

# **ANTI-ANGINAL AND ANTI-ISCHEMIC DRUGS**

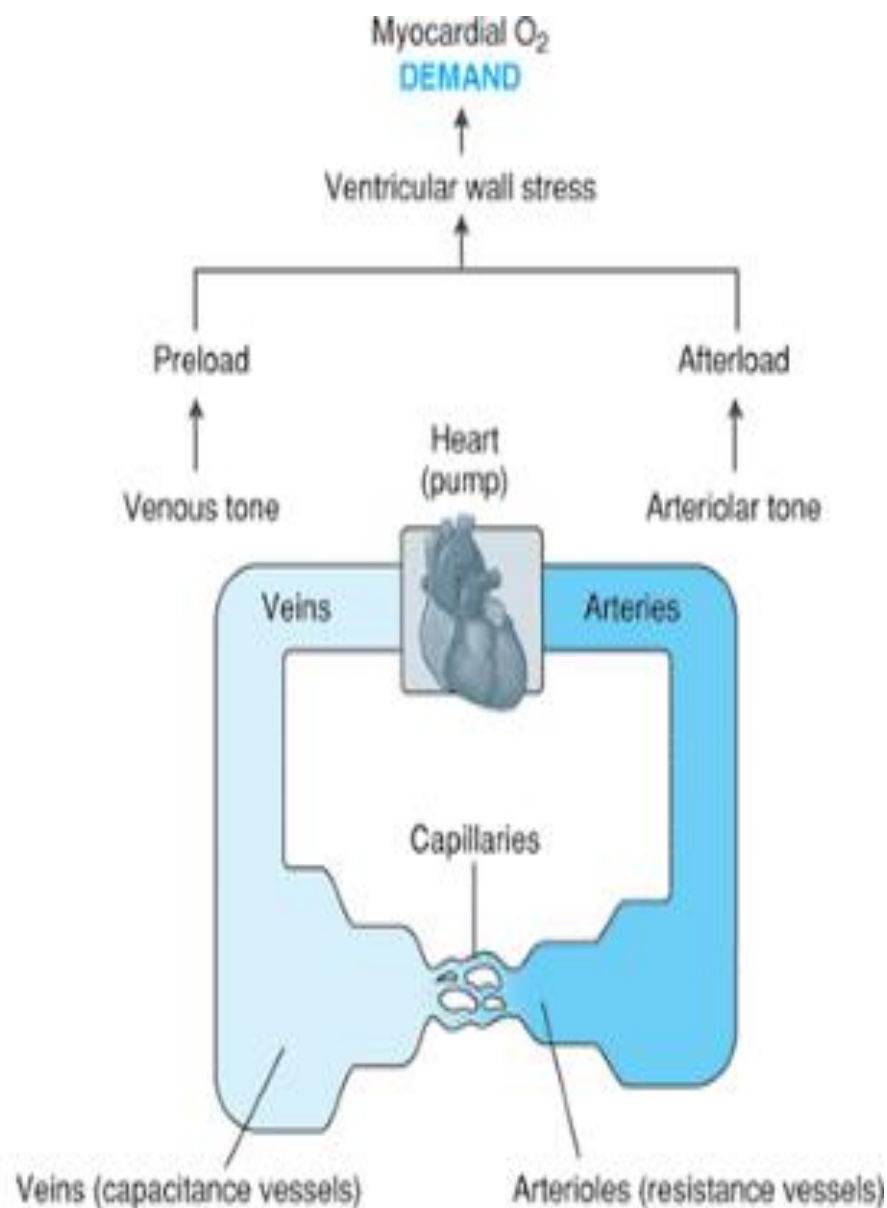
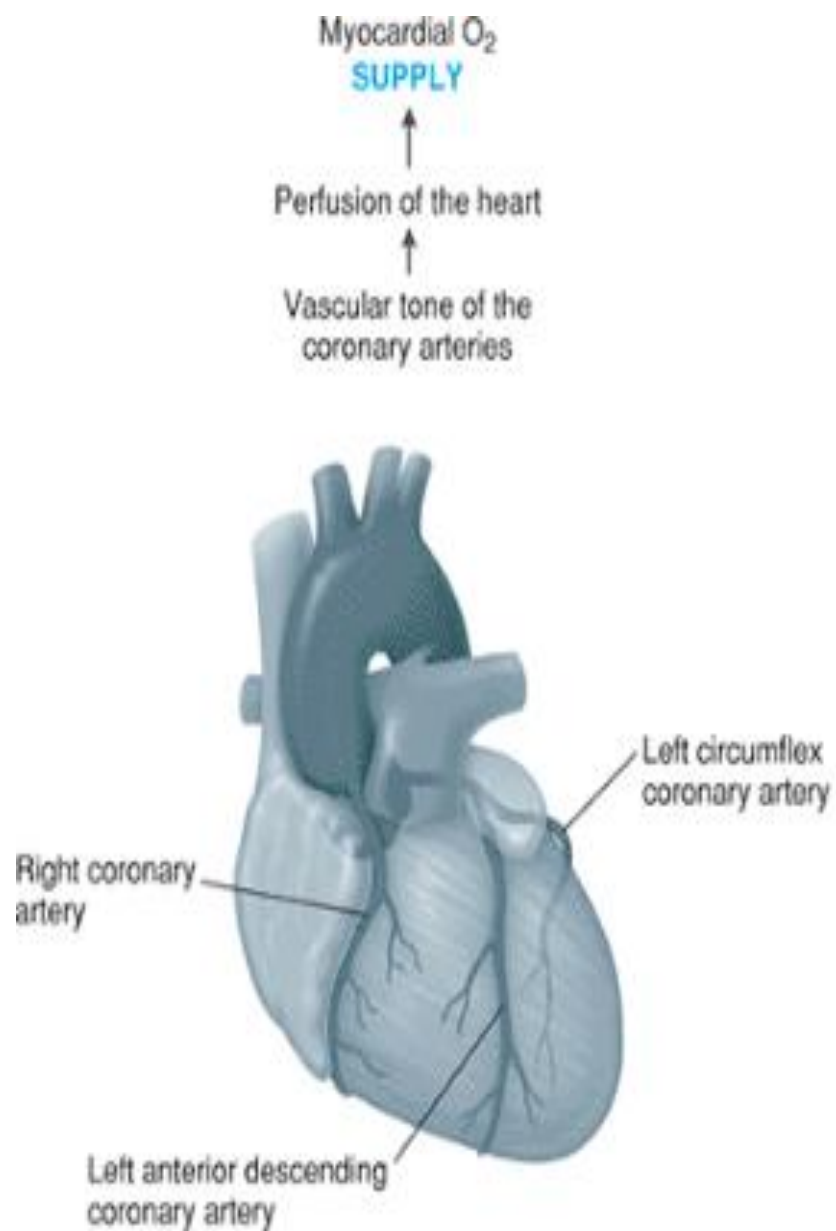
## **Definitions**

**Ischemia:** Is the inadequate blood supply to a part of the body, even to the point of complete deprivation.

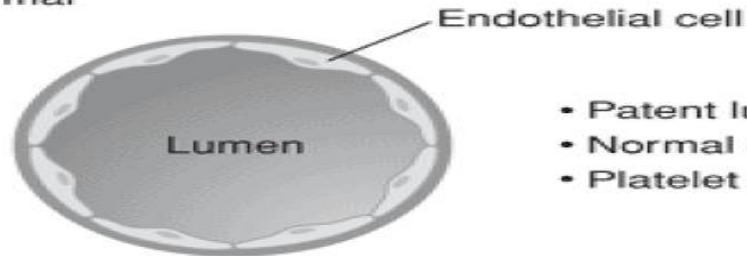
**Ischemic heart disease (IHD):** It is defined as acute or chronic form of cardiac disability arising from imbalance between between the myocardial supply and demand for oxygenated blood eg. Angina pectoris and myocardial infarction .

**Angina pectoris:** It is a clinical syndrome of **IHD** resulting from transient myocardial ischemia.

It is characterized by pain in the substernal or pre-cordial region of the chest which is aggravated by an increase in the demand of the heart and relieved by decrease in the work of the heart. Often pain radiated to left arm, neck, jaw or right arm.

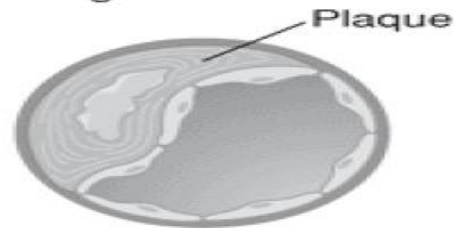


**A Normal**



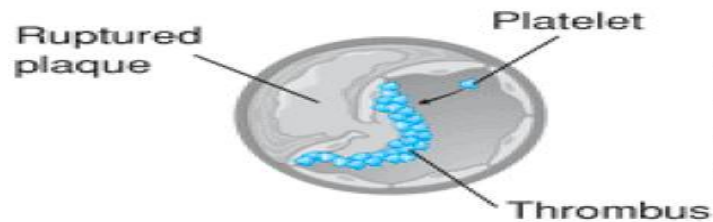
- Patent lumen
- Normal endothelial function
- Platelet aggregation inhibited

**B Stable angina**



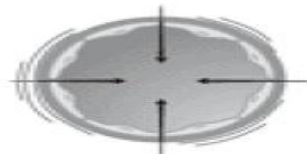
- Lumen narrowed by plaque
- Inappropriate vasoconstriction

**C Unstable angina**



- Plaque ruptured
- Platelet aggregation
- Thrombus formation
- Unopposed vasoconstriction

**D Variant angina**



- No overt plaques
- Intense vasospasm

## Types of angina

# Classification

## 1. Nitrates

- a) *Short acting*: Glyceryl trinitrate (GNT, Nitoglycerine)
- b) *Long acting*: Isosorbide dinitrate, Isosorbide mononitrate, Erythrityl tetranitrate

## 2. $\beta$ - blockers: Propranolol, Metoprolol, Atenolol

## 3. Calcium channel blockers

- a) *Phenyl alkylamine*: Verapamil
- b) *Benzothiazepine*: Diltiazem
- c) *Dihydropyridines*: Nifedipine, Nimodipine, Lacidipine, Lercanidipine, Benidipine

## 4. Potassium channel opener: Nicorandil

## 5. Others: Dipyridamole, Trimetazidine, Ranolazine, Ivabradine, Oxyphendrine

## **Pharmacology of nitrates**

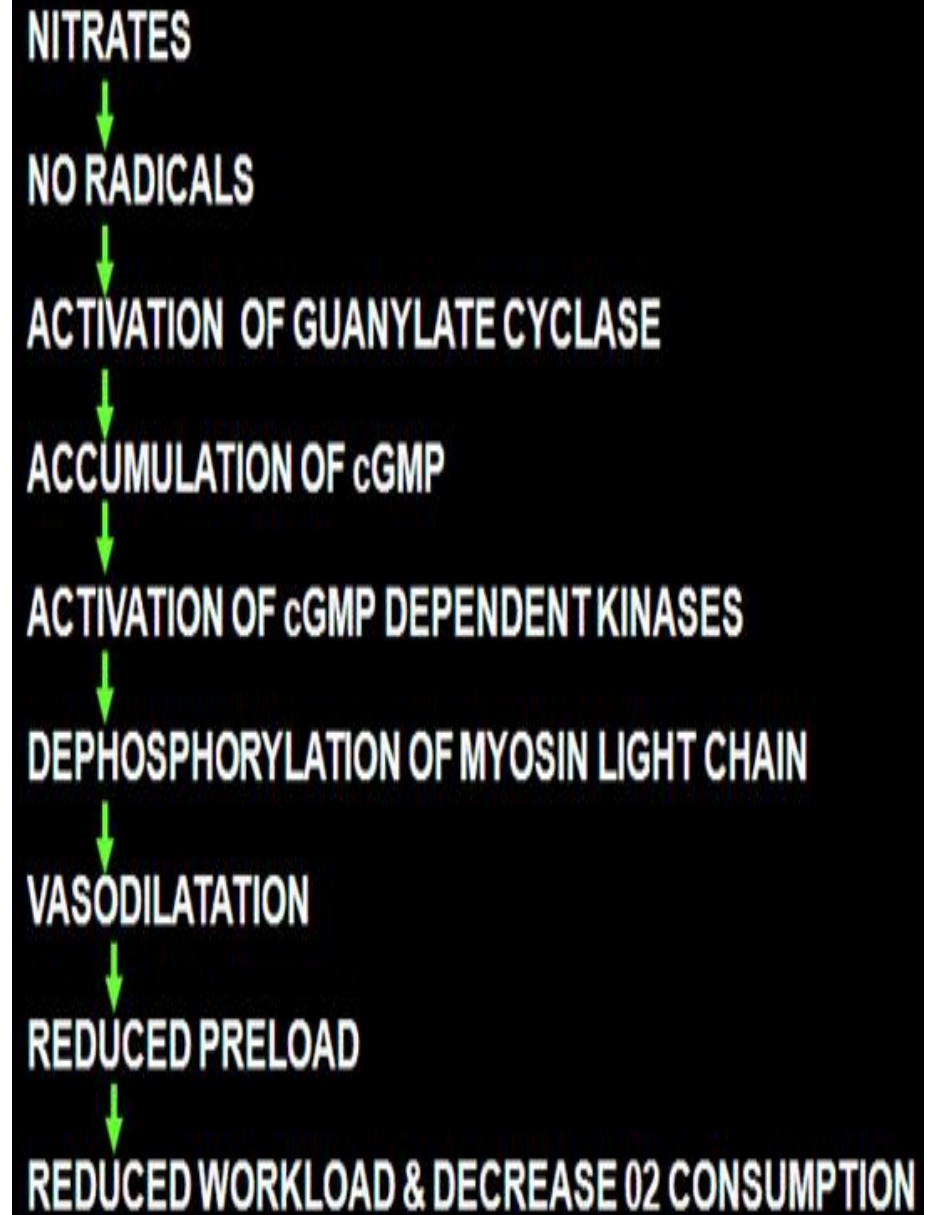
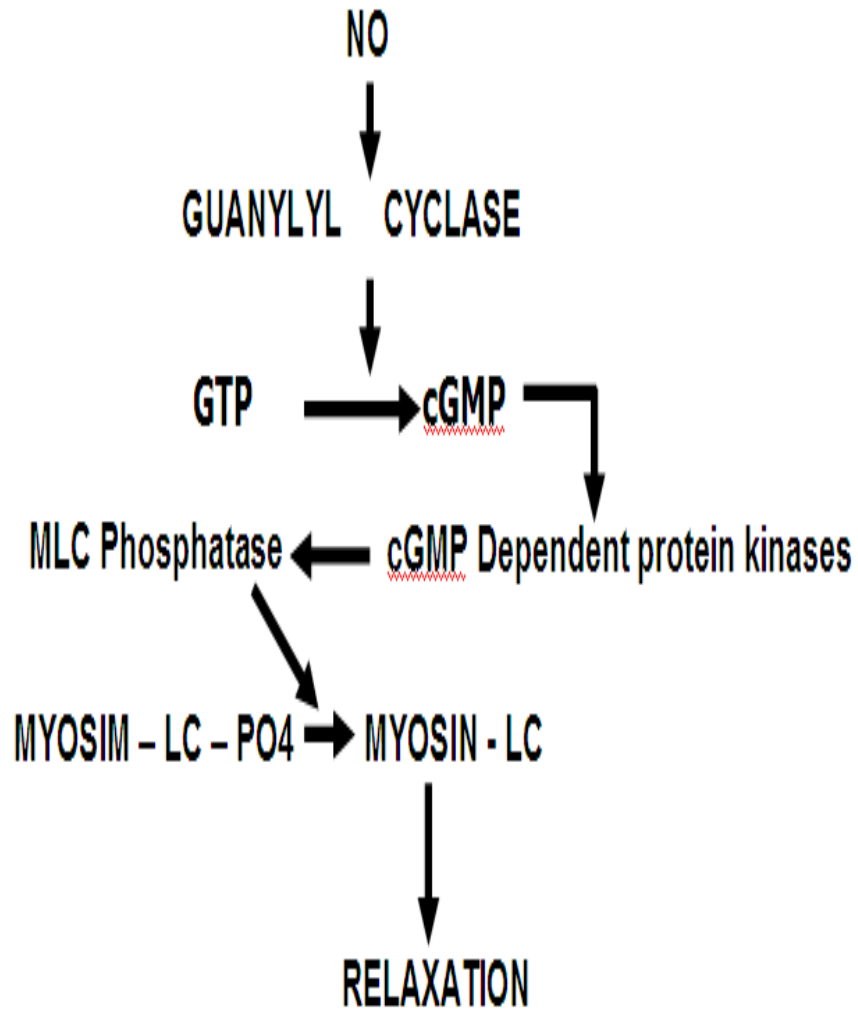
### **Nitroglycerin**

1. Preload reduction
2. After-load reduction
3. Redistribution of coronary flow
4. Relief in angina

### **Pharmacokinetics**

Nitrates are lipid soluble well absorbed from buccal mucosa, intestine and skin therapeutic nitrates and is available in forms that provide a range of durations of action from 10–20 min (sublingual) to 8–10 h (transdermal). They undergo extensive first pass metabolism in liver. Rapidly denitrated by glutathione reductase and mitochondrial aldehyde dehydrogenase.

NITRATES + ENDOTHELIAL CELLS (SH)



**Mode of action of organic nitrates**

## **Tolerance**

1. Tolerance may result from a reduced capacity of the vascular smooth muscle to convert nitroglycerin to NO
2. Multiple mechanisms have been proposed to account for nitrate tolerance, including
  - i) Volume expansion
  - ii) Neurohumoral activation
  - iii) Cellular depletion of sulfhydryl groups, and the generation of free radicals.
  - iv) Inactivation of mitochondrial aldehyde dehydrogenase, an enzyme implicated in biotransformation of nitroglycerin

## **Adverse drug reactions**

The most common toxic effects of nitrates are the responses evoked by vasodilation.

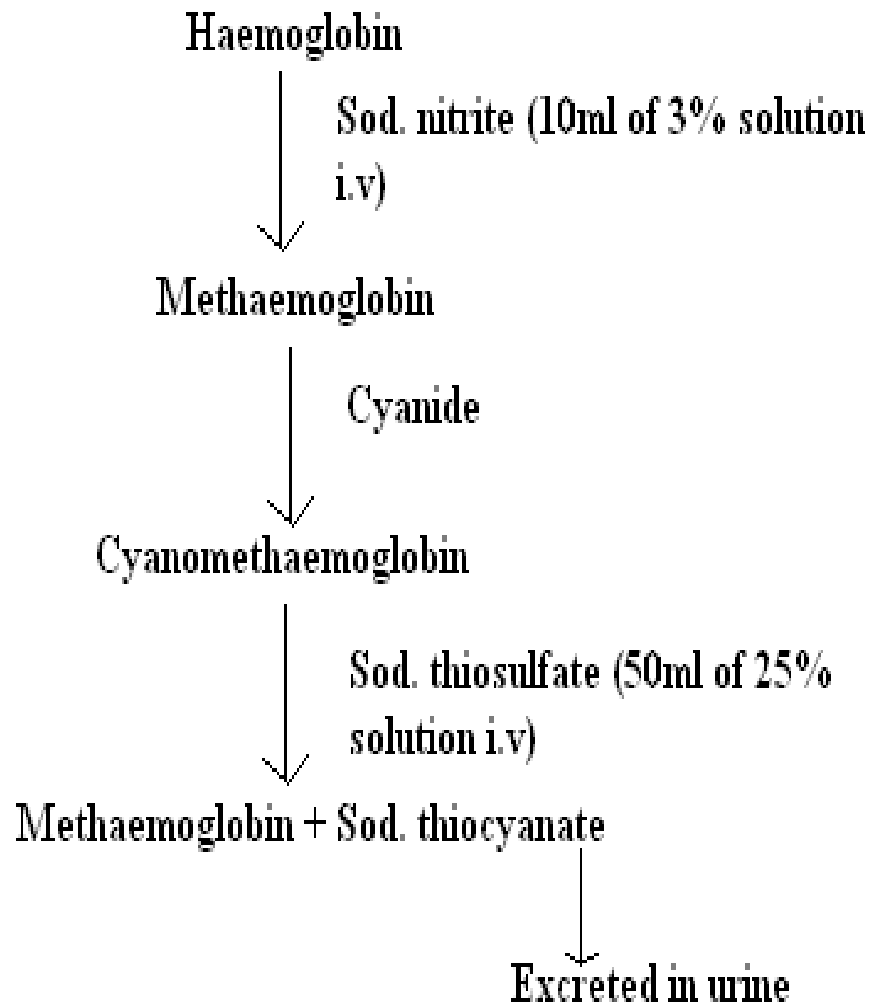
1. These include tachycardia (from the baroreceptor reflex)
2. Orthostatic hypotension (a direct extension of the venodilator effect), and
3. Throbbing headache from meningeal artery vasodilatation.

## **Drug interaction**

Nitrates + Sildenafil can lead to severe hypotension, myocardial infarction and death

## Uses

1. Angina pectoris
2. Acute coronary syndromes
3. Myocardial infarction (MI)
4. CHF and acute LVF
5. Biliary colic
6. Esophageal spasm
7. Cyanide poisoning



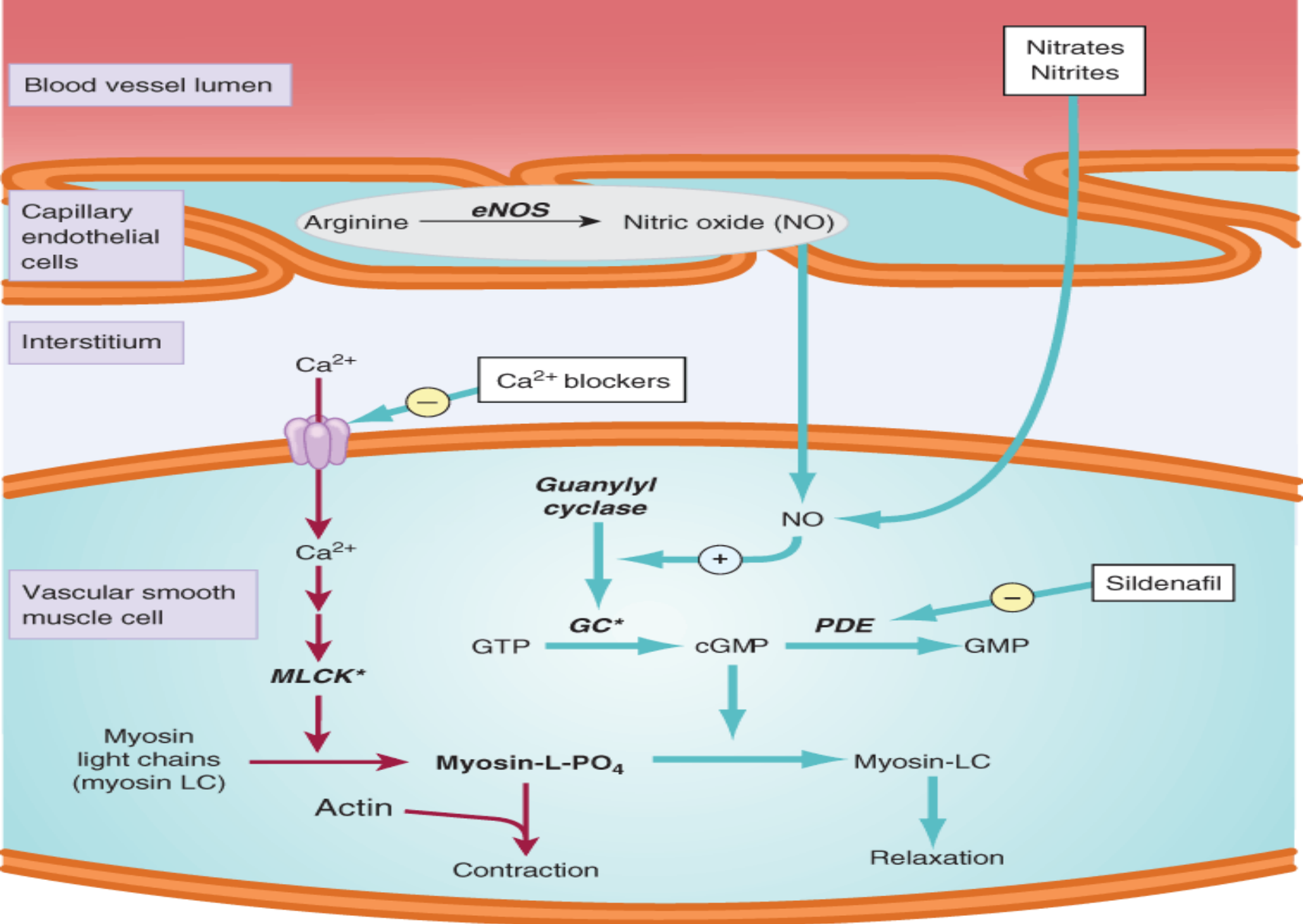
## **β- blockers**

1. Adrenergic receptor antagonists are effective in reducing the severity and frequency of attacks of exertional angina and in improving survival in patients who have had an MI.
2. These agents are not useful for vasospastic angina and, if used in isolation, may worsen the condition.
3. ***Timolol, metoprolol, atenolol, and propranolol*** have been shown to exert cardioprotective effects. The effectiveness of adrenergic receptor antagonists in the treatment of exertional angina is attributable primarily to a fall in myocardial O<sub>2</sub> consumption at rest and during exertion,
4. The decrease in myocardial O<sub>2</sub> consumption is due to a negative chronotropic effect (particularly during exercise), a negative inotropic effect, and a reduction in arterial blood pressure (particularly systolic pressure) during exercise.

# **Calcium channel blockers**

## **Mechanism of Action**

1. Calcium channel blockers block voltage-gated L-type calcium channels, the calcium channels most important in cardiac and smooth muscle.
2. By decreasing calcium influx during action potentials in a frequency- and voltage-dependent manner, these agents reduce intracellular calcium concentration and muscle contractility.



## **Adverse drug reactions**

1. The calcium channel blockers cause constipation, pretibial edema, nausea, flushing, and dizziness.
2. More serious adverse effects include heart failure, AV blockade, and sinus node depression; these are most common with verapamil and least common with the dihydropyridines.

## **Use**

1. Verapamil and Diltiazem may be used to treat AV nodal arrhythmia.
2. Calcium blockers are effective as prophylactic therapy in both
3. Effort and vasospastic angina.
4. Nifedipine has also been used to abort acute anginal
5. In severe atherosclerotic angina, these drugs are particularly valuable when combined with nitrates.
6. In addition to well-established uses in angina, hypertension, and supraventricular tachycardia, some of these agents are used in migraine, preterm labor, stroke, and Raynaud's phenomenon.

## **Potassium channel opener: Nicorandil**

1. This a novel antianginal drug activates ATP sensitive  $K^+$  channels leading to hyperpolarization of vascular smooth muscle.
2. It also acts as a NO donor and relaxes blood vessels by increasing cGMP.
3. Coronary blood flow is increased, dilatation of both epicardial conducting vessels and deeper resistance vessel.
4. Mitochondrial  $K^+_{ATP}$  channel opening exert myocardial protection by preconditioning which appears to reduce myocardial stunning, arrhythmias and infarct size.

## **Side effect**

1. Flushing, palpitation, weakness, headache, dizziness
2. Large painful aphthous ulcers of mouth.

## Newer Drugs

**A) Ranolazine** appears to act mainly by reducing a late, prolonged sodium current in myocardial cells.

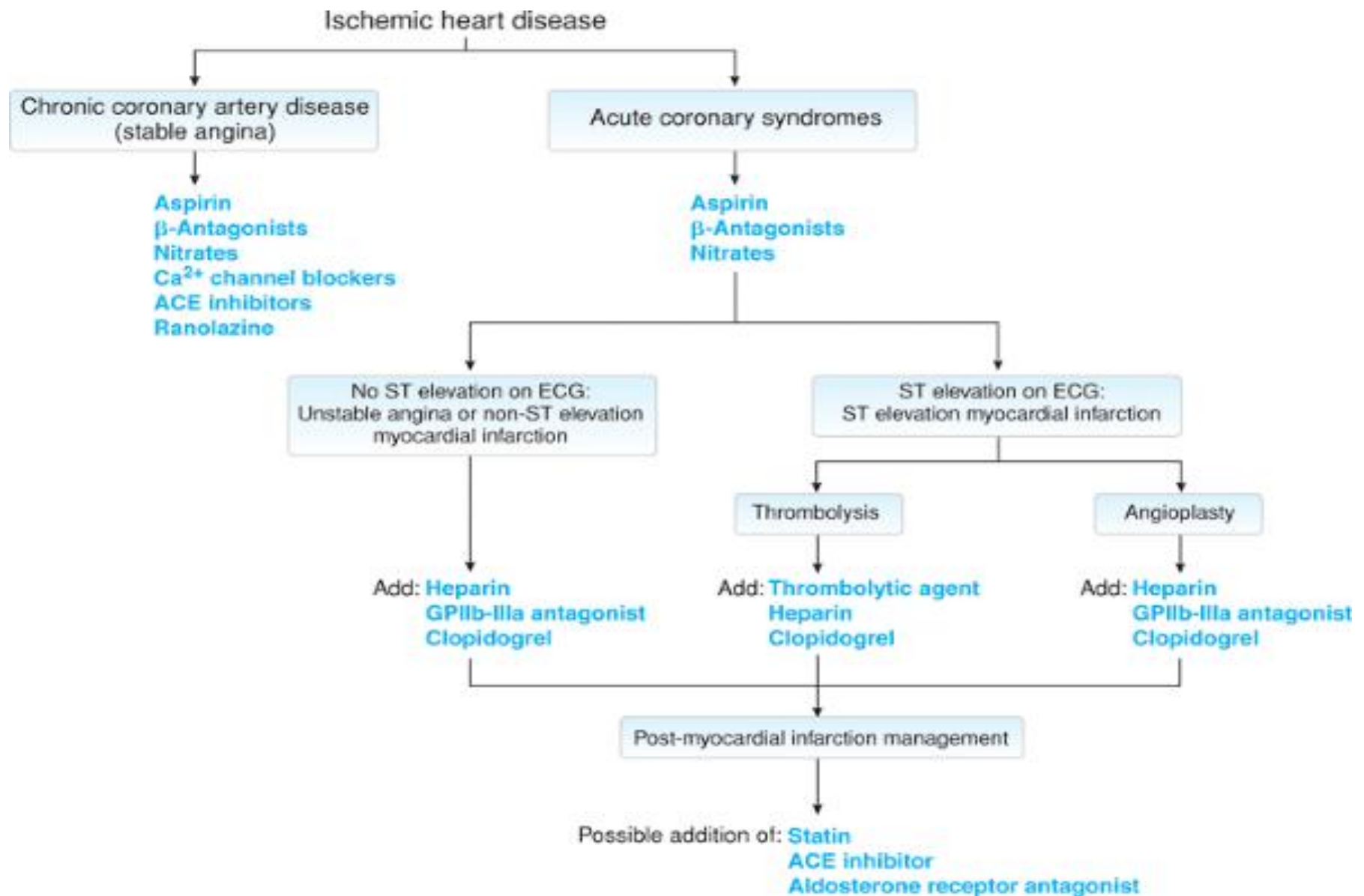
1. The decrease in intracellular sodium causes an increase in calcium expulsion via the Na/Ca transporter and a reduction in cardiac force and work.
2. Ranolazine is moderately effective in angina prophylaxis.

## **B) Dipyridamole**

1. It is a powerful coronary dilator; increases total coronary flow by preventing uptake and degradation of **adenosine**.
2. It dilates resistance vessels and abolishes autoregulation.
3. Inhibit platelet aggregation.
4. Not useful as an anti-anginal drug but used for prophylaxis of Coronary and cerebral thrombosis in post-MI and post stroke patients.

### C) Trimetazidine

1. It is a novel antianginal drug acts by nonhaemodynamic mechanism.
2. Anginal frequency is reduced and exercise capacity is increased.
3. Mechanism of action not known .
4. But may improve cellular tolerance to ischemia by
  - i) Inhibiting mitochondrial long chain **3-ketoacyl-CoA-thiolase (LC<sub>3</sub>-KAT)** a key enzyme in fatty acid oxidation and increasing glucose metabolism in myocardium.
  - ii) Limiting intracellular acidosis and Na<sup>+</sup> and Ca<sup>++</sup> accumulation during ischemia.
  - iii) Protecting against O<sup>·</sup> free radical induced membrane damage



## Pharmacologic management of acute coronary syndromes