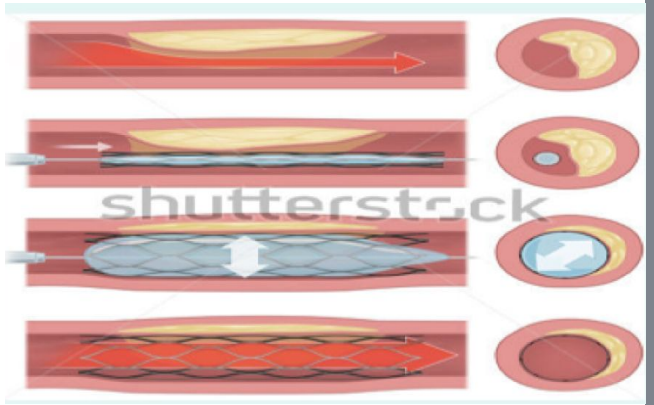
✧is more potent than ticlopidine
✧Longer duration of action than ticlopidine
✧ Less frequency of administration (given once daily).
✧Less side effects **(less neutropenia).**
✧Bioavailability is unaffected by food.
✧ **Clopidogrel has replaced ticlopidine**

Indications:

✧For patients with a history of **recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease.**
✧For patients with **acute coronary syndrome** (unstable angina/ MI): either those managed medically or with percutaneous coronary intervention (PCI) with or without stent.

acute coronary syndrome = unstable angina with MI

Coronary angioplasty (percutaneous coronary intervention, PCI) is a procedure used to open clogged heart arteries. Angioplasty involves temporarily inserting and inflating a tiny balloon to help widen the artery.



New ADP Pathway Inhibitors

Prasugrel	Ticagrelor
Irreversible inhibitor of the P2Y12 receptor	Reversible inhibitor of the P2Y12 receptor

-**both have more rapid onset of action than clopidogrel**

-**both drugs do not need hepatic activation** (are not prodrugs)

Uses:

to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed by PCI.

Adverse effects:

-both increase bleeding risk

-Ticagrelor causes **dyspnea**

Glycoprotein IIb/ IIIa receptor inhibitors

Abciximab:

⁎MOA: inhibits platelet aggregation by preventing the binding of fibronigen, von Willebrand factor, and other adhesive molecules to GPIIb/IIIa receptor sites on activated platelets

⁎Given I.V. infusion.

⁎is used with heparin and aspirin as adjunct to PCI* for the prevention of cardiac ischemic complications.

*percutaneous coronary intervention

Tirofiban & Eptifibatide:

⁎Tirofiban (non-peptide drug)

⁎Epitafibatide (peptide drug)

⁎MOA: Act by occupying the site on glycoprotein IIb/ IIIa receptor that is required to bind the platelet to fibrinogen (act as fibrinogen- mimetic agents).

⁎They are given intravenously for the reduction of incidence of thrombotic complications during coronary angioplasty (PCI)

★ Note that Glycoprotein IIb/ IIIa receptor is required for platelet aggregation with each others and with fibrinogen and von Willbrand factor.

Dipyridamole

It is a vasodilator and antiplatelet

MOA:

Inhibits phosphodiestrase thus increases cAMP causing decreased synthesis of thromboxane A2 and other platelet aggregating factors.

Phosphodiesterase enzymes that normally break down cAMP

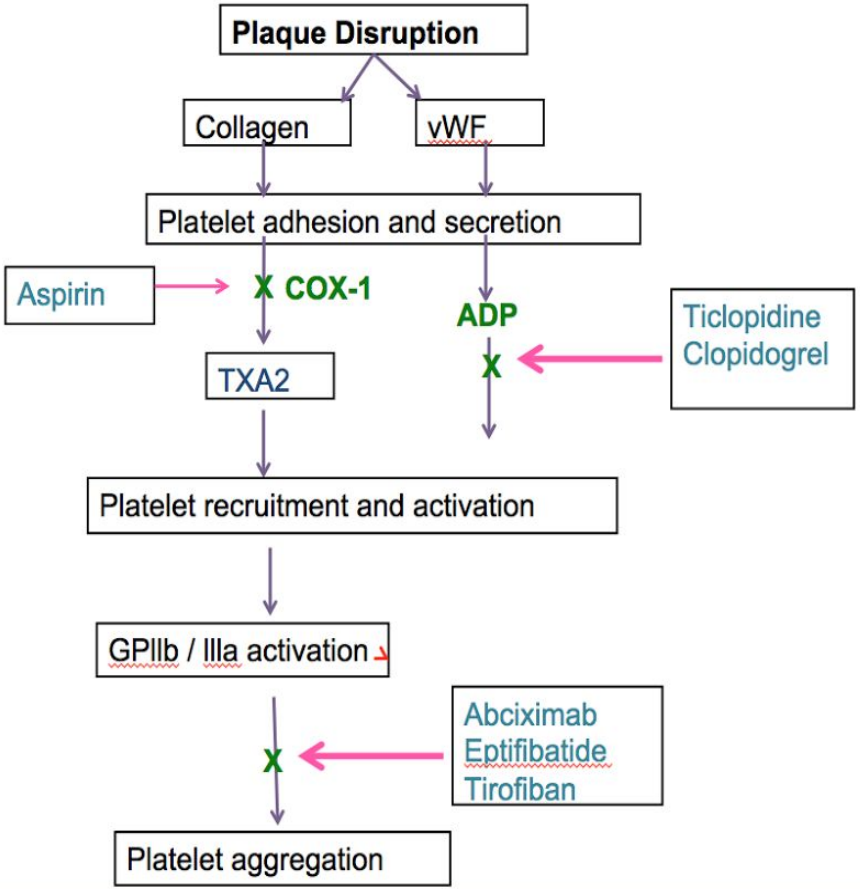
Uses of dipyridamole

- **Given orally.**
- **Adjunctive therapy for prophylaxis of thromboembolism in cardiac valve replacement (with warfarin).**
- **Secondary prevention of stroke and transient ischemic attack (with aspirin).**

Adverse Effects:

- Headache
- Postural hypotension

Mechanisms of action
of antiplatelet drugs



Summary

Mechanism of action	Drug	ROA
Inhibition of thromboxane A2 synthesis via inhibiting COX-1	Aspirin	Oral
ADP receptor antagonists	Clopidogrel Ticlopidine	Oral
GP IIb / IIIa receptor antagonists	Abciximab Tirofiban Eptifibatide	I.V.
Phosphodiestrase (PDE) inhibitor	Dipyridamole	Oral

MCQs

1)A 45- year-old male who came to the ER with MI and underwent PCI. From history, he is on phenytoin. Which is the best protective drug to give in this case ?

A- Prasugrel
B- ticlopidine
C- clopidogrel

2)A 55-year- old male came to GP with severe abdominal pain after meals & hyperacidity . Endoscopy shows gastric ulcer. From history, he is a heavy smoker for 25 years and taking drug A as cardio protection. What's drug A that can be the cause of his illness ?

A- dipyridamole
B- aspirin
C- abciximab

3)Which one of these drugs is reversible inhibitor of the P2Y12 receptor:

A-ticlopidine
B-Prasugrel
C-Ticagrelor

4) Drug is given by I.V :

A-Tirofiban
B-Ticagrelor
C-Dipyridamole

5)one of Dipyridamole side effect is :

A- peptic ulcer
B- hypertension
C- postural hypotension

1)A
2)B
3)C
4)A
5)C

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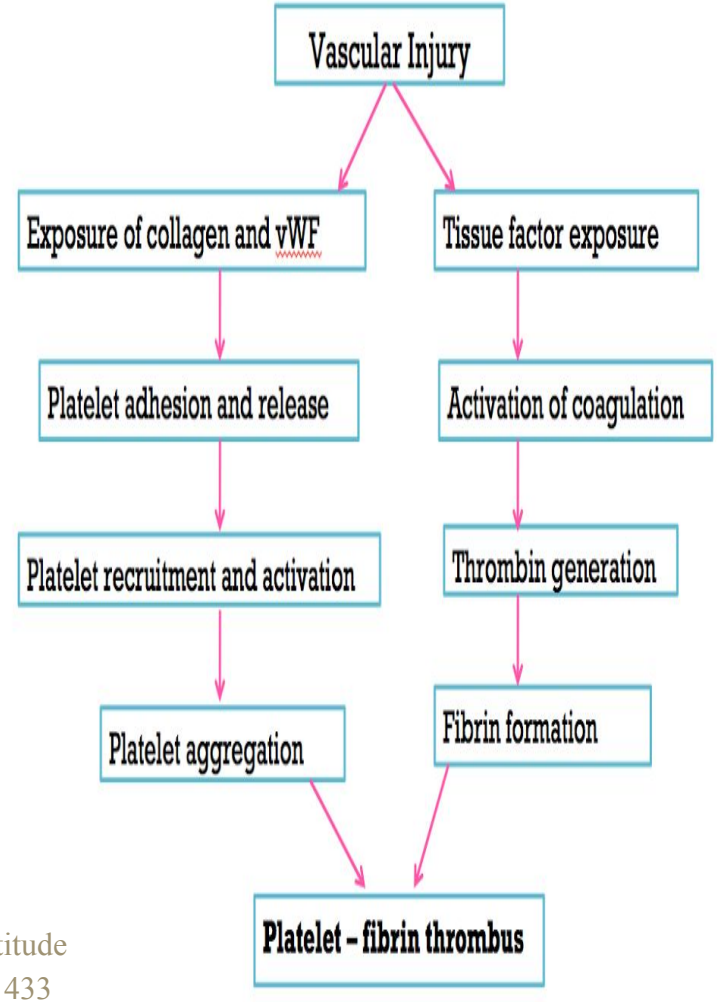

SAQs

1) **What is the Mechanism of Aspirin ?**

Irreversible inhibition of cyclooxygenase enzyme (COX-1) via acetylation..

2) **What is the indications for Clopidogrel ?**

recent myocardial infarction (MI)

recent stroke

established peripheral arterial disease.

acute coronary syndrome

3) **Name the ADP inhibitor which causes dyspnea .**

Ticagrelor

4) **What is the difference between abciximab and Tirofiban ?**

binding to all GPIIb/IIIa receptor sites on activated platelets.

bind the platelet to fibrinogen on glycoprotein IIb/ IIIa receptor .

Good luck!

Done by Pharmacology team

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For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com