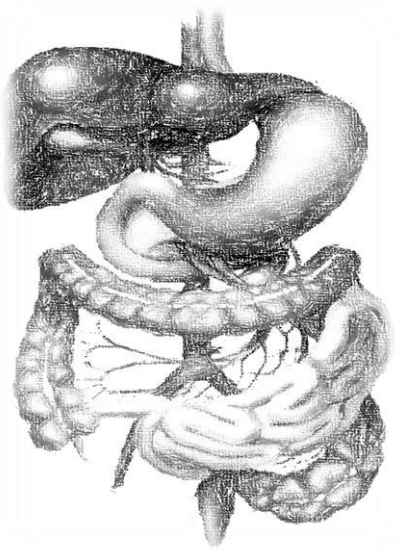
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



Antiplatelet Drugs

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

Color index

- extra information and further explanation
- important
- doctors notes
- Drugs names
- Mnemonics

Kindly check the editing file before studying this document

Introduction

Platelets and Vessels

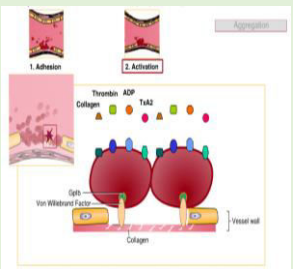
- In healthy vessels, **nitric oxide** and **prostacyclin** (released by endothelial cells lining the blood vessels) **inhibit** platelets aggregation.
- **Damage** to the vessel wall leads to interaction between (1) Platelets, (2) Endothelial cells and (3) Coagulation factors which lead to formation of the **CLOT:**

THROMBUS:
is the CLOT that adheres to vessel wall

EMBOLUS:
is the CLOT that floats in the blood

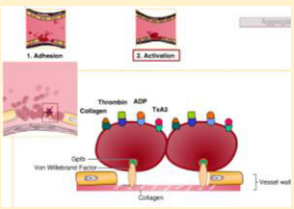
- THROMBOSIS: is the formation of unwanted clot within the blood vessel, producing life threatening conditions such as:
  - Acute myocardial infarction (MI)
  - Acute ischemic stroke
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)

Role of Platelets in Homeostasis

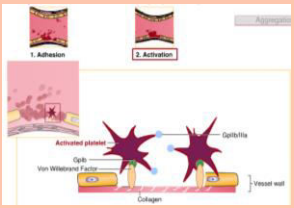


Following vascular injury**, von Willebrand factor** binds to collagen in the exposed subendothelium at the site of injury.

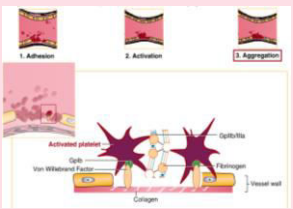
The other site of the "**rod-formed**" von Willebrand factor binds to the platelet receptor **GPIb** and platelets are thereby anchored to the site of the injured endothelium. This is called **adhesion**.



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

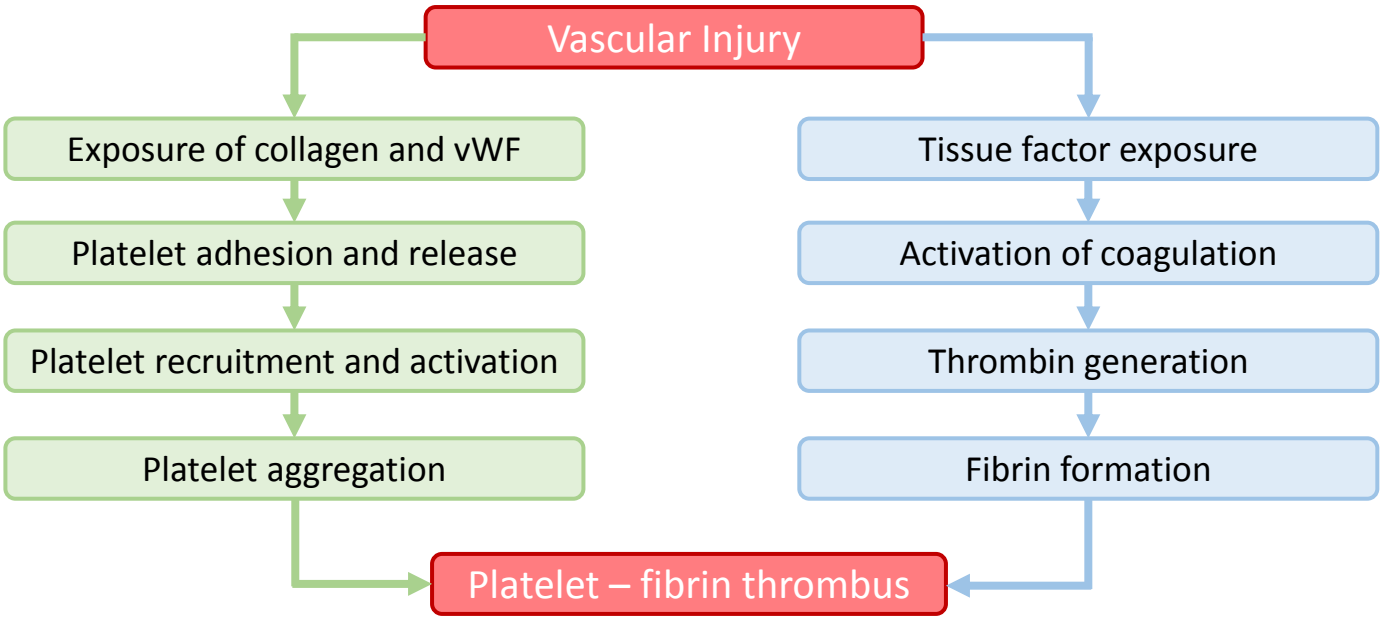


As a result of agonist binding, platelets undergo a **shape change** and new structures such **as phospholipids and GPIIb/IIIa receptors** are exposed on the cell membrane. This is called **activation**



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.

To understand !



Drugs used in thrombosis

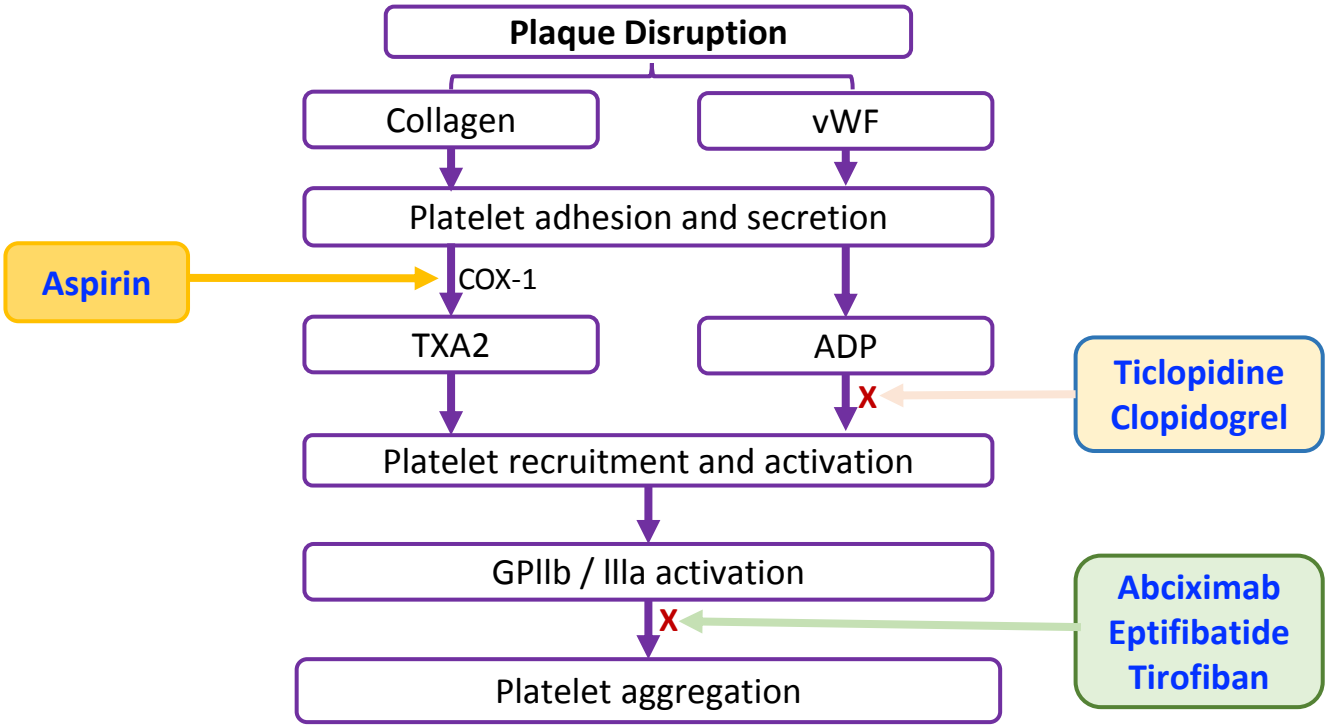
Anticoagulants	Antiplatelets	Thrombolytics or Fibrinolytics
drugs which prevent clotting by inhibiting **clotting factors** (coagulation process) (used in prevention and treatment of thrombosis).	drugs which prevent and inhibit **platelet activation and aggression** (used as prophylactic therapy in high risk patients).	act by **dissolving existing or already formed thrombi or emboli** (used in the acute treatment of thrombosis).

Classification of Antiplatelet Drugs

بنجيب لكم دوا ونقولكم ايش الميكانزيم

- **Arachidonic acid pathway inhibitors** **e.g.** Aspirin
- **Phospho-diesterase inhibitors** **e.g.** Dipyridamole
- **ADP inhibitors** **e.g.** Ticlopidine Clopidogrel
- **Glycoprotein IIb/IIIa inhibitors** **e.g.** Abciximab – Eptifibatide - Tirofiban

Mechanisms of action of antiplatelet drugs



Arachidonic acid pathway inhibitors

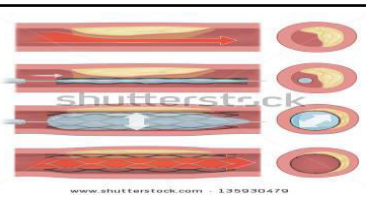
Drug	**Aspirin** (Acetylsalicylic Acid)
M.O.A	• **Irreversible** inhibition of **cyclooxygenase enzyme** (COX-1) via acetylation. • Small dose inhibits **thromboxane** (TXA2) synthesis in platelets <u>But</u> not **prostacyclin** (PGI_2) synthesis in endothelium (larger dose).
Use	• **Prophylaxis of thromboembolism** **e.g.** prevention of transient ischemic attack, ischemic stroke and myocardial infarction. الذبحة الصدريه اللي تجي وقت الراحة • **Prevention of ischemic events** in patients with <u>unstable</u> **angina pectoris.** • can be combined with other antiplatelet drugs (clopidogrel) or anticoagulants (heparin).
Dose	• **Low-dose aspirin** (81 mg enteric coated tablet/day) is the most common dose used to prevent a heart attack or a stroke. Given as prophylaxis
ADRs	• Risk of peptic ulcer. Because it inhibits prostaglandin synthesis • Increased incidence of GIT bleeding (**aspirin prolongs bleeding time**)

ADP pathway inhibitors

الدين كله أدب
البنت حلاها بالأدب
(ADP= dine)
(ADP= Grel/Girl)

	Ticlopidine	Clopidogrel
Drug	اتكلوا بالدين	صار كلو بدو قيرل — Better!
M.O.A	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).	
P.K	• 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	Bye to you (P2Y) من الأدب نقول
Use	Secondary prevention of ischemic complications after myocardial infarction, ischemic stroke and unstable angina.	
ADRs	• Sever neutropenia, CBC should be done monthly during treatment. • Bleeding (prolong bleeding time). • G.I.T : nausea, dyspepsia, diarrhea. • Allergic reactions.	اتكلوا بالدين، لأن ديننا وسطي (neutralize = neutropenia) (ticlopidine) Worse with ticlopidine
Drug Interactions	**inhibit CYT P450** causing **increased plasma levels** of drugs such as phenytoin and carbamazepine.	
Notes	can't be taken with food	• 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 Why clopidogril had replaced ticlopidine?
Indication	• 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. كلها زي بعض الا الاسبيرين بروفيلاكسس	

*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
	البنت حلاها بالأدب (ADP= Grel/Girl) — More preferred than the old ones	
M.O.A	Irreversible inhibitor of the P2Y12 receptor	Reversible inhibitor of the P2Y12 receptor — يرتبط معه تكا ويروح ما يطول
P.K	• both have more rapid onset of action than clopidogrel • both drugs do not need hepatic activation. not prodrug	
Use	to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed by PCI.	
ADRs	• both increase bleeding risk	• both increase bleeding risk • dyspnea — باقي تكا يا بنتي ويروح نفسي

Glycoprotein IIb/ IIIa receptor inhibitors

Strongest pathway

	Abciximab	Tirofiban (Non peptide drug)	Eptifibatide (peptide drug)
	عيسى زيي راح بخرايطها — شفت أي بي سي زيها أبيك تحفظ الخريطة	من شافوه طاروا فيه باين	ايدي فيه بالتايد ويروح
M.O.A	inhibits platelet aggregation by preventing the binding of fibronigen, von Willebrand factor, and other adhesive molecules to **GPIIb/IIIa** receptor sites on activated platelets prevent the activation and final step of aggregation	Act by occupying the site on glycoprotein IIb/ IIIa receptor that is required to bind the platelet to fibrinogen **(act as fibrinogen-mimetic agents)**.	
P.K	Given I.V. infusion	They are given intravenously	
Use	Used with heparin and aspirin as adjunct to PCI for the prevention of cardiac ischemic complications.	Used for the reduction of incidence of thrombotic complications during coronary angioplasty (PCI)	
Notes	Glycoprotein IIb/ **IIIa receptor is required for platelet aggregation with each others** and with fibrinogen and von Willbrand factor.		

Phosphodiesterase Inhibiter

Drug	Two **mole** of **phosph**ate **Di**pyrida**mole** = **Phosph**o**d**iesterase **Dipyridamole**
M.O.A	• It is a **vasodilator.** • Inhibits phosphodiestrase (an enzyme that normally break down **cAMP**) thus increases cAMP and decreased synthesis of thromboxane A2 and other platelet aggregating factors.
Use	• Given orally. • Adjunctive therapy for prophylaxis of thromboembolism in cardiac valve replacement (**with warfarin**). • Secondary prevention of stroke and transient ischemic attack (**with aspirin**). used in combination with other drugs due to its Weakness
ADRs	• Headache • Postural hypotension Because it's a vasodialator

Summary

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

Summary

1-Arachidonic acid pathway inhibitors: Aspirin

-M.O.A:
Irreversible inhibition of COX-1 via acetylation
-Use:
Prophylaxis of thromboembolism and Prevention of ischemic events
-Dose: Low-dose aspirin
-ADRs:
Risk of peptic ulcer
Increased incidence of GIT bleeding

2-Phosphodiesterase inhibitors: Dipyridamole

-M.O.A:
Inhibits phosphodiesterase & It is a vasodilator
-Use:
Adjunctive therapy for prophylaxis of thromboembolism (with warfarin) & Secondary prevention of stroke and transient ischemic attack (with aspirin)
-ADRs:
Headache & Postural hypotension

3-ADP pathway inhibitors: Ticlopidine & Clopidogrel

-M.O.A:
Irreversibly inhibit ADP receptor of subtype P2Y12
-P.K: orally, pro-drugs,
have slow onset of action
-Use: Secondary prevention
For patients with **acute coronary syndrome** (unstable angina/ MI)→clopidogrel
-ADRs:
Sever neutropenia→ Ticlopidine
-interactions:
inhibit CYT P450

4-New ADP Pathway Inhibitors:

Prasugrel: Irreversible inhibitor of the P2Y12 receptor
Ticagrelor: Reversible inhibitor of the P2Y12 receptor & cause dyspnea
-Use:
reduce the rate of thrombotic cardiovascular events
-ADRs:
increase bleeding risk
No risk of Neutropenia.

5-Glycoprotein IIb/IIIa inhibitors:

Abciximab:
-M.O.A:
inhibits the binding to GPIIb/IIIa receptor
-P.K: I.V. infusion→ acute case / during surgery(such as coronary angioplasty)
-Use:
with heparin and aspirin as adjunct to PCI for the prevention of cardiac ischemic complications
Eptifibatide –Tirofiban:
-M.O.A:
act as fibrinogen- mimetic agents
-P.K: I.V. infusion

MCQs

Q1: Which of the P2Y12 ADP receptor antagonists reversibly binds the receptor

A. Tirofiban. *B. Ticagrelor.* *C. Ticlopidine.*

Q2: A 56-year-old man came to the emergency room with complaints of swelling, redness, and pain in his right leg. The patient is diagnosed with acute DVT and requires treatment with an antiplatelet immediately. Which one of the following can be used in his case ?

A. Tirofiban. *B. Ticagrelor.* *C. Ticlopidine.*

Q3: A 59-year-old female presents to the emergency room and she is diagnosed with valvular atrial fibrillation. She requires valve replacement surgery immediately. Which one of the following Antiplatelet can be used in her case during surgery ?

A. Tirofiban. *B. Ticagrelor.* *C. Ticlopidine.*

Q4: All of the following Antiplatelet drugs act as ADP inhibitors except :

A.Tirofiban. *B. Ticagrelor.* *C. Ticlopidine.*

Q5: All of the following Antiplatelet drugs act by blocking the adhesion or activation of platelet except* :

A. Aspirin. *B. Tirofiban.* *C. Ticlopidine.*

Q6: Which one of the following Antiplatelet drugs act as fibrinogen mimetic agent and block GP IIb / IIIa receptors in platelet ?

A. Aspirin. *B. Epitafibatide.* *C. Prasugrel.*

Q7: Which one of the following Antiplatelet drugs can be used in patient with liver diseases ?**

A. Clopidogrel. *B. Ticlopidine.* *C. Ticagrelor.*

*Q5: Tirofiban act mainly on aggregation phase of platelet.

** Q7: the new ADP such as Ticagrelor do not need hepatic activation.because they are not prodrug

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

MCQs

Q8: Which of the following is a common serious side effect of ticlopidine ?

A. Prolong Bleeding. *B. Postural hypotension.* *C. Neutropenia.*

Q9: Which one of the following Antiplatelet drugs should be monitored by complete blood count for the patient every month ?

A. Clopidogrel. *B. Ticlopidine.* *C. Ticagrelor.*

Q10: Which one of the following Antiplatelet drugs is not recommended to be used in patient who is on phenytoin as anti-epileptic drug ?

A. Tirofiban. *B. Ticlopidine.* *C. Abciximab.*

Q11: Which one of the following Antiplatelet drugs can cause dyspnea as adverse effect ?

A. Tirofiban. *B. Ticagrelor.* *C. Ticlopidine.*

Q12: Which one of the following Antiplatelet drugs can cause postural hypotension as adverse effect ?

A. Prasugrel. *B. Clopidogrel.* *C. Dipyridamole.*

Q13: Which one of the following drugs is the most potent as Antiplatelet ?

A. Abciximab. *B. Aspirin..* *C. Clopidogrel.*

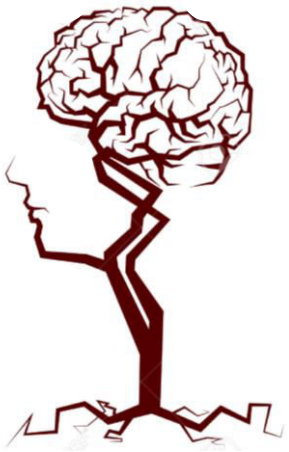
Q14: Which one of the following Antiplatelet drugs act by blocking GP IIb/IIIa and inhibit platelet aggregation ?

A. Abciximab. *B. Ticagrelor.* *C. Prasugrel.*

Q15: Which one of the following Antiplatelet drugs is given intravenously and can be used during operation and acute emergency case ?

A. Abciximab. *B. Aspirin.* *C. Clopidogrel.*

8) C
9) B
10) B
11) B
12) C
13) A
14) A
15) A



إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

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فيصل العباد

References :

1- 436 Prof. Yieldez slides