

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**

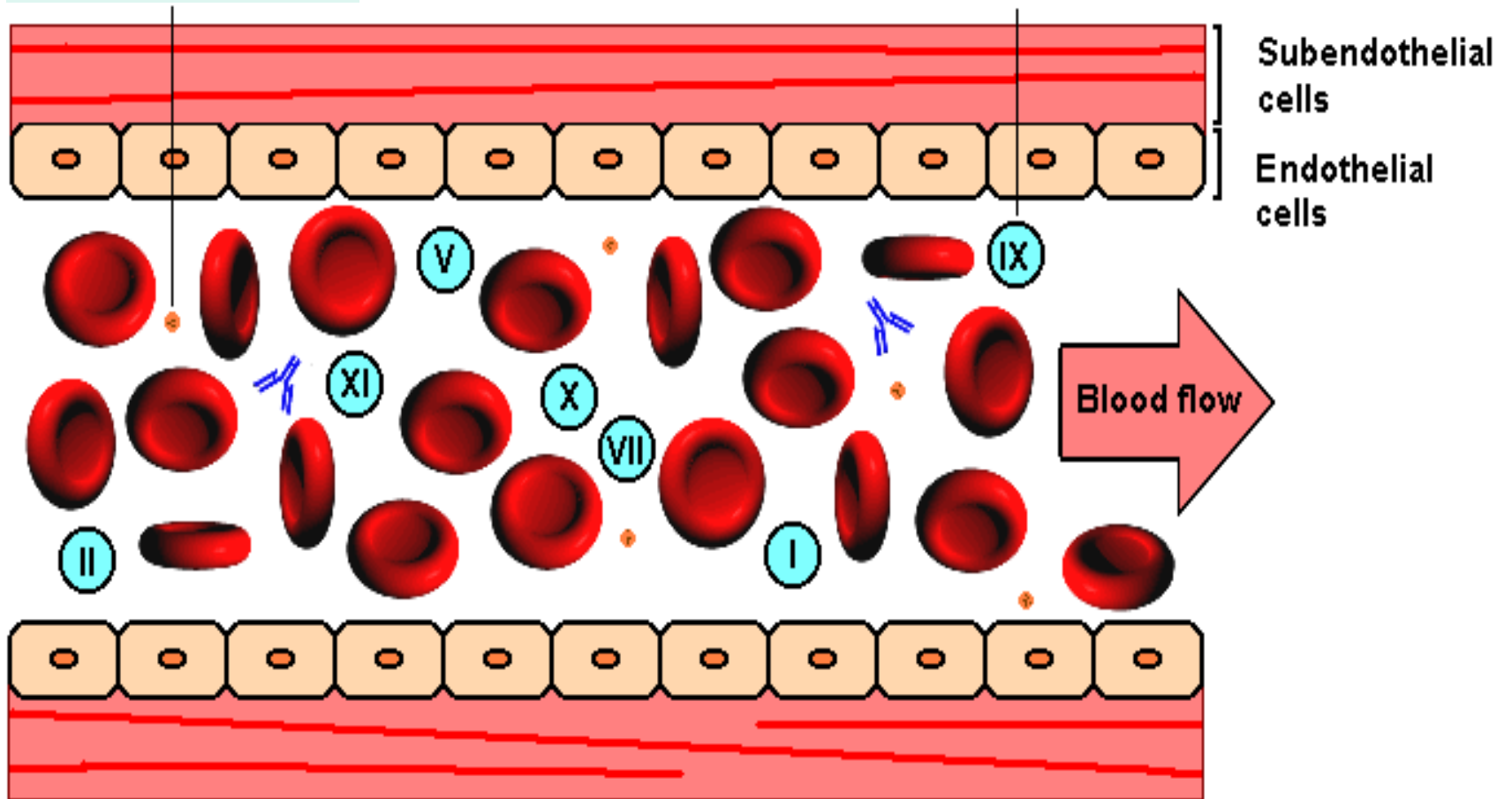
Clot

- **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

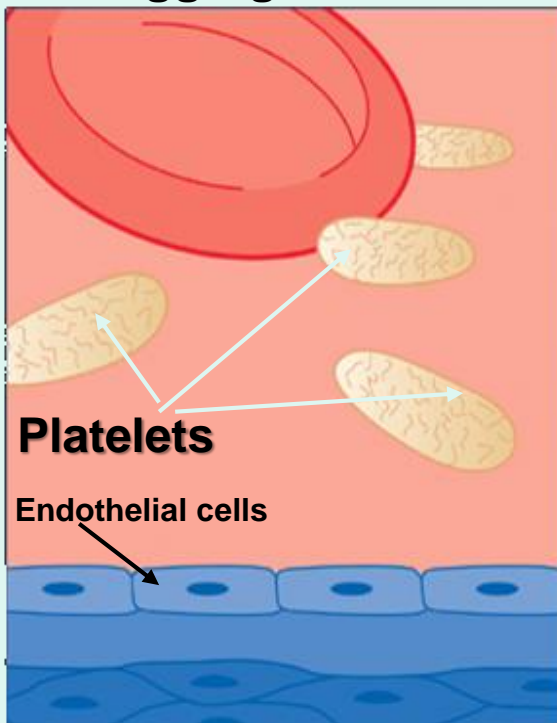
Coagulation Factors



Platelet Adhesion and Activation

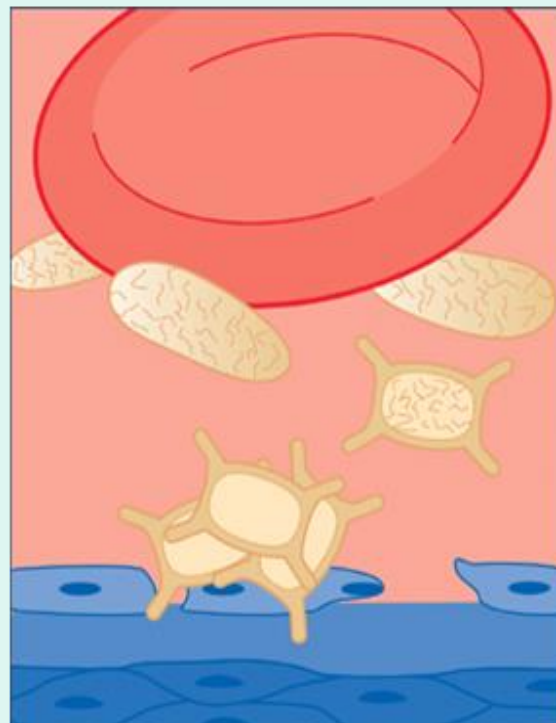
Healthy vascular endothelium

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

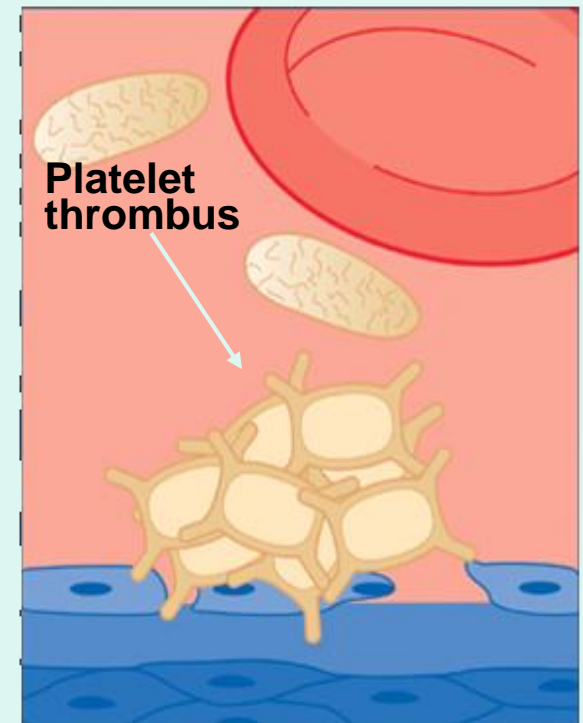


Injured endothelium

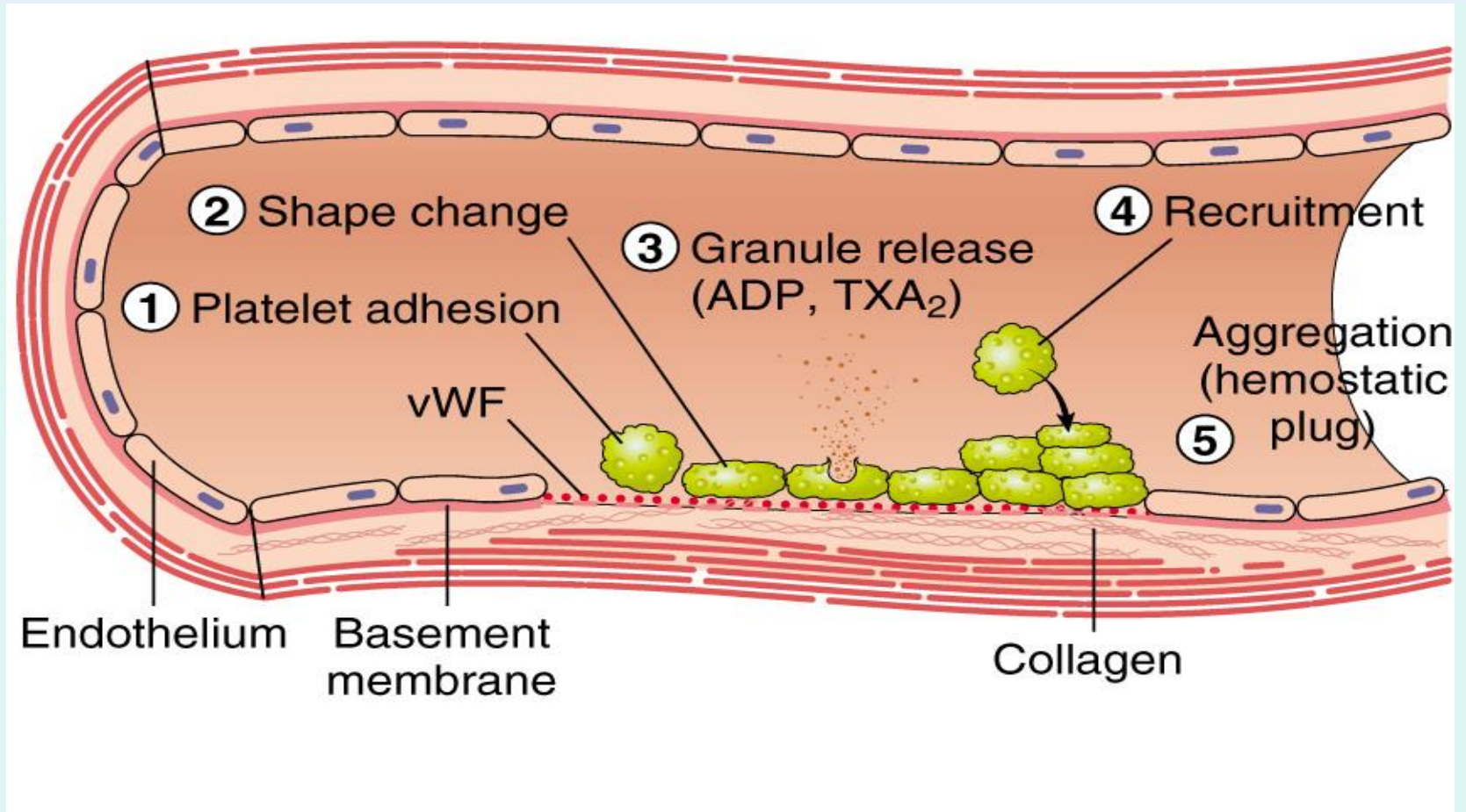
Platelets adhere to damaged endothelium become activated



Aggregation of platelets into a thrombus

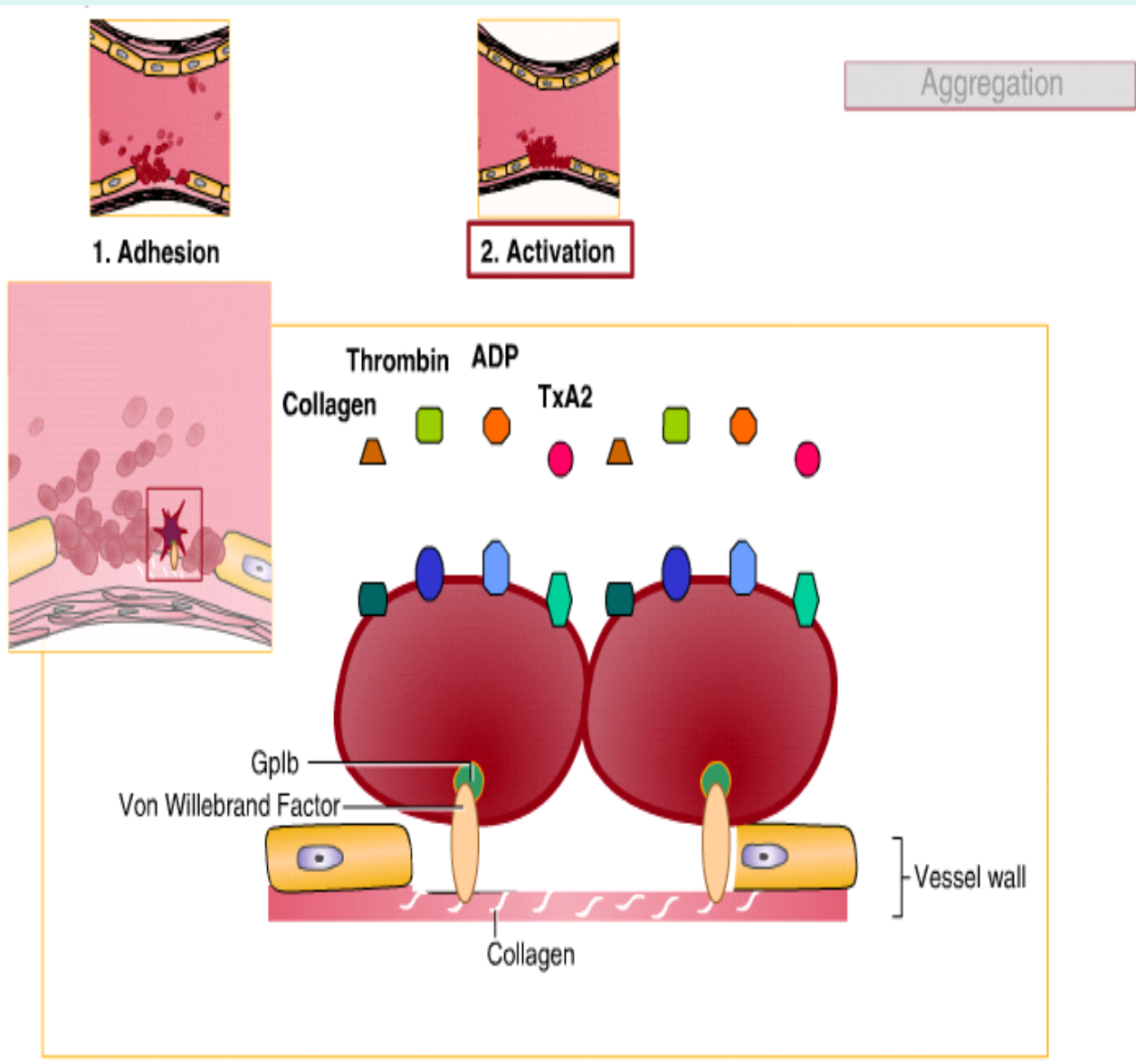


In case if there is an endothelial injury



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



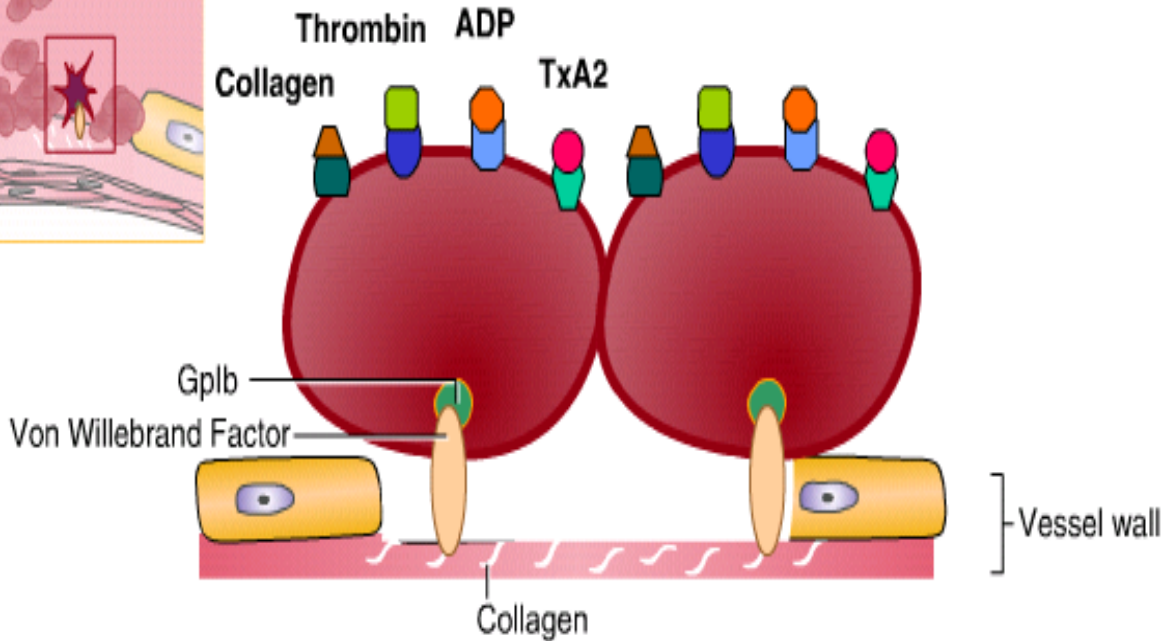
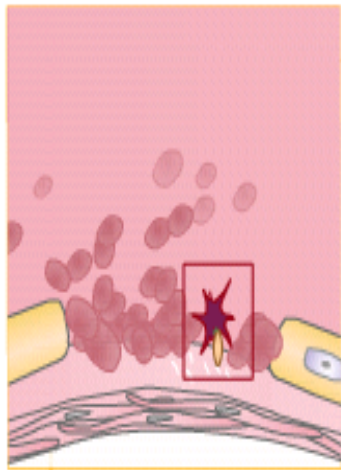
1. Adhesion



2. Activation

Aggregat

-Following adhesion, agonists such as **collagen**, **thrombin**, **ADP**, and **thromboxane A₂** activate platelets by binding to their respective platelet receptors.



The role of platelets in hemostasis



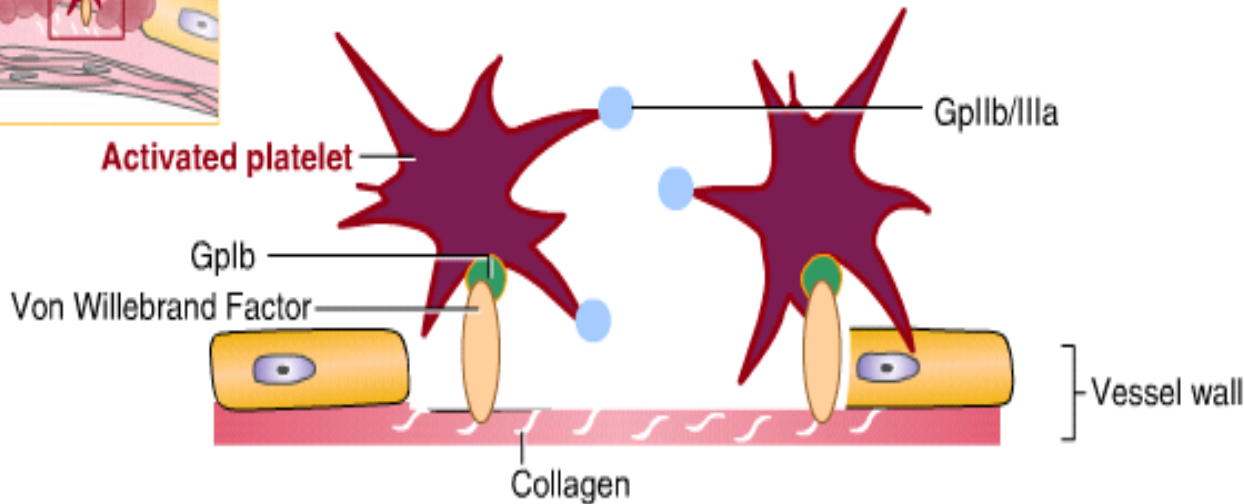
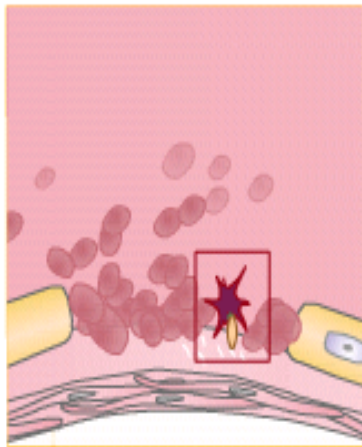
1. Adhesion



2. Activation

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**



The role of platelets in hemostasis



1. Adhesion

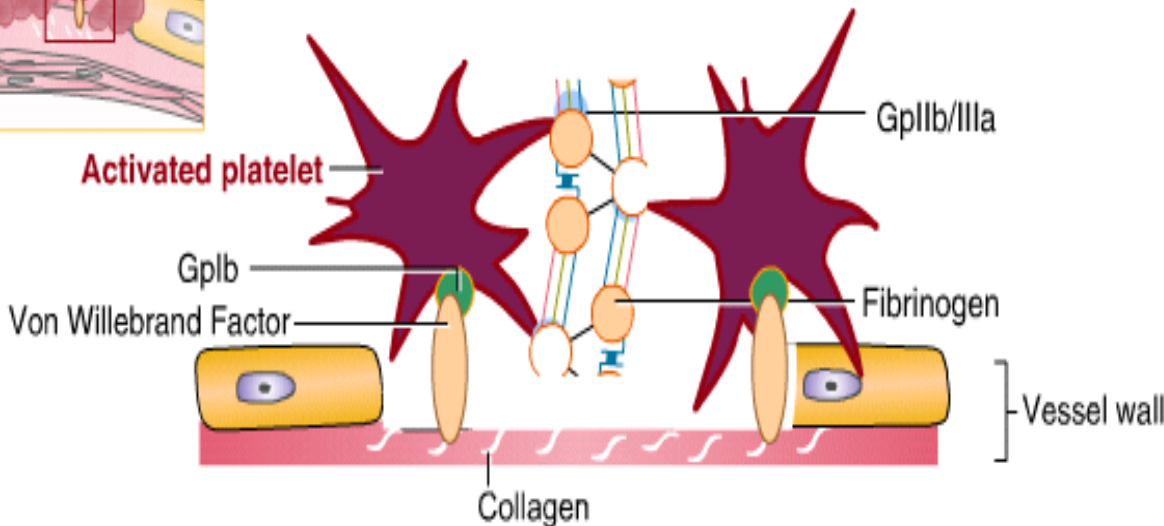


2. Activation



3. Aggregation

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 But not prostacyclin (PGI₂) 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.

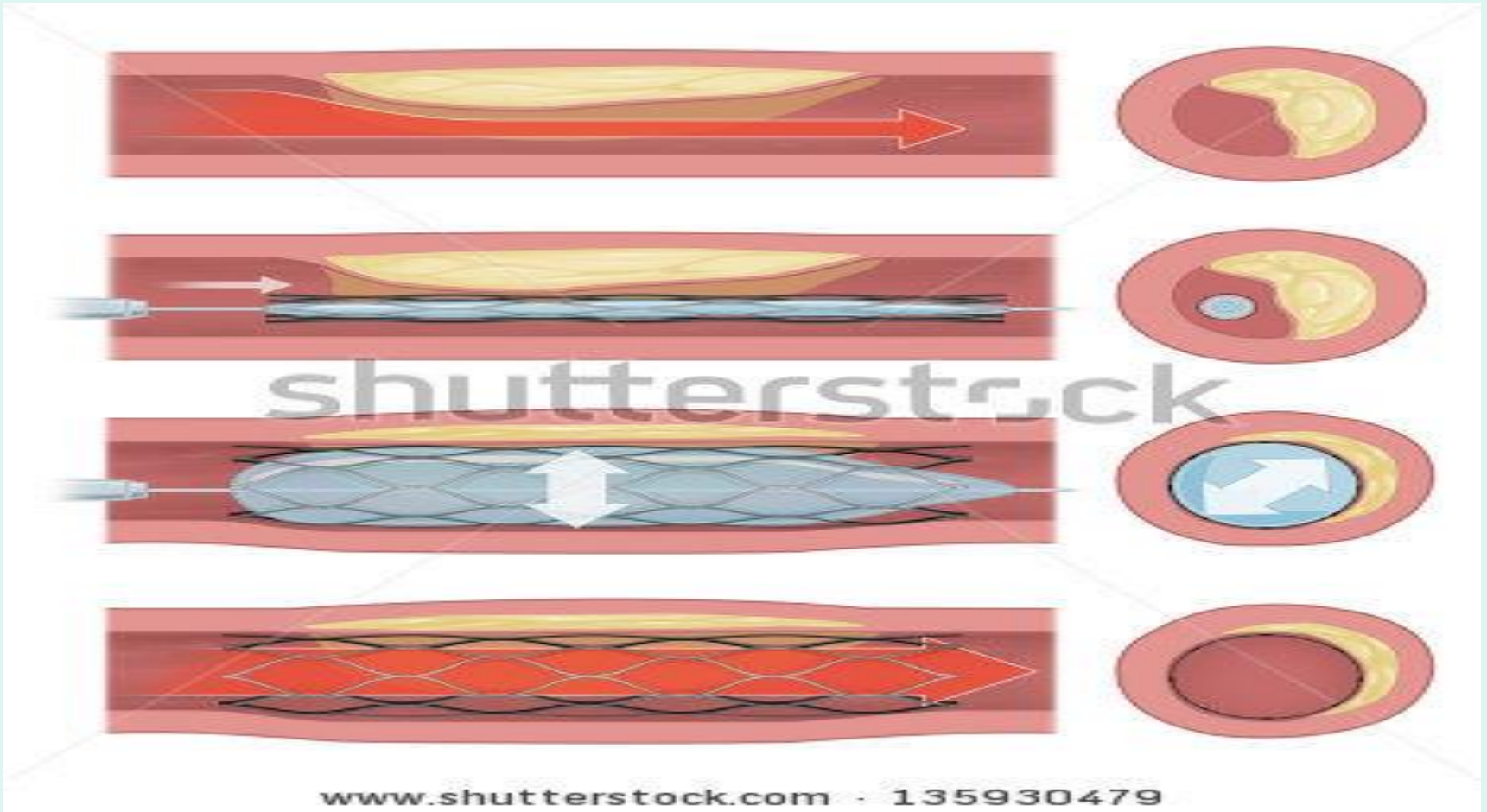
Clopidogrel

- 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

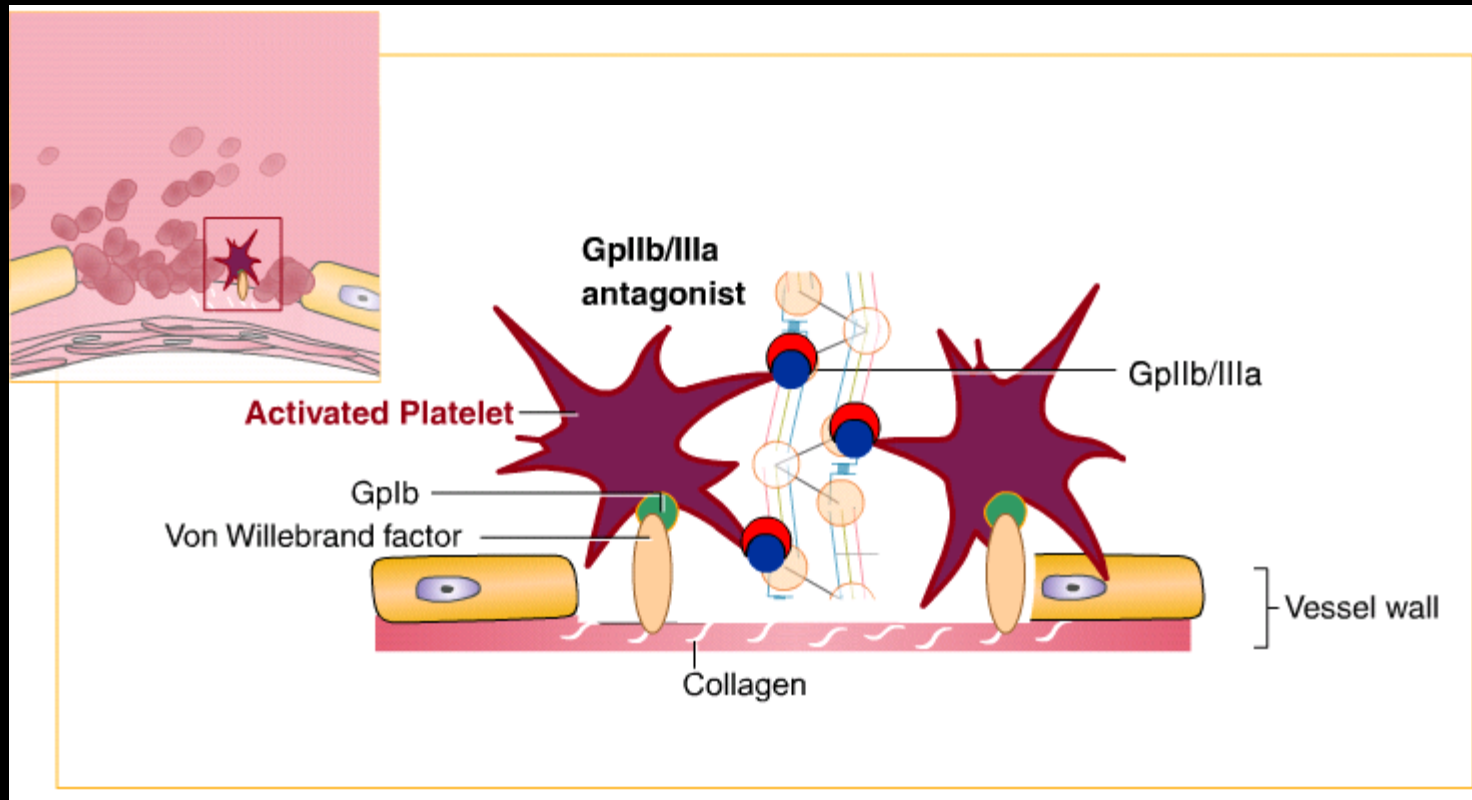
Abciximab, tirofiban & eptifibatide

- **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)
- **Eptifibatide** (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 phosphodiesterase (an enzyme that normally break down cAMP) thus increases cAMP and decreased synthesis of thromboxane A₂ and other platelet aggregating factors.

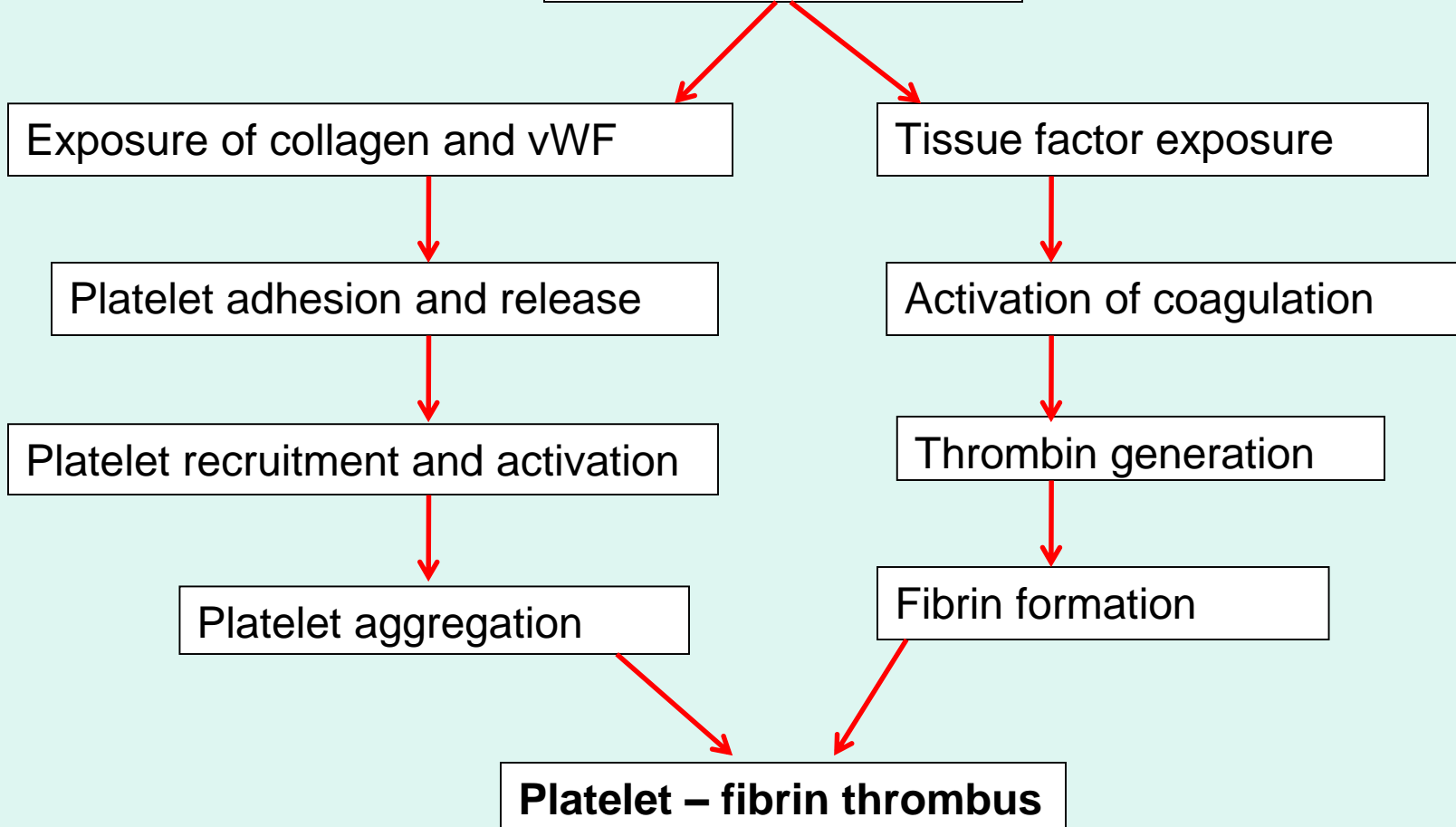
Uses of dipyridamole

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

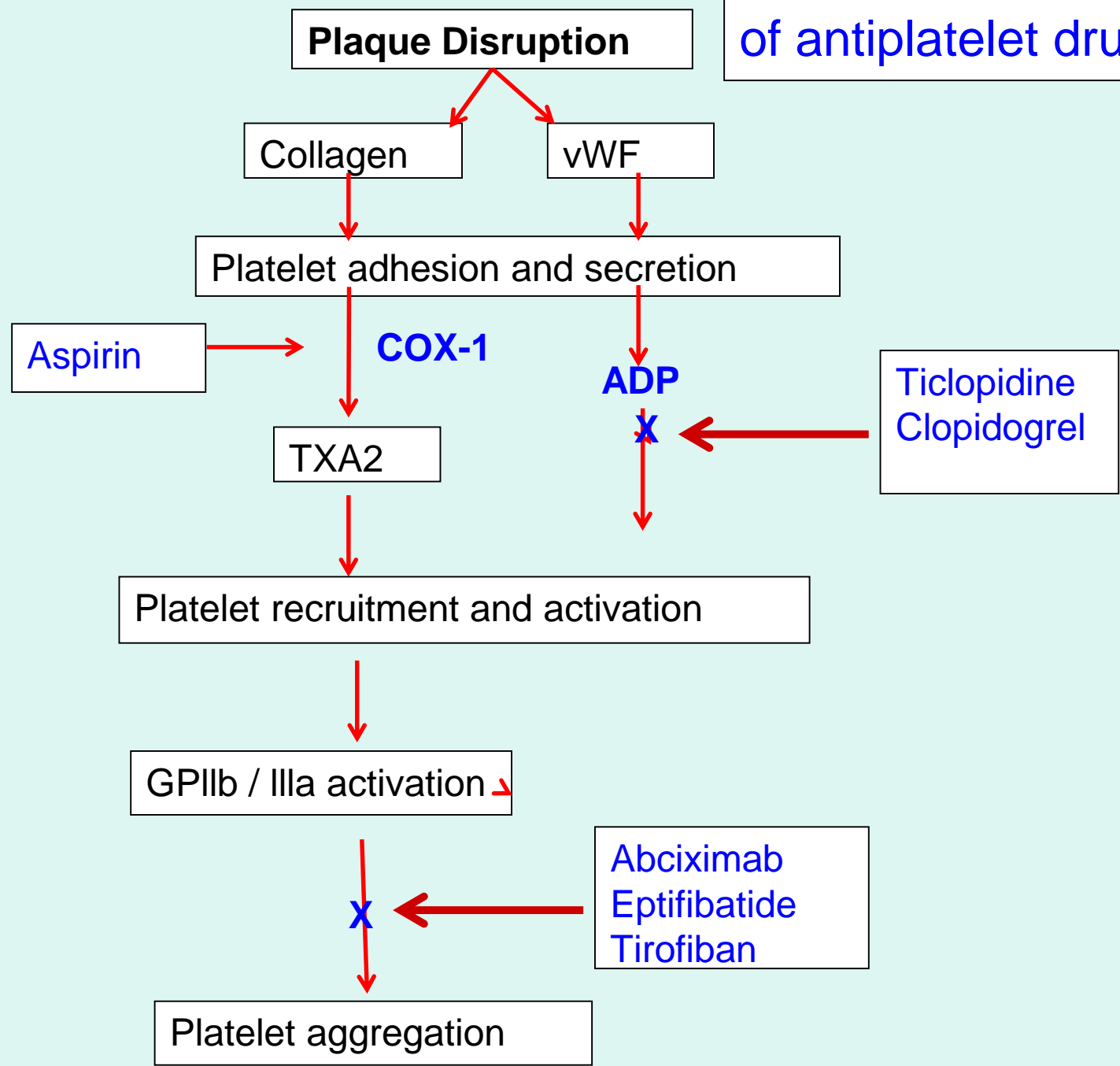
Adverse Effects:

- **Headache**
- **Postural hypotension**

Vascular Injury



Mechanisms of action of antiplatelet drugs



SUMMARY

Mechanism of action	Drug	ROA
Inhibition of thromboxane A ₂ synthesis via inhibiting COX-1	Aspirin	Oral
ADP receptor antagonists	Clopidogrel Ticlopidine	Oral
GP IIb / IIIa receptor antagonists	Abciximab Tirofiban Eptifibatide	I.V.
Phosphodiesterase (PDE) inhibitor	Dipyridamole	Oral

NEVER EVER
GIVE UP

