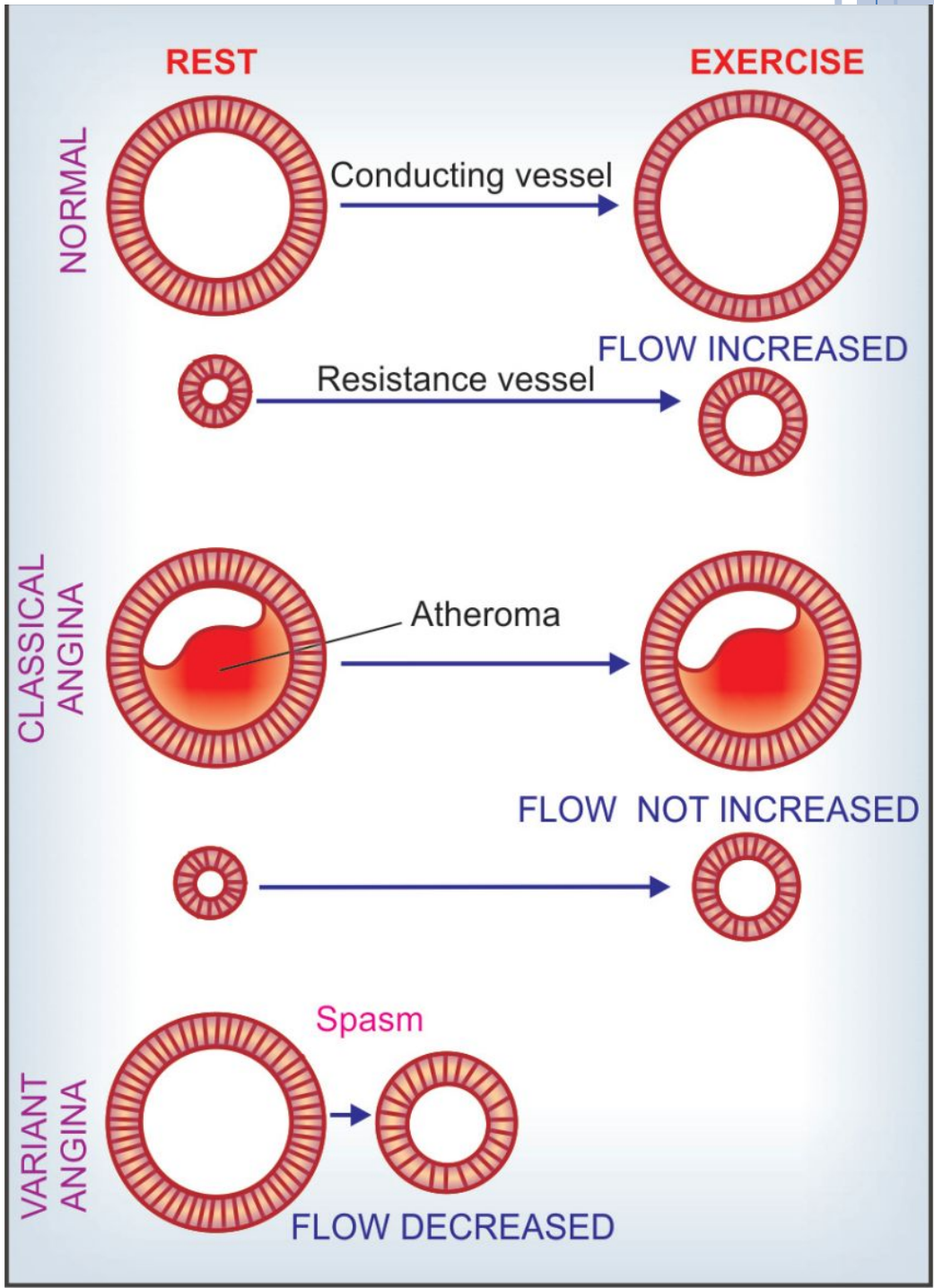
ANTIANGINAL DRUGS

Angina pectoris is the ischemic heart disease, anginal pain occurring when oxygen delivery to the heart is inadequate for myocardial requirement.

Classic angina (angina of effort or exercise) is due to coronary atherosclerotic occlusion

Vasospastic or variant angina (Prinzmetal) is due to a reversible decrease in coronary blood flow



Drug strategies in classic and vasospastic angina involve:

- ↑ oxygen delivery by ↓ vasospasm
- ↓ cardiac oxygen requirements by decreasing peripheral vascular resistance and (or) cardiac output

Drugs are used to eliminate angina pectoris attacks or to prevent attacks (systematic treatment).

Classification

- **Nitrates**

Short acting: Nitroglycerine

***Long acting*:**

Isosorbide dinitrate (short acting by sublingual route), Isosorbide mononitrate

- **Drugs, blocking calcium channels of L-type:**

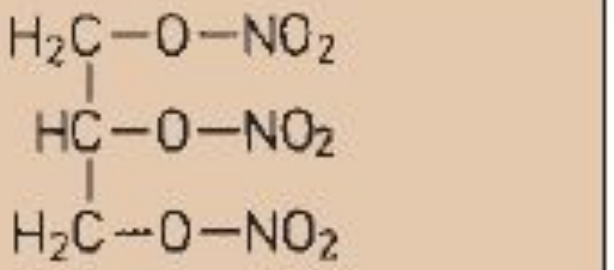
***Phenyl alkylamine*:** Verapamile,

Benzothiazepine: Diltiazem

Dihydropyridines: Nifedipine, Felodipine, Amlodipine, Nitrendipine

- **Potassium channels activator:** Nicorandil
- Amiodarone
- **B-adrenoblockers**
- **Bradycardic drugs:** Ivabradine, Falipamile
- **Myotropic drugs dilating coronary vessels:** Dipiridamole
- **Improving metabolism:** Trimetazidine
- **Reflex inhibitors of the coronary spasm:** Validol

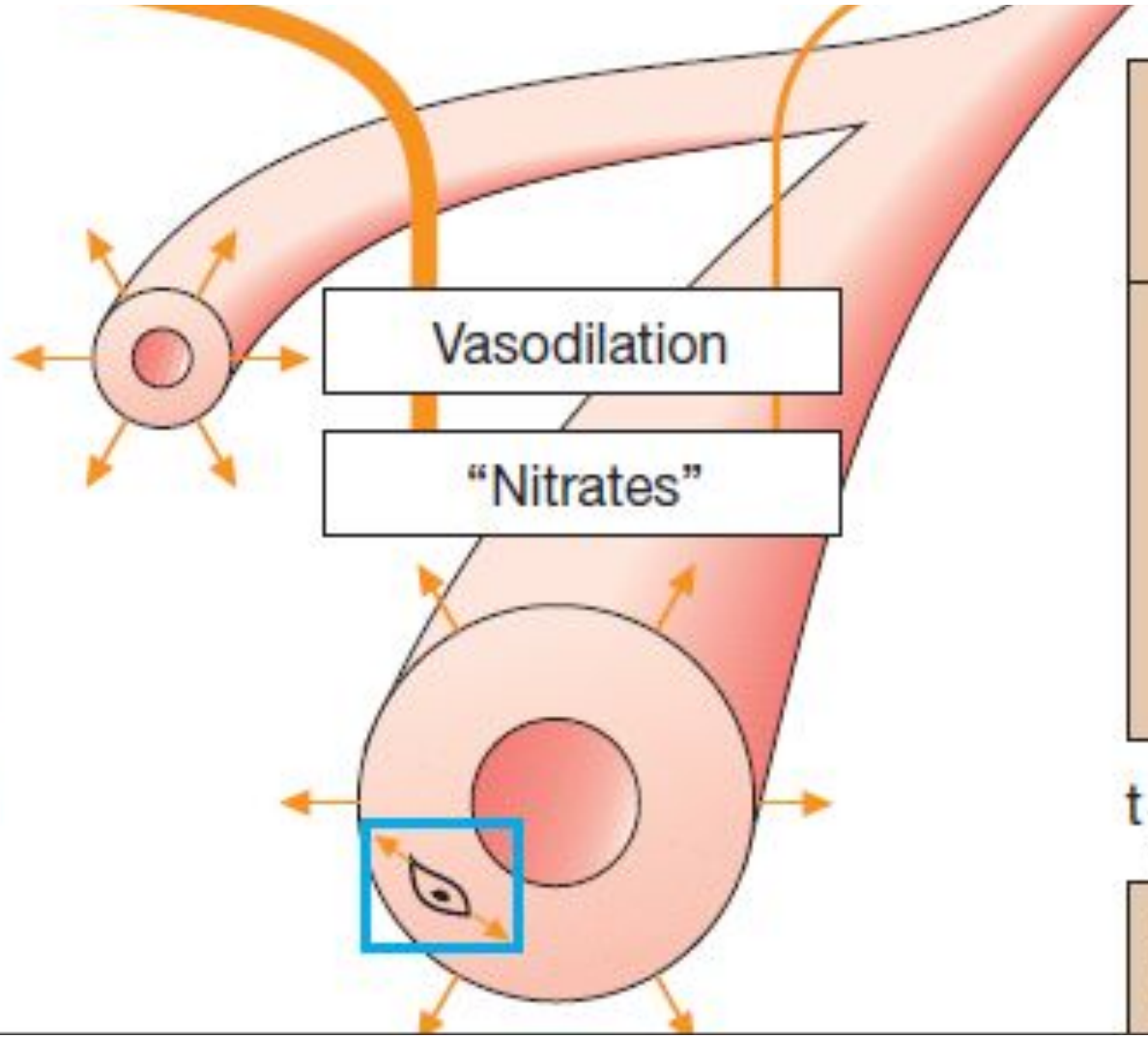
Route:
e.g., sublingual,
transdermal



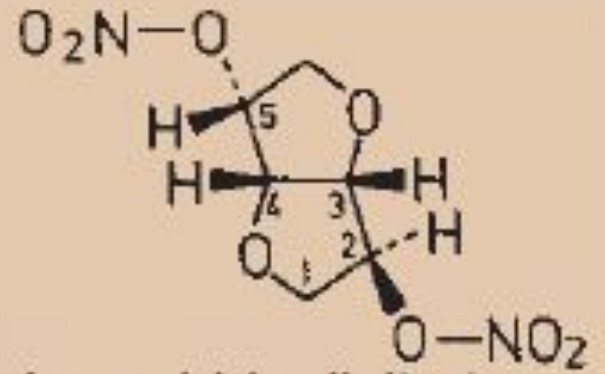
Glyceryl trinitrate
Nitroglycerin

NO ← $t_{1/2}$ ~ 2 min

Inactivation



Route:
e.g., sublingual,
oral, transdermal



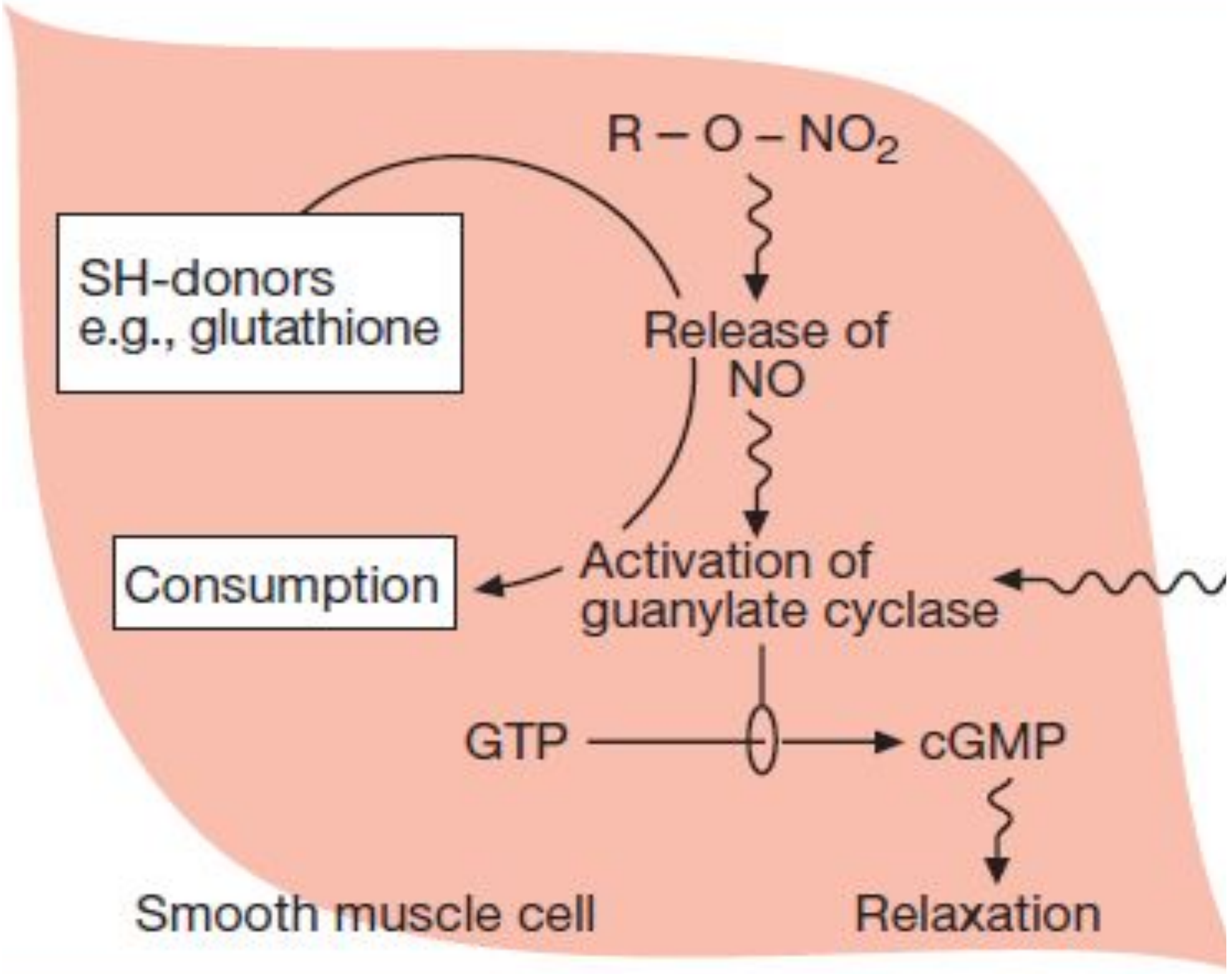
Isosorbide dinitrate

$t_{1/2}$ ~ 30 min → NO

5-Isosorbide mononitrate,
an active metabolite

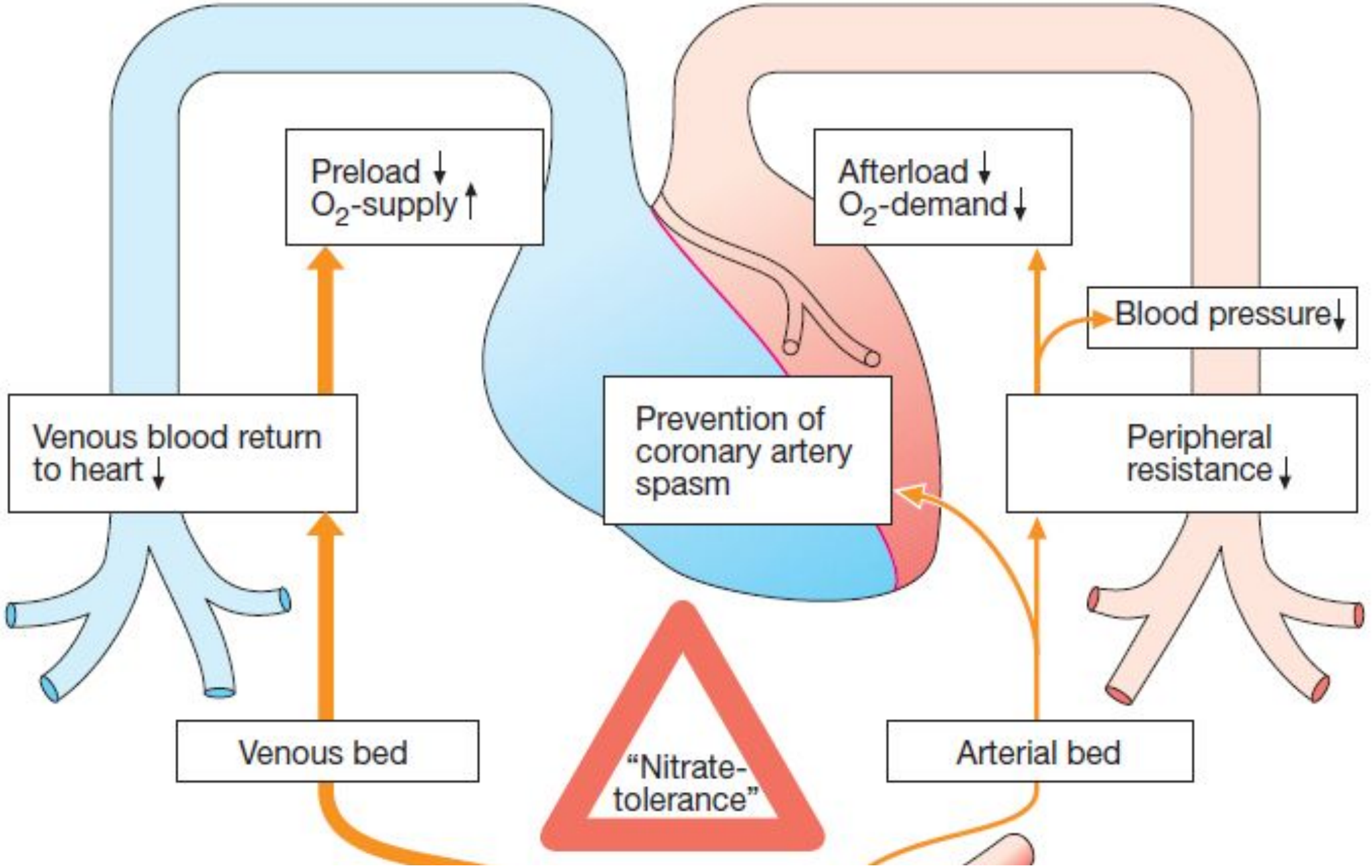
The mechanism of action of Nitroglycerine

- Nitroglycerine releases nitric oxide, which forms S-nitrosothioles.
- These substances activate soluble cytosolic guanylyl cyclase.
- The content of cGMP is increased.
- Free cytosolic Ca2+ ion content is decreased that leads to vascular smooth muscle relaxation.


R – O – NO2
SH-donors
e.g., glutathione
Release of
NO
Consumption
Activation of
guanylate cyclase
GTP
cGMP
Smooth muscle cell
Relaxation

Hemodynamic changes

- Dilation of the peripheral veins → decrease of venous return to the heart→ ↓ preload → decrease in cardiac work
- Dilation of the peripheral arteries → decrease in peripheral vascular resistance and arterial blood pressure → decrease afterload →
- **decrease in myocardial oxygen demand**


Preload ↓
O_2-supply ↑
Afterload ↓
O_2-demand ↓
Blood pressure ↓
Venous blood return to heart ↓
Prevention of coronary artery spasm
Peripheral resistance ↓
Venous bed
"Nitrate-tolerance"
Arterial bed

Increase in blood supply to the ischemic myocardial area because:

- Dilation of major coronary arteries;
- Decrease in diastolic ventricular wall tension and improvement of coronary circulation;
- Suppression of the central links of the coronary constricting reflexes;
- Improving of collateral circulation.

Indications for use:

- Relief of angina attack.
- Prevention of attacks.
- Acute myocardial infarction.

Adverse effects

- Hypotension, collapse, faint. Hyperemia of the face, neck.
- Headache, dizziness, increased intraocular and intracranial pressure. Tachycardia.
- Tolerance.
- Reflux esophagitis, heartburn.

Drug	Beginning of effect	Duration of effect
Nitroglycerine (tabl., caps, inhalation) + IV forms	1-3 min	30 min
Trinitrolong (polymeric lamina)	1 – 3 min	3 – 5 h

Drug form		Beginning of effect	Duration of effect
Slow released	2,6 and 6,4 mg tablets	10 – 20 min	4 – 8 h
Nitroderm-TTS 5 or 10 mg patch		Slow	Till applied, max 24 hr

Drug	Beginning of effect	Duration of effect
Isosorbide dinitrate	Sublingually – 3 – 5 min Orally – 20 – 30 min	4 – 5 h
Isosorbide dinitrate retard	20 – 30 min	6 - 12 h
Isosorbide mononitrate	40 – 60 min	6-8 - 10 h

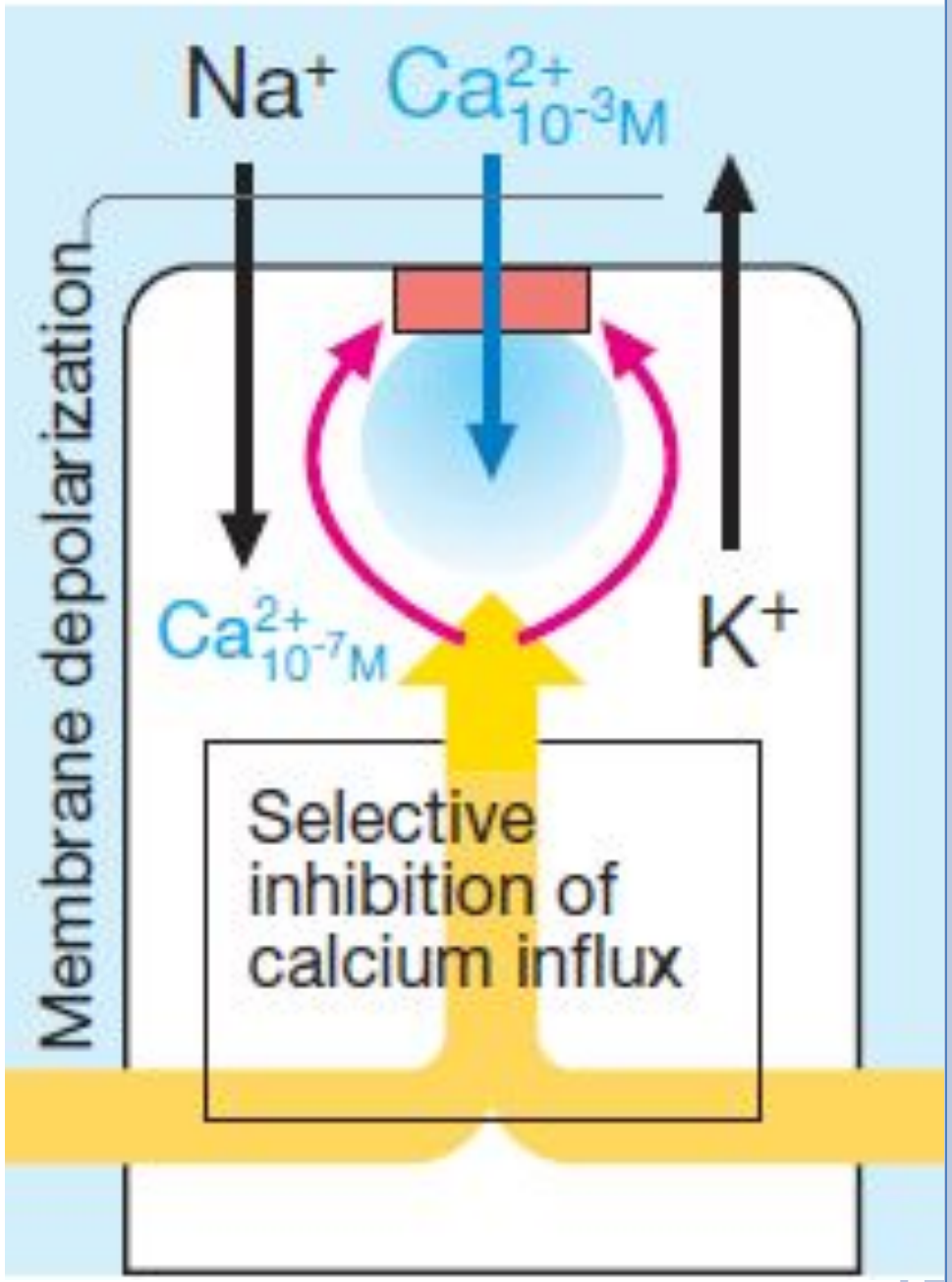
AMIODARONE

- **Antianginal activity.** Blocks α and β ar, glucagon's receptors, ↓ heart rate, ↓ arterial blood pressure, ↓oxygen demand, dilates coronary vessels, improves coronary circulation.
- **Antiarrhythmic effect.** Blocks Ca, K, Na channels, ↑ the duration of the action potential. ↓ automatism, the conductance, the excitability of the sinoatrial and atrioventricular nodes.

- It is administered once every 24 h. Effect develops slowly , after several weeks. It can be injected IV (effect after 1-2 h).
- **Indications:** Ischemic heart disease, supraventricular and ventricular tachyarrhythmia.
- **Adverse effects:** dyspepsia, bradycardia, AV-blockade, staining of the skin and of the cornea in a gray-blue color, thyroid dysfunction.

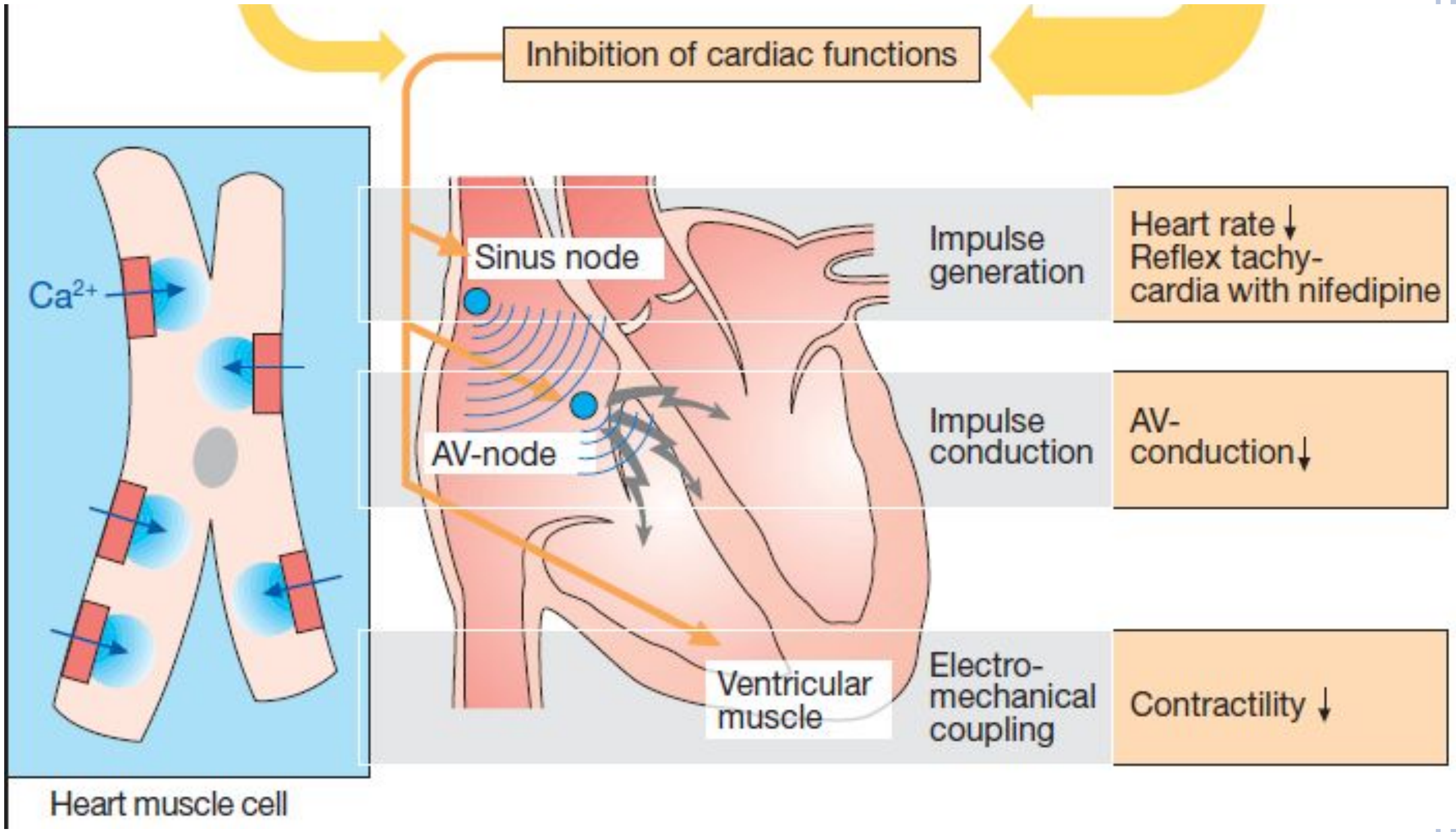
Drugs blocking calcium channels of L-type

- Block Ca^{2+} channels of the sinus node, AV node;
- Ca^{2+} channels in the myocardium;
- Ca^{2+} channels of blood vessels



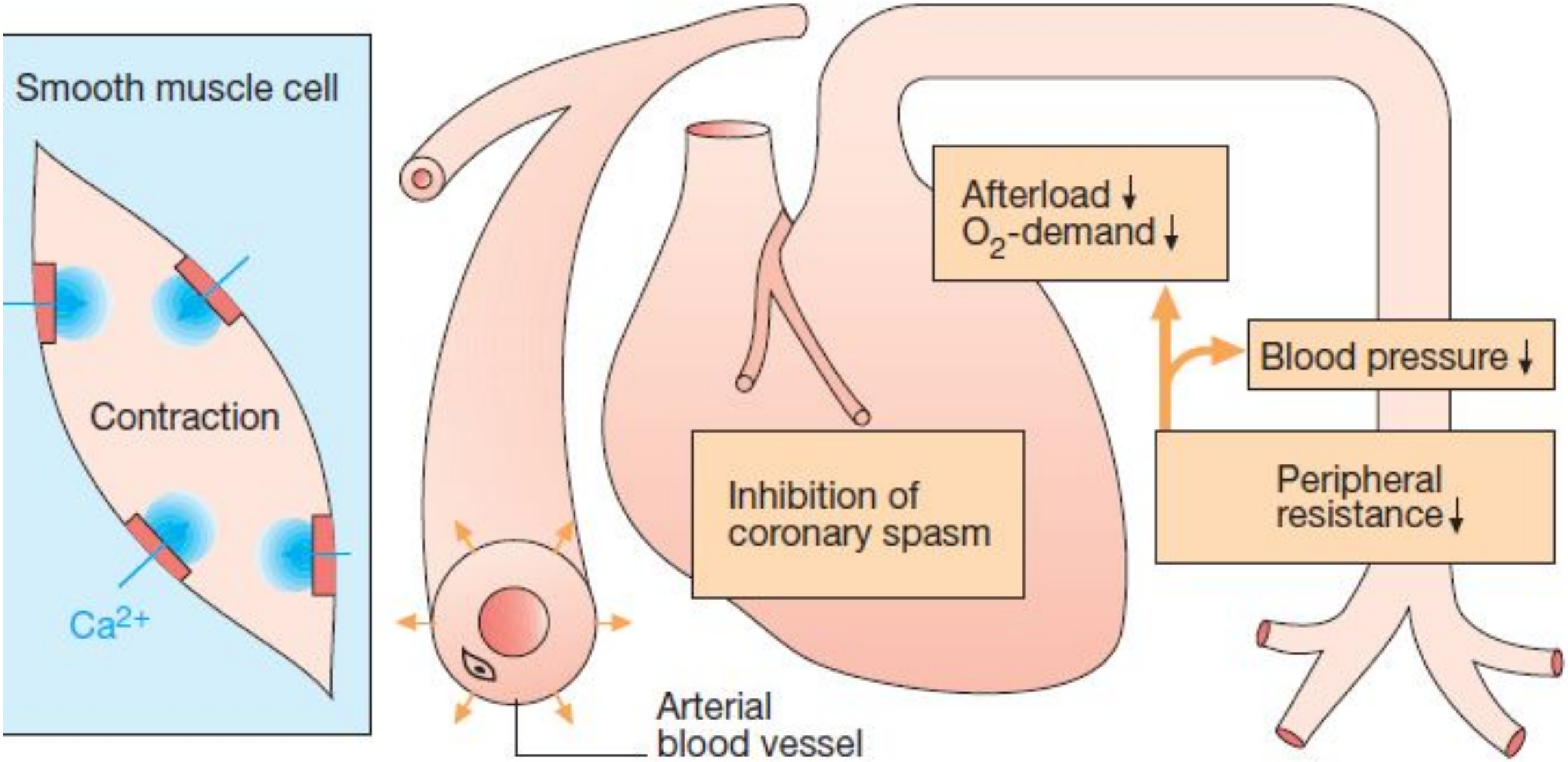
Verapamil , Diltiazem

- ↓depolarization (automaticity) in the sinus and AV nodes, ↑ERP;
- ↓HR, intensity of heart contractions, decrease in cardiac work, ↓systolic BP, ↓ oxygen demand;
- Expand peripheral vessels, ↓BP, ↓ tone of the arteries, ↓ afterload, ↓ O_2 demand;
- Dilate the coronary vessels, ↑blood delivery (O_2), ↓ platelet aggregation.
- They are applied orally and IV (Verapamil). Indications: hypertension, supraventricular tachyarrhythmia, coronary heart disease.
- Adverse effects: AV block, hypotension, nausea, vomiting, constipation, edema of ankles, allergic reactions.


Inhibition of cardiac functions
Ca2+
Heart muscle cell
Sinus node
AV-node
Ventricular muscle
Impulse generation
Impulse conduction
Electro-mechanical coupling
Heart rate ↓
Reflex tachy-cardia with nifedipine
AV-conduction ↓
Contractility ↓

Nifedipine, Amlodipine

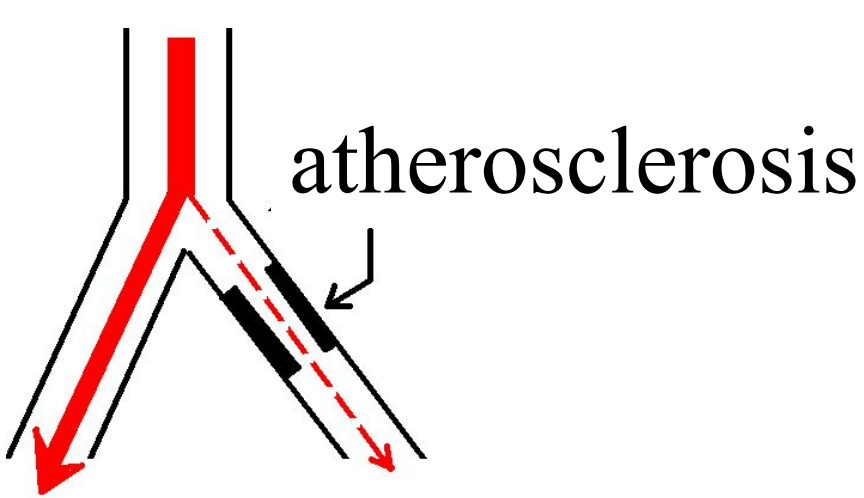
- Dilate large arteries and arterioles, ↓blood pressure, afterload and O_2 demand;
- Dilate coronary vessels, ↑ delivery of blood and O_2.
- ↓ force of heart contractions;
- They are used orally, the effect of N. lasts up to 6 hours, tablet retard- up to 24 hours. Amlodipine is active during 24 h.
- Adverse effects: reflex tachycardia, hypotension, flushing of the face, headache, feeling of heat, edema of ankles, constipation, withdrawal syndrome.


Smooth muscle cell
Contraction
Ca^{2+}
Afterload ↓
O_2-demand ↓
Blood pressure ↓
Inhibition of coronary spasm
Peripheral resistance ↓
Arterial blood vessel
Vasodilation in arterial bed

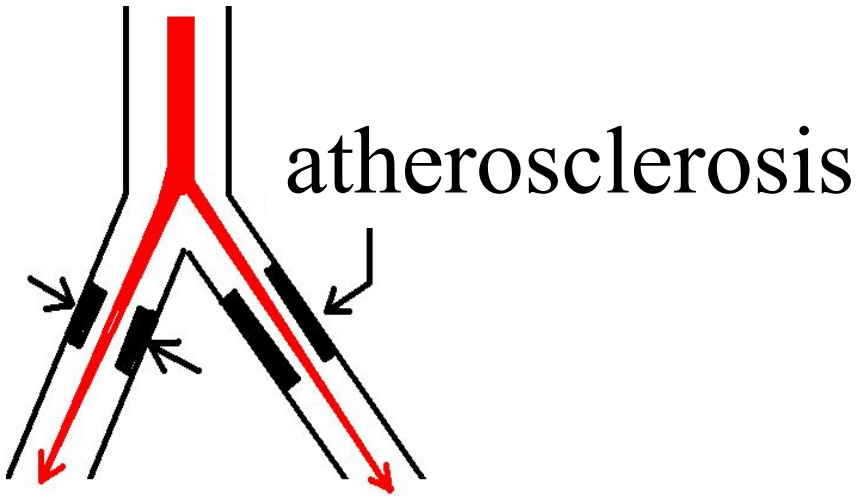
Effect	Nifedipine	Diltiazem	Verapamil
Hypotensive effect	+++	++	++
Antianginal	+++ (vasospastic)	+++	+++
Antiarrhythmic	+	++	+++
Cardiac contraction intensity	↓	↓↓	↓↓↓
AV conduction	0↓	↓	↓↓
Heart rate (automatism of SA node)	↑	↓	↓↓

B-adrenoblockers

- Decrease cardiac contraction rate and intensity
- Decrease in myocardial oxygen demand;
- Anxiolytic effect.
- Indications: supraventricular and ventricular tachyarrhythmias, coronary heart disease, hypertension.



ischemia



redistribution of blood flow

Ivabradine

- Selectively blocks Na^+ and K^+ channels of the sinoatrial node, prolongs slow diastolic depolarization, ↓ automatism of the sinoatrial node;
- Causes bradycardia; Lengthens diastole;
- Decreases cardiac oxygen demand;
- Improves endocardial blood circulation.
- It is used orally twice a day for the treatment of coronary heart disease and chronic heart failure.
- Adverse effects: reversible visual problems.

Dypiridamole

- It causes the suppression of adenosine reuptake (by myocardium or erythrocytes); inhibits adenosine desamidase enzyme. Myocardium accumulates increased concentrations of adenosine. And adenosine dilates coronary arteries. Oxygen supply is improved.
- D. inhibits platelet aggregation.
- But! D. dilates vessels in the normal part of the myocardium and this further decreases blood and oxygen supply of the ischemic zone.

Trimetazidine is the cardioprotective drug

- Inhibits 3-ketoacil-KOA thiolase enzyme isoform, inhibits the oxidation of fatty acids; ↑ oxidation of glucose, ↑ formation of ATP and creatine phosphate; ↓ oxygen demand.
- It prevents a decrease in ATP content in cardiac myocytes, maitains energy recourses of the cells, normalizes ion channels functions and ion kinetics. So, T. increases the resistance of cardiac myocytes to ischemia.
- It is used orally 2-3 times a day.
- Side effects: dyspepsia, headache, dizziness, insomnia.

Validol

- It is a 25-30% menthol solution in a ester of isovalerianic acid. Some validol drops on a sugar cube or a tablet is inserted under the tongue (up to complete resorption).
- The drug causes reflex improvement of coronary circulation by irritating oral mucous membranes. If the pain does not subside after 2-3 min, validol can be considered ineffective.
- The drug is indicated for the treatment of early and mild angina pectoris.