# Pharmacology

Dentistry Department

3rd Grade

## Antianginal Drugs

Dr. Ali Al-Athari

## Angina overview:

- **Atherosclerotic disease of the coronary arteries**, also known as **coronary artery disease (CAD)** or **ischemic heart disease (IHD)**, is the most common cause of mortality worldwide.
- **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 anginal pain**.
- **Typical angina pectoris is a characteristic sudden, severe, crushing chest pain that may radiate to the neck, jaw, back, and arms.** Patients may also present with dyspnea or atypical symptoms such as indigestion, nausea, vomiting, or diaphoresis.

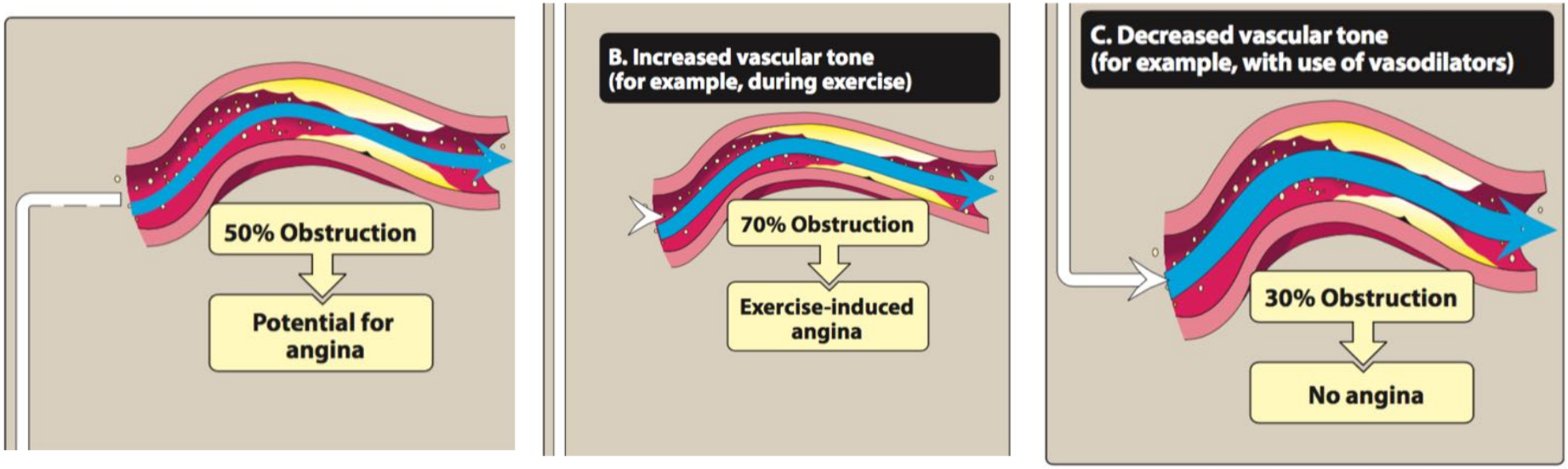
TYPES OF ANGINA :

## A. Stable angina, effort-induced angina, classic or typical angina

- **Classic angina is the most common form of angina** and, therefore, is also called **typical angina pectoris**. 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).**
- **Atypical presentations are more common in women, diabetic patients, and the elderly**.

- **Classic angina** is caused by **the reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis.**
- Due to the **fixed obstruction, the blood supply cannot increase, and the heart becomes vulnerable to ischemia whenever there is increased demand,** such as that produced by **physical activity, emotional stress or excitement**, or any other cause of increased cardiac workload
- Typical angina pectoris is promptly relieved by **rest or *nitroglycerin***.
- When the pattern of the chest pains and the amount of effort needed to trigger the chest pains do not vary over time, the angina is named **"stable angina."**

## A. Stable angina, effort-induced angina, classic or typical angina



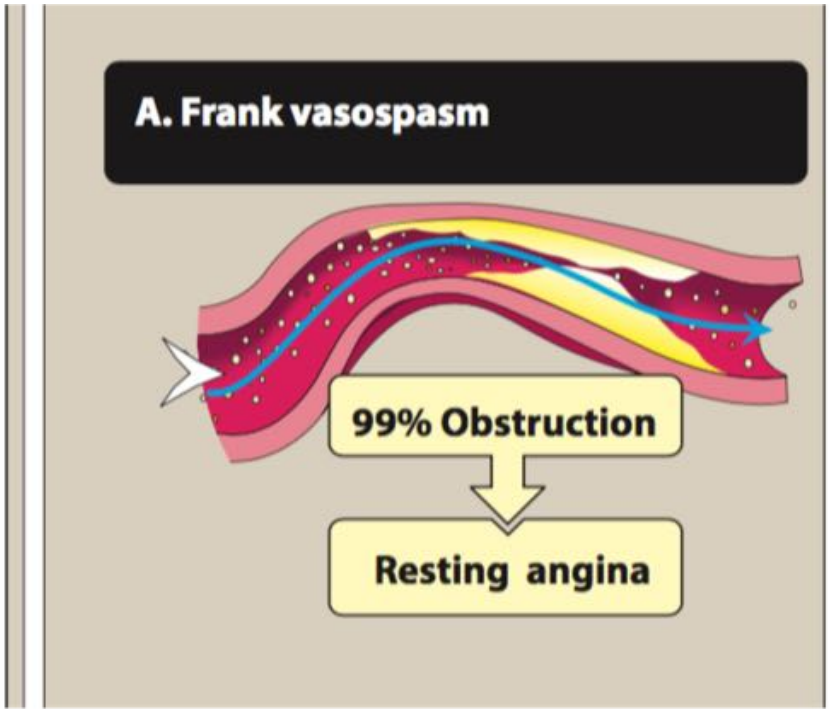
## B. Unstable angina

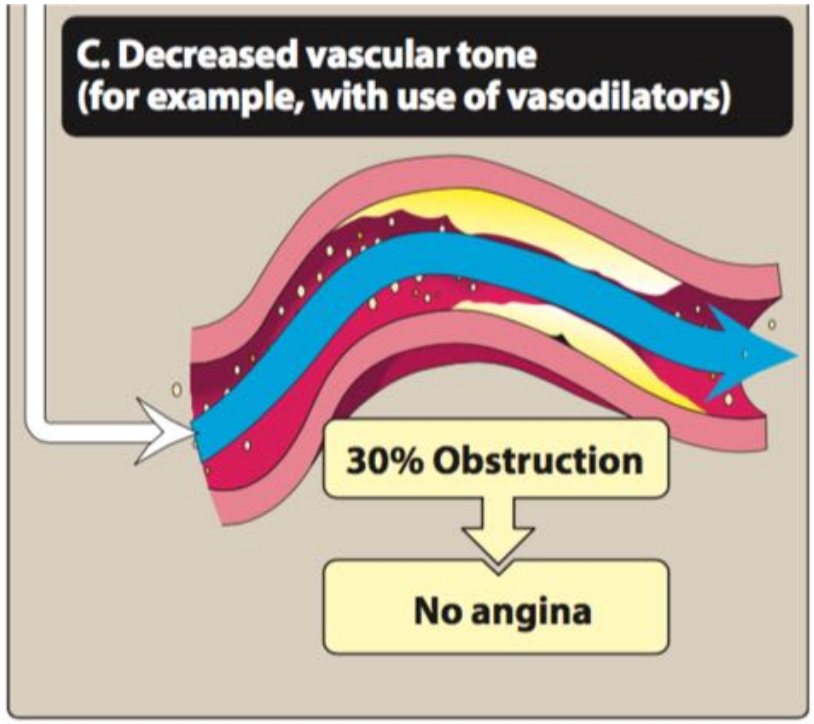
- **Unstable angina is classified between stable angina and MI**.
- In unstable angina, **chest pain occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort**.
- Any episode of rest angina **longer than 20 minutes**, any **sudden development of shortness of breath is suggestive of unstable angina**.
- **The symptoms are not relieved by rest or *nitroglycerin***.
- Unstable angina is **a form of acute coronary syndrome and requires hospital admission and more aggressive therapy to prevent progression to MI and death.**

## C. Prinzmetal, variant, vasospastic, or rest angina

- Prinzmetal angina is an uncommon pattern of **episodic angina that occurs at rest and is due to coronary artery spasm.**
- **Symptoms are caused by decreased blood flow to the heart muscle from the spasm of the coronary artery.**
- 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.**

## C. Prinzmetal, variant, vasospastic, or rest angina



**D. 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.**
- Most cases occur from **disruption of an atherosclerotic lesion, followed by platelet activation of the coagulation cascade and vasoconstriction. This process culminates in intra- luminal thrombosis and vascular occlusion**.
- 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.**
- [Note: **In unstable angina, no increases of biomarkers of myocardial necrosis are present.]**

# Antianginal drugs:

## 1-β-ADRENERGIC BLOCKERS: (propranolol, metoprolol and atenolol)

- The β-adrenergic blockers **decrease the oxygen demands of the myocardcardium 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 can be used to increase exercise duration and tolerance in patients with effort-induced angina.
- **β-Blockers are recommended as initial antianginal therapy in all patients** unless contraindicated. [Note: **The exception to this rule is vasospastic angina, in which β-blockers are ineffective and may actually worsen symptoms**.]
- β-Blockers **reduce the risk of death and MI in patients who have had a prior MI.**
- Agents **with intrinsic sympathomimetic activity (ISA) such as *pindolol* should be avoided in patients with angina and those who have had a MI.**
- It is **important not to discontinue β-blocker therapy abruptly. The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.**

## 2-CALCIUM CHANNEL BLOCKERS:

- Calcium is essential for muscular contraction. **Calcium influx is increased in ischemia** because of the membrane depolarization that hypoxia produces. In turn, this promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia.
- **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.**
- These agents primarily affect the resistance of peripheral and coronary arteriolar smooth muscle.
- **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.**

## 2-CALCIUM CHANNEL BLOCKERS:

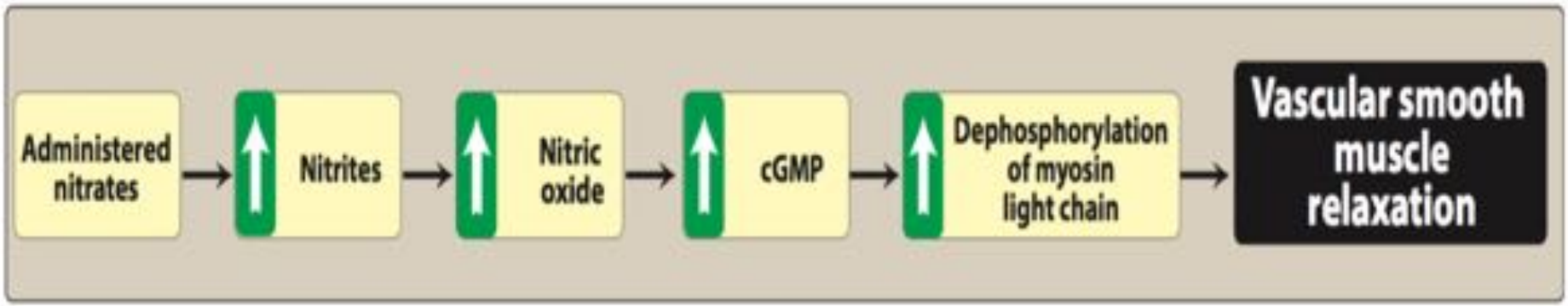
- [***Verapamil*** **mainly affects the myocardium, whereas** ***amlodipine*** **exerts a greater effect on smooth muscle in the peripheral vasculature.** ***Diltiazem*** **is intermediate in its actions.]**
- ***Amlodipine and Nifedipine:*** function mainly as **an arteriolar vasodilator.** This drug has **minimal effect on cardiac conduction**. The vasodilatory effect of these agents is useful in the treatment of **variant angina caused by spontaneous coronary spasm.**
- ***Diltiazem:*** **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.**
- ***Verapamil:*** **slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand.** *Verapamil* has greater negative inotropic effects than *amlodipine*, but it is a weaker vasodilator. *Verapamil* is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities.

## 3-ORGANIC NITRATES: (Nitroglycerin, *Isosorbide mononitrate and isosorbide dinitrate* )

- These compounds cause a **reduction in myocardial oxygen demand, followed by relief of symptoms.** They are effective **in stable, unstable, and variant angina.**

**Mechanism of action:**

- **Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions** and then to **nitric oxide**, which activates **guanylate cyclase** and **increases** the cells' cyclic guanosine monophosphate **(cGMP). Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation .**



- 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.** This is believed to be their main mechanism of action in the treatment of angina.
- Nitrates also **dilate the coronary vasculature, providing an increased blood supply to the heart muscle.**

**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*** .
- **For prompt relief of an angina attack precipitated by exercise or emotional stress, sublingual (or spray form) *nitroglycerin*** is **the drug of choice.** All patients suffering from angina should have ***nitroglycerin*** on hand to treat acute angina attacks.
- **Significant first-pass metabolism of *nitroglycerin*** occurs **in the liver**. Therefore, it is commonly administered via the **sublingual or transdermal route (patch),** thereby avoiding the hepatic first-pass effect.
- *Oral **Isosorbide mononitrate and isosorbide dinitrate** they have* improved bioavailability and **long duration of action due to its stability against hepatic breakdown.**

**Adverse effects:**

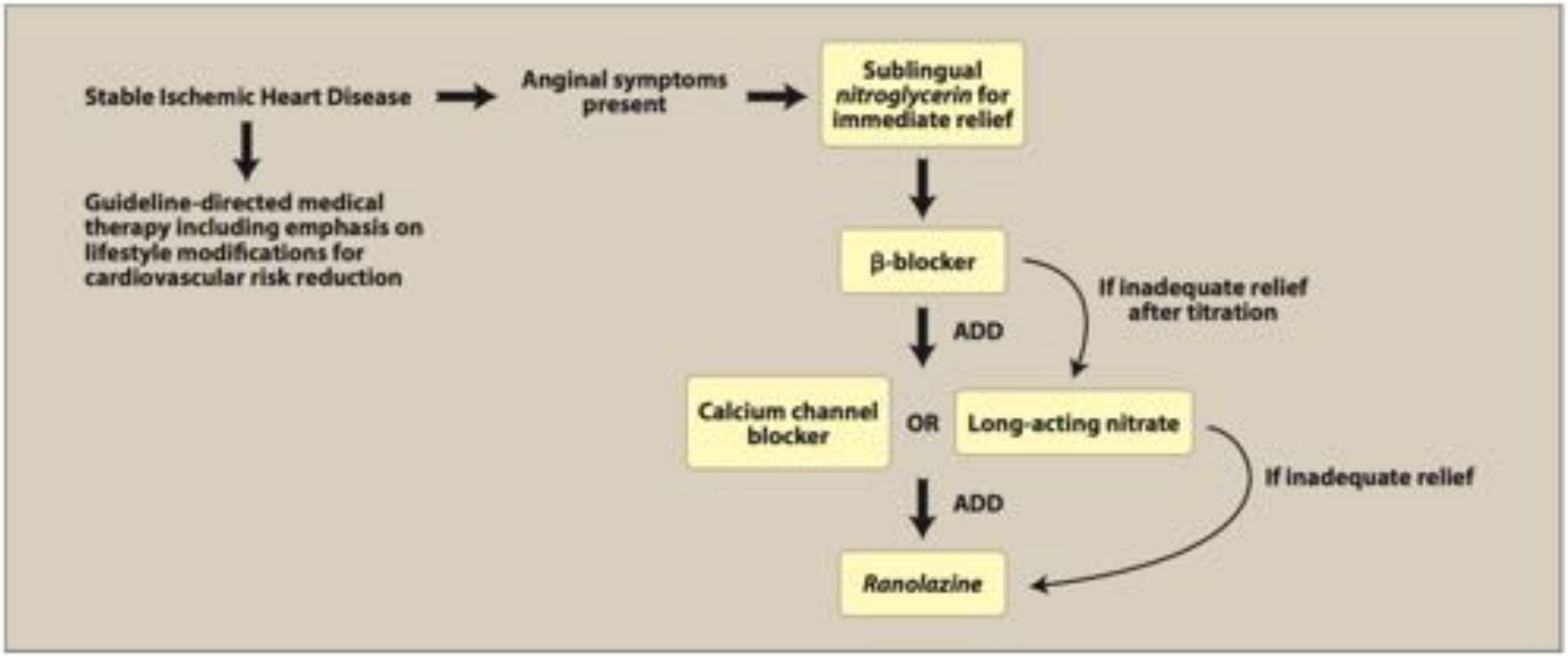
- **Headache** is the most common adverse effect of **nitrates.**
- High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia.
- **Phosphodiesterase type 5 inhibitors such as *sildenafil*** potentiate the action of the **nitrates.** To preclude the dangerous hypotension 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.** ***This interval of 10 to 12 hours is usually taken at night because demand on the heart is decreased at that time.***

## 4-SODIUM CHANNEL BLOCKER :

### *Ranolazine:*

- **inhibits the late phase of the sodium current (late $I_{Na}$), improving the oxygen supply and demand equation.**
- **Inhibition of late $I_{Na}$ reduces intracellular sodium and calcium overload,** thereby improving diastolic function.
- ***Ranolazine* has antianginal as well as antiarrhythmic properties. It is indicated for the treatment of chronic angina** and may be used alone or in combination with other traditional therapies.
- It is most often used in patients who have failed other antianginal therapies.

**Treatment algorithm for improving symptoms in patients with stable angina:**

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