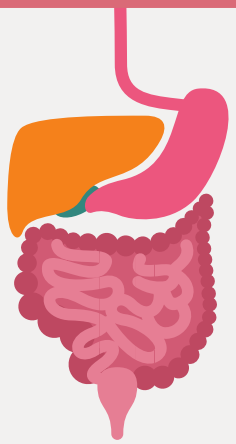
Anti-platelet drugs



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

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Drugs names | Doctors notes | Important | Extra

« **باذلًا وسعي** في استنقاذها من الهلاك والمرض، والألم والقلق »

شكر وتقدير

قال رسول الله صلى الله عليه وسلم:

"إذا مات ابن آدم انقطع عمله إلا من ثلاث، صدقة جارية، أو **علم ينتفع به**، أو ولد صالح يدعو له"

كل الشكر والتقدير لأعضاء فريق علم الأدوية الكرام على عملهم الرائع خلال هذا البلوك، جزاهم الله خير الجزاء:

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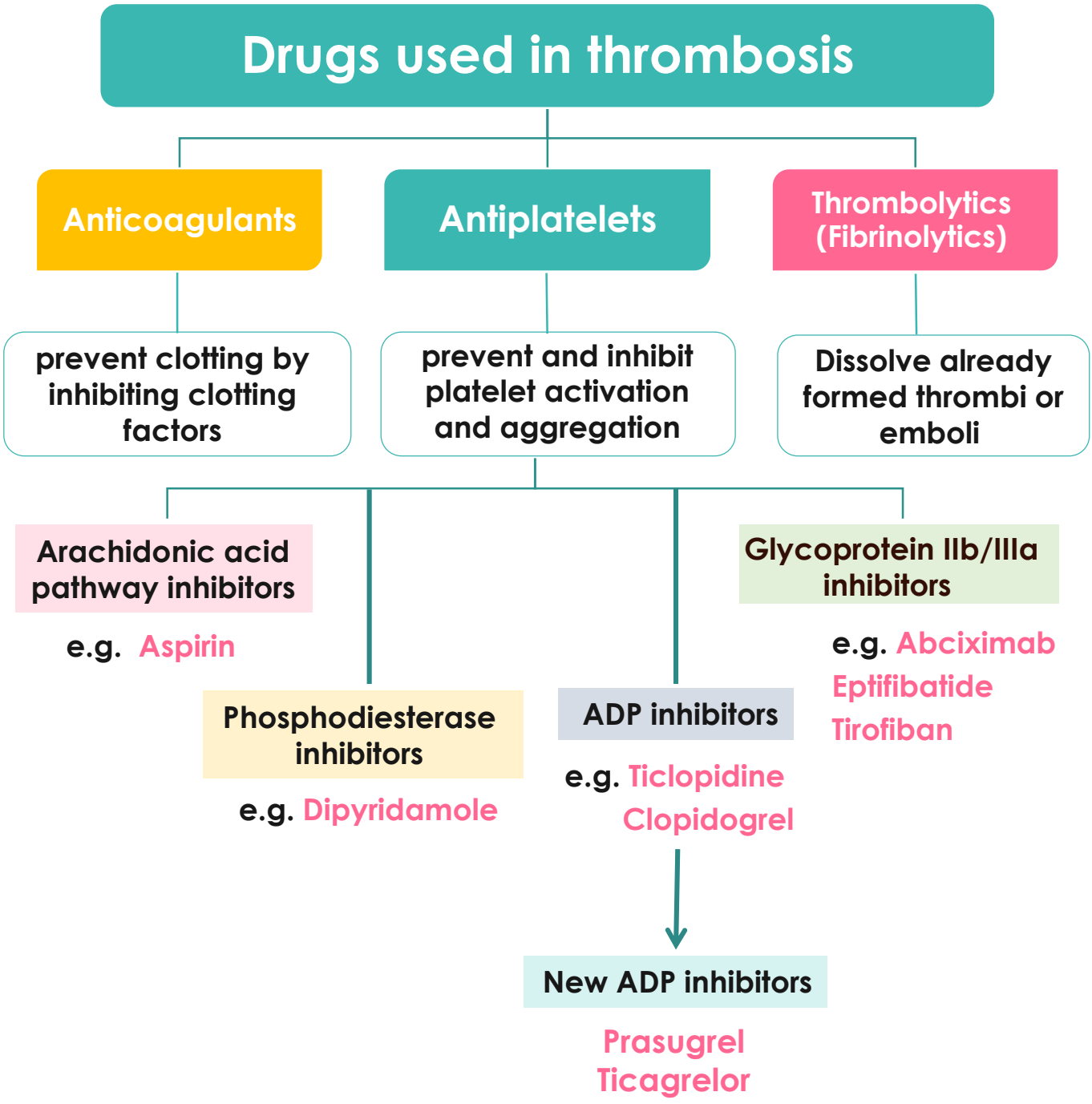
أثير النشوان & خالد أبوراس

Mind Map



3:22 min

To Understand Better

The role of platelets in hemostasis

Following vascular injury, von Willebrand factor binds to collagen in the exposed sub endothelium 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 A2** 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.

2:00 min

To Understand Better

Platelets and vessels

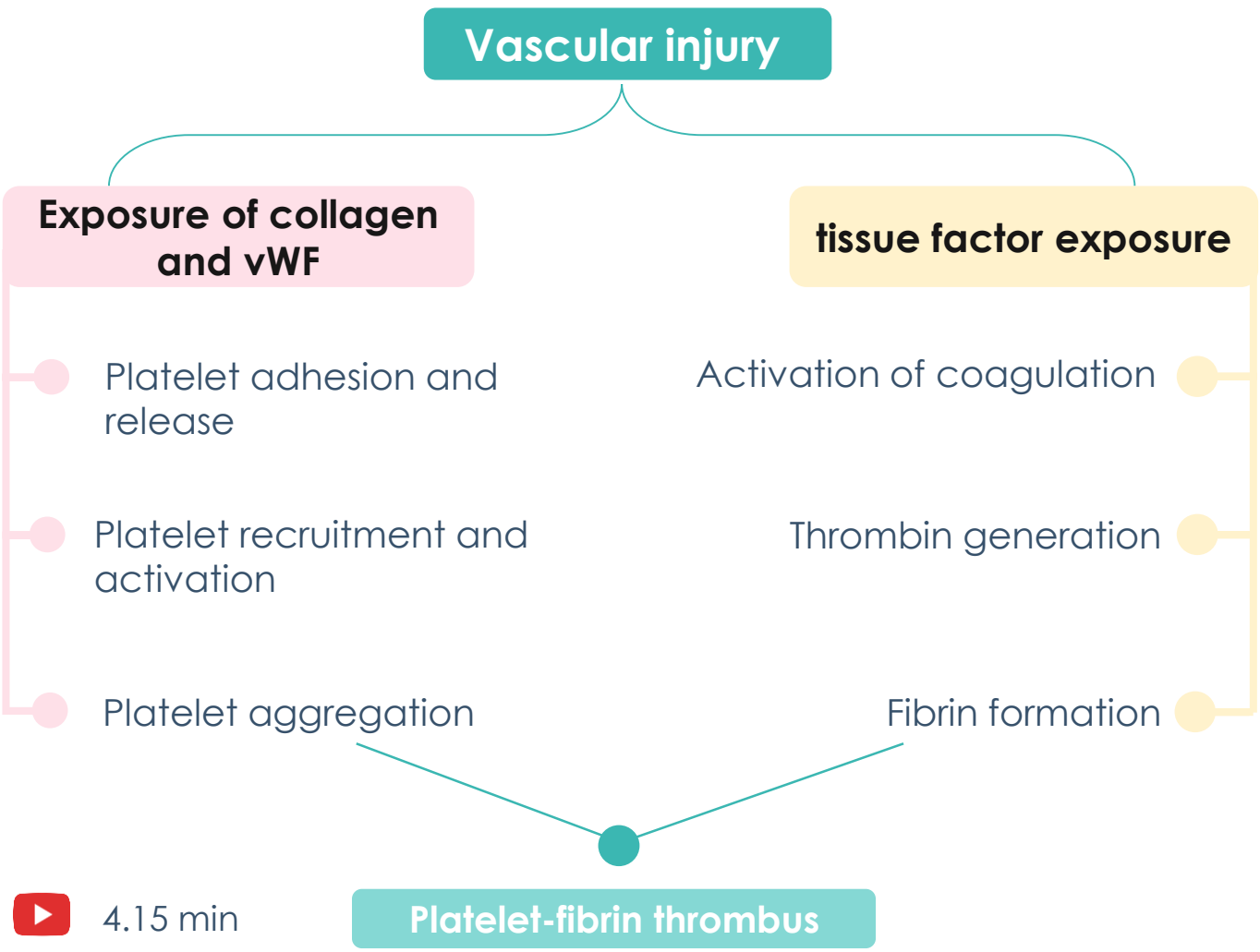
In **healthy** vessels, nitric oxide and prostacyclin (released by endothelial cells lining the blood vessels) **inhibit** platelets aggregation.

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

CLOT

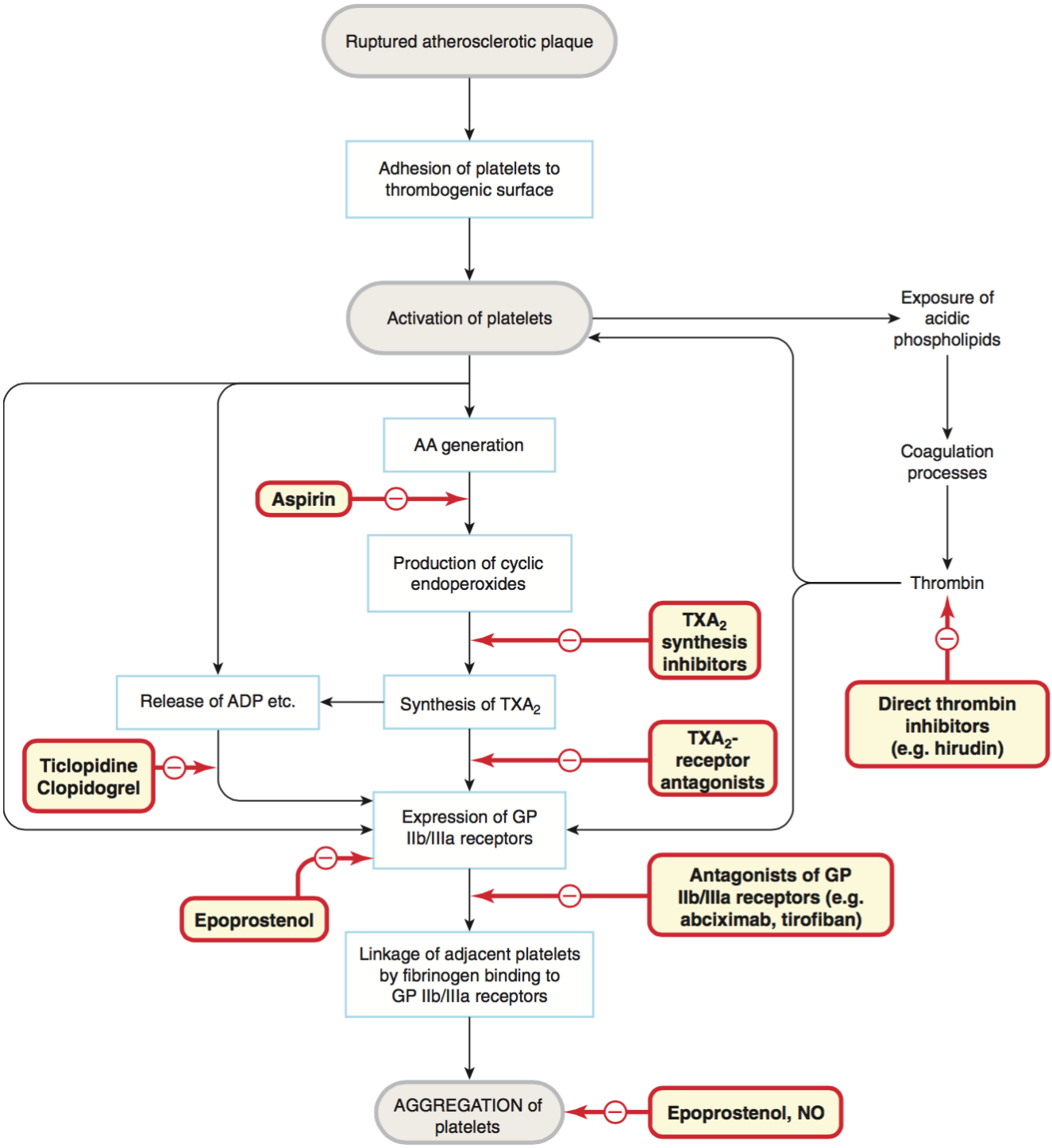
- **THROMBUS:** is the CLOT that adheres to vessel wall
- **EMBOLUS**: is the CLOT that floats in the blood
- **THROMBOSIS:** is the formation of unwanted clot within the blood vessel, producing life threatening conditions such as:
  - **Acute myocardial infarction (MI)**
  - **Acute ischemic stroke (AIS)**
  - **Deep vein thrombosis (DVT)**
  - **Pulmonary embolism (PE)**

1:53 min



4.15 min

Make your life easy by this diagram ☺



Drugs used in thrombosis:

1-Anticoagulate	2-Antiplatelets	3-Thrombotics or Fibrinolytic
Drugs which prevent clotting by inhibiting clotting factors (coagulation process) **used in prevention and treatment of thrombosis.** Mainly used for **venous** thrombus	Drugs which prevent and inhibit platelet activation and aggression. **used as prophylactic therapy in high risk patients.** Mainly used for **arterial** thrombus	Act by dissolving existing or already formed thrombi or emboli. **used in the acute treatment of thrombosis.**

Classification of antiplatelet

1. **Arachidonic acid pathway inhibitors** e.g. Aspirin
2. **ADP inhibitors** e.g. Ticlopidine – Clopidogrel (plavix)
3. **Glycoprotein IIb/IIIa inhibitors** e.g. Abciximab Eptifibatide - Tirofiban
4. **Phosphodiesterase inhibitors** e.g. Dipyridamole Not used nowadays

Arachidonic acid pathway inhibitors

Drug	Aspirin (acetylsalicylic acid –ASA-)
MOA	✓ Irreversible inhibition of cyclooxygenase enzyme (**COX-1**) via acetylation. (irreversible =long acting → عشان كذا نسأل قبل العملية إذا المريض يأخذ أسبرين أو لا، وإذا إيه نقول له وقفها قبل العملية ب١٠ أيام تقريبًا.) ✓ **Small dose** inhibits thromboxane (TXA2) synthesis in platelets But not prostacyclin (PGI2) synthesis in endothelium (**larger dose**).
Dose	○ Low-dose aspirin (81 mg enteric coated tablet/day) is the most common dose used to prevent a heart attack or a stroke. ○ Used orally.
Indications	○ **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). ○ *Aspirin* is the only NSAID that irreversibly exhibits antithrombotic efficacy.
ADRs	○ Risk of peptic ulcer. → bc they inhibit the prostaglandins synthesis. ○ Increased incidence of GIT bleeding (aspirin prolongs bleeding time)

ADP pathway inhibitors

Ticlopidine & Clopidogrel

MOA

- 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).
- Diagram shows their MOA

P.K.

- Given **orally**. (75 mg)
- Have **slow onset of action** (3 - 5 days) so you have to plan to use it before enough time.
- **Pro-drugs**, they have to be activated in the liver.
- Bound to plasma proteins

Indications

- **Secondary prevention of ischemic complications** after myocardial infarction, ischemic stroke and unstable angina.
  - **Primary prevention:** aims to prevent disease or injury before it occurs.
  - **Secondary prevention:** aims to reduce the impact of disease or injury that has already occurred.
  - **Tertiary prevention:** aims to soften the impact of an ongoing illness or injury that has lasting effect.
- *Ticlopidine* is approved for the prevention of **transient ischemic attacks** and strokes for patients with a prior **cerebral thrombotic** event.
- Compared to *ticlopidine*, ***clopidogrel*** is the preferred agent in ischemic heart disease events.

ADRs

- **Sever neutropenia** (low WBCs) \ agranulocytosis, **CBC** should be done monthly during treatment. (more sever w\ *Ticlopidine* → reserve its use for pts who cannot take aspirin or clopidogrel).
- **Bleeding** (prolong bleeding time). → pts should be careful when driving\playing.
- G.I.T : nausea, dyspepsia, diarrhea.
- Allergic reactions.

Drug interaction

- **Inhibit CYT P450** causing increased plasma levels of drugs such as phenytoin and carbamazepine.(Antiepileptic drugs)

Clopidogrel (Plavix)

P.K

- **More potent** with **Longer duration** of action than ticlopidine.
- Less frequency of administration **(given once daily).** → better compliance
- Less side effects **(less neutropenia)** → it is rarely associated with 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.
- * Coronary angioplasty **(percutaneous coronary intervention, PCI** القسطرة **):** 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

Drug	Prasugrel	Ticagrelor
MOA	○ **Irreversible** inhibitor of the P2Y12 receptor.	○ **Reversible** inhibitor of the P2Y12 receptor. → Better
P.K	○ **Both** have more **rapid** onset of action than **clopidogrel.** ○ **Both** drugs **do not need hepatic activation**. (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**.	
ADRs	○ Both increase **bleeding** risk. ○ **Ticagrelor causes dyspnea**.	

Glycoprotein IIb/IIIa receptor inhibitors

Glycoprotein IIb/ IIIa receptor is required for platelet aggregation with each other and with fibrinogen and von Willbrand factor.

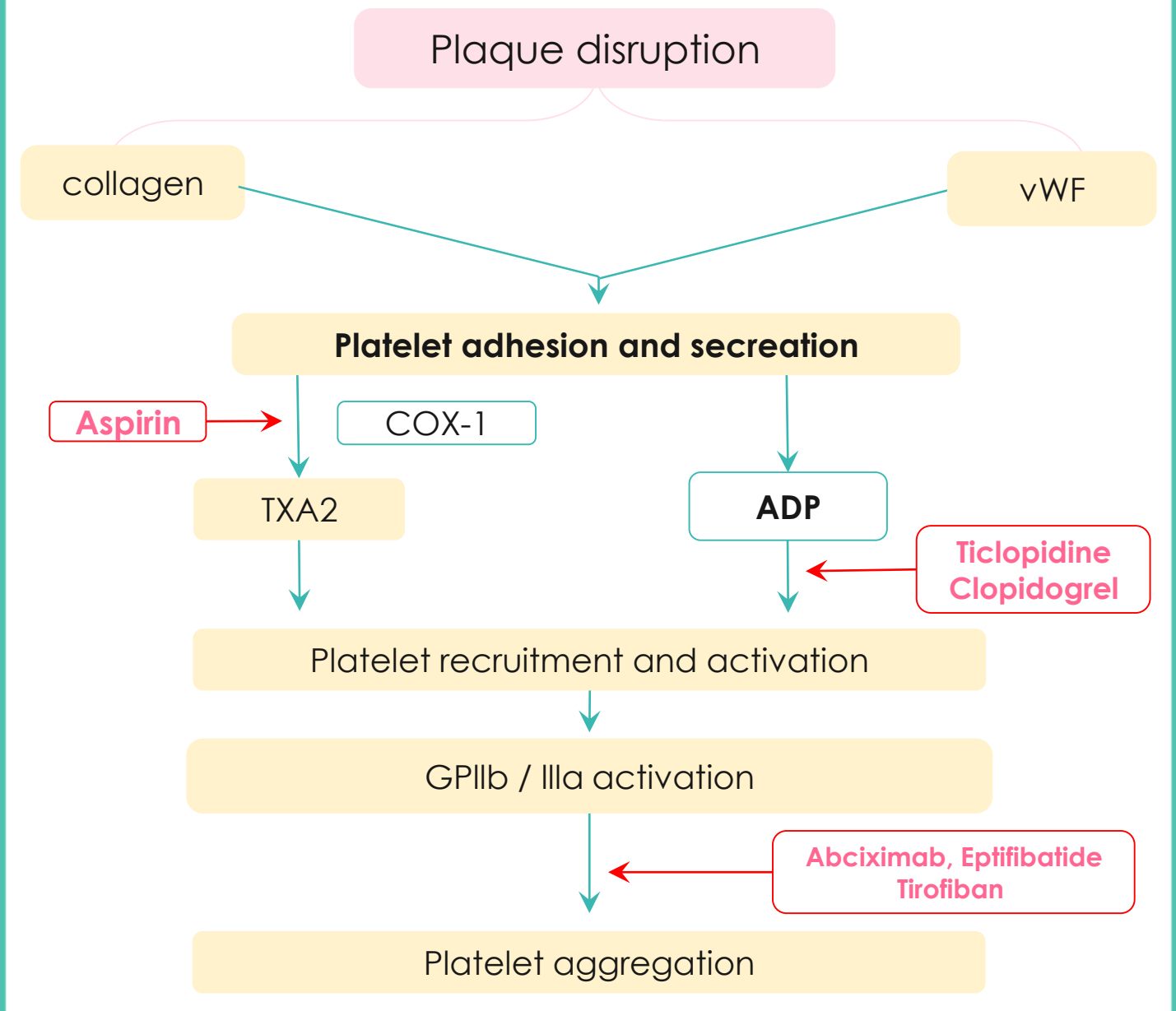
They are the very potent anti-platelet drugs, why? Bc GPIIb\IIa is the final step which enhances the **platelet aggregation** (when it binds to **fibrinogen**)

Drug	Abciximab	Tirofiban	Eptifibatide
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. ○ (chimeric monoclonal antibody directed against the IIb/IIIa complex)	○ Act by **occupying the site** on **glycoprotein IIb/ IIIa receptor** that is required to bind the platelet to **fibrinogen** (act as **fibrinogen-mimetic agents**).	
	○ Monoclonal antibodies, reversibly inhibit the binding of fibrin & other ligands to the platelet GP IIb\IIIa R, which is involved in platelet cross-linking. Diagram shows their MOA		
P.K	○ Given **IV** (Abciximab) Infusion.	○ Non-peptide drug	○ Peptide drug
		○ They are given **IV**. → PCI يستخدم أثناء	
	○ They are given IV, not like the previous drugs!		
Uses	○ Used with **heparin** and **aspirin** as adjunct to **PCI** for the prevention of cardiac ischemic complications.	○ For the **reduction of incidence of thrombotic complications during coronary angioplasty (PCI).**	

Phosphodiesterase inhibitors

Drug	**Dipyridamole** (weak, less used now)
MOA	○ (It is a **vasodilator**). ○ Inhibits phosphodiestrase (an enzyme that normally break down cAMP) thus **increases cAMP** causing **decreased synthesis of thromboxane A2** and other platelet aggregating factors.
P.K	○ Given **orally**. (like aspirin & ADP inhibitors)
Uses	○ **Adjunctive** therapy for **primary prophylaxis** of thromboembolism in **cardiac valve replacement** (with **warfarin**) → effective for inhibiting embolization from prosthetic heart valves ○ **Secondary prevention** of stroke and transient ischemic attack (**with aspirin**).
ADRs	○ Headache. ○ Postural hypotension. → bc it is a vasodilator.

Quick summary



Summary from the slides

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

Summary -1

Drug	Arachidonic acid pathway inhibitors (**Aspirin**)	Phosphodiesterase inhibitors (**Dipyridamole**)
MOA	- 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)	- Inhibits phosphodiestrase thus increases cAMP causing decreased synthesis of thromboxane A2 and other platelet aggregating factors.
P.K	- Low-dose aspirin (81 mg enteric coated tablet/day) is the most common dose used to prevent a heart attack or a stroke	- It is a vasodilator - Given orally.
Uses	- Prophylaxis of thromboembolism - Prevention of ischemic events - can be combined with other antiplatelet drugs (clopidogrel) or anticoagulants (heparin).	- Adjunctive therapy for prophylaxis of thromboembolism in cardiac valve replacement (with warfarin). - Secondary prevention of stroke and transient ischemic attack (with aspirin).
ADRs	- Risk of peptic ulcer. - Increased incidence of GIT bleeding (aspirin prolongs bleeding time)	- Headache - Postural hypotension

Summary -2

Drug	Glycoprotein IIb/IIIa inhibitors (Abciximab – Eptifibatide -Tirofiban)	New ADP Pathway Inhibitors (Prasugrel - Ticagrelor)
MOA	- Abciximab: inhibits platelet aggregation by preventing the binding of fibronigen, von Willebrand factor, and other adhesive molecules to GPIIb/IIIa receptor sites on activated platelets - Tirofiban (non-peptide drug) - Epitafibatide (peptide drug) Act by occupying the site on glycoprotein IIb/ IIIa receptor that is required to bind the platelet to fibrinogen (act as fibrinogen- mimetic agents).	- Prasugrel: Irreversible inhibitor of the P2Y12 receptor - Ticagrelor: Reversible inhibitor of the P2Y12 receptor - both have more rapid onset of action than clopidogrel - both drugs do not need hepatic activation
P.K	Given I.V. infusion.	
Uses	- Abciximab is used with heparin and aspirin as adjunct to PCI for the prevention of cardiac ischemic complications. Tirofiban & Eptifibatide They are given intravenously for the reduction of incidence of thrombotic complications during coronary angioplasty (PCI)	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 Ticagrelor causes dyspnea

Drug	ADP inhibitors → (Ticlopidine - Clopidogrel)
MOA	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 - For clopidogrel: More potent, Longer duration of action, Less frequency of administration (given once daily). Less side effects (less neutropenia). Bioavailability is unaffected by food. Clopidogrel has replaced ticlopidine
Indications	Secondary prevention of ischemic complications after myocardial infarction, ischemic stroke and unstable angina. for Clopidogrel: 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.
ADRs	Sever neutropenia Bleeding G.I.T : nausea, dyspepsia, diarrhea. Allergic reactions.
Interaction	inhibit CYT P450 causing increased plasma levels of drugs such as phenytoin and carbamazepine.

Extra helpful summaries

Antiplatelet drugs

- **Aspirin** inhibits cyclo-oxygenase irreversibly. Low doses very effectively (> 95%) inhibit platelet thromboxane (TX) A_2 synthesis and reduce the risk of thrombosis.
- **Clopidogrel** is a prodrug. Given by mouth, it irreversibly inhibits $P2Y_{12}$ receptors and thereby inhibits platelet responses to ADP. Its clinical effect is additive with aspirin. **Prasugrel** is similar.
- Antagonists of GPIIb/IIIa receptors include a monoclonal antibody (**abciximab**) and several synthetic molecules (e.g. **tirofiban**). They inhibit diverse agonists, for example ADP and TXA_2, because different pathways of activation converge on GPIIb/IIIa receptors. They are administered intravenously for short-term treatment.
- **Dipyridamole** inhibits phosphodiesterase and adenosine uptake. It is used in addition to aspirin in some patients with stroke or transient ischaemic attack.
- **Epoprostenol** (synthetic PGI_2) is chemically unstable. Given as an intravenous infusion, it acts on I prostanoid (IP) receptors on vascular smooth muscle and platelets (Ch. 17), stimulating adenylyl cyclase and thereby causing vasodilatation and inhibiting aggregation caused by any pathway (e.g. ADP or TXA_2).

Clinical uses of antiplatelet drugs

The main drug is **aspirin**. Other drugs with distinct actions (e.g. **dipyridamole**, **clopidogrel**) can have additive effects, or be used in patients who are intolerant of aspirin. Uses of antiplatelet drugs relate mainly to arterial thrombosis and include:

- *acute myocardial infarction*
- high risk of myocardial infarction, including a history of *myocardial infarction*, *angina or intermittent claudication* (see Ch. 22)
- following *coronary artery bypass grafting*
- *unstable coronary syndromes* (**clopidogrel** is added to **aspirin**)
- following coronary artery *angioplasty* and/or *stenting* (intravenous glycoprotein IIb/IIIa antagonists, e.g. **abciximab**, are used in some patients in addition to aspirin)
- *transient cerebral ischaemic attack* ('ministrokes') or *thrombotic stroke*, to prevent recurrence (**dipyridamole** can be added to **aspirin**)
- *atrial fibrillation*, if oral anticoagulation is contraindicated.

Other antiplatelet drugs such as **epoprostenol** (PGI_2; see Ch. 17) have specialised clinical applications (e.g. in *haemodialysis* or *haemofiltration*, Ch. 28, or in *pulmonary hypertension*, Ch. 22).

MCQs

1- Which of the following is arachidonic acid pathway inhibiter:
A- Dipyridamole
B- Aspirin
C- Clopidorel
D- Tirofiban

2- Which of the following is used as a secondary prevention in MI patients?
A- Dipyridamole
B- Aspirin
C- Clopidorel
D- Tirofiban

3- Choose the correct statement about ticlopidine:
A- It blocks GPIIb/IIIa receptors on platelet membrane
B- It prevents ADP mediated platelet adenylyl- cyclase inhibition
C- It inhibits thromboxane A2 synthesis in platelets
D- It does not prolong bleeding time

4- Combined therapy with dipyridamole and warfarin is recommended in subjects with the following:
A- Risk factors for coronary artery disease
B- Prosthetic heart valves
C- Cerebral thrombosis
D- Buerger's disease

5- Ticlopidine is recommended for the following except:
A- To reduce neurological sequelae of stroke
B- Transient ischaemic attacks
C- To prevent occlusion of coronary artery bypass graft

6- The following drug increases cyclic-AMP in platelets and inhibits their aggregation without altering levels of thromboxane A2 or prostacyclin:
A- Aspirin
B- Dipyridamole
C- Abciximab

7- Indications for the use of antiplatelet drugs include the following except:
A- Secondary prophylaxis of myocardial infarction
B- Unstable angina pectoris
C- Disseminated intravascular coagulation
D- Stroke prevention in patients with transient ischaemic attacks

8- A 50-year-old man presents to the emergency depart- ment with acute-onset left-sided crushing chest pain. An ECG shows ST elevations in II, III, and aVF. He is immediately rushed to the catheterization lab and three stents are placed. Because of the insertion of stents, he has started on ticlopidine. Which of the following is a common side effect of ticlopidine?
A- Gastric ulcers
B- Neutropenia
C- Osteoporosis
D- Seizures

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

Thank you for checking our team!

Pharmacology 435

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Sources:

1. 435's slides.
2. Rang & Dale's pharmacology, chapter 24, 7th edition.
3. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 20, 5th edition.
4. Basic & Clinical Pharmacology by Katzung, chapter 34, 12th edition.