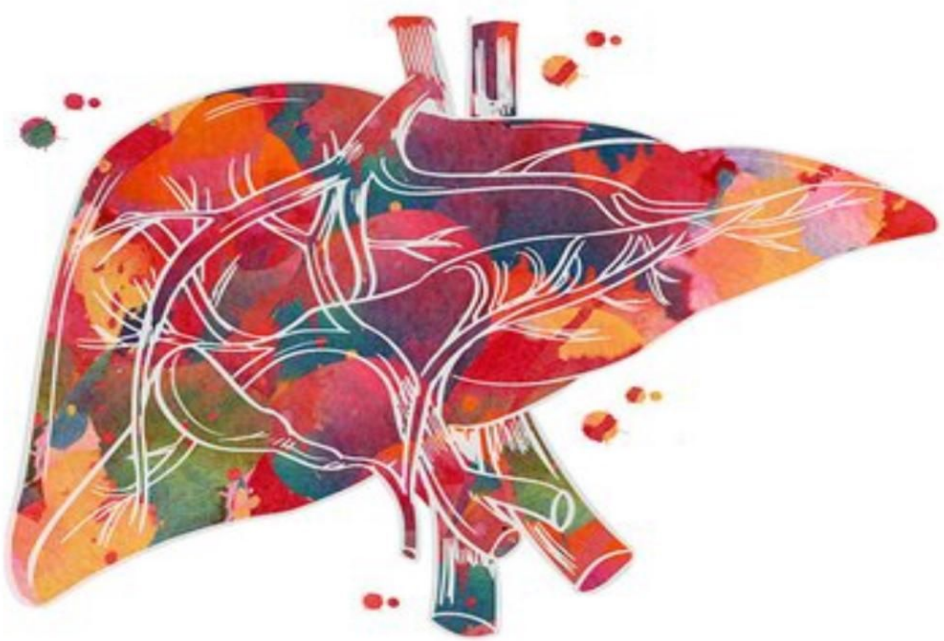
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY



# Anti-Platelet 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.

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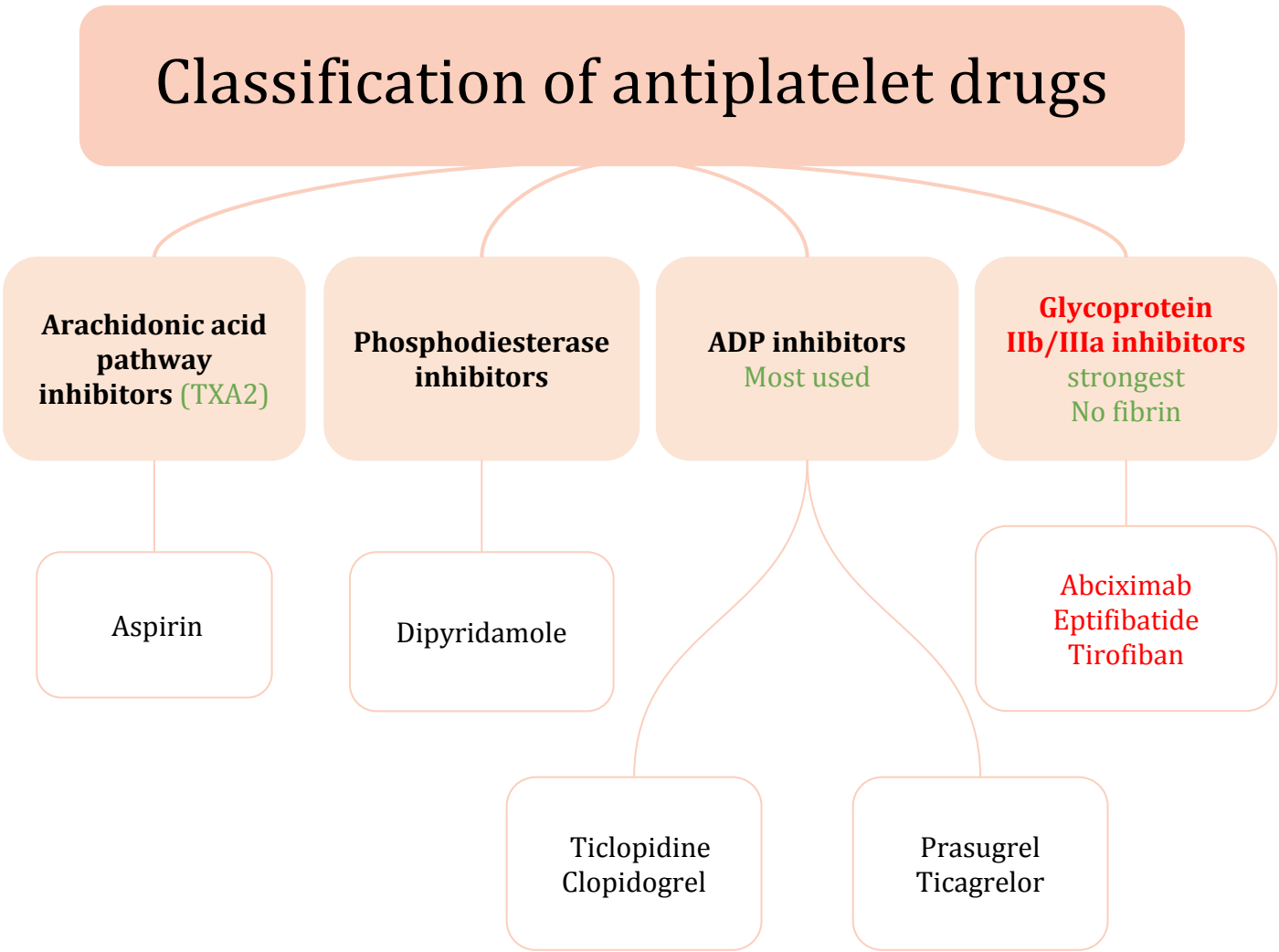
Editing File

Color index: Important Note Extra

# Mind Map

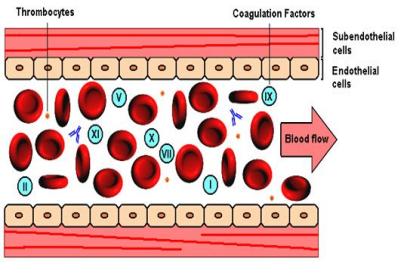

Classification of antiplatelet drugs
Arachidonic acid pathway inhibitors (TXA2)
Phosphodiesterase inhibitors
ADP inhibitors
Most used
Glycoprotein IIb/IIIa inhibitors
strongest
No fibrin
Aspirin
Dipyridamole
Ticlopidine
Clopidogrel
Prasugrel
Ticagrelor
Abciximab
Eptifibatide
Tirofiban

# Platelets and vessels

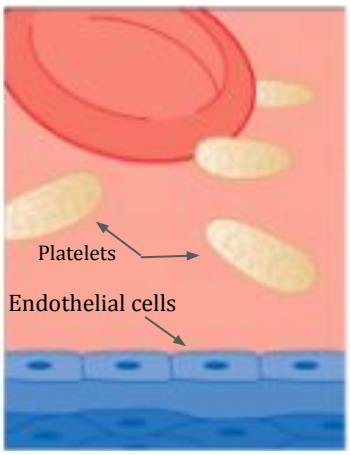
- In healthy vessels, nitric oxide (vasodilator)and prostacyclin (released by endothelial cells lining the blood vessels) inhibit platelets aggregation. (endogenous anti-platelet)
- Damage to the vessel wall leads to interaction between Platelets, Endothelial cells and Coagulation factors which lead 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 (AIS)
  ➔ Deep vein thrombosis (DVT)
  ➔ Pulmonary embolism (PE)

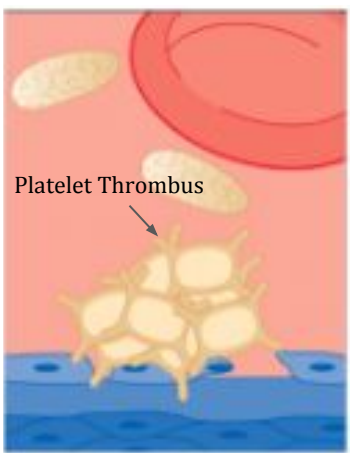



# Platelet Adhesion and Activation




Healthy vascular endothelium: chemical mediators such as prostacyclin ($PGI_2$), nitric oxide act as inhibitors of platelet aggregation

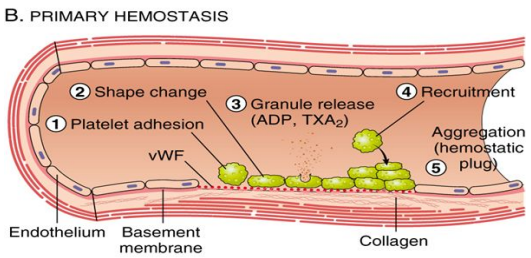
Injured endothelium: Platelets adhere to damaged endothelium become activated




Aggregation of platelets into a thrombus

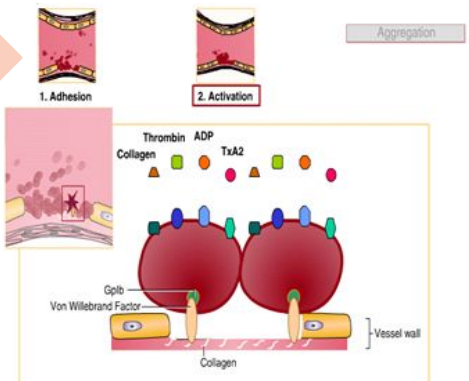
# In case if there is an endothelial injury

Platelet activation; receptors present on the platelets are activated by the collagen of the connective tissues, platelets release mediators like adenosine diphosphate (ADP), thromboxanes A2



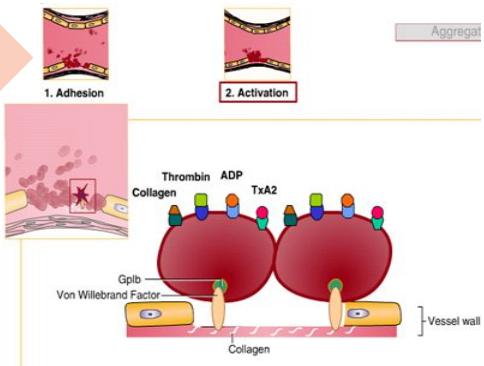

# The role of platelets in Hemostasis

1



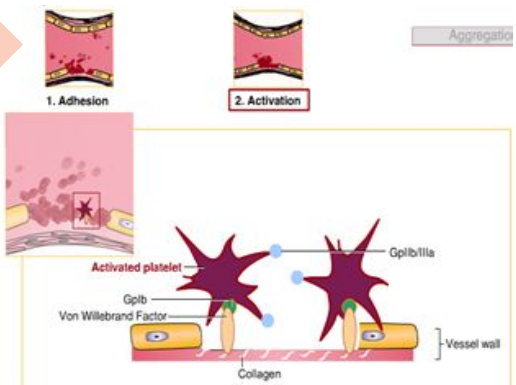

- Following vascular injury, von Willebrand factor binds to collagen in the exposed subendothelium at the site of injury.
- The other site of the "rod-formed" von Willebrand factor binds to the platelet receptor GPIb and platelets are thereby anchored to the site of the injured endothelium. This is called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

2



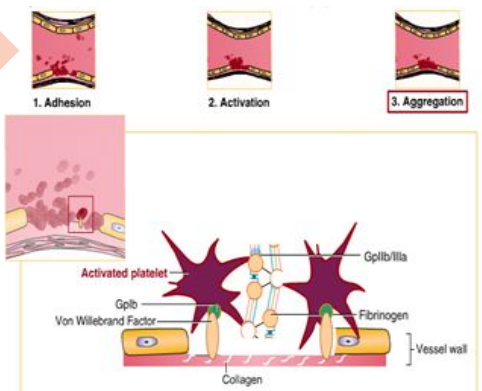

Following adhesion, agonists such as collagen, thrombin, ADP, and thromboxane A2 Activate (degranulated) platelets by binding to their respective platelet receptors.

3




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

4




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.

**Prof. Yieldez stressed on the importance on knowing M.O.A of each drug.**

# Drugs used in thrombosis

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

**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.

## Arachidonic acid pathway inhibitors

| Drug | Aspirin (Acetylsalicylic Acid) |
|---|---|
| M.O.A | • Irreversible (its action will stay throughout the lifespan of the platelet; 7days) inhibition of cyclooxygenase enzyme ( COX-1 ) via acetylation.<br>• Small dose inhibits thromboxane (TXA2) synthesis in platelets But not prostacyclin (PGI2) synthesis in endothelium (larger dose). |
| Uses | • Prophylaxis of thromboembolism e.g. prevention of transient ischemic attack, ischemic stroke and myocardial infarction.<br>• Prevention of ischemic events in patients with unstable angina pectoris(chest pain at rest) .<br>• can be combined with other antiplatelet drugs (clopidogrel) or anticoagulants (heparin). Because aspirin is weak |
| Dose | • Low-dose aspirin (81 mg enteric coated tablet/day ) is the most common dose used to prevent a heart attack or a stroke. |
| ADRs | • Risk of peptic ulcer.<br>• Increased incidence of GIT bleeding (aspirin prolongs bleeding time) |

**Prof. Yieldez stressed on the importance on knowing M.O.A of each drug.**

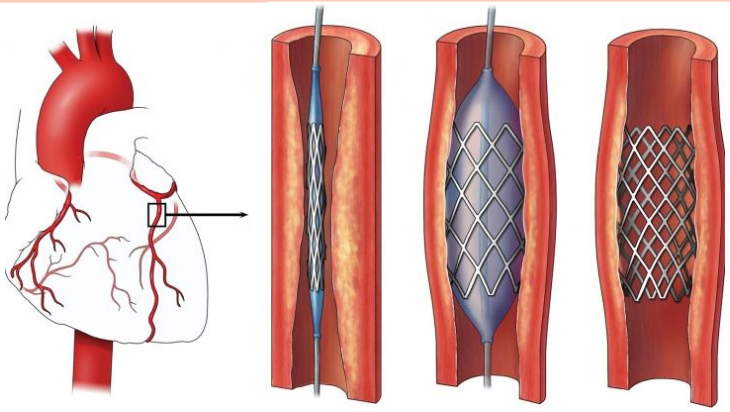
# ADP pathway inhibitors

| Drug | Ticlopidine | Clopidogrel |
|---|---|---|
| **M.O.A** | • These drugs specifically and irreversibly inhibit ADP receptor of subtype P2Y12, (Purine 2Y12) which is required for platelets activation thus prevent platelet aggregation.<br>• P2Y12 is purinergic receptor and is a chemoreceptor for adenosine diphosphate (ADP). | |
| **P.K** | • Are given orally.<br>• Have slow onset of action (3 - 5 days)<br>• **Pro-drugs**, they have to be activated in the liver<br>• Bound to plasma proteins<br>**P.K ONLY for Clopidogrel:**<br>➔ More potent than ticlopidine.<br>➔ Longer duration of action than ticlopidine.<br>➔ Less frequency of administration (given once daily ).<br>➔ Less side effects (**less neutropenia**).<br>➔ Bioavailability is unaffected by food.<br>➔ Clopidogrel has replaced ticlopidine | |
| **Clinical Uses** | • Secondary prevention of ischemic complications after myocardial infarction, ischemic stroke and unstable angina. + atrial fibrillation | |
| **Indications ONLY for Clopidogrel** | • For patients with a history of recent **myocardial infarction (MI)** (the best alternative for aspirin), recent stroke, or established peripheral arterial disease.<br>• For patients with acute coronary syndrome (unstable angina/ MI): either those managed medically or with percutaneous coronary intervention ( PCI ) with or without stent. Give Clopidogrel during the procedure. | |
| **ADRs** | • **Sever neutropenia,** CBC should be done monthly during treatment Especially with Ticlopidine<br>• Bleeding ( prolong bleeding time )<br>• G.I.T : nausea, dyspepsia, diarrhea<br>• Allergic reactions | |
| **Drug interactions** | inhibit CYT P450 causing increased plasma levels of drugs such as phenytoin and carbamazepine. | |

**Prof. Yieldez stressed on the importance on knowing M.O.A of each drug.**

# ADP pathway inhibitors

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.
Can be with or without a stent.
It's a non-surgical procedure.

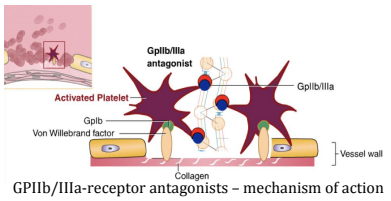


## New ADP Pathway Inhibitors

| Drug | Prasugrel | Ticagrelor |
|---|---|---|
| M.O.A | Irreversible inhibitor of the P2Y12 receptor | Reversible inhibitor of the P2Y12 receptor |
| P.K | • Both have more rapid onset of action than clopidogrel.<br>• Both drugs do not need hepatic activation. They are NOT prodrugs | |
| Indications | • 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<br>• Ticagrelor causes dyspnea | |

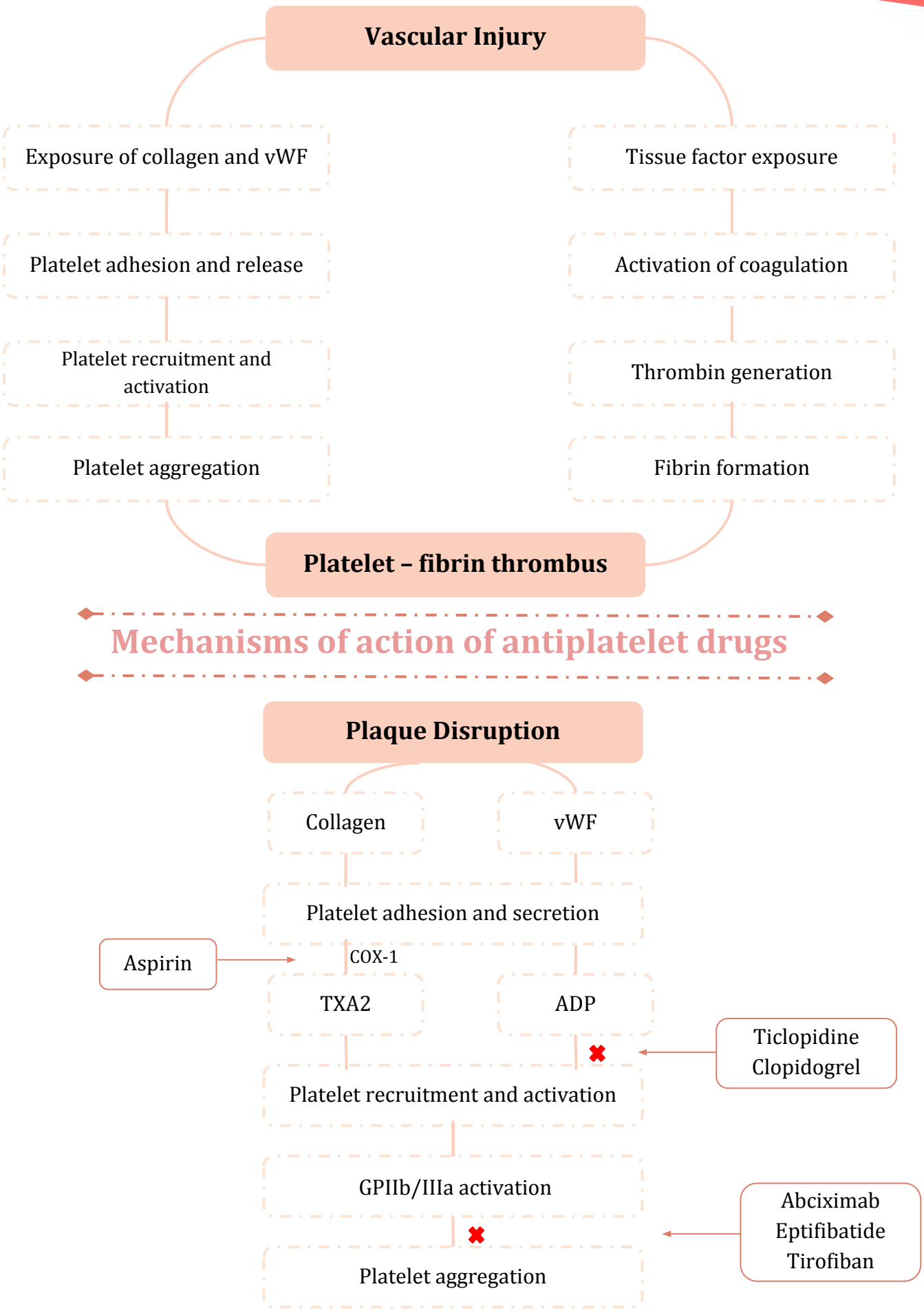
**Prof. Yieldez stressed on the importance on knowing M.O.A of each drug.**

# Glycoprotein IIb/ IIIa receptor inhibitors

| Drug | Abciximab | Tirofiban (non-peptide drug) | Eptifibatide (peptide drug) |
|---|---|---|---|
| M.O.A | inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive molecules to **GPIIb/IIIa receptor** sites on activated platelets | 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. | Given intravenously | |
| Indications | Is 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) | |
| Note | Glycoprotein IIb/ IIIa receptor is required for platelet aggregation with each others and with fibrinogen and von Willebrand factor. |  GPIIb/IIIa-receptor antagonists – mechanism of action | |

# Phosphodiesterase inhibitor

| Drug | Dipyridamole |
|---|---|
| M.O.A | • It is a vasodilator<br>• Inhibits phosphodiesterase thus increases cAMP causing decreased synthesis of thromboxane A2 and other platelet aggregating factors. |
| P.K | • Given orally. |
| Indications | • Adjunctive therapy for prophylaxis of thromboembolism in cardiac valve replacement (with warfarin).<br>• Secondary prevention of stroke and transient ischemic attack (with aspirin). |
| ADRs | • Headache<br>• Postural hypotension |


Vascular Injury
Exposure of collagen and vWF
Tissue factor exposure
Platelet adhesion and release
Activation of coagulation
Platelet recruitment and activation
Thrombin generation
Platelet aggregation
Fibrin formation
Platelet – fibrin thrombus
Mechanisms of action of antiplatelet drugs
Plaque Disruption
Collagen
vWF
Platelet adhesion and secretion
Aspirin
COX-1
TXA2
ADP
Ticlopidine
Clopidogrel
Platelet recruitment and activation
GPIIb/IIIa activation
Abciximab
Eptifibatide
Tirofiban
Platelet aggregation

# Summary

| Arachidonic acid pathway inhibitors | | |
|---|---|---|
| **Drug** | **Aspirin** | |
| **M.O.A** | Irreversible Inhibition of thromboxane A2 synthesis via **inhibiting COX-1** | |
| **Use** | Oral prophylaxis with other antiplatelet drugs (clopidogrel) or heparin. | |
| **ADRs** | prolongs bleeding time | |
| **ADP pathway inhibitors** | | |
| **Drug** | **Ticlopidine** | **Clopidogrel** |
| **M.O.A** | irreversibly **inhibit ADP** receptor of subtype P2Y12 | |
| **Uses** | Orally - **Clopidogrel:** with acute coronary syndrome or with percutaneous coronary intervention ( PCI ) | |
| **ADRs** | Severe neutropenia but less with **Clopidogrel** | |
| **Drug interactions** | inhibit CYT P450 causing increased plasma levels of drugs such as phenytoin and carbamazepine. | |
| **New ADP Pathway Inhibitors** | | |
| **Drug** | **Prasugrel** | **Ticagrelor** |
| **Glycoprotein IIb/ IIIa receptor inhibitors** | | |
| **Drug** | **Tirofiban** / **Eptifibatide** | **Abciximab** |
| **M.O.A** | occupy the binding site of fibrinogen ( **fibrinogen- mimetic agents** ). | preventing the binding of fibrinogen & VWF, to **GPIIb/IIIa receptor** |
| **Use** | IV during PCI | **IV** with heparin and aspirin |
| **Phosphodiesterase inhibitor** | | |
| **Drug** | **Dipyridamole** | |
| **M.O.A** | **Inhibits phosphodiesterase** | |

# MCQs

Q1- A patient with unstable angina came to you complaining of increased GIT bleeding, tests confirmed a prolonged bleeding time, while taking medical history you discovered that the patient was prescribed an antiplatelet drug. Which one of the following drugs was most likely used?

A- Abciximab
B- Aspirin
C- Ticagrelor
D- Dipyridamole

Q2- Which one of the following adverse side effects of Ticlopidine must you be very careful with?

A- Bleeding
B- Nausea
C- Allergic reactions
D- Severe neutropenia

Q3- Which one of the following drugs inhibits the P2Y12 receptor reversibly?

A- Ticlopidine
B- Prasugrel
C- Ticagrelor
D- Clopidogrel

Q4- Which one of the following drugs can be combined with other antiplatelet drugs like clopidogrel or heparin?

A- Aspirin
B- Prasugrel
C- Ticagrelor
D- Clopidogrel

Q5- Which one of the following is a prodrug that has to be activated in the liver?

A- Aspirin
B- Prasugrel
C- Clopidogrel
D- Ticagrelor

Q6- Which one of the following ways of admission is used for GPIIb/IIIa inhibitors?

A- Subcutaneous
B- Oral
C- Intravenous
D- Intramuscular

Q7- Which one of the following drugs is not used in the management of ischemic events during PCI?

A- Tirofiban
B- Prasugrel
C- Aspirin
D- Clopidogrel

Q8- Which one of the following antiplatelet drugs may cause increased levels of coadministered drugs?

A- Ticagrelor
B- Prasugrel
C- Aspirin
D- Clopidogrel

1-B
2-D
3-C
4-A
5-C
6-C
7-C
8-D

# SAQ:

Q1: A/ Mention 2 antiplatelet drugs used in patients with unstable angina and explain the mechanism of action of each.

Aspirin → Irreversible inhibition of COX 1
Clopidogrel → Irreversible inhibition of ADP receptors subtype P2Y12

B/ Mention 1 important ADR for each drug.

Aspirin → Increased incidence of GIT bleeding
Clopidogrel → Severe neutropenia

Q2: A/ What is the mechanism of action of Dipyridamole?

Inhibition of phosphodiesterase leading to increased cAMP and decreased TXA2

B/ Mention two indications of Dipyridamole.

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

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## Thanks for those who worked on this lecture:

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References:

✓ Doctors' slides and notes


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