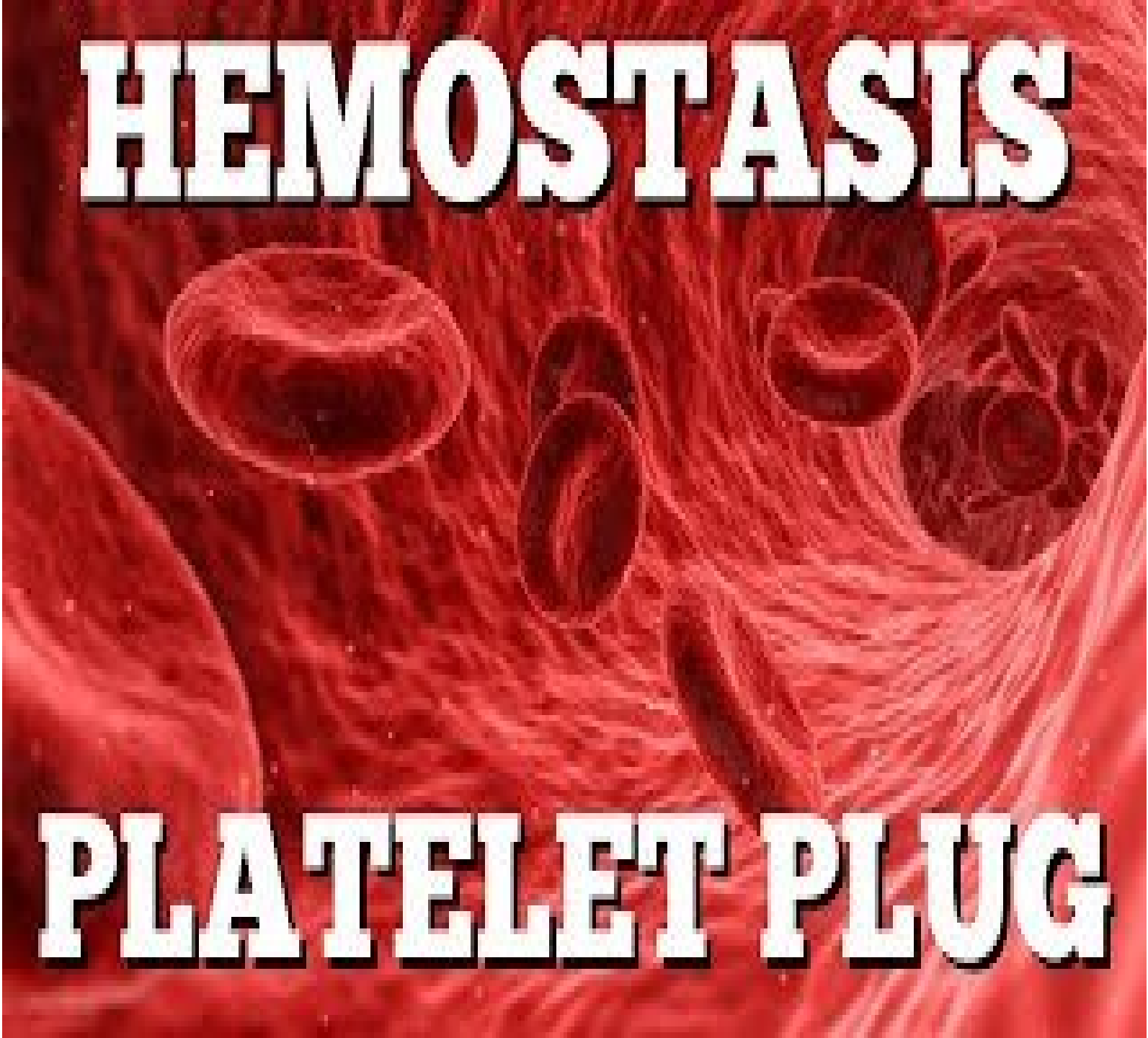


Anticoagulants & antiplatelets

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BCPS

A microscopic view of blood vessels, showing red blood cells and platelets. The vessels are filled with a dense network of red blood cells, and several platelets are visible, some of which are aggregating to form a platelet plug.

HEMOSTASIS

PLATELET PLUG

INTRODUCTION

Thrombosis, the formation of an unwanted clot within a blood vessel, is the most common abnormality of hemostasis. Thrombotic disorders include acute myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE), and acute ischemic stroke. These conditions are treated with drugs such as anticoagulants and fibrinolytics. Bleeding disorders related to the failure of hemostasis are less common than thromboembolic disorders. Bleeding disorders include hemophilia, which is treated with transfusion of recombinant factor VIII and vitamin K deficiency.

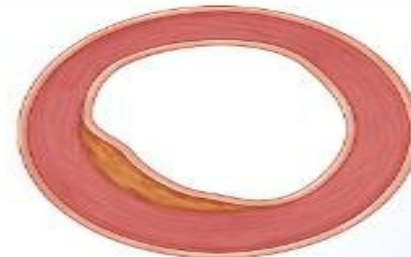
ANTICOAGULANTS
ANTIPLATELETS
THROMBOLYTICS
TREATMENT OF BLEEDING

NOMANCLATURE AND MAIN HISTOLOGY	SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS	EARLIEST ONSET	MAIN GROWTH MECHANISM	CLINICAL COLLERLATION
Initial lesion • histologically "normal" • macrophage infiltration • isolated foam cells		from first decade		clinically silent
Fatty streak mainly intracellular lipid accumulation				
Intermediate lesion • intracellular lipid accumulation • small extracellular lipid pools		from third decade	growth mainly by lipid addition	
Atheroma • intracellular lipid accumulation • core of extracellular lipid				
Fibroatheroma • single or multiple lipid cores • fibrotic/calcific layers		from fourth decade	increased smooth muscle and collagen increase	clinically silent or overt
Complicated lesion • surface defect • hematoma-hemorrhage • thrombosis			thrombosis and/or hematoma	

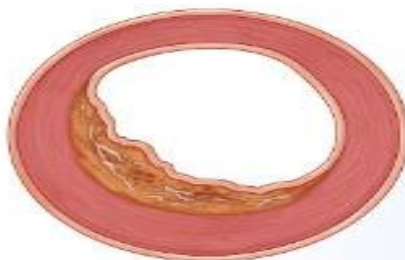
Thrombus Versus Embolus

A clot that adheres to a vessel wall is called a “thrombus,” whereas an intravascular clot that floats in the blood is termed an “embolus.” Thus, a detached thrombus becomes an embolus. Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients. Arterial thrombosis most often occurs in medium-sized vessels(ESCHEMIC STROK) rendered thrombogenic by atherosclerosis. Arterial thrombosis usually consists of a platelet-rich clot . In contrast, venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade. Venous thrombosis typically involves a clot that is rich in fibrin(PE), with fewer platelets than are observed with arterial clots

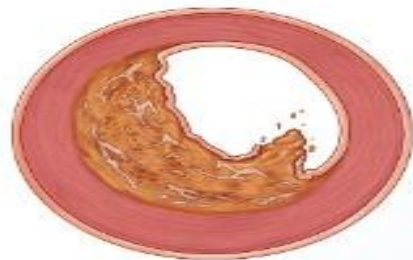
Atherosclerosis - narrowing of the arteries



Plaque begins to form in the lining of the artery.



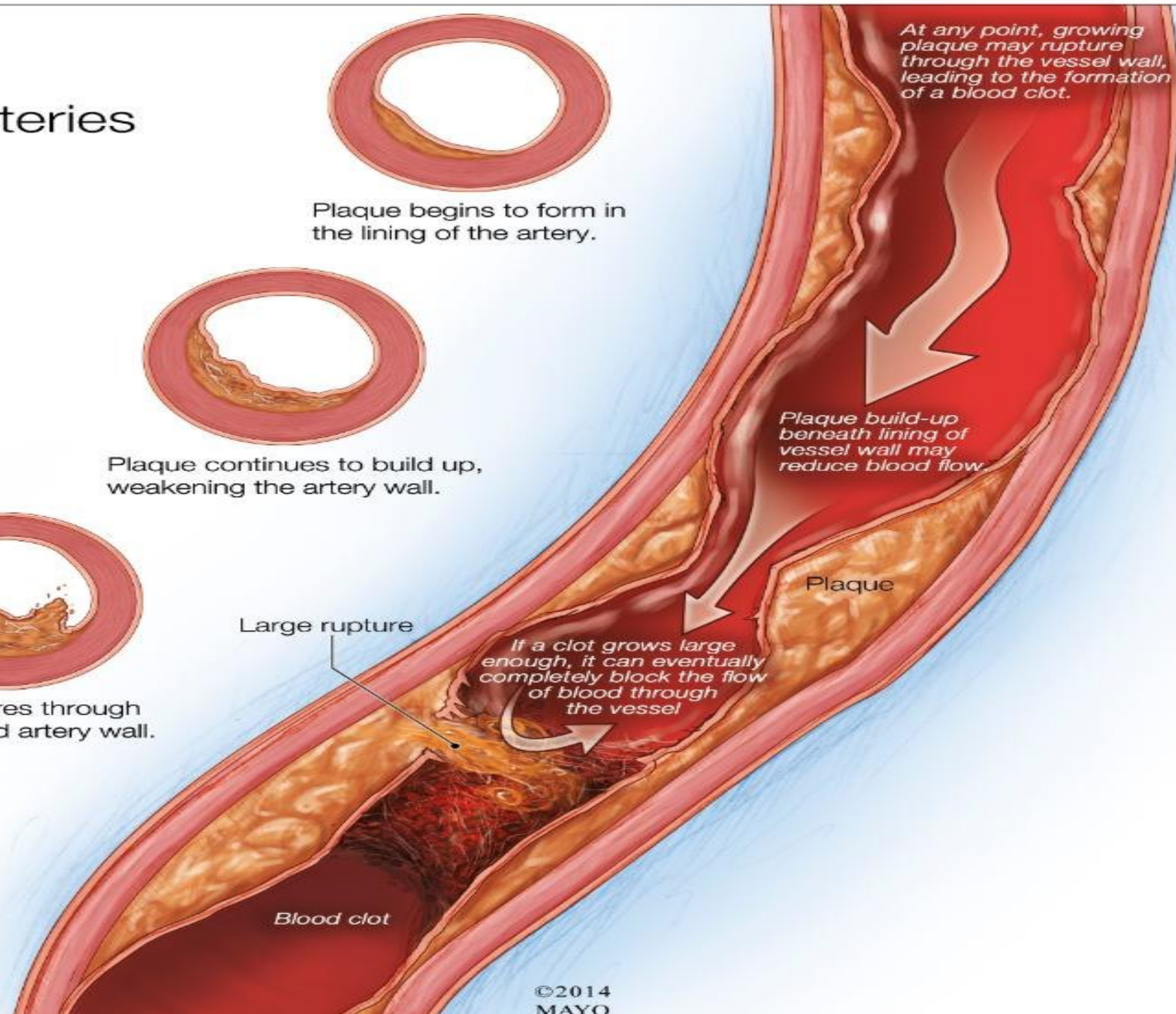
Plaque continues to build up, weakening the artery wall.



Plaque ruptures through the weakened artery wall.



A blood clot forms around the ruptured plaque and may eventually cut off blood flow completely.



Platelet Response to Vascular Injury

Physical trauma to the vascular system, such as a puncture or a cut, initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade. These interactions lead to hemostasis or the cessation of blood loss from a damaged blood vessel. Platelets are central in this process. Initially, there is vasospasm of the damaged blood vessel to prevent further blood loss. The next step involves the formation of a platelet–fibrin plug at the site of the puncture. The creation of an unwanted thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system, rather than external physical trauma.

ARACHIDONIC ACID

Cyclooxygenase Pathway

COX-1 / COX-2

Prostaglandin G2 (PGG2)

Prostaglandin H2 (PGH2)

Tissue
specific
synthesases

PGD2

PGE2

PGF2 α

PGI2

Prostacyclin

TXA2

Thromboxane A2

5- Lipoxygenase Pathway

Hydroperoxyeicosatetraenoic acid

5HPETE

5HETE

Leukotriene B4

Leukotriene A4

Leukotriene C4

Leukotriene D4

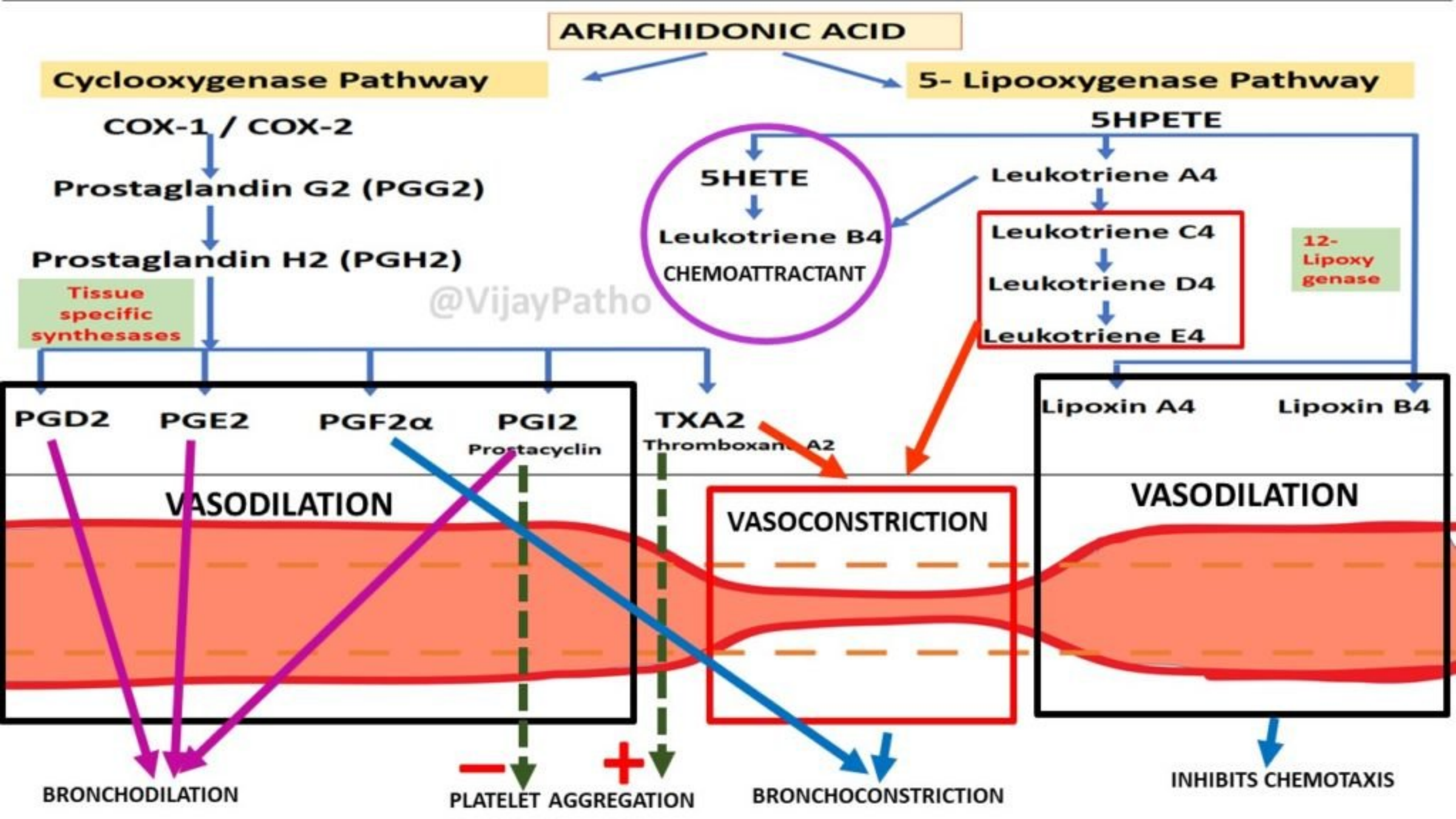
Leukotriene E4

Lipoxin A4

Lipoxin B4

12-
Lipox-
genase

@VijayPatho



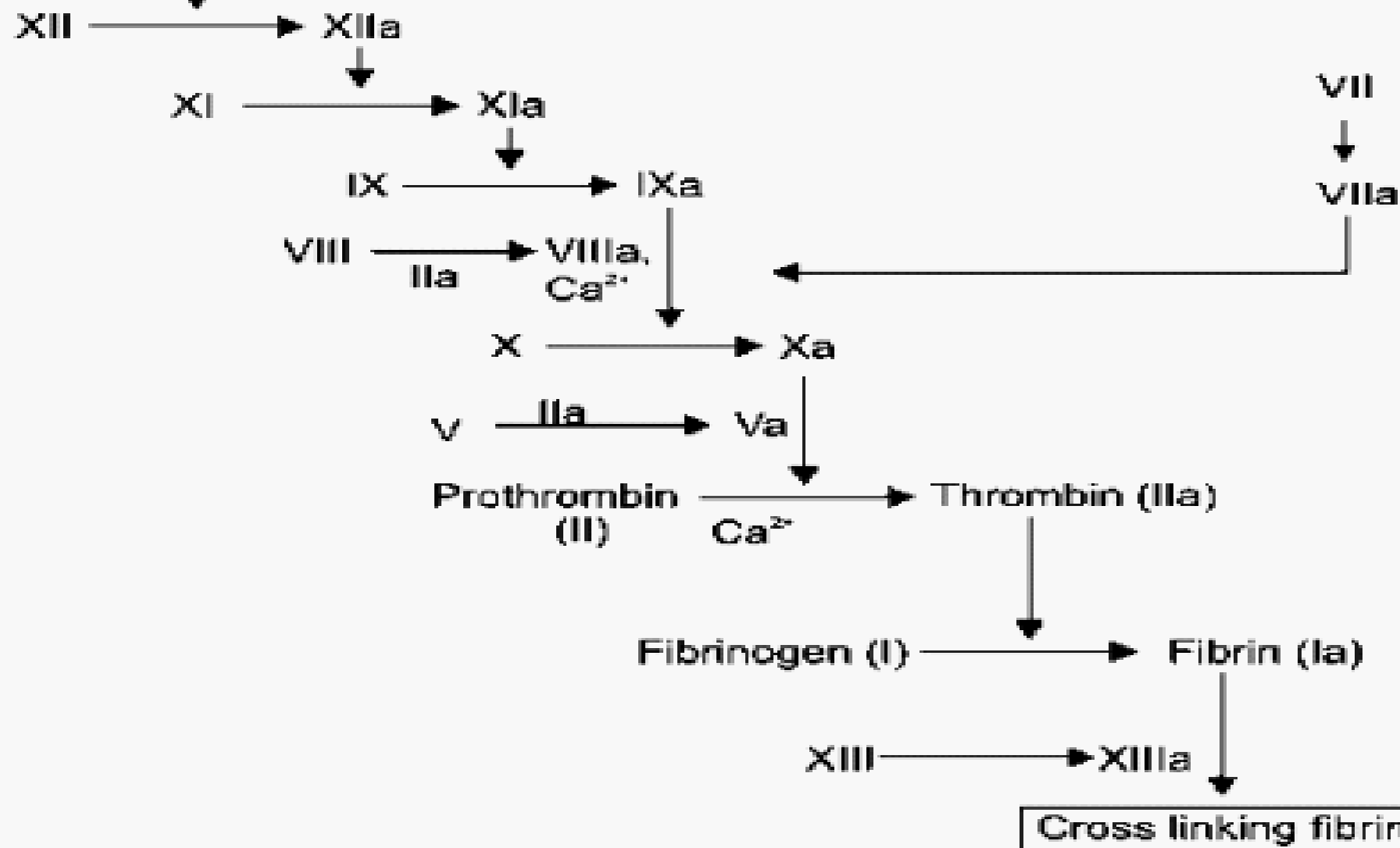
Intrinsic pathway

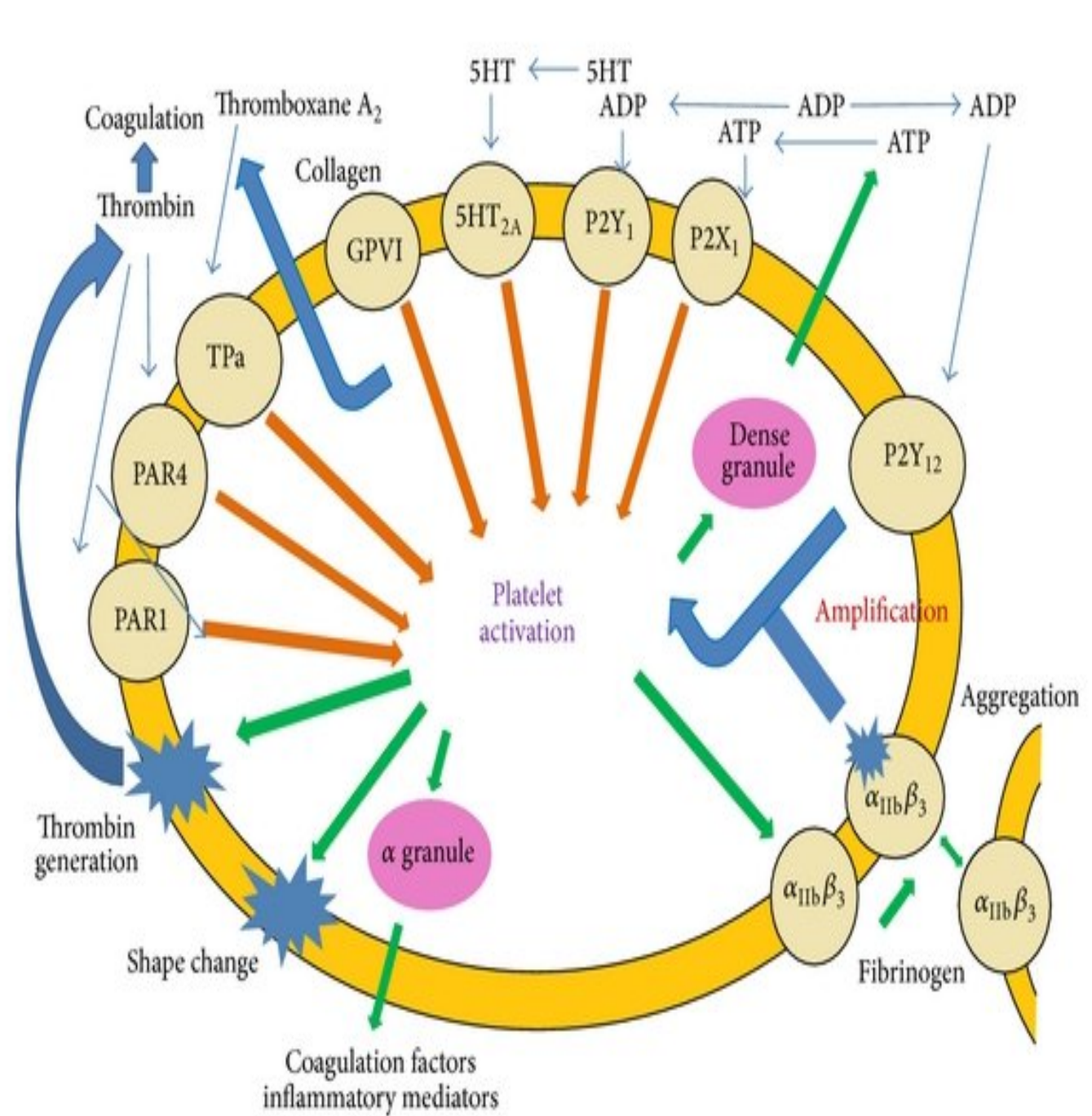
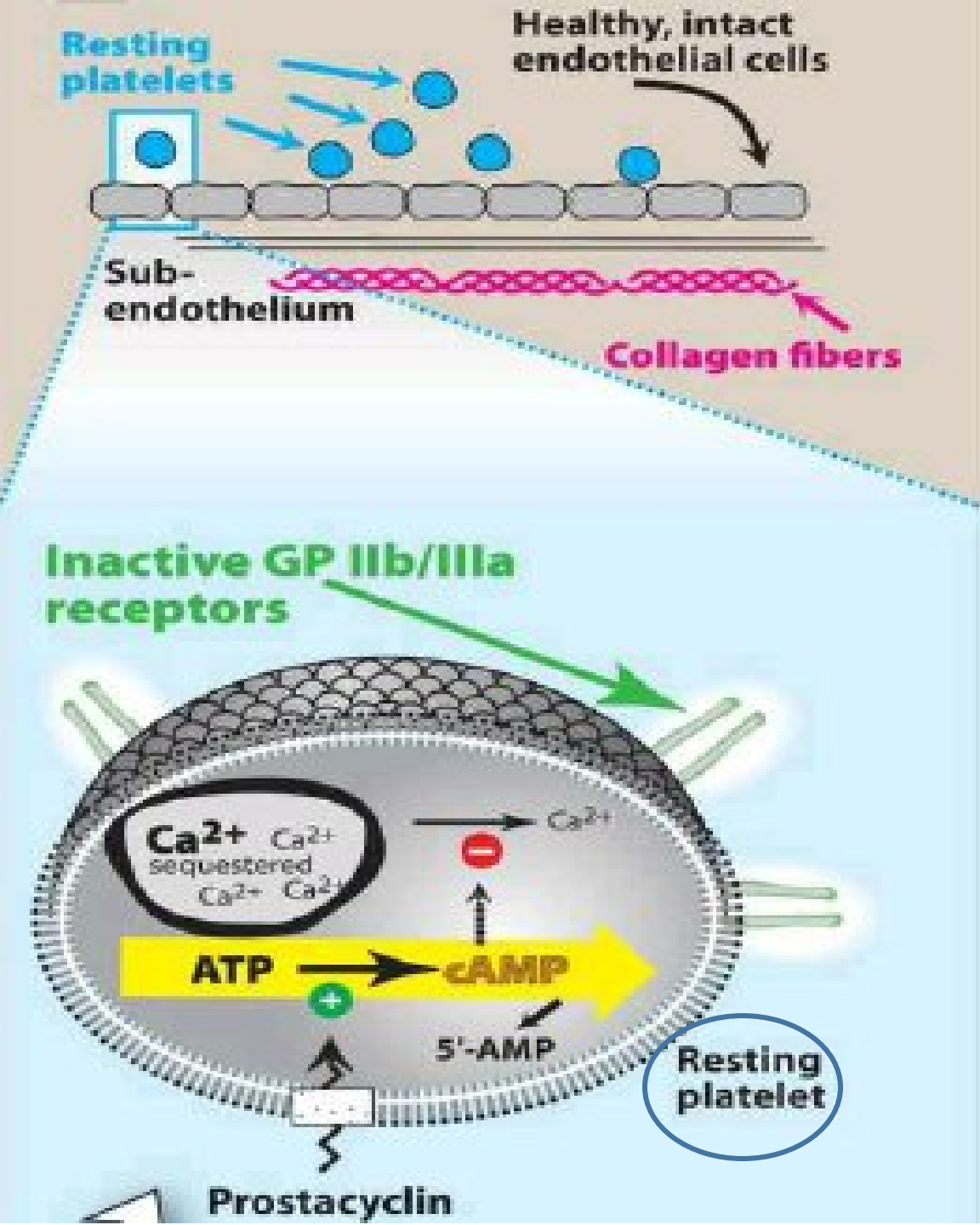
Extrinsic pathway

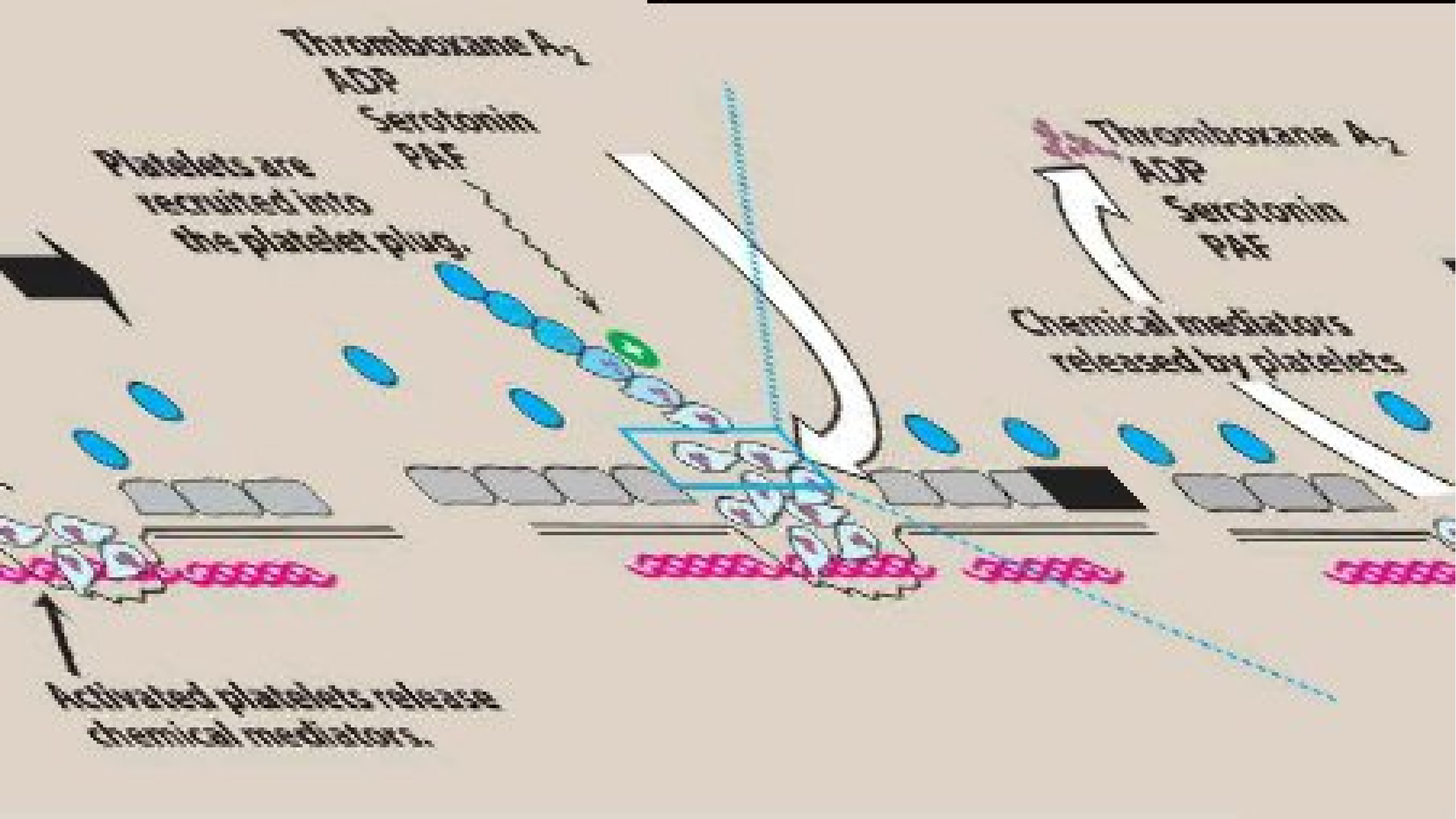
Injury to blood vessels

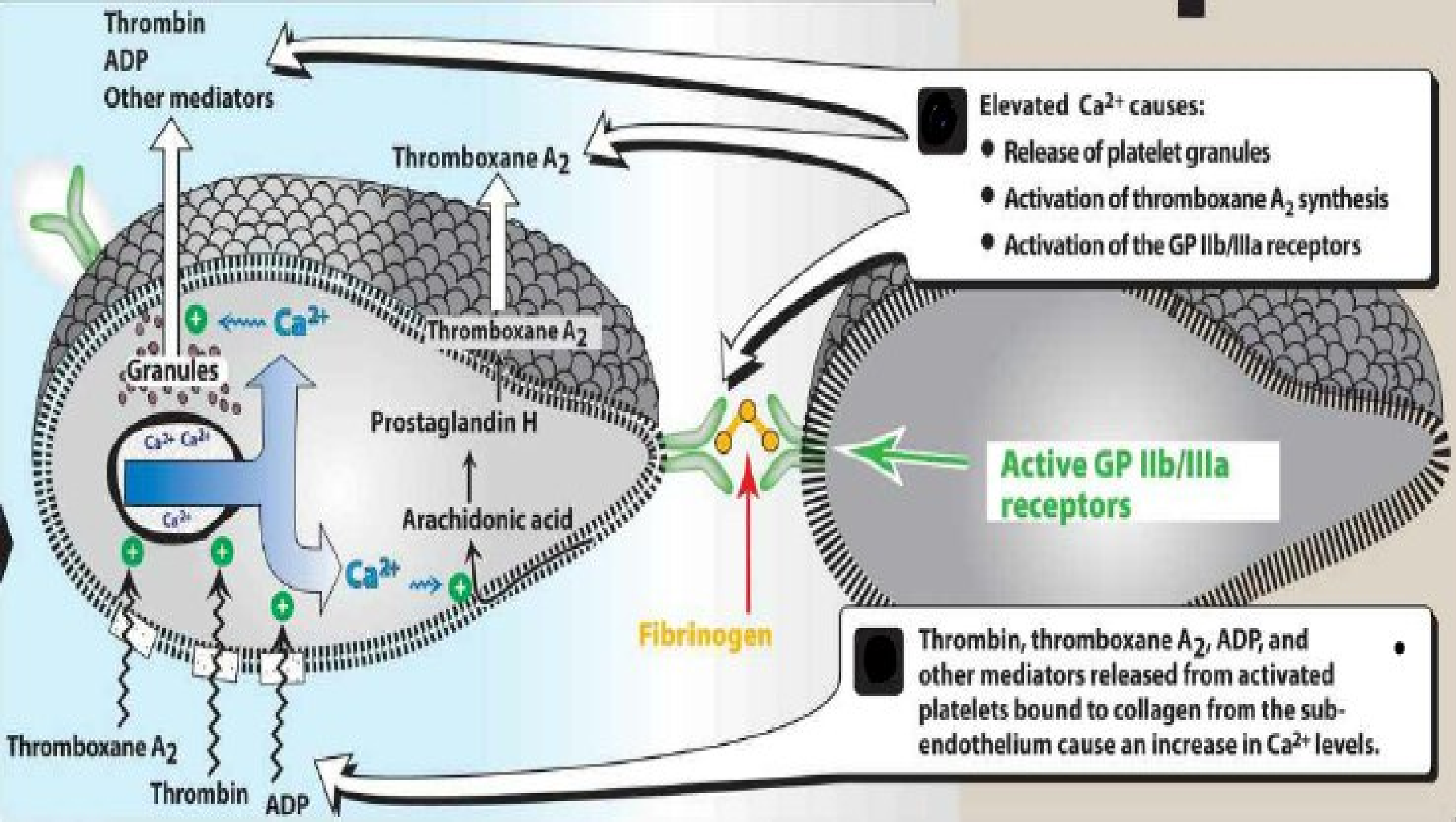
Tissue factor

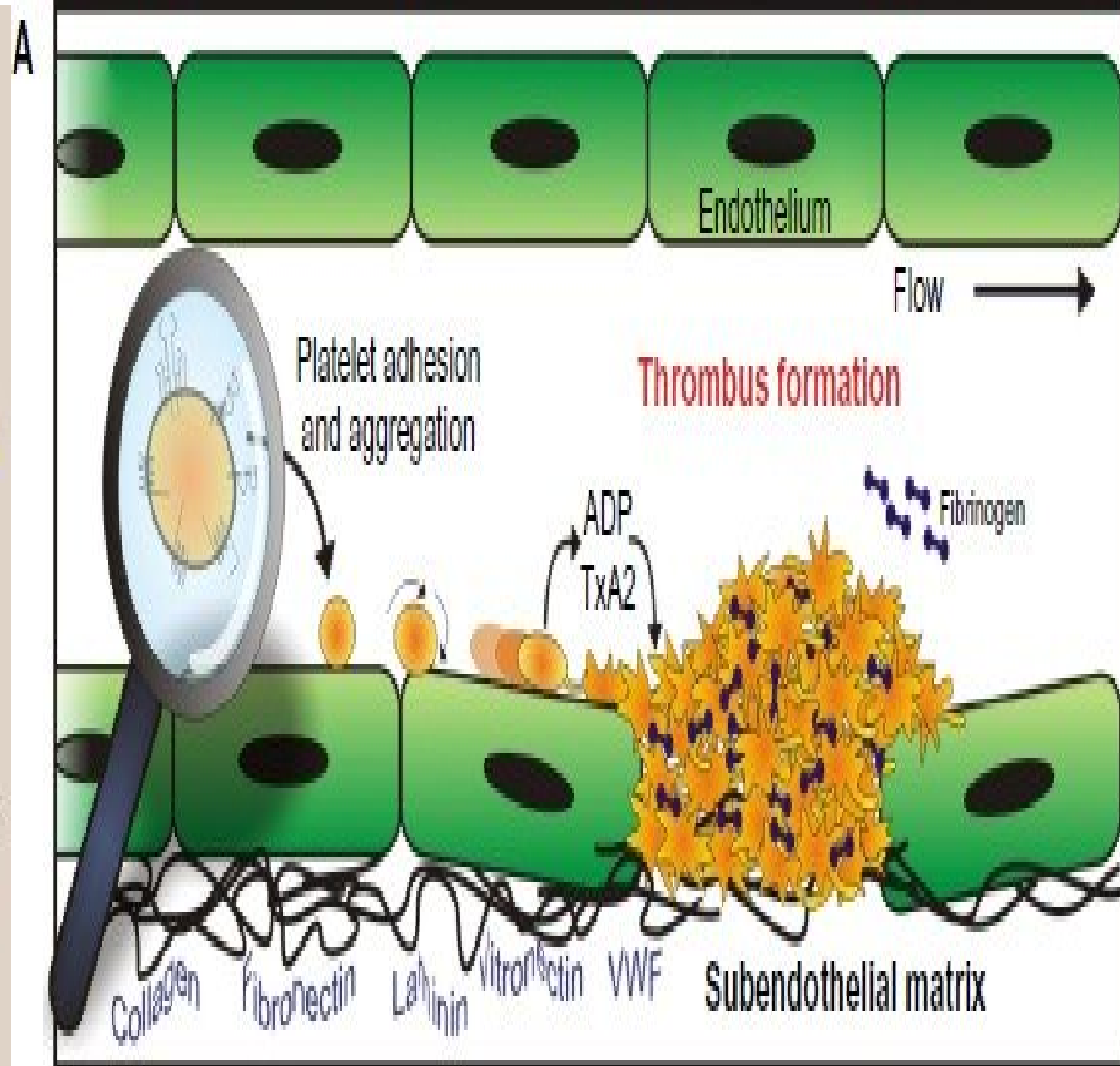
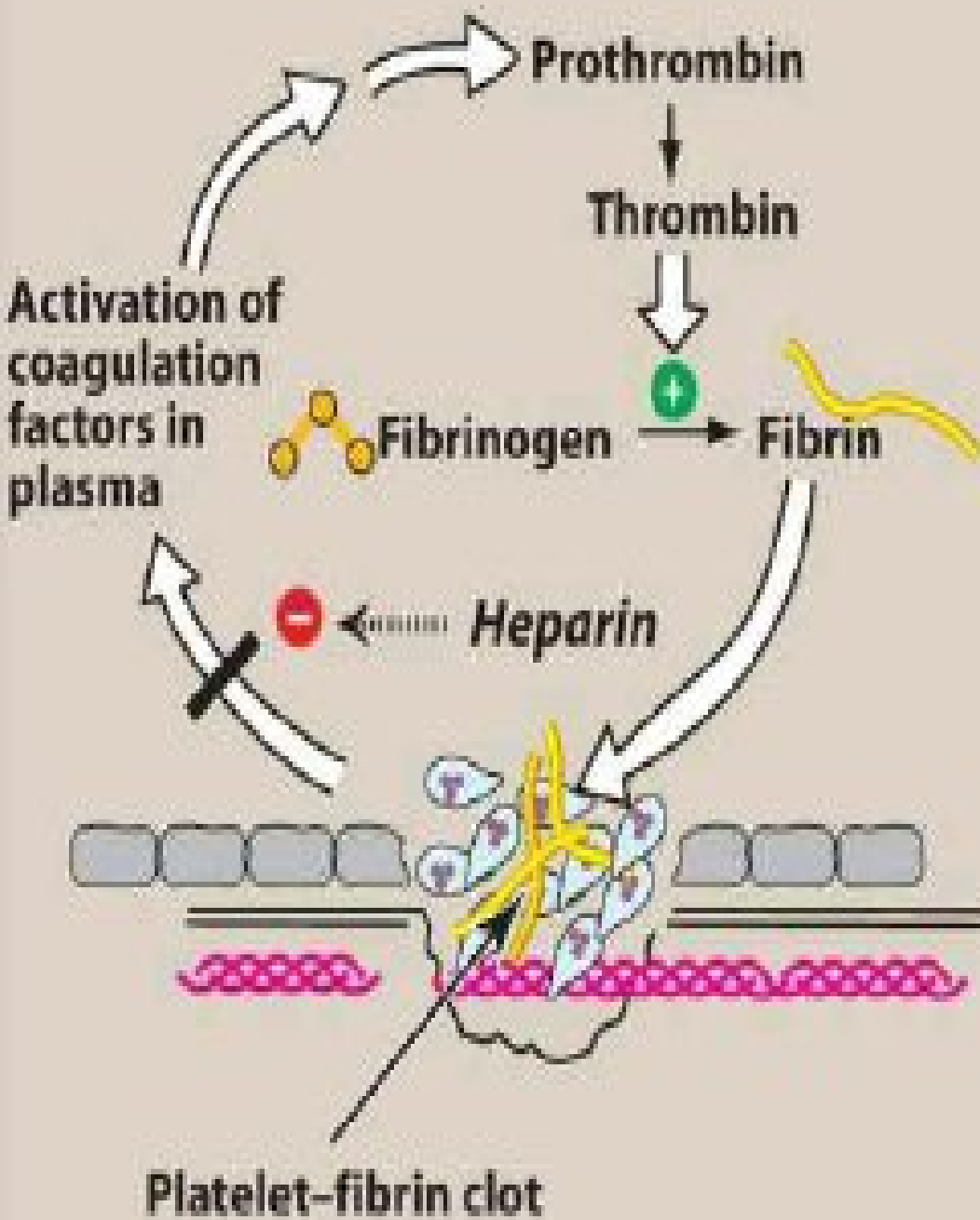
Epomedicine.com











Chemical mediators synthesized by endothelial cells

Prostacyclin is synthesized by intact endothelial cells and acts as an inhibitor of platelet aggregation. Prostacyclin (also known as prostaglandin I₂) binds to platelet membrane receptors that are coupled to the synthesis of cyclic adenosine monophosphate (cAMP), an intracellular messenger. Elevated levels of intracellular cAMP are associated with a decrease in intracellular calcium. Decreased intracellular calcium prevents platelet activation and the subsequent release of platelet aggregation agents. Damaged endothelial cells synthesize less prostacyclin than healthy cells. With less prostacyclin to bind platelet receptors, less intracellular cAMP is synthesized; this leads to platelet aggregation.

Roles of thrombin, thromboxanes, and collagen

The platelet membrane also contains receptors that can bind thrombin, thromboxanes, and exposed collagen. In the intact, normal vessel, circulating levels of thrombin and thromboxane are low, and the intact endothelium covers collagen in the subendothelial layers. The corresponding platelet receptors are, thus, unoccupied, and as a result, platelet activation and aggregation are not initiated. However, when occupied, each of these receptor types triggers a series of reactions leading to the release into the circulation of intracellular granules by the platelets. This ultimately stimulates platelet aggregation.

Platelet adhesion

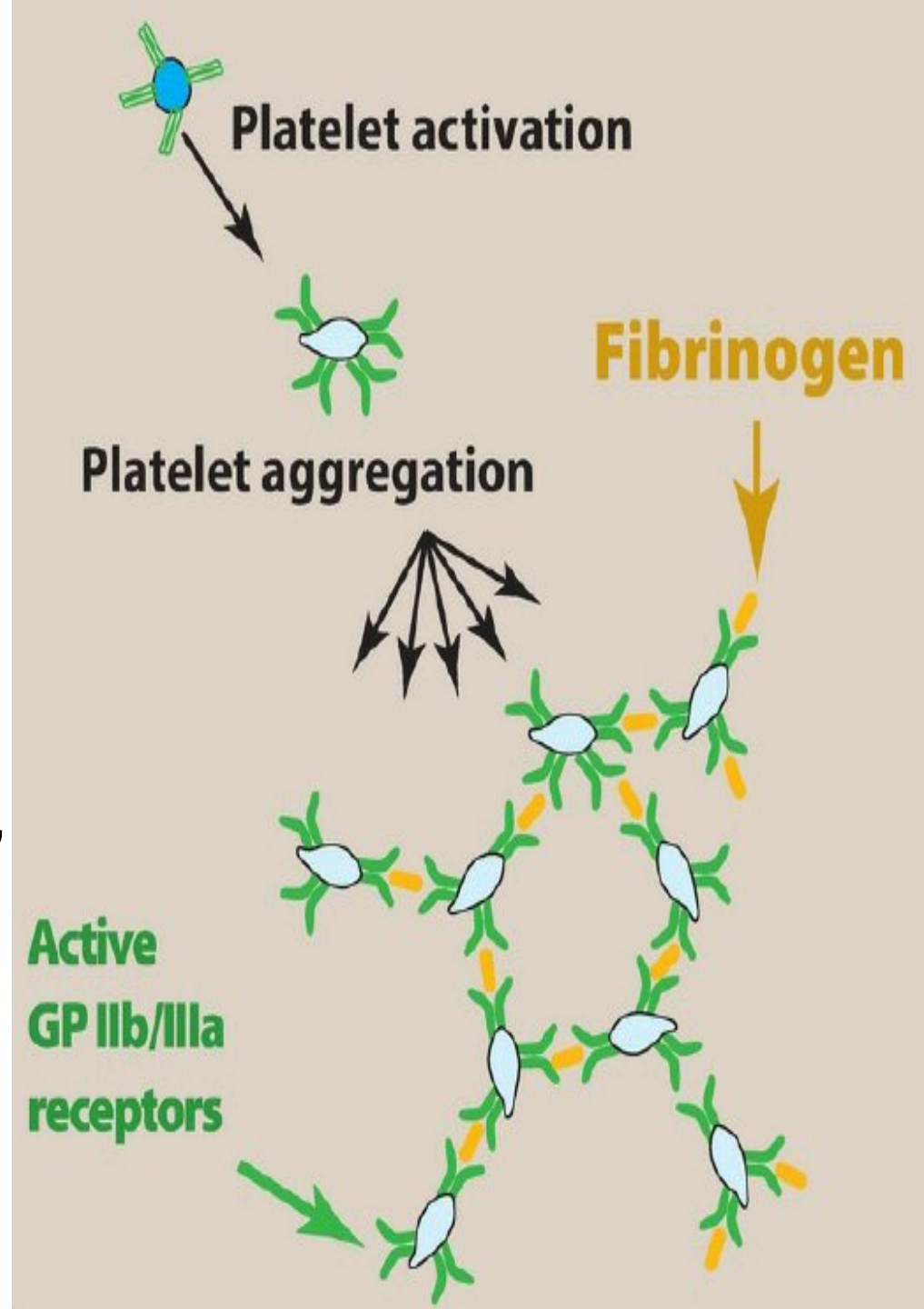
When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the subendothelium. This triggers a complex series of chemical reactions, resulting in platelet activation.

Platelet activation

Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue. This causes morphologic changes in platelets and the release of platelet granules containing chemical mediators, such as adenosine diphosphate (ADP), thromboxane A₂, serotonin, platelet activation factor, and thrombin. These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby. These receptors function as sensors that are activated by the signals sent from the adhering platelets. The previously dormant platelets become activated and start to aggregate. These actions are mediated by several messenger systems that ultimately result in elevated levels of calcium and a decreased concentration of cAMP within the platelet.

Platelet aggregation

The increase in cytosolic calcium accompanying activation is due to a release of sequestered stores within the platelet. This leads to 1) the release of platelet granules containing mediators, such as ADP and serotonin that activate other platelets; 2) activation of thromboxane A₂ synthesis; and 3) activation of glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen and, ultimately, regulate platelet–platelet interaction and thrombus formation. Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation. This leads to an avalanche of

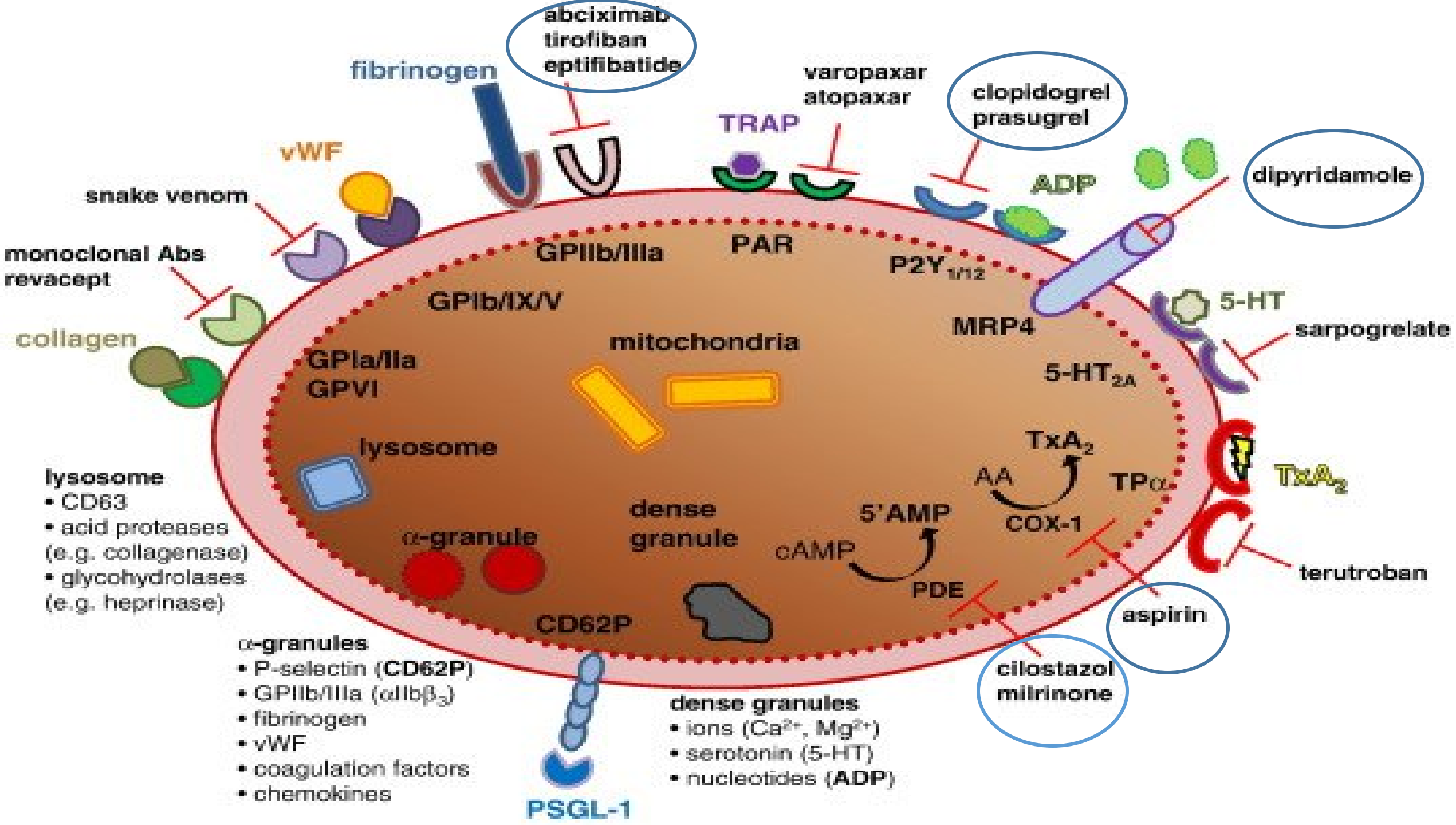


Formation of a clot

Local stimulation of the coagulation cascade by tissue factors released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (factor IIa). In turn, thrombin, a serine protease, catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the clot. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet–fibrin plug.

Fibrinolysis

During clot formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators in the tissue. Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal.



Platelet Aggregation Inhibitors

The platelet aggregation inhibitors inhibit cyclooxygenase-1 (COX-1), block GP IIb/IIIa, or block ADP receptors, thereby interfering with the signals that promote platelet aggregation. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.

Aspirin

Mechanism of action

Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids. Arachidonic acid is first converted to prostaglandin H₂ by COX-1. Prostaglandin H₂ is further metabolized to thromboxane A₂, which is released into plasma. Thromboxane A₂ promotes the aggregation process that is essential for the rapid formation of a hemostatic plug.

Aspirin inhibits thromboxane A₂ synthesis by acetylation of a serine residue on the active site of COX-1, thereby irreversibly inactivating the enzyme. This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thereby preventing platelet aggregation. The inhibitory effect is rapid, and aspirin-induced suppression of thromboxane A₂ and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days. Repeated administration of aspirin has a cumulative effect on the function of platelets. Aspirin is the only antiplatelet agent that irreversibly inhibits platelet function.

Therapeutic use

Aspirin is used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI. Complete inactivation of platelets occurs with 75 mg of aspirin given daily. The recommended antiplatelet dose of aspirin ranges from 50 to 325 mg daily.

Pharmacokinetics

When given orally, aspirin is absorbed by passive diffusion and quickly hydrolyzed to salicylic acid in the liver. Salicylic acid is further metabolized in the liver and some is excreted unchanged in the urine. The half-life of aspirin ranges from 15 to 20 minutes and for salicylic acid is 3 to 12 hours.

Adverse effects

Higher doses of aspirin increase drug-related toxicities as well as the probability that aspirin may also inhibit prostacyclin production. Bleeding time is prolonged by aspirin treatment, causing complications that include an increased incidence of hemorrhagic stroke and gastrointestinal (GI) bleeding, especially at higher doses of the drug.

Nonsteroidal anti-inflammatory drugs, such as ibuprofen, inhibit COX-1 by transiently competing at the catalytic site. Ibuprofen, if taken within the 2 hours prior to aspirin, can obstruct the access of aspirin to the serine residue and, thereby, antagonize platelet inhibition by aspirin. Therefore, immediate-release aspirin should be taken at least 60 minutes before or at least 8 hours after ibuprofen.

P2Y12 receptor antagonists

Ticlopidine, clopidogrel , prasugrel , ticagrelor, and cangrelor are P2Y12 ADP receptor inhibitors that also block platelet aggregation but by a mechanism different from that of aspirin. All of these agents are administered orally, with the exception of cangrelor, which is an injectable formulation.

Mechanism of action

These drugs inhibit the binding of ADP to the P2Y12 receptor on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other. Ticagrelor and cangrelor bind to the P2Y12 ADP receptor in a reversible manner. The other agents bind irreversibly. The maximum inhibition of platelet aggregation is achieved in 2 minutes with intravenous (IV) cangrelor, 1 to 3 hours with ticagrelor, 2 to 4 hours with prasugrel, 3 to 4 days with ticlopidine, and 3 to 5 days with

Therapeutic use

Clopidogrel is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and in those with established peripheral arterial disease. It is also approved for prophylaxis of thrombotic events in acute coronary syndromes (unstable angina or non-ST-elevation MI). Additionally, clopidogrel is used to prevent thrombotic events associated with percutaneous coronary intervention (PCI) with or without coronary stenting.

Ticlopidine is similar in structure to clopidogrel. It is indicated for the prevention of transient ischemic attacks (TIA) and strokes in patients with a prior cerebral thrombotic event. However, due to life-threatening hematologic adverse reactions, ticlopidine is generally reserved for patients who are intolerant to other therapies. Prasugrel is approved to decrease thrombotic cardiovascular events in patients with acute coronary syndromes (unstable angina, non-ST-elevation MI, and ST-elevation MI managed with PCI). Ticagrelor is approved for the prevention of arterial thromboembolism in patients with unstable angina and acute MI, including those undergoing PCI. Cangrelor is approved as an adjunct during PCI to reduce thrombotic events in select patients.

Pharmacokinetics

These agents require oral loading doses for quicker antiplatelet effect, except cangrelor that has a fast onset of action with intravenous administration. Food interferes with the absorption of ticlopidine but not with the other agents. After oral ingestion, the drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by the cytochrome P-450 (CYP) system to active metabolites. Elimination of the drugs and metabolites occurs by both the renal and fecal routes. Clopidogrel is a prodrug, and its therapeutic efficacy relies on its active metabolite, which is produced via metabolism by CYP 2C19. Genetic polymorphism of CYP 2C19 leads to a reduced clinical response in patients who are “poor metabolizers” of clopidogrel. Tests are currently available to identify poor metabolizers, and it is recommended that other antiplatelet agents (prasugrel or ticagrelor) be prescribed for these patients. In addition, other drugs that inhibit CYP 2C19, such as

Adverse effects

These agents can cause prolonged bleeding for which there is no antidote. Ticlopidine is associated with severe hematologic reactions that limit its use, such as agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia. Clopidogrel causes fewer adverse reactions, and the incidence of neutropenia is lower. However, TTP has been reported as an adverse effect for both clopidogrel and prasugrel (but not for ticagrelor). Prasugrel is contraindicated in patients with history of TIA or stroke. Prasugrel, ticagrelor, and cangrelor carry black box warnings for bleeding. Additionally, ticagrelor carries a black box warning for diminished effectiveness with concomitant use of aspirin doses above 100 mg

Glycoprotein IIb/IIIa inhibitors

1. Mechanism of action

The GP IIb/IIIa receptor plays a key role in stimulating platelet aggregation. A chimeric monoclonal antibody fragment, abciximab, inhibits the GP IIb/IIIa receptor complex. By binding to GP IIb/IIIa, abciximab blocks the binding of fibrinogen and von Willebrand factor and, consequently, aggregation does not occur. Eptifibatide and tirofiban act similarly to abciximab, by blocking the GP IIb/IIIa receptor. Eptifibatide is a cyclic peptide that binds to GP IIb/IIIa at the site that interacts with the arginine–glycine–aspartic acid sequence of fibrinogen. Tirofiban is not a peptide, but it blocks the same site as eptifibatide.

Therapeutic use

These agents are given intravenously, along with heparin and aspirin, as an adjunct to PCI for the prevention of cardiac ischemic complications.

Abciximab is also approved for patients with unstable angina not responding to conventional medical therapy when PCI is planned within 24 hours.

Pharmacokinetics

Abciximab is given by IV bolus, followed by IV infusion, achieving peak platelet inhibition within 30 minutes. The metabolism of abciximab is unknown. After cessation of abciximab infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours. When IV infusion of eptifibatide or tirofiban is stopped, both agents are rapidly cleared from the plasma. Eptifibatide and its metabolites are excreted by the kidney.

Tirofiban is excreted largely unchanged by the kidney and to a lesser extent in the feces.

The major adverse effect of these agents is bleeding, especially if used with anticoagulants

Dipyridamole

MRP4

Dipyridamole, a coronary vasodilator, increases intracellular levels of cAMP by inhibiting phosphodiesterase, thereby resulting in decreased thromboxane A₂ synthesis. The drug may potentiate the effect of prostacyclin and, therefore, decrease platelet adhesion to thrombogenic surfaces. Dipyridamole is used for stroke prevention and is usually given in combination with aspirin. Dipyridamole has variable bioavailability following oral administration. It is highly protein bound. The drug undergoes hepatic metabolism, mainly glucuronidation, and is excreted primarily in the feces. Patients with unstable angina should not use dipyridamole because of its vasodilating properties, which may worsen ischemia (coronary steal phenomenon). Dipyridamole commonly causes headache and dizziness and can lead to orthostatic hypotension (especially if administered IV).

Cilostazol

Cilostazol is an oral antiplatelet agent that also has vasodilating activity. Cilostazol and its active metabolites inhibit phosphodiesterase type III, which prevents the degradation of cAMP, thereby increasing levels of cAMP in platelets and vascular tissues. The increase in cAMP prevents platelet aggregation and promotes vasodilation of blood vessels, respectively. Cilostazol is approved to reduce the symptoms of intermittent claudication. Cilostazol is extensively metabolized in the liver by the CYP 3A4 and 2C19 isoenzymes. As such, this agent has many drug interactions that require dose modification. The primary route of elimination is via the kidney. Headache and GI side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain) are the most common adverse effects observed with cilostazol. Rarely, thrombocytopenia or leukopenia has been reported. Phosphodiesterase type III inhibitors have been shown to increase mortality in patients with

Acute coronary syndrome (ACS)

Antiplatelet recommendations

Aspirin

- (a) An irreversible cyclooxygenase-1 inhibitor blocking the formation of thromboxane A₂– and thromboxane A₂–mediated platelet activation
- (b) Given to all patients (class I)
- (c) Established first-line therapy in ACS; reduces the incidence of recurrent MI and death
- (d) LD is necessary for aspirin-naïve patients; avoid enteric coated initially because of delayed and reduced absorption.
 - (1) Dosing is 162–325 mg for patients at initial presentation of ACS.
 - (2) Dosing is 81–325 mg for those who are undergoing PCI, depending on chronic aspirin therapy regimen.
- (e) Aspirin is given indefinitely at a preferred dose of 81 mg after ACS with or without PCI (class I).
 - (1) High dose (greater than 160 mg) is associated with more bleeding than lower dose (less than 160 mg).
 - (2) High doses (greater than 160 mg) have not been shown to improve outcomes after ACS more effectively than lower doses (less than 160 mg).

Dual antiplatelet therapy (DAPT) with aspirin plus a P2Y₁₂ receptor inhibitor is indicated for all patients after ACS for at least 12 months. The duration of initial treatment with DAPT is at least 75–100 days, and then

P2Y12 inhibitors

- P2Y12 inhibitor therapy is given to all patients (class I).
 - Choice of oral P2Y12 inhibitor depends on an ischemia-guided therapy or early invasive approach and pharmacokinetic differences.
- (1) Prasugrel should not be administered to patients with a history of stroke or transient ischemic attack (class III).
- (2) The efficacy of ticagrelor is decreased in patients treated with higher doses of aspirin (greater than 300 mg daily) compared with lower doses (less than 100 mg daily).
- Clopidogrel and ticagrelor are preferred for a medical (i.e., ischemia-guided) strategy .
 - Clopidogrel, ticagrelor, and prasugrel are options for an early invasive strategy.
- (1) It is reasonable to choose ticagrelor over clopidogrel for P2Y12 inhibition in patients with NSTEMI-ACS or STEMI treated with an early invasive strategy or coronary stenting (class IIa).
- (2) It is reasonable to choose ticagrelor over clopidogrel for P2Y12 inhibition in

Antiplatelet Management Strategies According to ACS Presentation

NSTE-ACS Ischemia Guided	NSTE-ACS Invasive	STEMI Primary PCI	STEMI + Fibrinolytic	Antiplatelet Agent
Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
Clopidogrel TIC	Clopidogrel PRA ^a TIC ^a	Clopidogrel PRA TIC	Clopidogrel ^b	P2Y ₁₂ receptor antagonist
GP IIb/IIIa inhibitor	Greatest benefit when given to patients with high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or TIC ^c			GP IIb/IIIa inhibitor

It may be reasonable to choose TIC or PRA (in those who are not at high bleeding risk) over clopidogrel in patients treated with early invasive strategy for NSTEMI-ACS (class IIa, 2014 NSTEMI-ACS guideline).

^aPre-PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if > 24 hr after event.

^cBenefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with P2Y₁₂ inhibitor. It is reasonable (class IIa, 2014 NSTEMI-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTEMI-ACS treated with UFH and adequately pretreated with clopidogrel.

PCI = percutaneous coronary intervention; PRA = prasugrel; TIC = ticagrelor.

