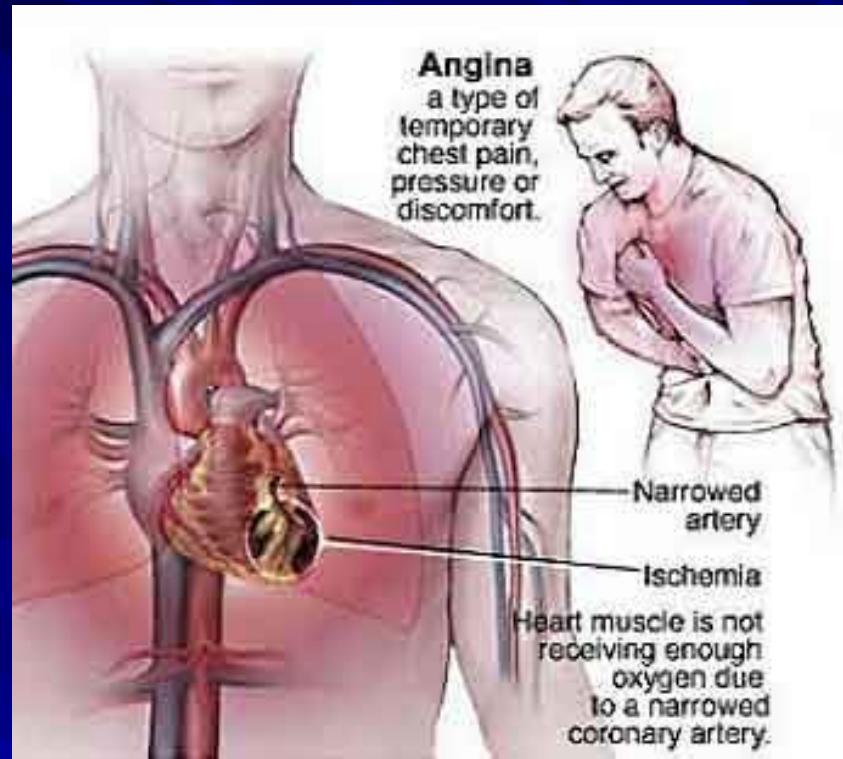




# **Drugs Used in Angina Pectoris**

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Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms. It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia.



- The imbalance between oxygen delivery and utilization may result during exertion, from a spasm of the vascular smooth muscle, or from obstruction of blood vessels caused by atherosclerotic lesions.

## **Types of Angina**

Angina pectoris has three overlapping patterns:

1. Stable or typical angina
2. Unstable angina
3. Prinzmetal's or variant angina.

## **Stable Angina (Typical Angina Pectoris):**

- It is caused by the reduction of coronary perfusion due to a fixed obstruction produced by coronary atherosclerosis. It is precipitated by physical activity, emotional excitement
- Typical angina pectoris is relieved by rest or nitroglycerin .

## **Unstable Angina**

- Lies between stable angina on the one hand and myocardial infarction on the other.
- It is unrelated to exercise
- Unstable angina requires hospital admission and more aggressive therapy to prevent death and progression to myocardial infarction.

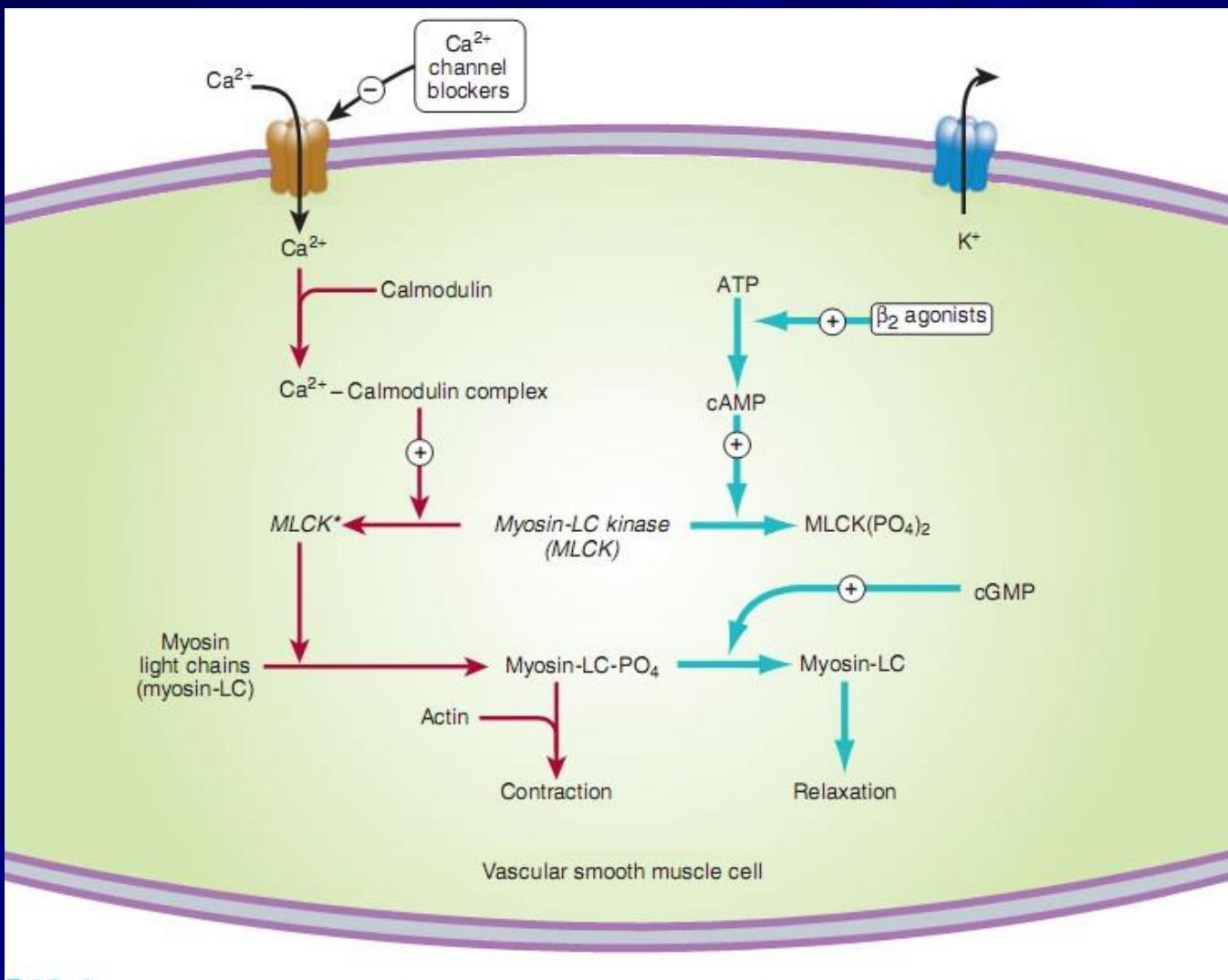
# **Prinzmetal's or Variant or Vasospastic Angina**

- It occurs at rest and is due to coronary artery spasm.
- It responds to coronary vasodilators, such as nitroglycerin and calcium-channel blockers.

## **Relaxtion of vascular smooth muscle occurs by several way:**

- Increasing cGMP
- Decreasing intracellular  $\text{Ca}^{+2}$
- Stabilizing or preventing depolarization of the vascular smooth muscle cell membrane
- Increasing cAMP in vascular smooth muscle cells

# Control of vascular smooth muscle contraction



## **Drugs used to treat Angina**

- Organic Nitrates
- $\beta$ -Adrenergic Blockers
- Calcium-Channel Blockers
- Newer Anti anginal Drugs

## Organic Nitrates

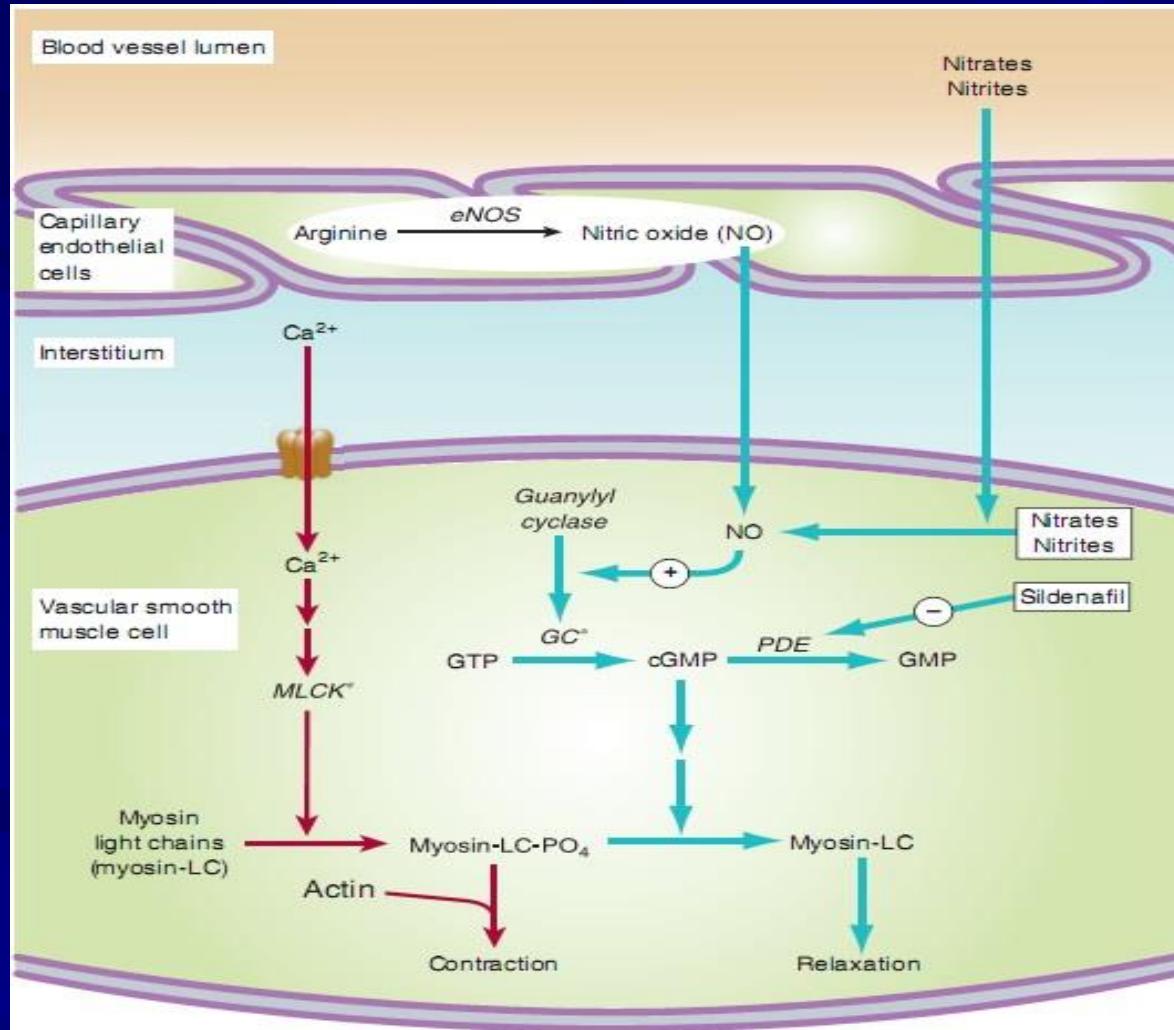
- These agents are simple nitric and nitrous acid esters of polyalcohols.
- Nitroglycerin (glyceryl trinitrate) may be considered the prototype of the group.
- All these agents are effective, but they differ in their onset of action and rate of elimination.
- Sublingual nitroglycerin is the drug of choice for relief of attack of angina precipitated by exercise or emotional stress

## Mechanism of Action

- Nitrates decrease coronary vasoconstriction or spasm
- Increase perfusion of the myocardium by relaxing coronary arteries.
- Relax veins
- Decreasing preload and myocardial oxygen consumption
- Nitroglycerin( glyceryl trinitrate) 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 (GMP). Elevated cGMP leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation

# Mechanism of action of nitrates.

MLCK (activated myosin light-chain kinase), GC (activated guanylyl cyclase). PDE (phosphodiesterase) .Enos (endothelial nitric oxide synthase)



## **Effects on the cardiovascular system**

At therapeutic doses, nitroglycerin has two major effects:

- It causes dilation of the large veins, resulting in pooling of blood in the veins. This diminishes preload (venous return to the heart) and reduces the work of the heart.
- Nitroglycerin dilates the coronary vasculature, providing an increased blood supply to the heart muscle.
- Nitroglycerin decreases myocardial oxygen consumption because of decreased cardiac work.

## **Beneficial and deleterious effects of nitrates in the treatment of angina.**

<b>Effect</b>	<b>Result</b>
<b>Potential beneficial effects</b>	
Decreased ventricular volume	Decreased myocardial oxygen requirement
Decreased arterial pressure	
Decreased ejection time	
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
<b>Potential deleterious effects</b>	
Reflex tachycardia	Increased myocardial oxygen requirement
Reflex increase in contractility	Increased myocardial oxygen requirement
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

## Pharmacokinetics

- Oral bioavailability of the organic nitrates eg, nitroglycerin and isosorbide dinitrate is low (< 10–20%).
- the sublingual route, which avoids the first-pass effect. Nitroglycerin and isosorbide dinitrate both are absorbed efficiently by this route and reach therapeutic blood levels within a few minutes.
- Duration of effect is (15–30 minutes).
- Oral preparations for longer duration of action can be given that contain an amount of drug sufficient to result in sustained systemic blood levels of the parent drug plus active metabolites
- Transdermal nitroglycerin is slow-release preparations

# Nitrate and nitrite drugs used in the treatment of angina

Drug	Dose	Duration of Action
<b>Short-acting</b>		
Nitroglycerin, sublingual	0.15–1.2 mg	10–30 minutes
Isosorbide dinitrate, sublingual	2.5–5 mg	10–60 minutes
Amyl nitrite, inhalant	0.18–0.3 mL	3–5 minutes
<b>Long-acting</b>		
Nitroglycerin, oral sustained-action	6.5–13 mg per 6–8 hours	6–8 hours
Nitroglycerin, 2% ointment, transdermal	1–1.5 inches per 4 hours	3–6 hours
Nitroglycerin, slow-release, buccal	1–2 mg per 4 hours	3–6 hours
Nitroglycerin, slow-release patch, transdermal	10–25 mg per 24 hours (one patch per day)	8–10 hours
Isosorbide dinitrate, sublingual	2.5–10 mg per 2 hours	1.5–2 hours
Isosorbide dinitrate, oral	10–60 mg per 4–6 hours	4–6 hours
Isosorbide dinitrate, chewable oral	5–10 mg per 2–4 hours	2–3 hours
Isosorbide mononitrate, oral	20 mg per 12 hours	6–10 hours

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## Adverse effects

- Throbbing Headache (From 30 - 60 % of patients)
- High doses of organic nitrates cause orthostatic hypotension, facial flushing, and tachycardia.
- long-acting preparations (oral, transdermal) or continuous intravenous infusions are used for more than a few hours without interruptioton may develop tolerance (tachyphylaxis) of isolated smooth muscle

- Sildenafil potentiates the action of the nitrates, this combination is contraindicated because of dangerous hypotension

## **β-Adrenergic Blockers**

Although they are not vasodilators (with the exception of carvedilol and nebivolol ,both of them are vasodilators ), β-blocking are useful in the management of effort angina.

## The beneficial effects of $\beta$ -blocking agents are related to

- Their hemodynamic effects
- Decrease the oxygen demands of the myocardium by lowering both the rate and the force of contraction of the heart
- They suppress the activation of the heart by receptors, and they reduce the work of the heart by decreasing heart rate, contractility, cardiac output, and blood pressure

# The 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

## **Verapamil (Diphenylalkylamine)**

- Mainly affects the myocardium
- Slows cardiac atrioventricular (AV) conduction directly, and decreases heart rate, contractility, blood pressure, and oxygen demand.
- Verapamil causes greater negative inotropic effects than nifedipine, but it is a weaker vasodilator.
- The drug is extensively metabolized by the liver; therefore, care must be taken to adjust the dose in patients with liver dysfunction

## **Nifedipine, Amlodipine, Nicardipine, and Felodipine (a dihydropyridine derivative)**

- Nifedipine exerts a greater effect on smooth muscle in the peripheral vasculature, it functions mainly as an arteriolar vasodilator, it has minimal effect on cardiac conduction or heart rate.
- Amlodipine, nicardipine, and felodipine, have similar cardiovascular characteristics except for amlodipine, which does not affect heart rate or cardiac output

## Diltiazem

- Diltiazem has cardiovascular effects that are similar to those of verapamil. Both drugs slow AV conduction
- Diltiazem reduces the heart rate, although to a lesser extent than verapamil, and also decreases blood pressure.
- It Can relieve coronary artery spasm so it is useful in patients with variant angina. It is metabolized by the liver.
- The incidence of adverse side effects is low (the same as those for other calcium-channel blockers).

- All calcium-channel blockers lower blood pressure. They may worsen heart failure due to their negative inotropic effect.
- Variant angina caused by spontaneous coronary spasm (either at work or at rest) rather than by increased myocardial oxygen requirement is controlled by organic nitrates or calcium-channel blockers; B-blockers are contraindicated

## Newer Antianginal Drugs

### Ranolazine

- It is a newer antianginal drug that appears to act by reducing a late sodium current that facilitates calcium entry via the sodium-calcium exchanger. The resulting reduction in intracellular calcium concentration reduces cardiac contractility and work.

## **Bradycardic Drugs ( Ivabradine)**

- Selective If sodium channel blockers, reduce cardiac rate by inhibiting the hyperpolarization-activated sodium channel in the sinoatrial node.
- Ivabradine appears to reduce anginal attacks with an efficacy similar to that of calcium channel blockers and  $\beta$  blockers.

## **Allopurinol**

- Allopurinol inhibits xanthine oxidase an enzyme that contributes to oxidative stress and endothelial dysfunction.
- A recent study suggests that high-dose allopurinol prolongs exercise time in patients with atherosclerotic angina.

# Summary Drugs Used In Angina Pectoris

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
<b>NITRATES</b>				
• Nitroglycerin	Releases nitric oxide in smooth muscle, which activates guanylyl cyclase and increases cGMP	Smooth muscle relaxation, especially in vessels • other smooth muscle is relaxed but not as markedly • vasodilation decreases venous return and heart size • may increase coronary flow in some areas and in variant angina	Angina: Sublingual form for acute episodes • oral and transdermal forms for prophylaxis • IV form for acute coronary syndrome	High first-pass effect, so sublingual dose is much smaller than oral • high lipid solubility ensures rapid absorption • Toxicity: Orthostatic hypotension, tachycardia, headache • Interactions: Synergistic hypotension with phosphodiesterase type 5 inhibitors (sildenafil, etc)
<ul style="list-style-type: none"> <li>• <i>Isosorbide dinitrate</i>: Very similar to nitroglycerin, slightly longer duration of action</li> <li>• <i>Isosorbide mononitrate</i>: Active metabolite of the dinitrate; used orally for prophylaxis</li> </ul>				
<b>BETA BLOCKERS</b>				
• Propranolol	Nonselective competitive antagonist at $\beta$ adrenoceptors	Decreased heart rate, cardiac output, and blood pressure • decreases myocardial oxygen demand	Prophylaxis of angina • for other applications, see Chapters 10, 11, and 13	Oral and parenteral, 4–6 h duration of action • Toxicity: Asthma, atrioventricular block, acute heart failure, sedation • Interactions: Additive with all cardiac depressants
<ul style="list-style-type: none"> <li>• Atenolol, metoprolol, others: <math>\beta_1</math>-Selective blockers, less risk of bronchospasm, but still significant</li> <li>• See Chapters 10 and 11 for other <math>\beta</math> blockers and their applications</li> </ul>				
<b>CALCIUM CHANNEL BLOCKERS</b>				
• Verapamil, diltiazem	Nonselective block of L-type calcium channels in vessels and heart	Reduced vascular resistance, cardiac rate, and cardiac force results in decreased oxygen demand	Prophylaxis of angina, hypertension, others	Oral, IV, duration 4–8 h • Toxicity: Atrioventricular block, acute heart failure; constipation, edema • Interactions: Additive with other cardiac depressants and hypotensive drugs
• Nifedipine (a dihydropyridine)	Block of vascular L-type calcium channels > cardiac channels	Like verapamil and diltiazem; less cardiac effect	Prophylaxis of angina, hypertension	Oral, duration 4–6 h • Toxicity: Excessive hypotension, baroreceptor reflex tachycardia • Interactions: Additive with other vasodilators
<ul style="list-style-type: none"> <li>• Other dihydropyridines: Like nifedipine but slower onset and longer duration (up to 12 h or longer)</li> </ul>				

# Treatment of angina in patients with concomitant diseases. COPD = chronic obstructive pulmonary disease

CONCOMITANT DISEASE	DRUGS COMMONLY USED IN TREATING ANGINA		
NONE	Long-acting nitrate	β-Blockers	Ca <sup>2+</sup> channel blockers
RECENT MYOCARDIAL INFARCTION	Long-acting nitrate	β-Blockers	
ASTHMA, COPD	Long-acting nitrate		Ca <sup>2+</sup> channel blockers
HYPERTENSION	Long-acting nitrate	β-Blockers	Ca <sup>2+</sup> channel blockers
DIABETES	Long-acting nitrate		Ca <sup>2+</sup> channel blockers
CHRONIC RENAL DISEASE	Long-acting nitrate	β-Blockers	Ca <sup>2+</sup> channel blockers
KEY:		Drug class Commonly used drugs	Drug class Less effective drugs