- Antianginal Drugs
- Drugs affecting the blood (part 1)

Lecture 10

College of Pharmacy

By:

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➢ Antianginal Drugs

- Atherosclerotic lesions in coronary arteries can obstruct blood flow, leading to **an imbalance in myocardial oxygen supply** and **demand** that presents as **stable angina or an acute coronary syndrome** (myocardial infarction [MI] or unstable angina).
- Spasms of vascular smooth muscle may also impede cardiac blood flow, reducing perfusion and causing ischemia and angina pain.
- **Typical angina pectoris** is a characteristic **sudden, severe, crushing chest pain that may radiate to the neck, jaw, back, and arms**.
- All patients with ischemic heart disease (IHD) and angina should receive **guideline-directed medical therapy** with **emphasis on lifestyle modifications** and **management of modifiable risk factors** to **reduce cardiovascular morbidity and mortality.**

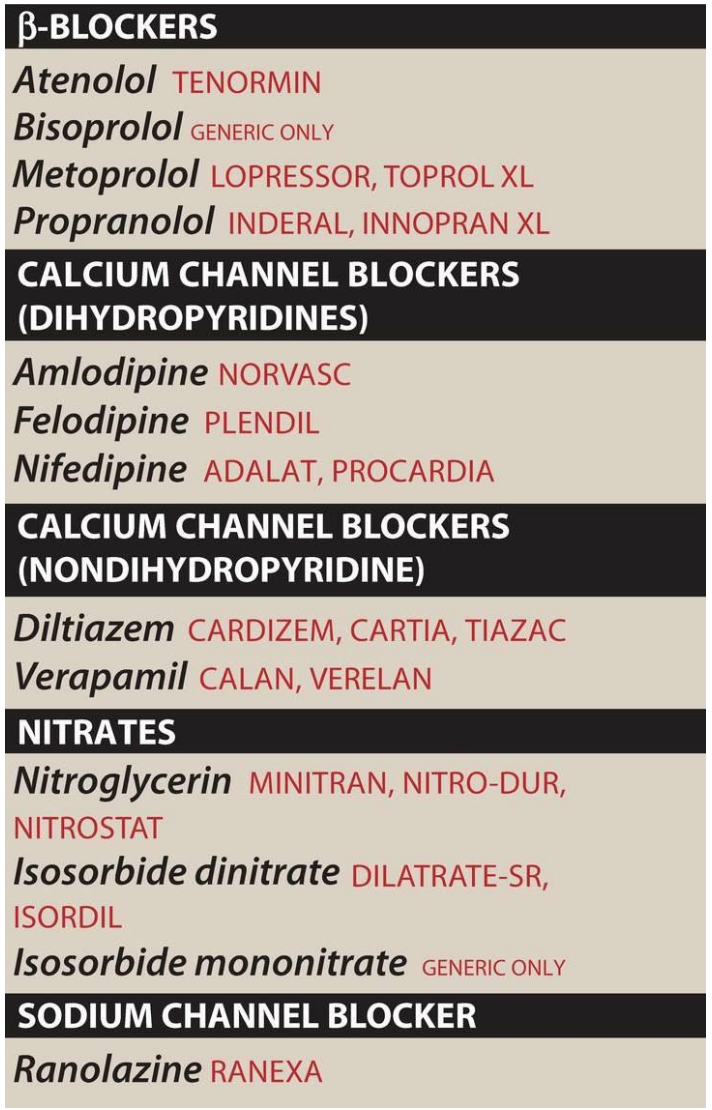

Figure 1: Summary of antianginal drugs.

Types of Angina

Angina pectoris has three patterns:

1) Stable, effort-induced, classic, or typical angina

- It is the **most common** form of angina.
- It is usually characterized by a **short-lasting burning, heavy, or squeezing feeling in the chest**.
- Some ischemic episodes may present "Atypically"—with extreme fatigue, nausea, or diaphoresis—while others may not be associated with any symptoms (silent angina).
- Classic angina is caused by the reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis. Increased myocardial oxygen demand, such as that produced by physical activity, emotional stress or excitement, or any other cause of increased cardiac workload, may induce ischemia. Typical angina pectoris is promptly relieved by **rest or nitroglycerin**.

2) Unstable angina

Unstable angina is **chest pain that occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort.** The **symptoms are not relieved by rest or nitroglycerin**. Unstable angina is a **form of acute coronary syndrome and hospital admission and more aggressive therapy to prevent progression to MI and death.**

3) Prinzmetal, variant, vasospastic, or rest angina

- It is an **uncommon pattern of episodic angina** that **occurs at rest** and is **due to decreased blood flow to the heart muscle caused by spasm of the coronary arteries.**
- Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure.
- Prinzmetal angina **generally responds promptly to coronary vasodilators, such as nitroglycerin and calcium channel blockers.**

4) Acute coronary syndrome

Acute coronary syndrome is an emergency that commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery. If **the thrombus occludes most of the blood vessel, and, if the occlusion is untreated, necrosis of the cardiac muscle may ensue. MI (necrosis) is typified** by **increases in the serum levels of biomarkers such as troponins and creatine kinase.** The acute coronary syndrome may present as St-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, or as unstable angina.

Treatment Strategies

- Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina:

β-blockers, calcium channel blockers, organic nitrates, and the sodium channel–blocking drug (Figure 1).

- These agents **help to balance the cardiac oxygen supply and demand equation** by **affecting blood pressure, venous return, heart rate, and contractility.** Figure 2 summarizes the treatment of angina in patients with concomitant diseases

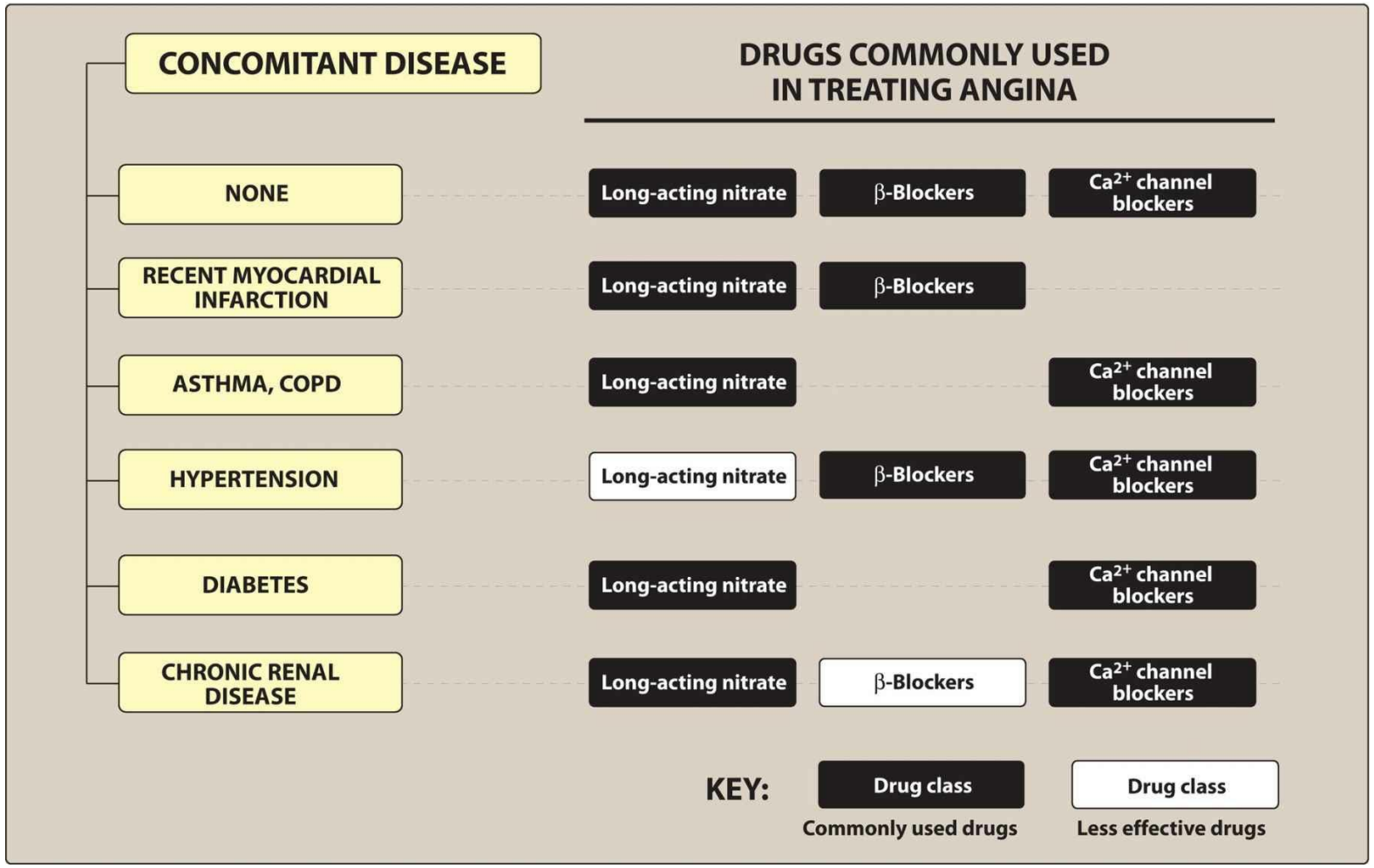

Figure 2: Treatment of angina in patients with concomitant diseases. COPD = chronic obstructive pulmonary disease.

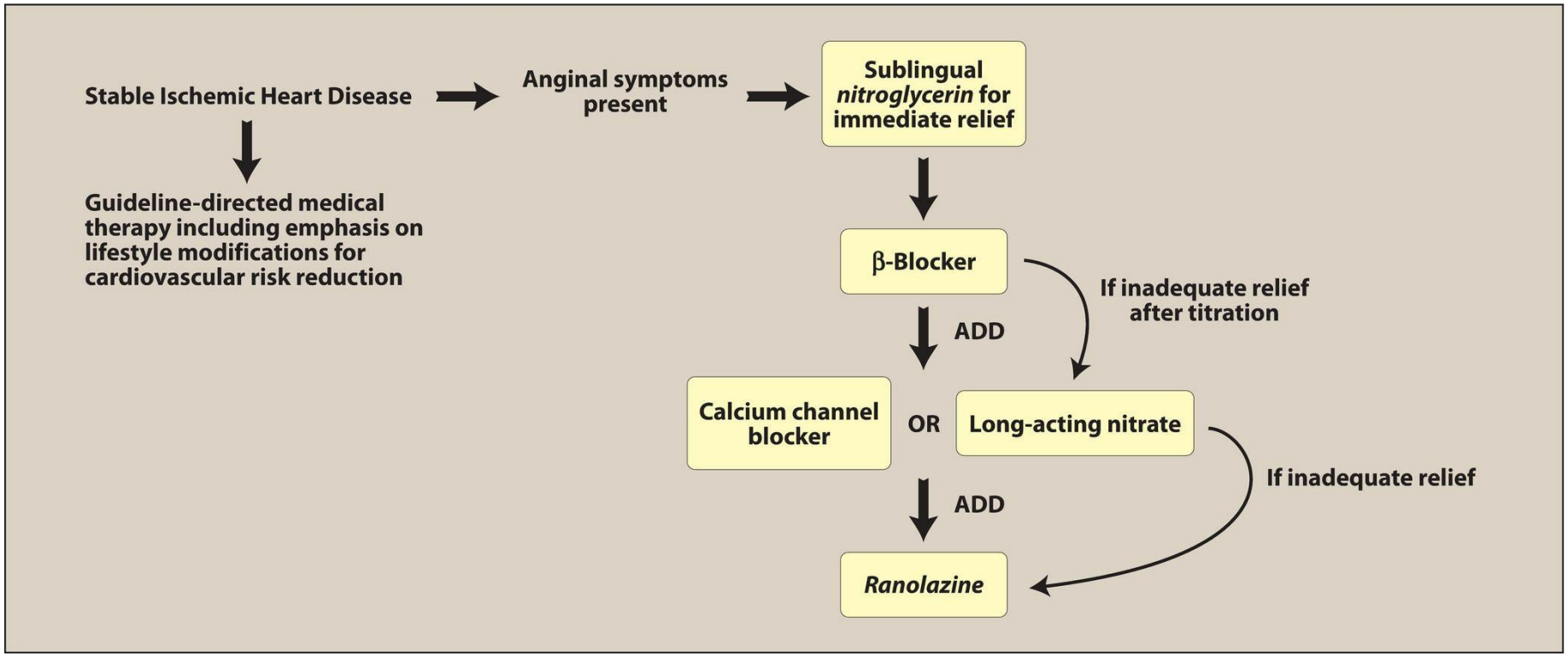

Figure 3: Treatment algorithm for improving symptoms in patients with stable angina.

β-Adrenergic Blockers

- The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β1 receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure.
- These agents reduce myocardial oxygen demand during exertion and at rest.
- As such, they can reduce both the frequency and severity of angina attacks.
- β-Blockers are recommended as initial antianginal therapy in all patients unless contraindicated.

- Propranolol is the prototype for this class of compounds, but it is not cardioselective. Thus, other β-blockers, such as metoprolol and atenolol, are preferred.
- β-Blockers should be avoided in patients with severe bradycardia; however, they can be used in patients with diabetes, peripheral vascular disease, and chronic obstructive pulmonary disease, as long as they are monitored closely.
- Nonselective β-blockers should be avoided in patients with asthma.
- The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.

Calcium Channel Blockers

- The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds.
- All calcium channel blockers are, therefore, arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance.
- In the treatment of effort-induced angina, calcium channel blockers reduce myocardial oxygen consumption by decreasing vascular resistance, thereby decreasing afterload.
- Their efficacy in vasospastic angina is due to relaxation of the coronary arteries.

A. Dihydropyridine calcium channel blockers

- **Amlodipine**, an oral dihydropyridine.
- The vasodilatory effect of amlodipine is useful in the treatment of variant angina caused by spontaneous coronary spasm.
- **Nifedipine** is another agent in this class; it is usually administered as an extended-release oral formulation.

B. Nondihydropyridine calcium channel blockers

- **Verapamil** slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand.
- Verapamil is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities.
- **Diltiazem** also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator.
- Diltiazem can relieve coronary artery spasm and is particularly useful in patients with variant angina.
- Nondihydropyridine calcium channel blockers can worsen heart failure due to their negative inotropic effect, and their use should be avoided in this population.

Organic Nitrates

These compounds cause a **reduction in myocardial oxygen demand**, followed by **relief of symptoms**.

A. Mechanism of action

Figure 4 shows the effects of nitrates and nitrites on smooth muscle.

- Nitrates such as nitroglycerin cause dilation of the large veins, which reduces preload (venous return to the heart) and, therefore, reduces the work of the heart.
- Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.

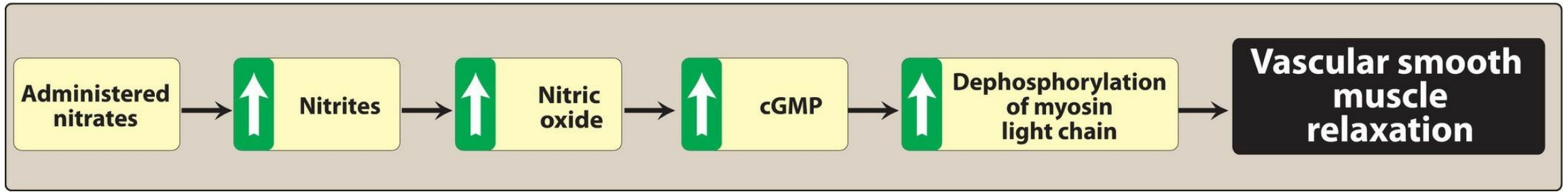

Figure 4: Effects of nitrates and nitrites on smooth muscle. cGMP = cyclic guanosine 3′,5′-monophosphate.

B. Pharmacokinetics

- Nitrates **differ in their onset of action and rate of elimination**. The onset of action varies from 1 minute for nitroglycerin to 30 minutes for isosorbide mononitrate (Figure 5).
- Sublingual nitroglycerin, available in tablet or spray formulation, is the drug of choice for prompt relief of an angina attack precipitated by exercise or emotional stress.
- Significant first-pass metabolism of nitroglycerin occurs in the liver. Therefore, it is commonly administered via the sublingual or transdermal route (patch or ointment).
- Isosorbide mononitrate owes its improved bioavailability and long duration of action to its stability against hepatic breakdown.
- Oral isosorbide dinitrate undergoes denitration to two mononitrates, both of which possess antianginal activity.

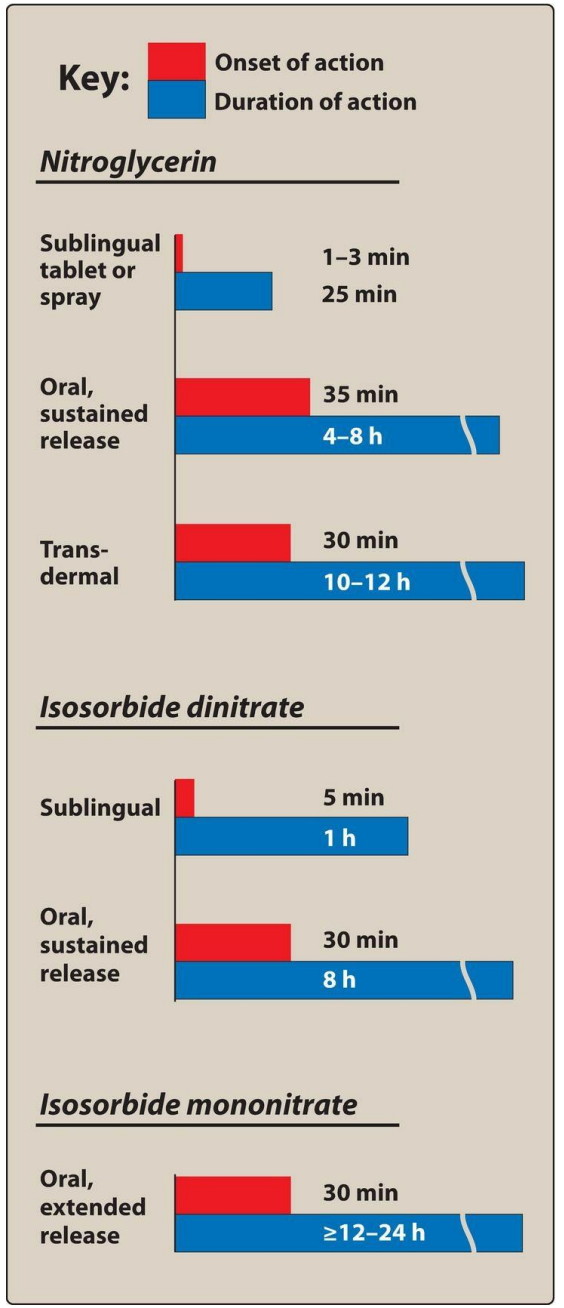

Figure 5: Time to peak effect and duration of action for some common organic nitrate preparations.

C. Adverse effects

- Headache is the most common adverse effect of nitrates.
- High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia.
- Phosphodiesterase type 5 inhibitors such as sildenafil potentiate the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.
- Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation.
- Tolerance can be overcome by providing a daily **“nitrate-free- interval”** to restore sensitivity to the drug. The nitrate-free- Interval of 10 to 12 hours is usually taken at night when myocardial oxygen demand is decreased.
- However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate free interval in patients with variant angina should occur in the late afternoon.
- Nitroglycerin patches are worn for 12 hours and then removed for 12 hours to provide the nitrate-free- interval.

Sodium Channel Blocker

- Ranolazine **inhibits the late phase of the sodium current (late I_{Na}), improving the oxygen supply and demand equation.**
- Ranolazine has antianginal as well as antiarrhythmic properties; and it is most often used in patients who have failed other antianginal therapies.
- Ranolazine is extensively metabolized in the liver.
- In addition, ranolazine can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.

DRUG CLASS	COMMON ADVERSE EFFECTS	DRUG INTERACTIONS	NOTES
β-Blockers *atenolol* *metoprolol* *propranolol*	Bradycardia, worsening peripheral vascular disease, fatigue, sleep disturbance, depression, blunt hypoglycemia awareness, inhibit β_2-mediated bronchodilation in asthmatics	β_2 Agonists (blunted effect); non-dihydropyridine calcium channel blockers (additive effects)	β_1-Selective agents preferred (*atenolol, metoprolol*). Avoid agents with ISA for angina therapy (*pindolol*).
Dihydropyridine calcium channel blockers *amlodipine* *felodipine* *nifedipine*	Peripheral edema, headache, flushing, rebound tachycardia (immediate-release formulations), hypotension	CYP 3A4 substrates (will increase drug concentrations)	Avoid short-acting agents as they can worsen angina (may use extended-release formulations)
Nondihydropyridine calcium channel blockers *diltiazem* *verapamil*	Bradycardia, constipation, heart failure exacerbations, gingival hyperplasia (*verapamil*), edema (*diltiazem*)	CYP 3A4 substrates (will increase drug concentrations); increase *digoxin* levels; β-blockers and other drugs affecting AV node conduction (additive effects)	Avoid in patients with heart failure Adjust dose of both agents in patients with hepatic dysfunction
Organic nitrates *isosorbide dinitrate* *isosorbide mononitrate* *nitroglycerin*	Headache, hypotension, flushing, tachycardia	Contraindicated with PDE5 inhibitors (*sildenafil* and others)	Ensure nitrate-free interval to prevent tolerance
Sodium-channel inhibitor *ranolazine*	Constipation, headache, edema, dizziness, QT interval prolongation	Avoid use with CYP 3A4 inducers (*phenytoin, carbamazepine, St. John's wort*) and strong inhibitors (*clarithromycin*, azole antifungals) and agents that prolong QT interval (*citalopram, quetiapine*, others)	No effect on hemodynamic parameters

Figure 6: Summary of characteristics of antianginal drugs. CYP = cytochrome P450; ISA = intrinsic sympathomimetic activity; PDE5 = phosphodiesterase type 5.

Anticoagulants and Antiplatelet Agents

- **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**, which is treated with vitamin K supplementation.
- **Anemias** caused by **nutritional deficiencies**, such as **the commonly encountered iron-deficiency anemia**, can be treated with either **dietary or pharmaceutical supplementation.**
- However, individuals with anemias that have a genetic basis, such **as sickle-cell disease can benefit from additional treatment.**

Figure 7 summarizes the drugs affecting the blood.

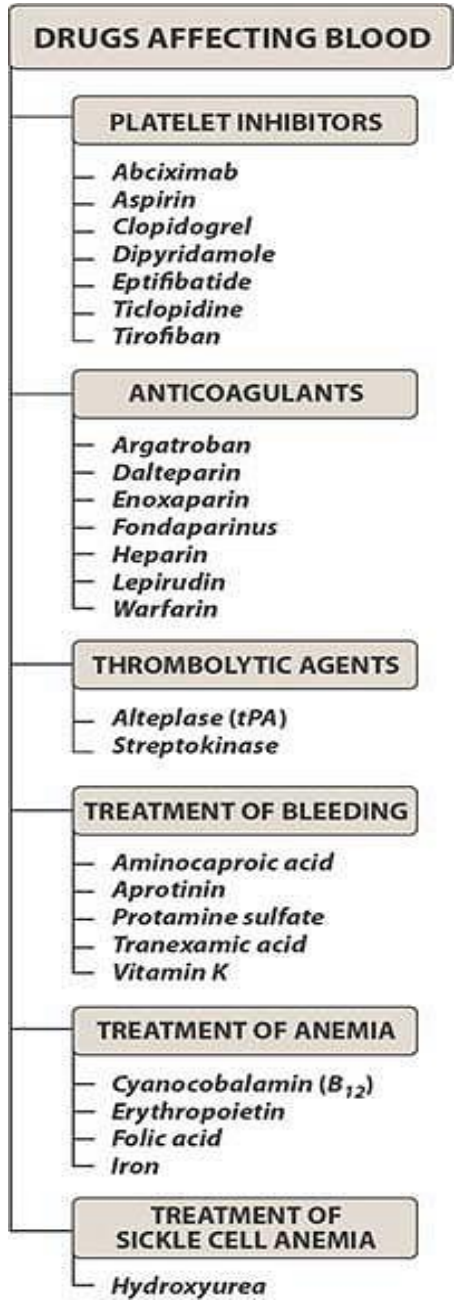

Figure 7: Summary of drugs used in treating dysfunctions of the blood

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.”**
- Both thrombi and emboli are dangerous.
- Arterial thrombosis most often occurs in medium-sized vessels 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, with fewer platelets than are observed with arterial clots.

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.

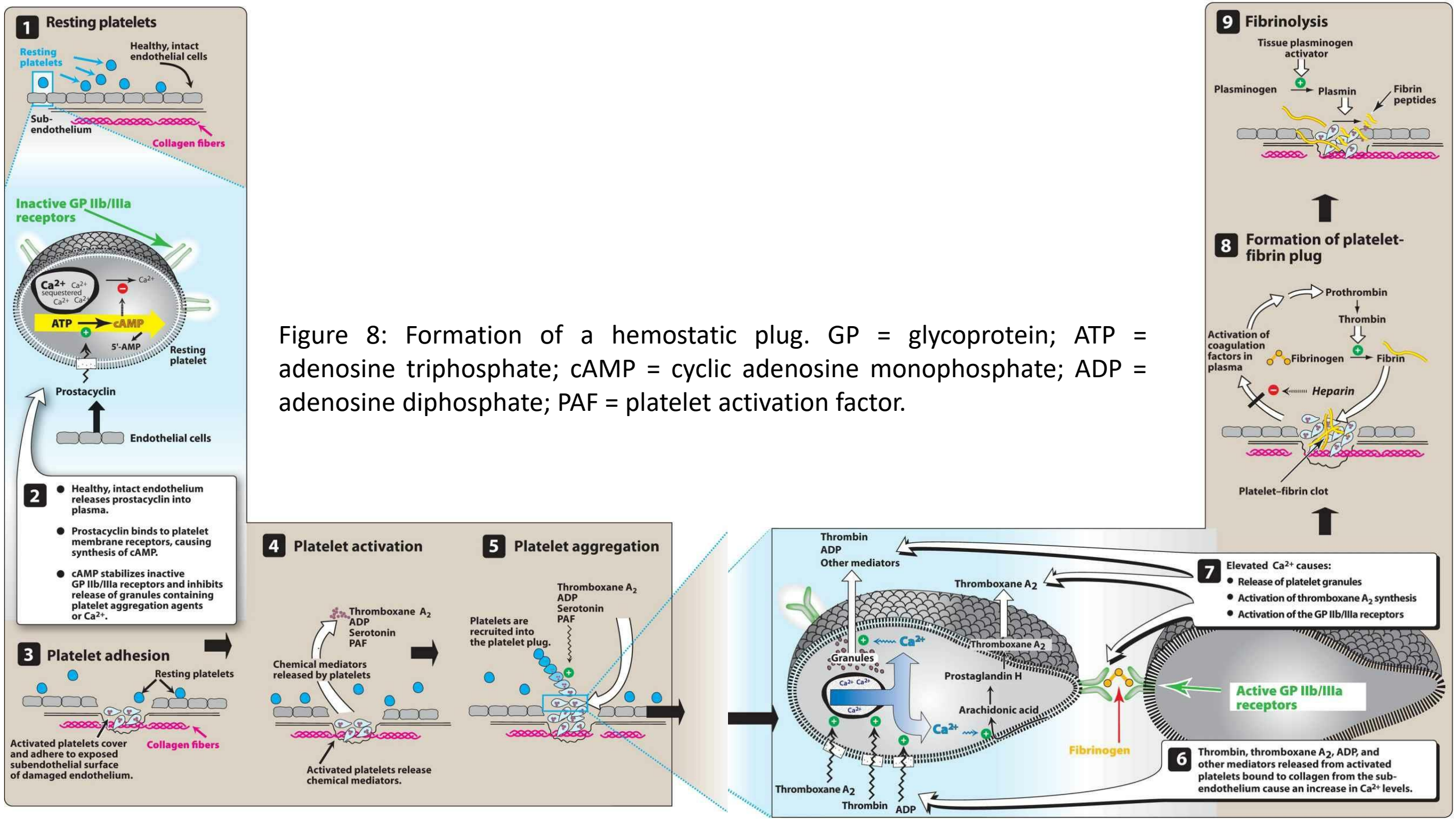

Figure 8: Formation of a hemostatic plug. GP = glycoprotein; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; ADP = adenosine diphosphate; PAF = platelet activation factor.

➢ Platelet Aggregation Inhibitors

- Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation.
- They 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
✓ As adjuncts to thrombin inhibitors or thrombolytic therapy in MI.

A. Aspirin

1. Mechanism of action

See figure 9.

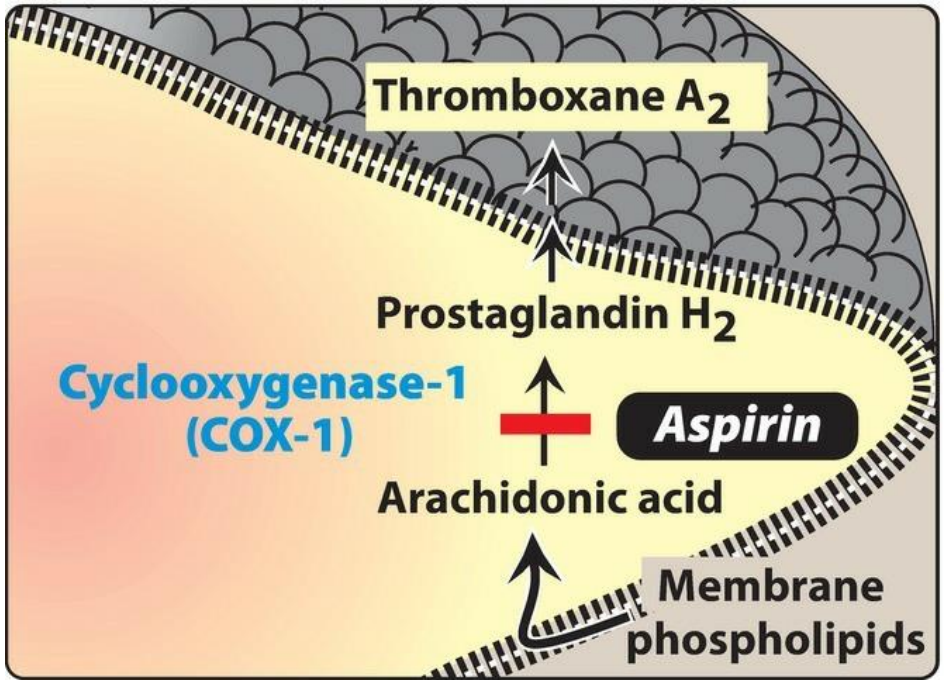

Figure 9: Aspirin irreversibly inhibits platelet cyclooxygenase-1.

- 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.

2. 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.
- The recommended antiplatelet dose of aspirin ranges from 50 to 325 mg daily.

3. 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.

4. Adverse effects

Higher doses of aspirin increase drug-related toxicities as well as the probability that aspirin may also inhibit prostacyclin production. For more details; see figure 12.

B. 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.

1. 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 (Figure 10).

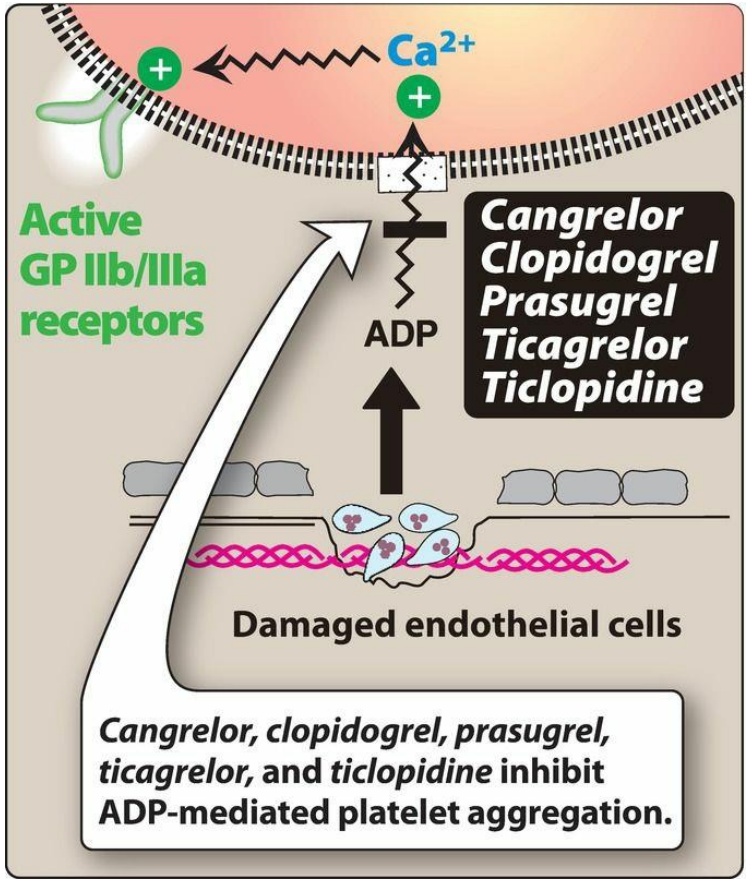

Figure 10: Mechanism of action of P2Y12 receptor antagonists. ADP = adenine diphosphate; GP = glycoprotein.

2. 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, prophylaxis of thrombotic events in acute coronary syndromes. Additionally, it is used to prevent thrombotic events associated with percutaneous coronary intervention (PCI) with or without coronary stenting.
- **Ticlopidine** 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, it 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.
- **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.

3. 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.
- In addition, other drugs that inhibit CYP 2C19, such as omeprazole and esomeprazole, should be avoided while on clopidogrel.

4. Adverse effects

These agents can cause prolonged bleeding for which there is no antidote. For more information; see figure 12.

C. Glycoprotein IIb/IIIa inhibitors

1. Mechanism of action

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 (Figure 11).

- **Eptifibatide and tirofiban** act similarly to abciximab.

2. 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.

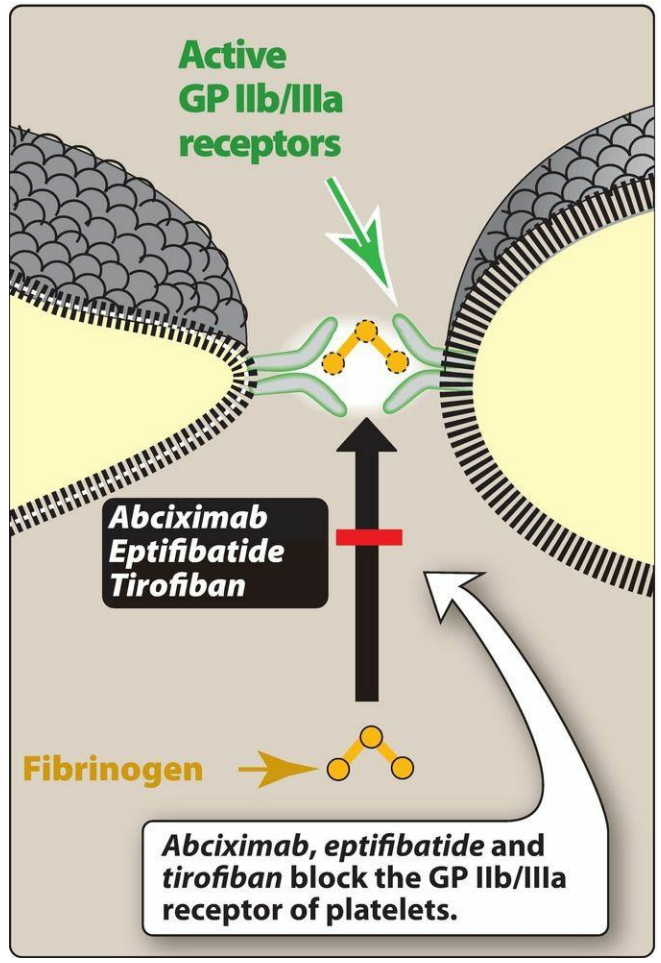

Figure 11: Mechanism of action of glycoprotein (GP) IIb/IIIa receptor blockers.

3. 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.

4. Adverse effects

The major adverse effect of these agents is bleeding, especially if used with anticoagulants. For more information; see figure 12.

D. Dipyridamole

- **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.

E. 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.

Medication	Adverse Effects	Drug Interactions	Monitoring Parameters
Oral Agents:			
Aspirin	Angioedema Bleeding Bronchospasm GI disturbances Reye syndrome SJS	Anticoagulants, P2Y12 inhibitors, NSAIDs—increased bleeding *cidofovir*—nephrotoxicity *probenecid*—decreased uricosuric effects	CBC LFT
Cilostazol	Bleeding GI disturbances Headache Peripheral edema SJS	Food (administer on empty stomach)	CBC
Clopidogrel	Bleeding SJS	Strong CYP2C19 inhibitors reduce antiplatelet effect (e.g., *omeprazole*)	CBC LFT
Dipyridamole	Bleeding Dizziness GI discomfort Rash	Salicylates—increased bleeding Thrombolytic agents—increased bleeding	None for oral administration
Prasugrel	Angioedema Bleeding Headache Hyperlipidemia Hypertension	Anticoagulants—increased bleeding Other antiplatelets—increased bleeding	CBC
Ticagrelor	Bleeding Dyspnea Headache Raised SCr	Strong CYP3A4 inhibitors (e.g., *ketoconazole*)—increased bleeding Strong CYP3A4 inducers (e.g., *rifampin*)—decreased efficacy	CBC LFT
Injectable Agents:			
Abciximab *Eptifibatide* *Tirofiban*	For all agents: Hypotension Nausea Vomiting Thrombocytopenia	For all agents: Increased bleeding: *Ginkgo biloba* Antiplatelets Salicylates SSRIs and SNRIs	For all agents: APTT clotting time H/H platelet count thrombin time

Figure 12: Summary of characteristics of platelet aggregation inhibitors. APTT = activated partial thromboplastin time, CBC = complete blood count, GI = gastrointestinal, H/H = hemoglobin and hematocrit, LFT = liver function test, NSAID = nonsteroidal anti-inflammatory drug, SCr = serum creatinine, SJS = Stevens-Johnson Syndrome, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Blood Coagulation

The coagulation process that generates thrombin consists of two interrelated pathways:

- The extrinsic system: is initiated by the activation of clotting factor VII by tissue factor (also known as thromboplastin). However, in response to vascular injury, tissue factor becomes exposed to blood. There, it can bind and activate factor VII, initiating the extrinsic pathway.

- The intrinsic systems: is triggered by the activation of clotting factor XII. This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.

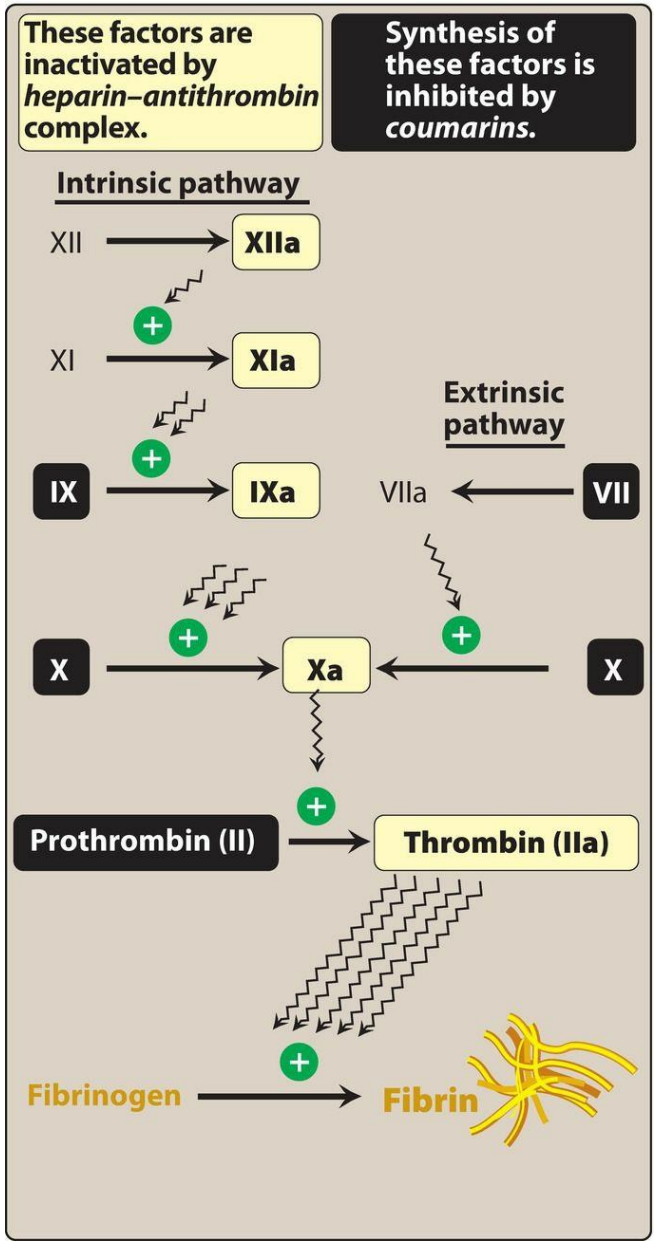

Figure 13: Formation of a fibrin clot. The active form of a clotting factor is denoted by the letter "a."

➢ Inhibitors of coagulation

Anticoagulants target various factors in the coagulation cascade, thereby **preventing formation of a stable fibrin meshwork.**

▪ Parenteral Anticoagulants

The anticoagulant drugs inhibit either the action of the coagulation factors (for example, **heparin**) or interfere with the synthesis of the coagulation factors **(warfarin).**

A. Heparin and low molecular weight heparins

- **Heparin** is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi.
- Heparin occurs naturally as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown. It is extracted for commercial use from porcine intestinal mucosa.
- Unfractionated heparin is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights.
- The realization that **low molecular weight forms of heparin (LMWHs)** can also act as anticoagulants led to the isolation of enoxaparin and dalteparin, produced by depolymerization of unfractionated heparin.

1. Mechanism of action

- Heparin acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors (Figure 14).
- In the absence of heparin, antithrombin III interacts very slowly with thrombin and factor Xa.
- When heparin molecules bind to antithrombin III, a conformational change occurs that catalyzes the inhibition of thrombin about 1000-fold.
- LMWHs complex with antithrombin III and inactivate factor Xa (including that located on platelet surfaces) but do not bind as avidly to thrombin.
- A unique pentasaccharide sequence contained in heparin and LMWHs permits their binding to antithrombin III (Figure 15).

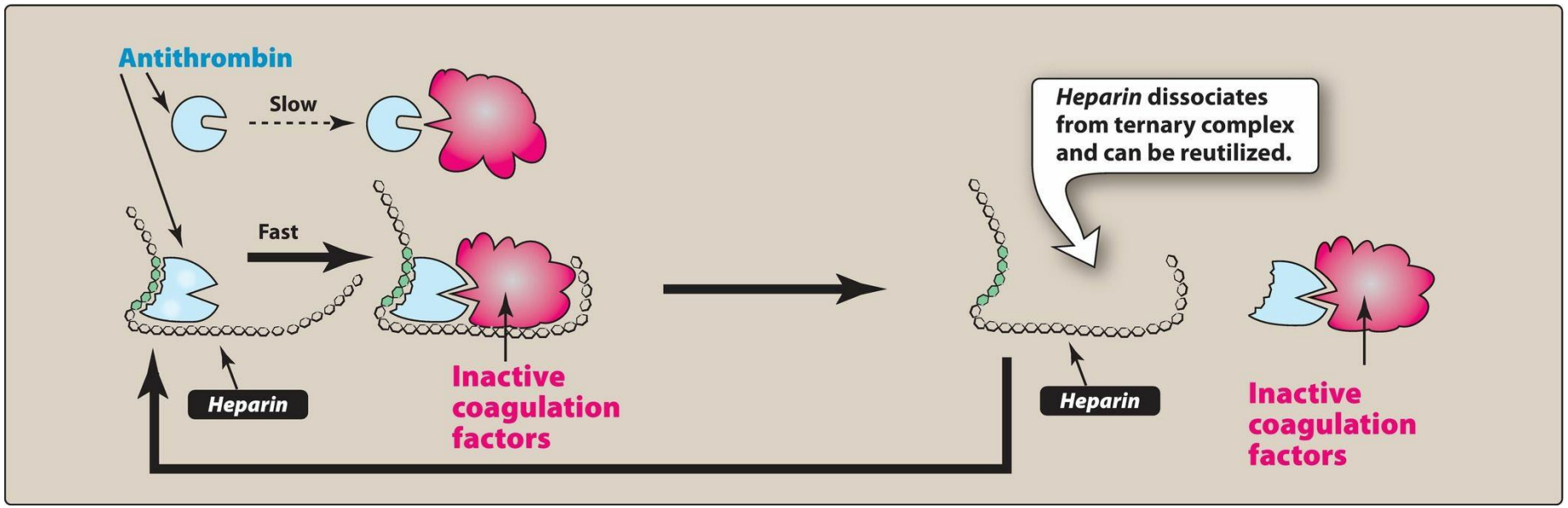

Figure 14: Heparin accelerates inactivation of coagulation factors by antithrombin.

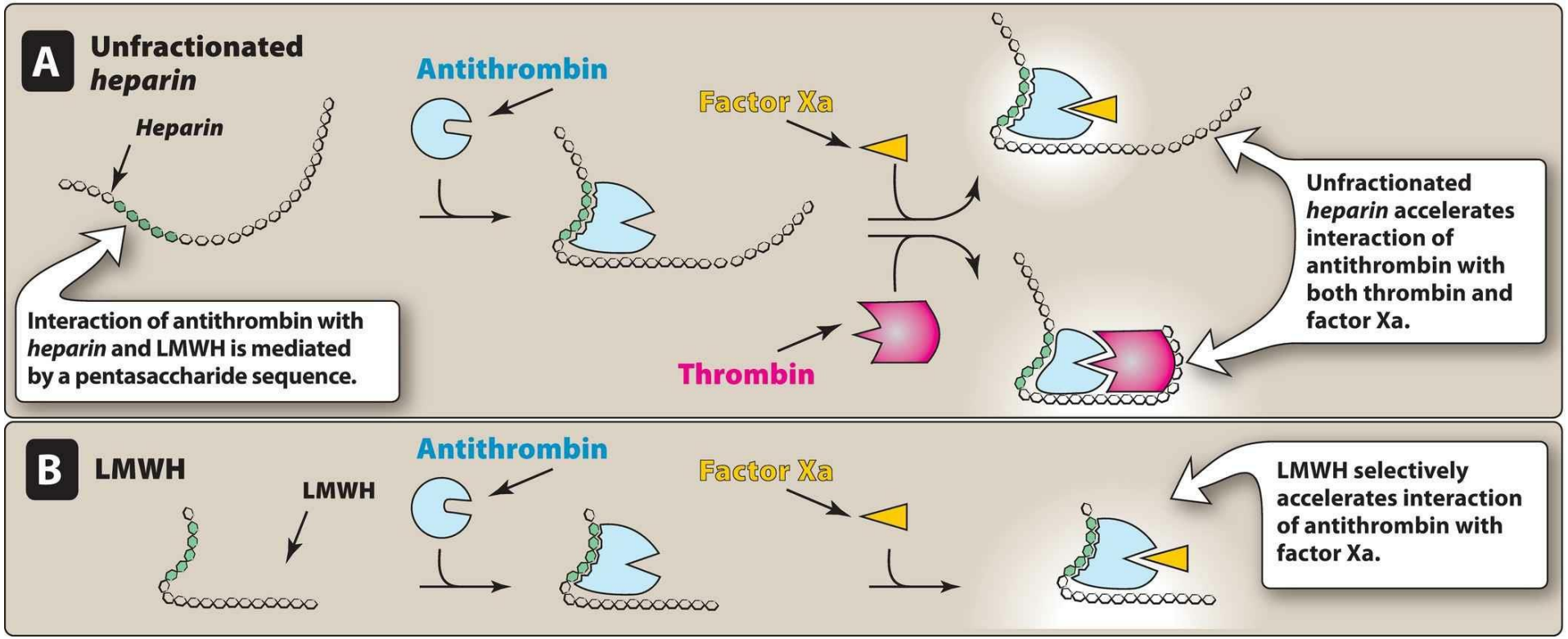

Figure 15: Heparin-mediated and low molecular weight heparin (LMWH)-mediated inactivation of thrombin or factor Xa.

2. Therapeutic use

- These agents are used for the treatment of acute venous thromboembolism (DVT or PE), prophylaxis of postoperative venous thrombosis in patients undergoing surgery and those with acute MI.
- These drugs are the anticoagulants of choice for treating pregnant women, because they do not cross the placenta, due to their large size and negative charge.
- LMWHs useful for both inpatient and outpatient therapy.

3. Pharmacokinetics

- Heparin must be administered subcutaneously or intravenously, because the drug does not readily cross membranes.
- The LMWHs are usually administered subcutaneously, enoxaparin can be administered intravenously in the treatment of MI.
- The anticoagulant effect with heparin occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection), the maximum anti–factor Xa activity of the LMWHs occurs about 4 hours after subcutaneous injection.
- In renally impaired, pregnant, and obese patients, monitoring of factor Xa levels is recommended with LMWHs.
- Heparin is taken up by the monocyte/macrophage system, and it undergoes depolymerization and desulfation to inactive products. The inactive metabolites, as well as some of the parent heparin undergo renal excretion.
- The LMWHs are primarily eliminated in the urine. Therefore, renal insufficiency prolongs the half-life of LMWH, and the dose of LMWH should be reduced in patients with renal impairment.
- The half-life of heparin is approximately 1.5 hours, whereas the half-life of the LMWHs is longer than that of heparin, ranging from 3 to 12 hours.

4. Adverse effects

- The chief complication of heparin and LMWH therapy is bleeding. Careful monitoring of the patient and laboratory parameters is required to minimize bleeding. Excessive bleeding may be managed by discontinuing the drug or by treating with protamine sulfate.
- Heparin may be antigenic. Possible adverse reactions include chills, fever, urticaria, and anaphylactic shock.
- Heparin-induced thrombocytopenia (HIT) is a serious condition, in which circulating blood contains an abnormally low number of platelets. This reaction is immune mediated and carries a risk of venous and arterial embolism.
- Heparin therapy should be discontinued when patients develop HIT or show severe thrombocytopenia.
- In cases of HIT, heparin can be replaced by another anticoagulant, such as argatroban.
- In addition, osteoporosis has been observed in patients on long-term heparin therapy.
- Heparin and LMWHs are contraindicated in patients who have hypersensitivity to heparin, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.


Thank You!