ANTI-PLATELET DRUGS

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Learning objectives

By the end of this lecture, students should be able to:

- 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.

Platelets and vessels

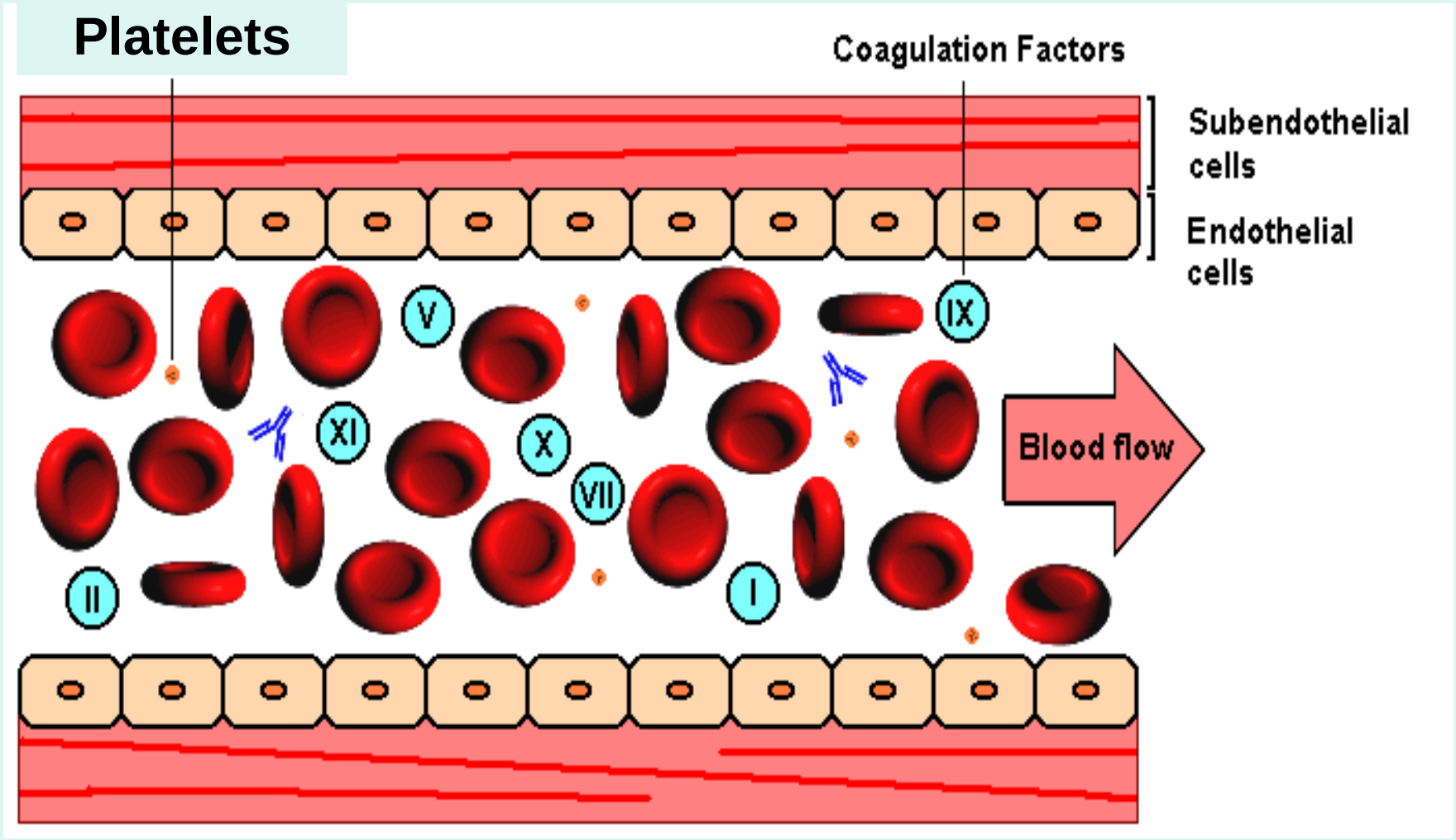
- In healthy vessels, nitric oxide and prostacyclin (released by endothelial cells lining the blood vessels) inhibit platelets aggregation.

- 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
- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)


Platelets
Coagulation Factors
Subendothelial cells
Endothelial cells
V
IX
XI
X
VII
II
I
Blood flow

Platelet Adhesion and Activation

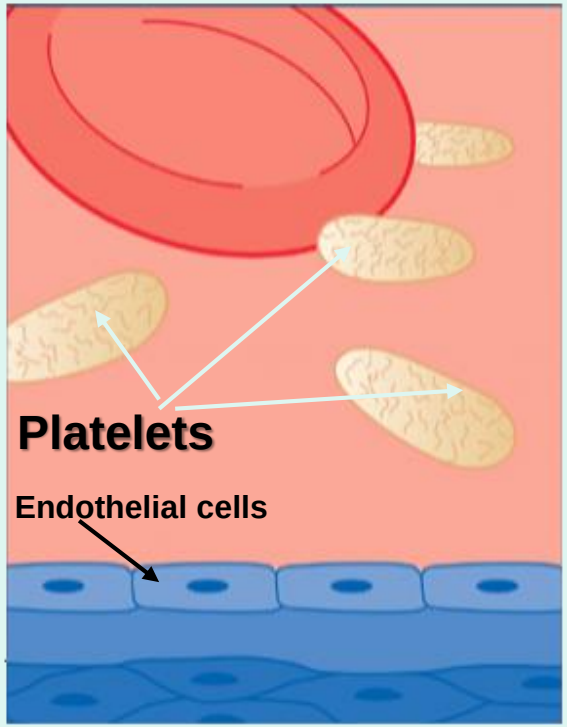
Healthy vascular endothelium

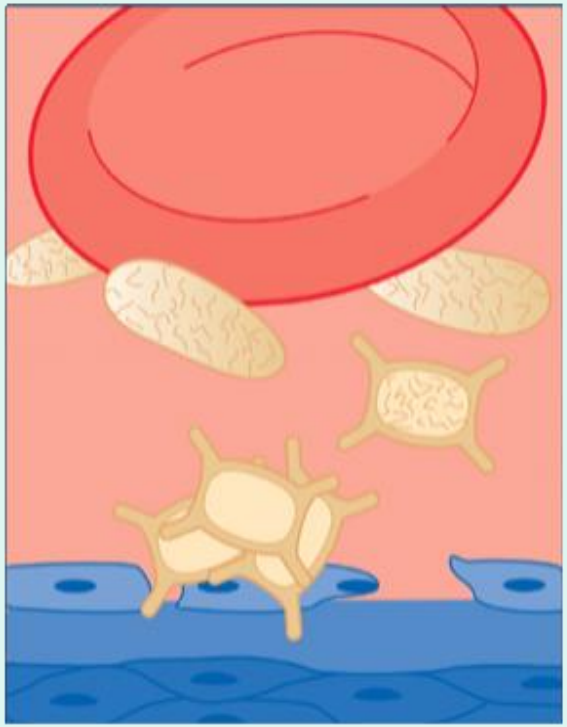
chemical mediators such as prostacyclin (PGI_2), nitric oxide act as inhibitors of platelet aggregation

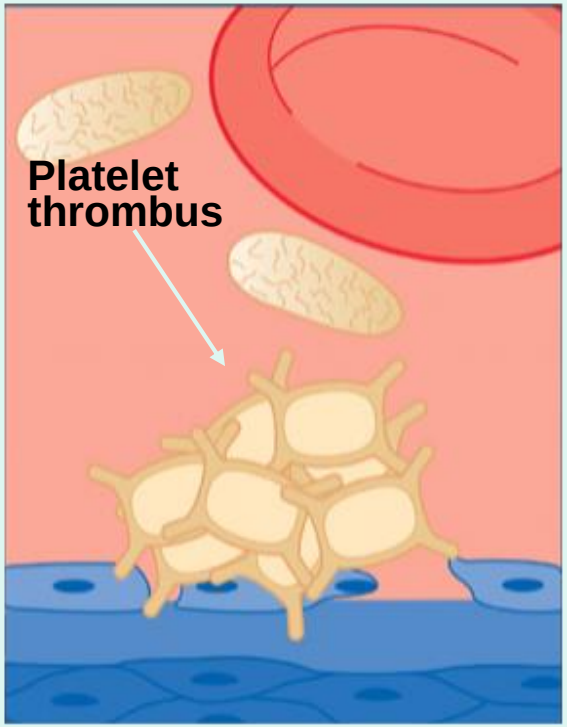
Injured endothelium

Platelets adhere to damaged endothelium become activated

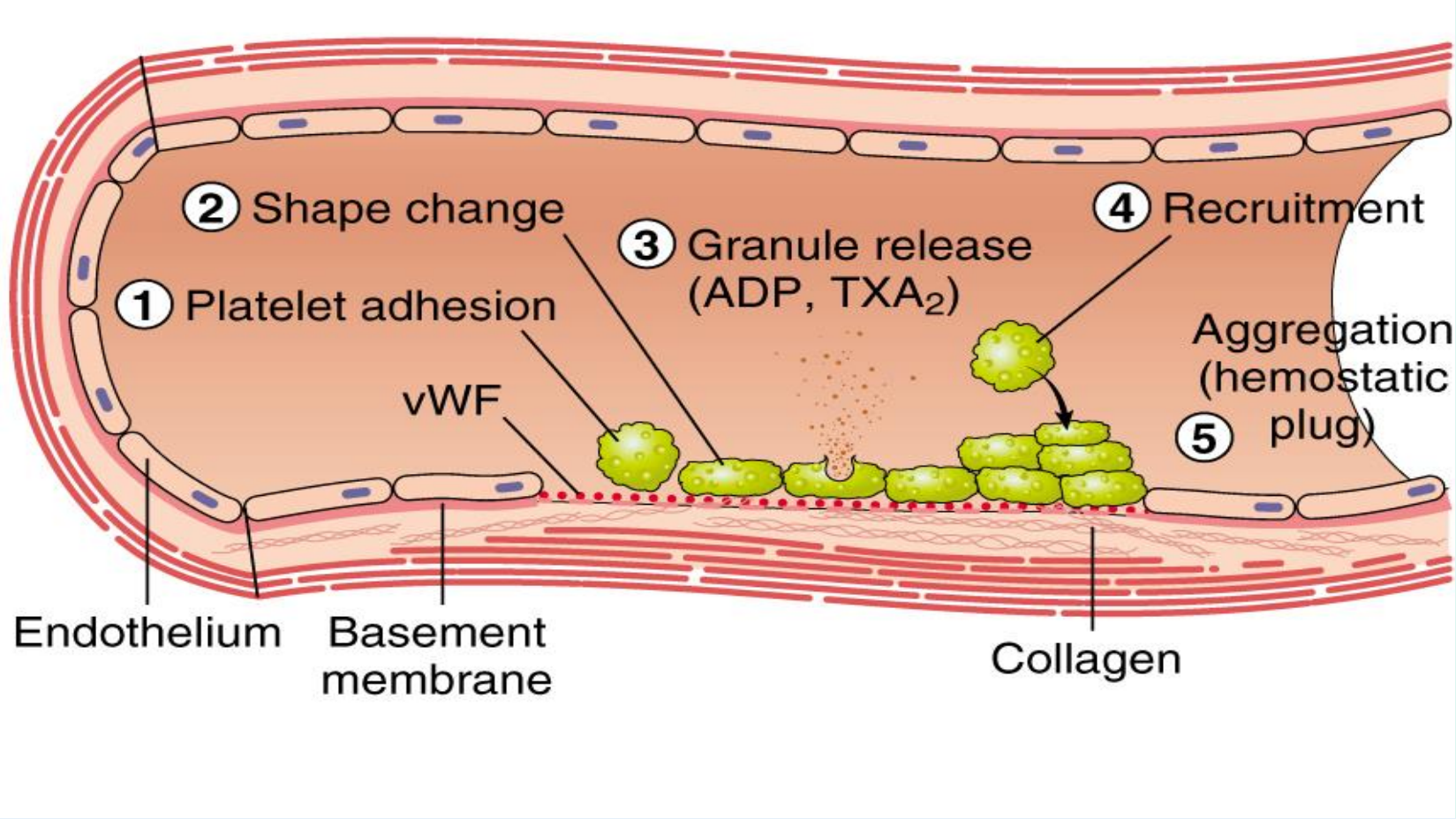
Aggregation of platelets into a thrombus





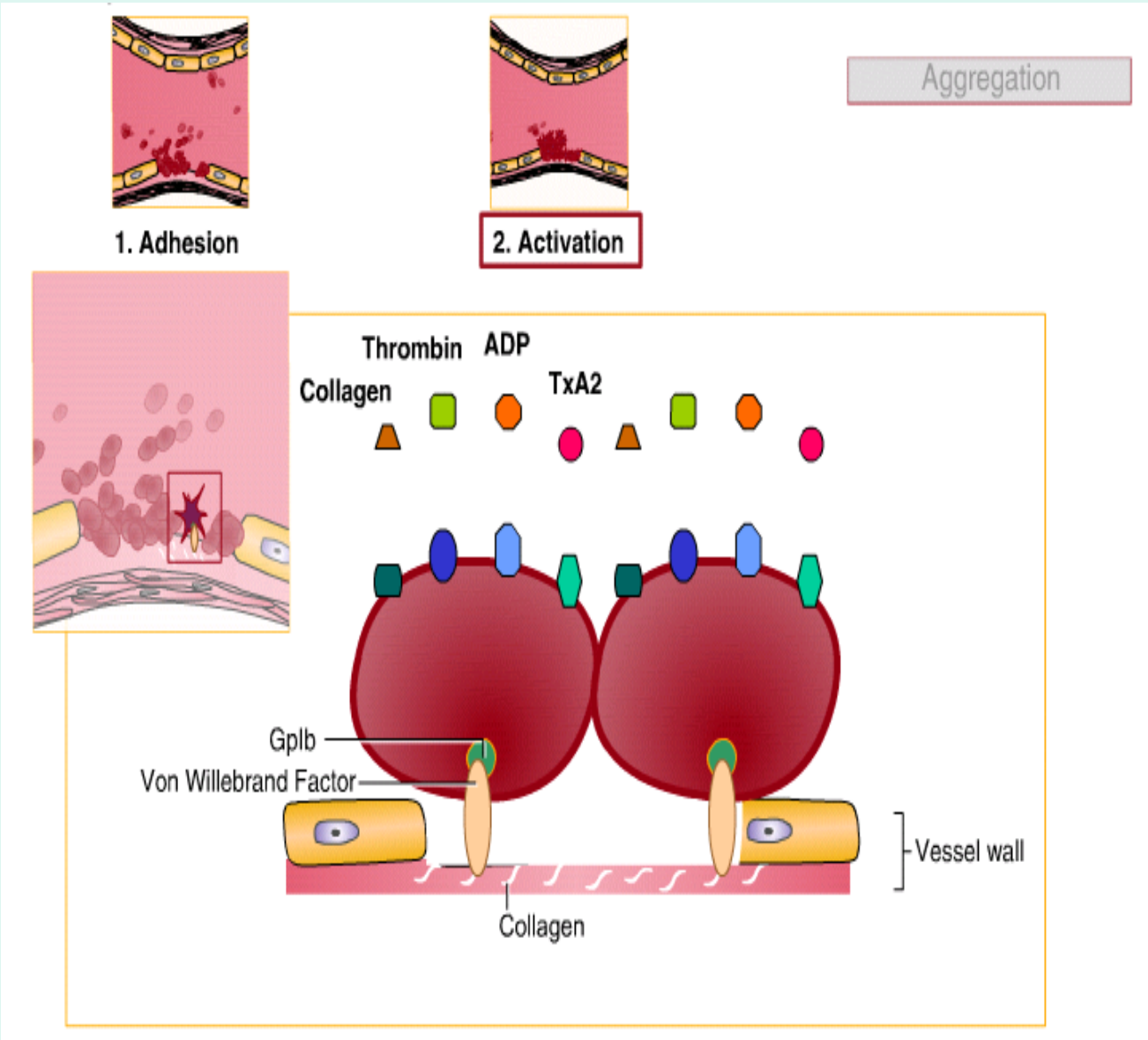


In case if there is an endothelial injury



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**

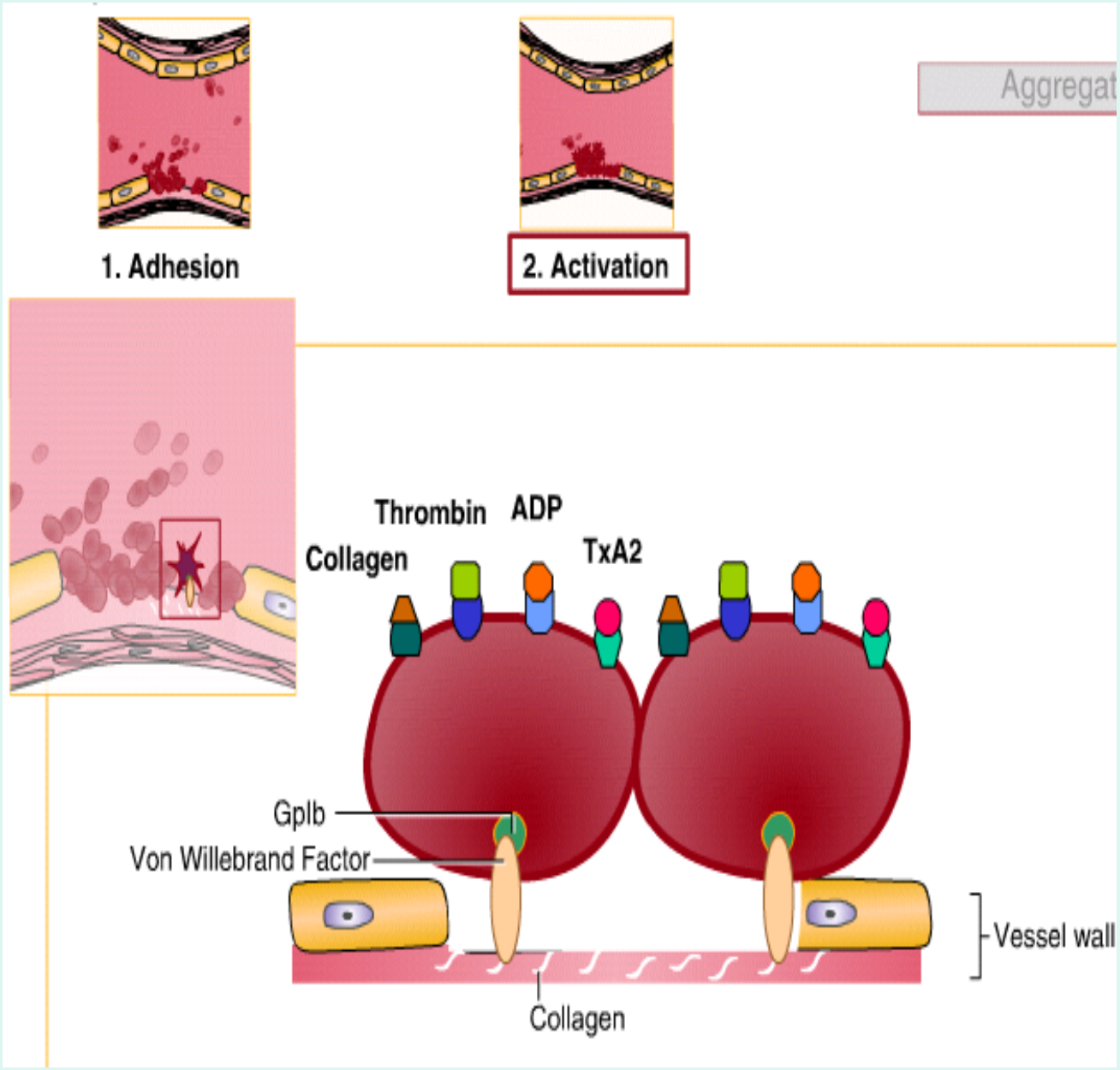
The role of platelets in hemostasis



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

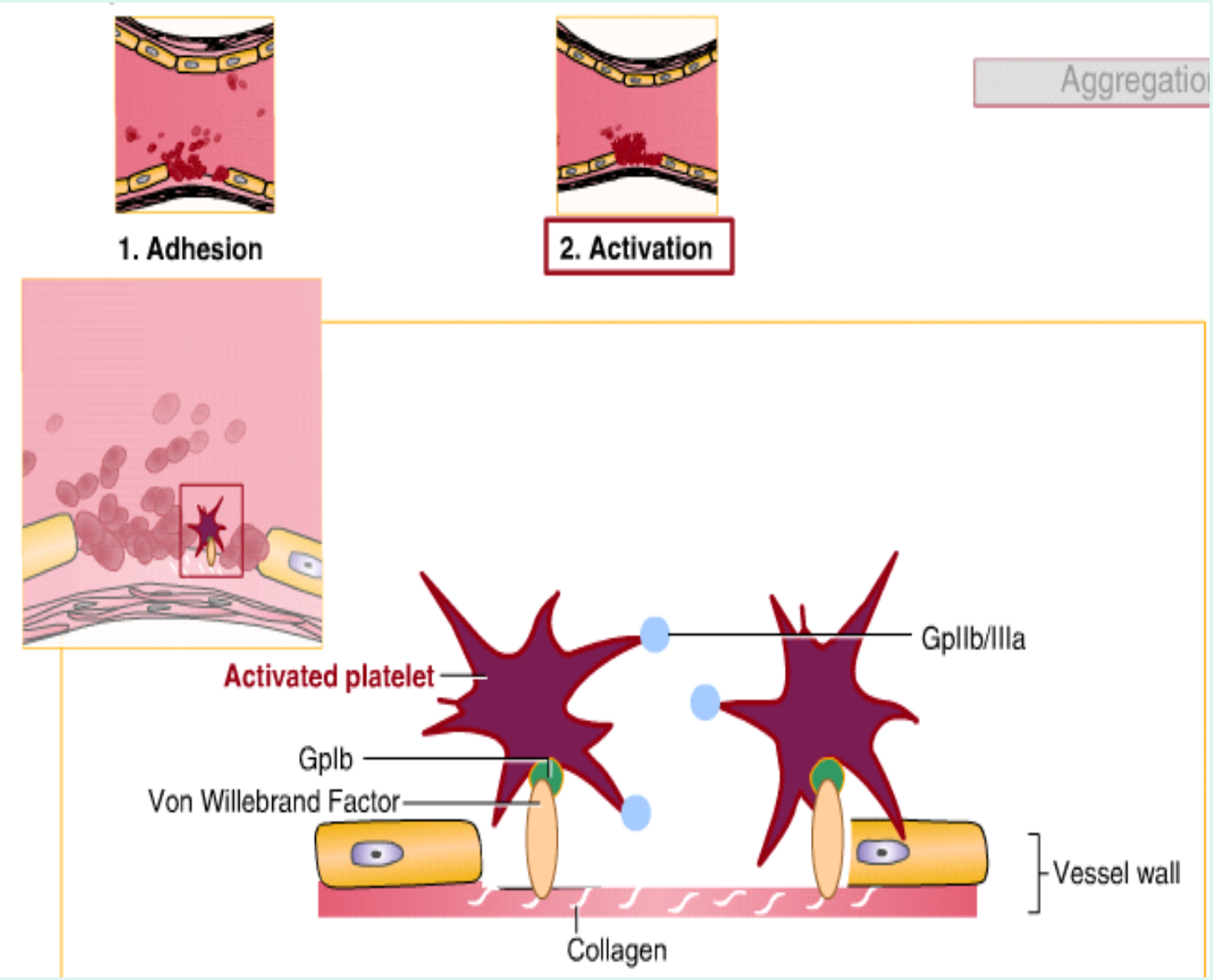
- The other site of the "rod-formed" von Willebrand factor binds to the platelet receptor GPIb and platelets are thereby anchored to the site of the injured endothelium. This is called adhesion.

The role of platelets in hemostasis



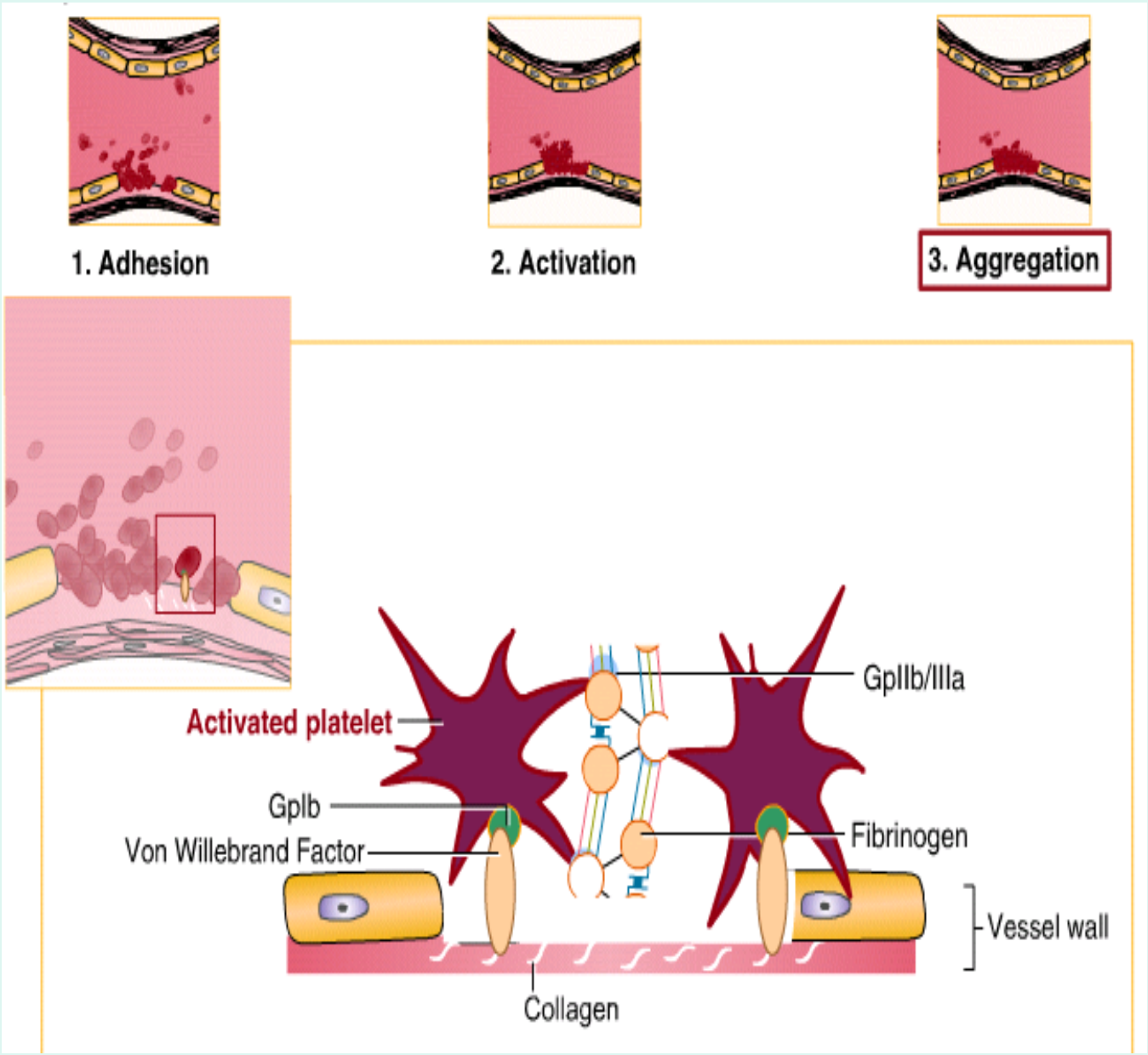
-**Following adhesion, agonists such as collagen, thrombin, ADP, and thromboxane A_2 activate platelets by binding to their respective platelet receptors.**

The role of platelets in hemostasis



- 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 role of platelets in hemostasis



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.

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.

Classification of antiplatelet drugs

- **Arachidonic acid pathway inhibitors**

  e.g. Aspirin

- **Phosphodiesterase inhibitors**

  e.g. Dipyridamole

- **ADP inhibitors**

  e.g. Ticlopidine - Clopidogrel

- **Glycoprotein IIb/IIIa inhibitors**

  e.g. Abciximab – Eptifibatide -Tirofiban

Arachidonic acid pathway inhibitors

Aspirin (Acetylsalicylic Acid)

Mechanism of action

- **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).**

Uses of aspirin

- **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 (81 mg enteric coated tablet/day) is the most common dose used to prevent a heart attack or a stroke.

Side effects of aspirin

- Risk of peptic ulcer.
- Increased incidence of GIT bleeding (aspirin prolongs bleeding time)

ADP pathway inhibitors

Ticlopidine & Clopidogrel

Mechanism of action

- 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).

ADP pathway inhibitors

- 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.

Adverse Effects of ADP inhibitors

- **Sever neutropenia,** CBC should be done monthly during treatment.
- **Bleeding** (prolong bleeding time).
- **G.I.T :** nausea, dyspepsia, diarrhea.
- **Allergic reactions.**

Drug interaction of ADP inhibitors :

- inhibit CYT P450 causing increased plasma levels of drugs such as phenytoin and carbamazepine.

Clopidogrel

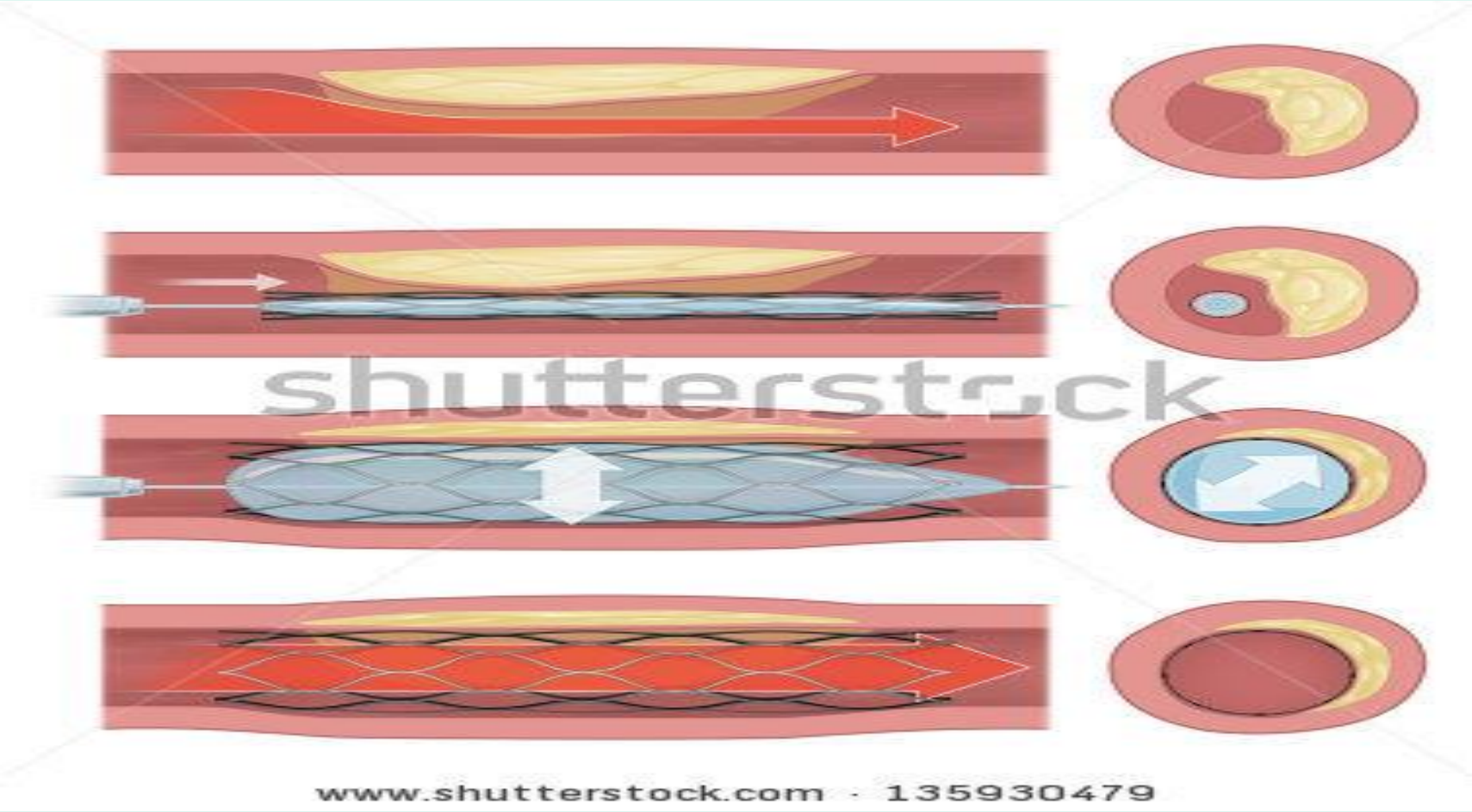
- is more potent than ticlopidine
- Longer duration of action than ticlopidine
- Less frequency of administration (given once daily).
- Less side effects **(less neutropenia).**
- Bioavailability is unaffected by food.
- **Clopidogrel has replaced ticlopidine**

Indications for 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.

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

- 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**

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

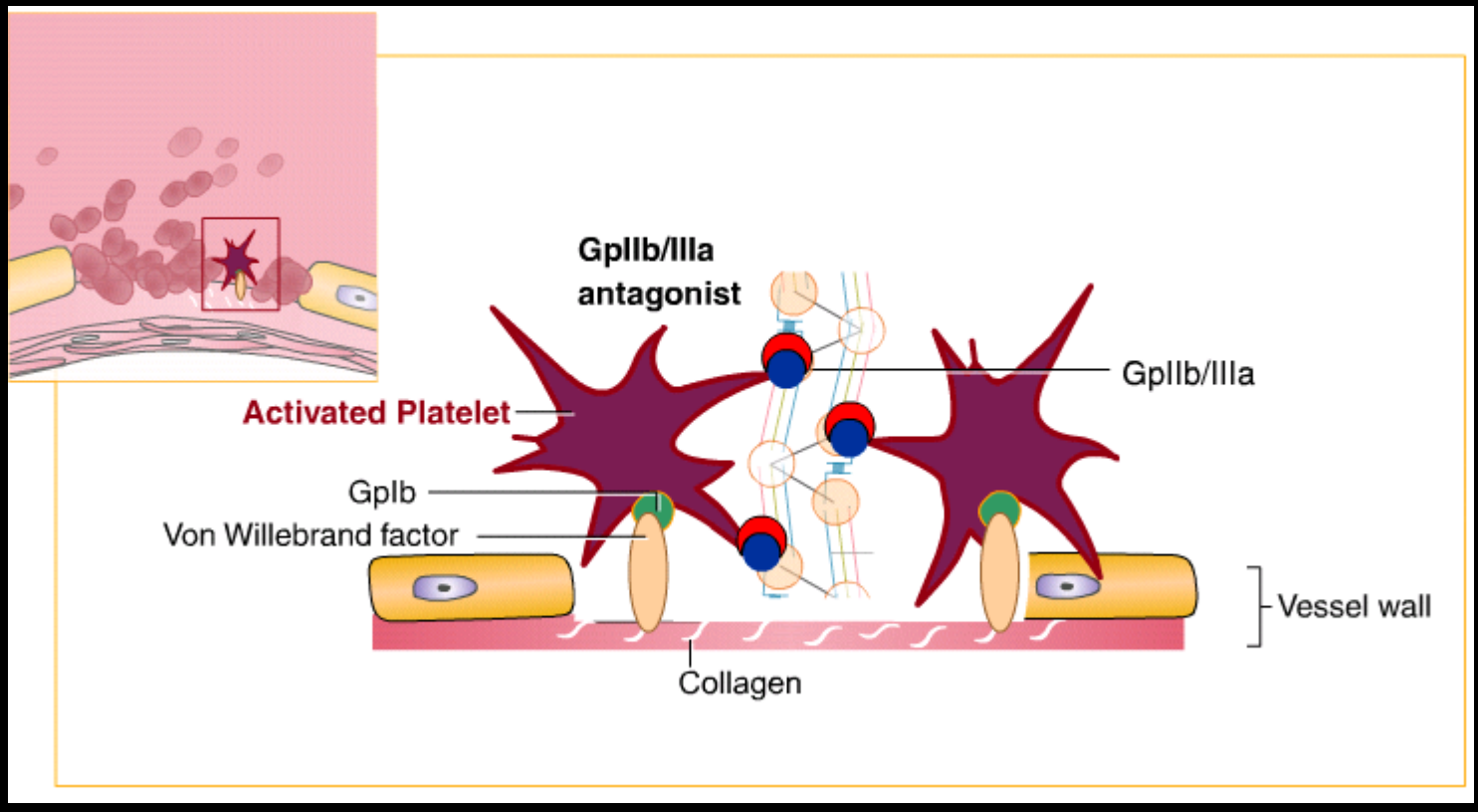
Abciximab, tirofiban & eptifibatide

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

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**

GPIIb/IIIa-receptor antagonists – mechanism of action



Abciximab

- **Given I.V. infusion.**

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

Tirofiban & Eptifibatide

- **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).**

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

Dipyridamole

- **It is a vasodilator**

Mechanism of action

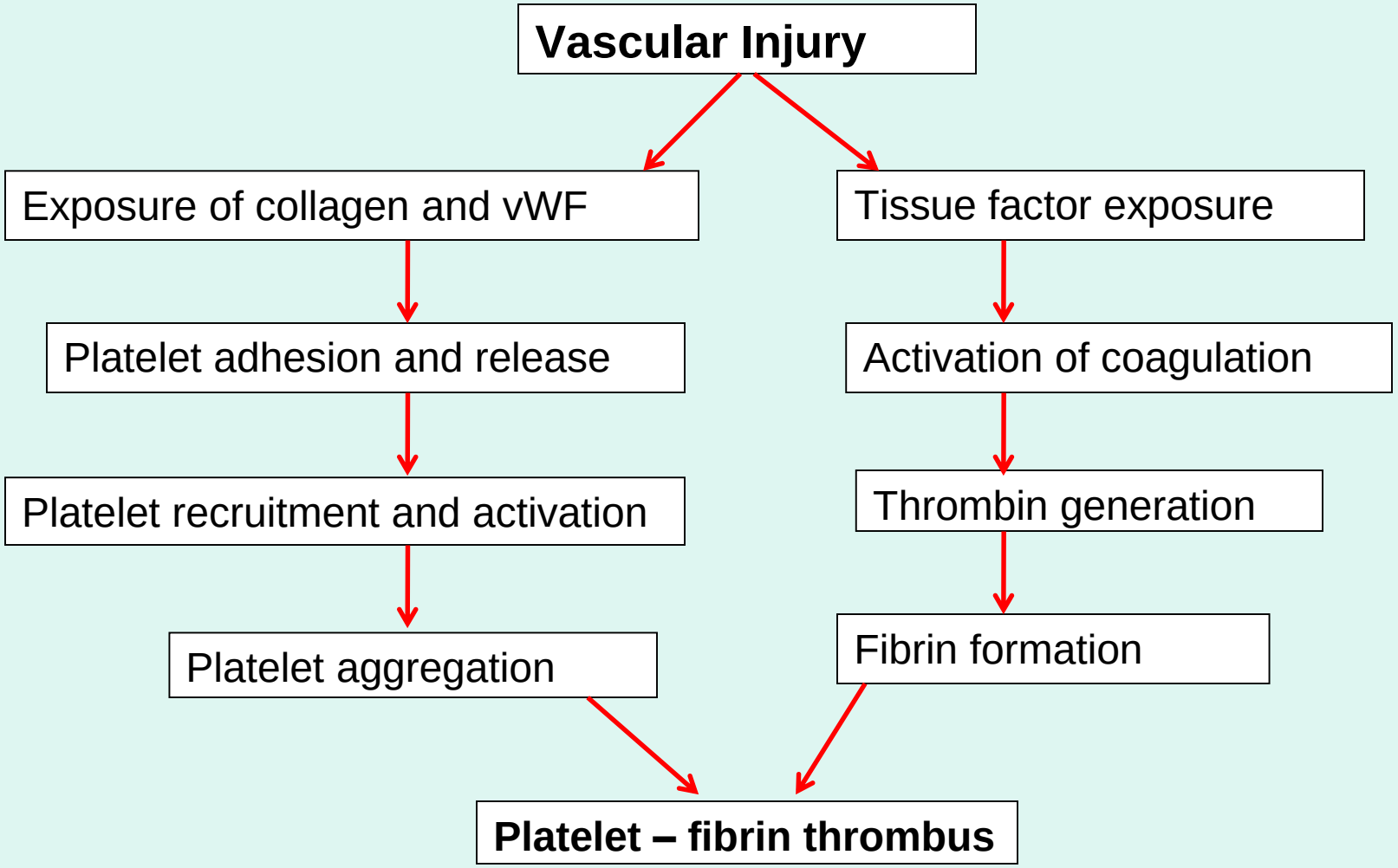
Inhibits phosphodiestrase (an enzyme that normally break down cAMP) thus increases cAMP and decreased synthesis of thromboxane A2 and other platelet aggregating factors.

Uses of dipyridamole

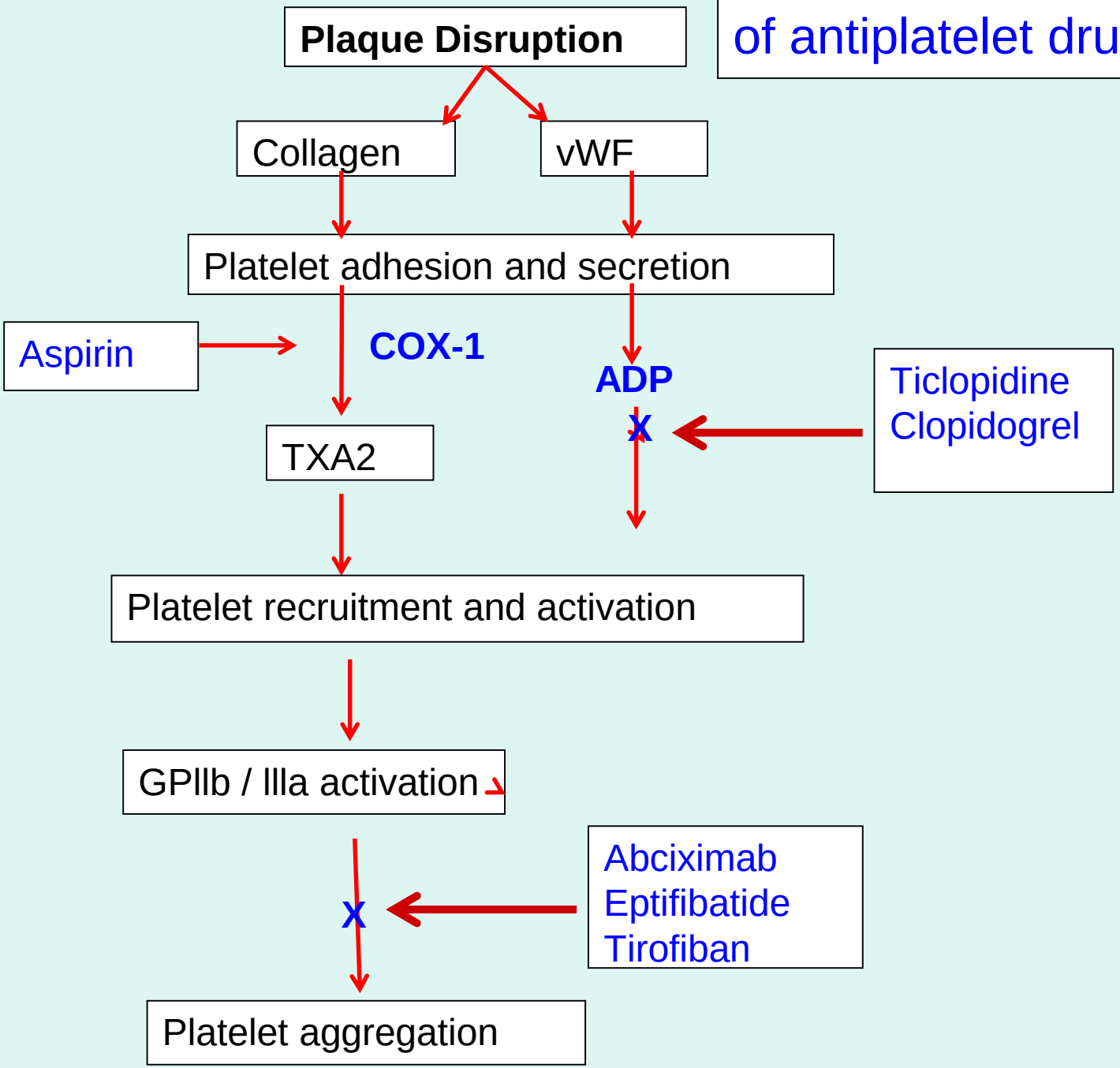
- Given orally.
- Adjunctive therapy for prophylaxis of thromboembolism in cardiac valve replacement (with warfarin).
- Secondary prevention of stroke and transient ischemic attack (with aspirin).

Adverse Effects:

- Headache
- Postural hypotension

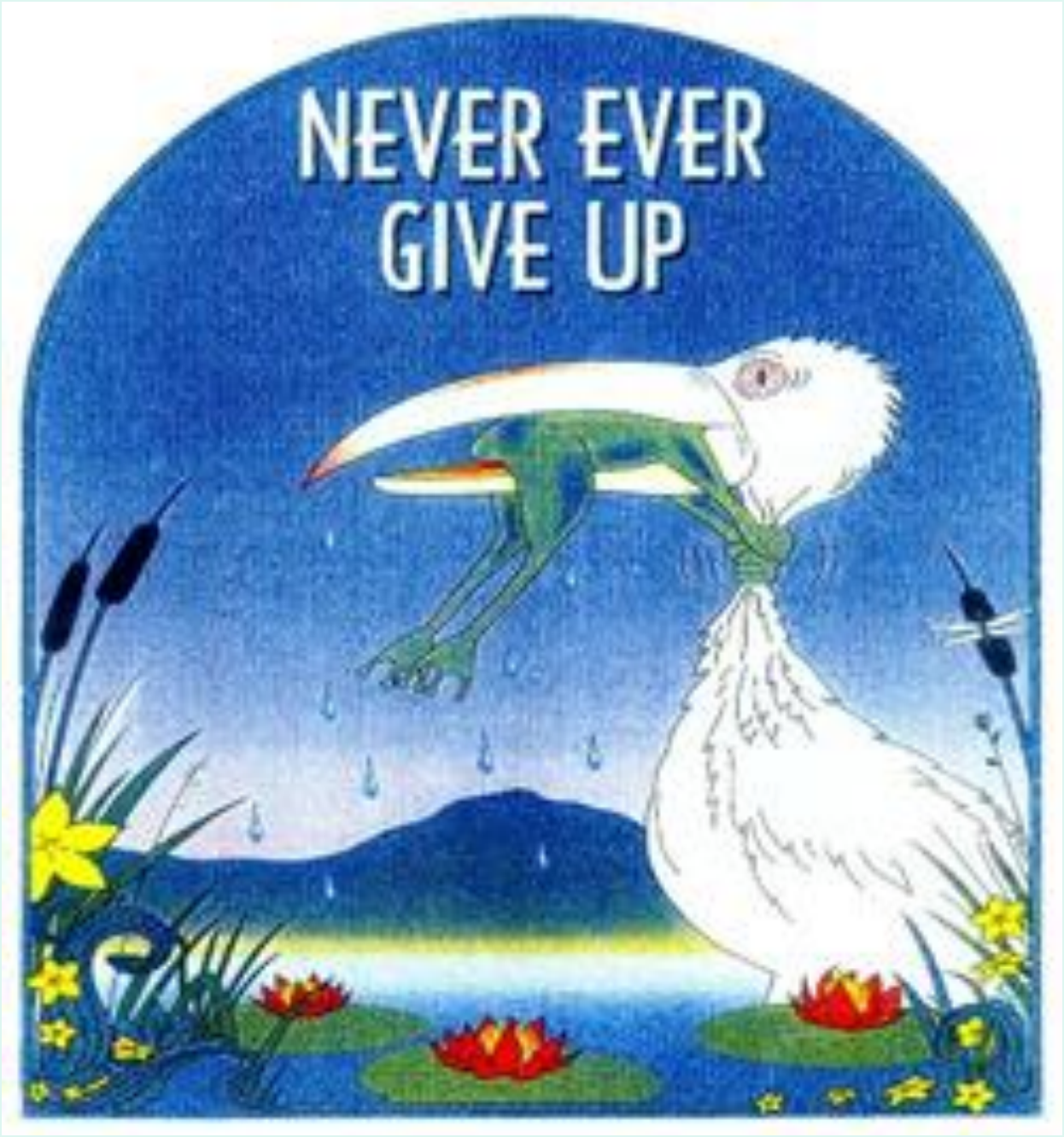

Vascular Injury
Exposure of collagen and vWF
Tissue factor exposure
Platelet adhesion and release
Activation of coagulation
Platelet recruitment and activation
Thrombin generation
Platelet aggregation
Fibrin formation
Platelet – fibrin thrombus

Mechanisms of action of antiplatelet drugs



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


NEVER EVER
GIVE UP