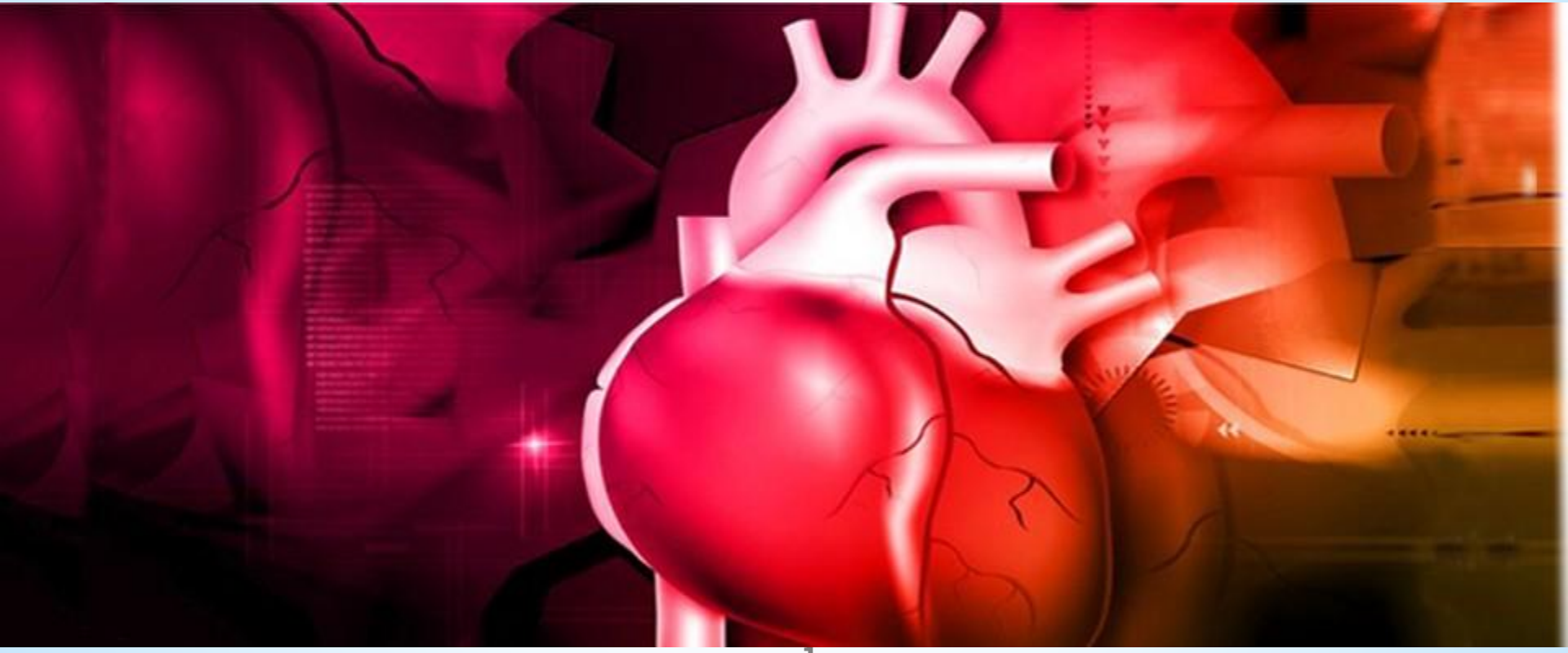
Zaporizhian State Medical University
Pharmacology Department

Lecture N1

ANTIANGINAL DRUGS.
DRUGS REGULATING CEREBRAL CIRCULATION.



Insufficiency of coronary circulation is the Syndrom of discrepancy between heart oxygen requirement and blood oxygen delivery.

It may be caused by:

- **Increased heart work as a result of:**
  - **Physical loading.**
  - **Psycho-emotional loading.**
- **Decreased blood circulation in myocardium as a result of:**
  - **Functional spasm of coronary blood vessels.**
  - **Organic narrowing of coronary blood vessels.**
    - **Atherosclerotic plaques in coronary blood vessels.**
    - **Thrombus in coronary blood vessels.**

Antianginal Agents

1.Organic Nitrates

2. β-Blockers

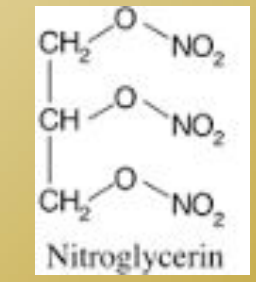
3. Calcium Channel Blockers

4. Angiotensin-Converting Enzyme Inhibitors

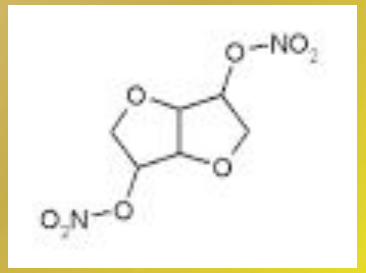
I. Nitrates:

Nitroglycerin – Tab. 0.5 mg,
Caps. with 1% oil solution,
amp. 1%-2 ml, vial 1%- 5 ml

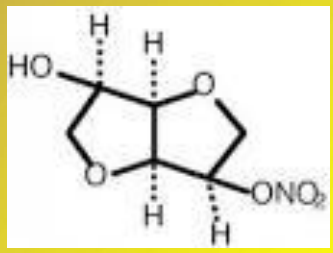
Nitrong-Mite – *Tab.* 2.5 mg
Nitrong-Forte – *Tab.* 6.5 mg



Sustac-Mite – *Tab.* 2.6 mg
Sustac-Forte – *Tab.* 6.4 mg



Isosorbide Dinitrate – *Tab. 10 and 20 mg*
Isosorbide Mononitrate – *Tab. 10 and 20 mg*



Drugs which at the same time increase the coronary blood flow and decrease oxygen demand of the myocardium.

Mechanism of action of organic nitrates:

- Molecular level.

Nitrogycerin and other organic nitrates

↓

Release of nitric oxide (NO)

↓

Activation of guanylyl cyclase in the smooth muscle cells

↓

Increase of amount of cGMP

↓

Decrease of Ca^{++} in cytoplasm

↓

Dephosphorylation of the light chains of myosin

↓

Relaxation of smooth muscles in next priority:

1. Large veines.
2. Large arteries.
3. Venules, arterioles, precapillary sphincters.

Nitroglycerin - tab. 0.0005 g (0.5 mg), amp. 1%-2 ml,
vial 1% spirituous sol. - 5 ml,

SL 0.5 mg (or spray forms) is considered to be the drug of choice to treat Acute Angina. Acts within 1-2 min;
peak blood level in 3-6 min due to direct absorption into systemic circulation (bypassing liver where ~ 90% is metabolized).

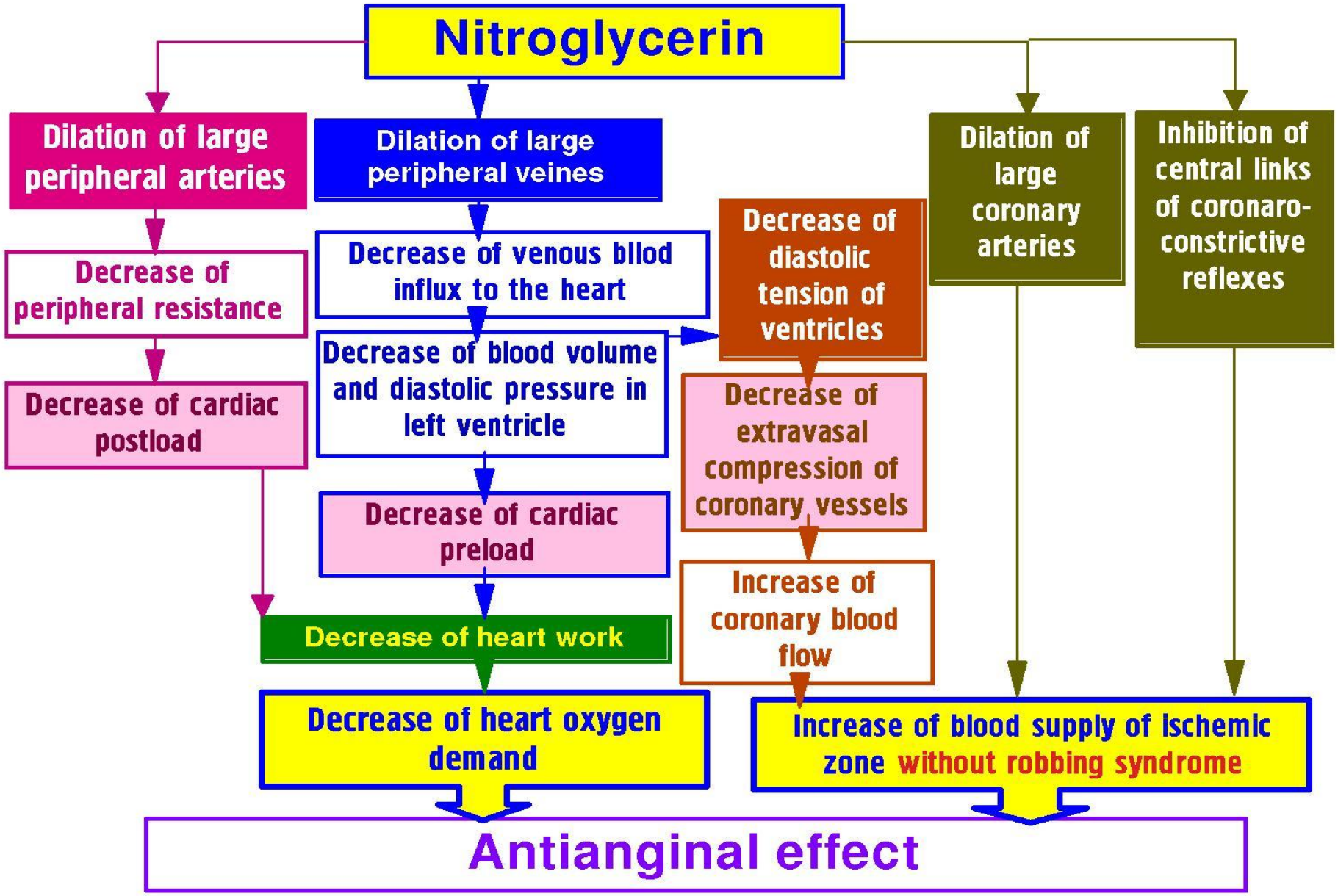
The total duration of effect is brief - 15–30 min.

The onset of action of for Sustained-Release Forms is within 20-60 min.

Duration of action for :

Mite-forms – 3-4 hours

Forte-forms – 6-8 hours

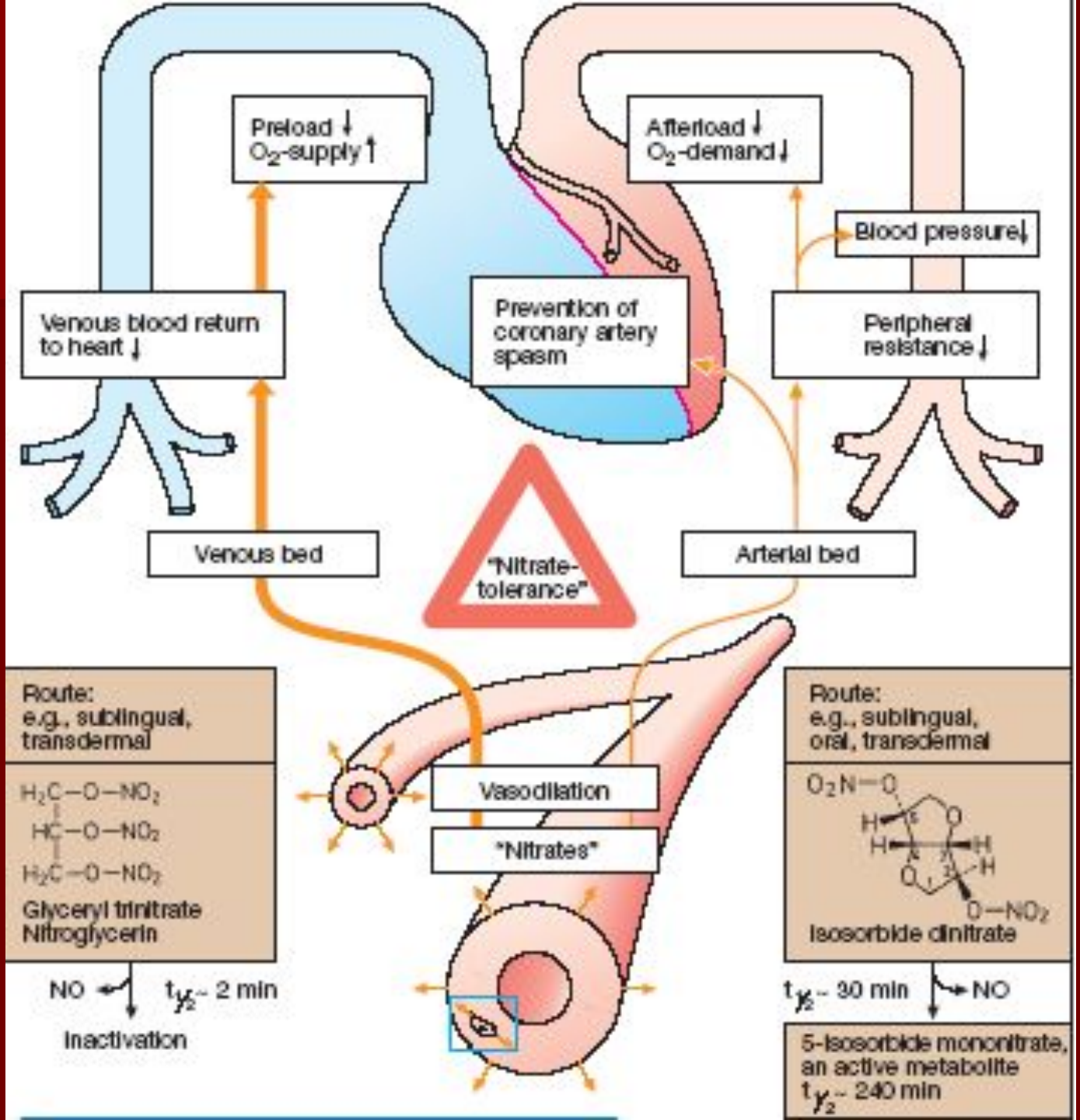

Nitroglycerin
Dilation of large peripheral arteries
Dilation of large peripheral veines
Dilation of large coronary arteries
Inhibition of central links of coronaro-constrictive reflexes
Decrease of peripheral resistance
Decrease of venous blood influx to the heart
Decrease of diastolic tension of ventricles
Decrease of cardiac postload
Decrease of blood volume and diastolic pressure in left ventricle
Decrease of extravasal compression of coronary vessels
Decrease of cardiac preload
Increase of coronary blood flow
Decrease of heart work
Decrease of heart oxygen demand
Increase of blood supply of ischemic zone without robbing syndrome
Antianginal effect

Clinucal uses of Nitroglycerine:

- Prophylaxis and Control of Angina Attack
- IV Infusion in Myocardial Infarction
- Pulmonary Stasis in Cardiac Insufficiency

Adverse Effects of Nitroglycerine:

- Headache (30-60%)
- Hypotension, Tachycardia
- Facial Flushing
- Tinnitus (Ringing in the Ears)


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
Route:
e.g., sublingual, transdermal
$H_2C-O-NO_2$
$HC-O-NO_2$
$H_2C-O-NO_2$
Glyceryl trinitrate
Nitroglycerin
NO
$t_{1/2}$ ~ 2 min
Inactivation
Vasodilation
"Nitrates"
Route:
e.g., sublingual, oral, transdermal
O_2N-O
$O-NO_2$
Isosorbide dinitrate
$t_{1/2}$ ~ 30 min
NO
5-Isosorbide mononitrate, an active metabolite
$t_{1/2}$ ~ 240 min

Overdose With Nitroglycerine:

Vasodilation and Methemoglobinemia -

- Hypotension, Throbbing Headache, Palpitations,
- Visual disturbances, Flushing of the skin,
- Sweating (with skin later becoming cold and cyanotic),
- Nausea and Vomiting, Colic, Bloody Diarrhea,
- Initial Hyperpnoea (in the Breathing Rate and/or in the Depth of breathing), Dyspnoea, then Slow Respiratory Rate,
- Bradycardia, Heart Block,
- Intracranial Pressure with Confusion, Fever, Tissue Hypoxia (from Methemoglobinemia)
- Cyanosis, and Metabolic Acidosis, Coma, Clonic Seizures and Circulatory Collapse

Treatment of overdose with nitroglycerine:

- Gastric Lavage; Activated Charcoal
- Oxygen therapy (Hyperbaric Oxygenation)

Antidotes:

- Ascorbic acid 5% solution 10-15 ml
  in Glucose 5% solution 500-800 ml IV infusion
- Methylene Blue (*Methylenum ceruleum*) 1% 7-10 ml or
  Chromosmon (1% *Methylene blue in 25% Glucose sol*.)

Symptomatic treatment:

- Sodium hydrocarbonate or Trisamine,
- Sulfocamphocaine (10% 3-4 ml), Mesaton,
- Noradrenaline hydrotartrate 0.2%-1 ml
  in Glucose 5% sol. 500 ml IV infusion in collapse.

β-Adrenoblockers:

Propranolol (*Anaprilin*) (β_1, β_2) – tab. 10 and 40 mg

Timolol (β_1, β_2) – tab. 0.01;0.02; eye drops 0.5%-5 ml

Oxprenolol (*Trasicor*) (β_1, β_2) – tab. 20 and 80 mg

Atenolol (β_1) – tab. 50 and 100 mg

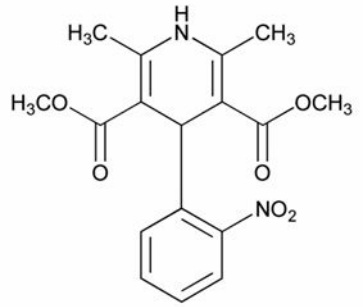
Metoprolol (β_1) – tab. 50 and 100 mg

Nadolol (*Corgard*) (β_1) – tab. 20; 40; 80 mg

Labetalol (β_1, α_1) - tab. 0.1; 0,2; amp 1%-5 ml

Carvediol (β_1, α_1) – tab. 12.5 and 25 mg

Ca^{2+} Channel Blockers



I. Diphenylalkylamines:

Verapamil

II. Dihydropyridines:

1st Generation:

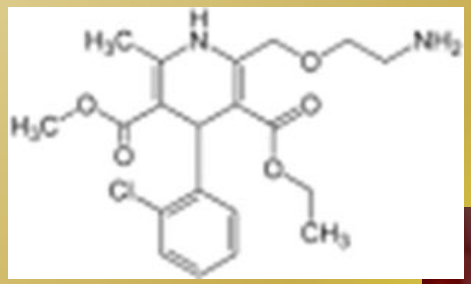
Nifedipine *(Adalat, Procardia)*

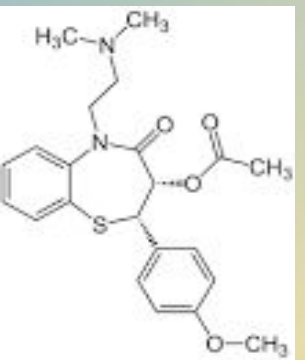
2nd Generation:

Amlodipine, Isradipine, Nicardipine

III. Benzothiazepines:

Diltiazem





Slow calcium channel blockers:

→ Agents which block high-threshold channels of L-type:

► 1. Agents acting on the myocardium predominantly (I class):

- Phenylalkylamine derivatives - Verapamil, Gallopamil, Thiapamil.

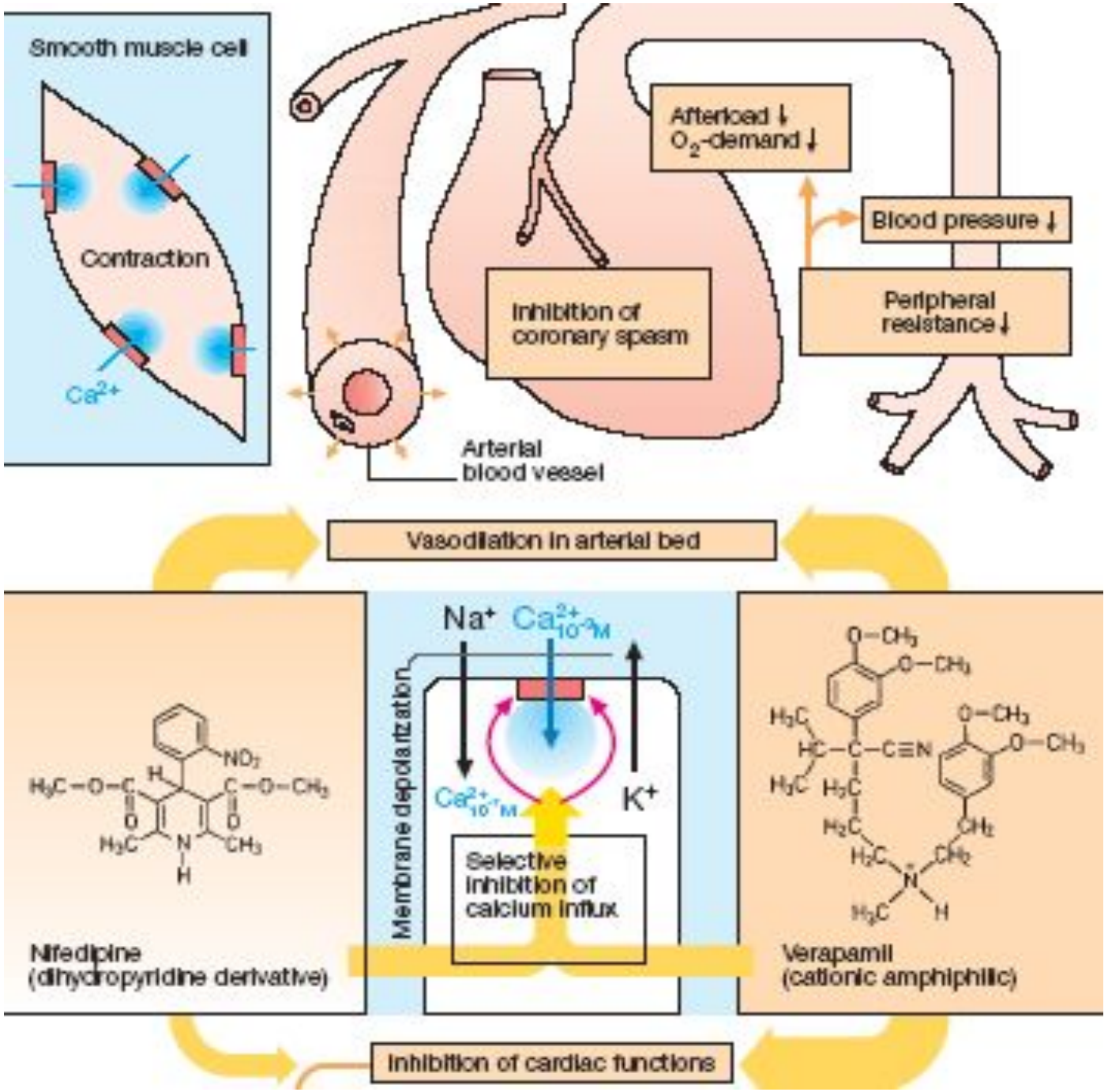
► 2. Agents acting on the arteries predominantly (II class):

- Dihydropyridine derivatives - Phenigidinum *[nifedipine]*, Nicardipine, Nisoldipine, Isradipine, Felodipine, Amlodipine, Lacidipine, etc.

► 3. Agents acting on both the myocardium and arteries (III class):

- Benzothiazepine derivatives - Diltiazem, Clentiazem.

→ Agents which block low-threshold or transitor channels of T-type - Mibefradile.


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
Na^+
$Ca^{2+}_{10^{-3}M}$
$Ca^{2+}_{10^{-7}M}$
K^+
Membrane depolarization
Selective inhibition of calcium influx
Nifedipine (dihydropyridine derivative)
Verapamil (cationic amphiphilic)
Inhibition of cardiac functions

Drug	Oral Bioavailability	Onset of Action (route)	Plasma Half-Life (hours)
Dihydropyridines			
Amlodipine	65–90%	No data available	30–50
Felodipine	15–20%	2–5 hours (oral)	11–16
Isradipine	15–25%	2 hours (oral)	8

Verapamil appears to have antianginal, antihypertensive and antiarrhythmic action.

It manages unstable and chronic stable angina by:

□ *Afterload* => □ *O_2 Consumption*.

It also □ myocardial *O_2* demand and cardiac work by:

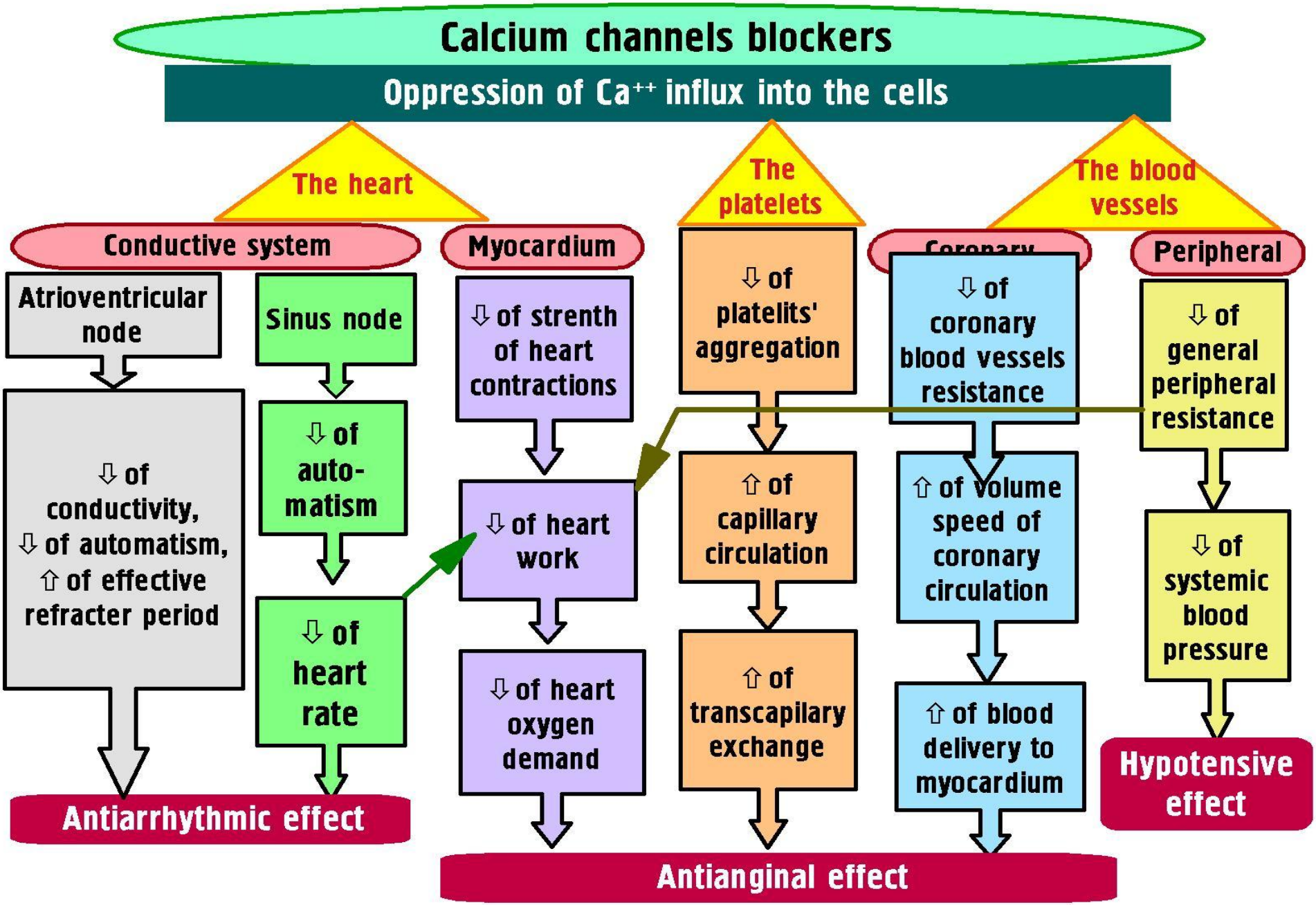
- *Exerting Negative Inotropic Effect* - □ Heart Rate: the drug *slows Cardiac Conduction directly* .

In patients with Prinzmetal's Variant Angina:

Relieving coronary artery spasm => myocardial □ *O_2 Delivery*

<u>Adverse Effects</u>:

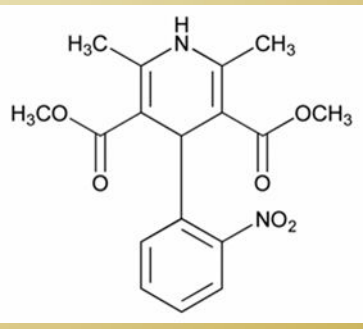
Myocardial Depression, including *Cardiac Arrest*, Bradycardia, AV block, Hypotension, Heart Failure, Constipation, Peripheral Edema.


Calcium channels blockers
Oppression of Ca++ influx into the cells
The heart
The platelets
The blood vessels
Conductive system
Myocardium
Coronary
Peripheral
Atrioventricular node
Sinus node
⇩ of strenth of heart contractions
⇩ of platelits' aggregation
⇩ of coronary blood vessels resistance
⇩ of general peripheral resistance
⇩ of conductivity, ⇩ of automatism, ⇧ of effective refracter period
⇩ of auto-matism
⇩ of heart work
⇧ of capillary circulation
⇧ of volume speed of coronary circulation
⇩ of systemic blood pressure
⇩ of heart rate
⇩ of heart oxygen demand
⇧ of transcapilary exchange
⇧ of blood delivery to myocardium
Hypotensive effect
Antiarrhythmic effect
Antianginal effect

Nifedipine – functions mainly as an *arteriolar vasodilator*.

It dilates systemic arteries, resulting in:

- *Total Peripheral Resistance*
- Systemic AP with slightly Increased Heart Rate,
- *Afterload*, and increased cardiac index.



- The vasodilation effect of *Nifidipine* is useful in the treatment of *Variant Angina* caused by spontaneous coronary spasm.
- In *Prinzmetal's angina*, *Nifedipine* inhibits coronary artery spasm, increasing myocardial *Oxygen Delivery.*

Adverse effects: Flushing, Headache, Tachycardia, Hypotension , Dizziness, Nausea, Constipation, and Peripheral Edema as side effects of its *vasodilation activity*.

Amlodipine is a Dihydropyridine compound – the 2nd Generation long-acting Ca^{2+} antagonist.

It blocks the inward movement of Ca^{2+} by binding to L-type Ca^{2+} channels in the Heart and in Smooth Muscle of the Coronary and Peripheral Vasculature =>

=> vascular smooth muscle relaxation dilating mainly arterioles.

The drug has an Intrinsic Natriuretic Effect.

It has *Antianginal, Hypotensive, Vasodilative* and Spasmolytic *Action*

Clinical Uses:

- Arterial Hypertension,
- Stable and Unstable angina,
- Prinzmetal's or Variant Angina Pectoris.

Peak effects occur within 1-2 hours and persist for 24 hours.

Adverse effects: headache, peripheral edema.

Ca^{2+} channel blockers are useful in the treatment of patients who also have asthma, hypertension, diabetes, and/or peripheral vascular disease.

The Angiotensin-Converting Enzyme (ACE) Inhibitors: Captopril, Lisinopril, Enalapril

block the ACE that cleaves Angiotensin I to form Angiotensin II – a potent vasoconstrictor.

They also the rate of Bradykinin inactivation.

- Vasodilation occurs as a result of the combined effects of diminished levels of Angiotensin II and the potent vasodilating effect of increased Bradykinin.

By reducing circulating angiotensin II levels, ACEIs:

 Aldesterone Secretion, resulting in decreased Na+ and water retention.

- Unlike β-blockers, ACEIs are effective in the management of patients with chronic CHF.
- ACE inhibitors are now a standard in the care of a patient following a Myocardial Infarction.

Other Antianginal Drugs

Antiplatelet agents:

Aspirin - 0.075 – 0.325 g daily blocks formation of PG Thromboxan A_2 (TXA_2) that causes platelets to change shape, to release their granules, and to aggregate.

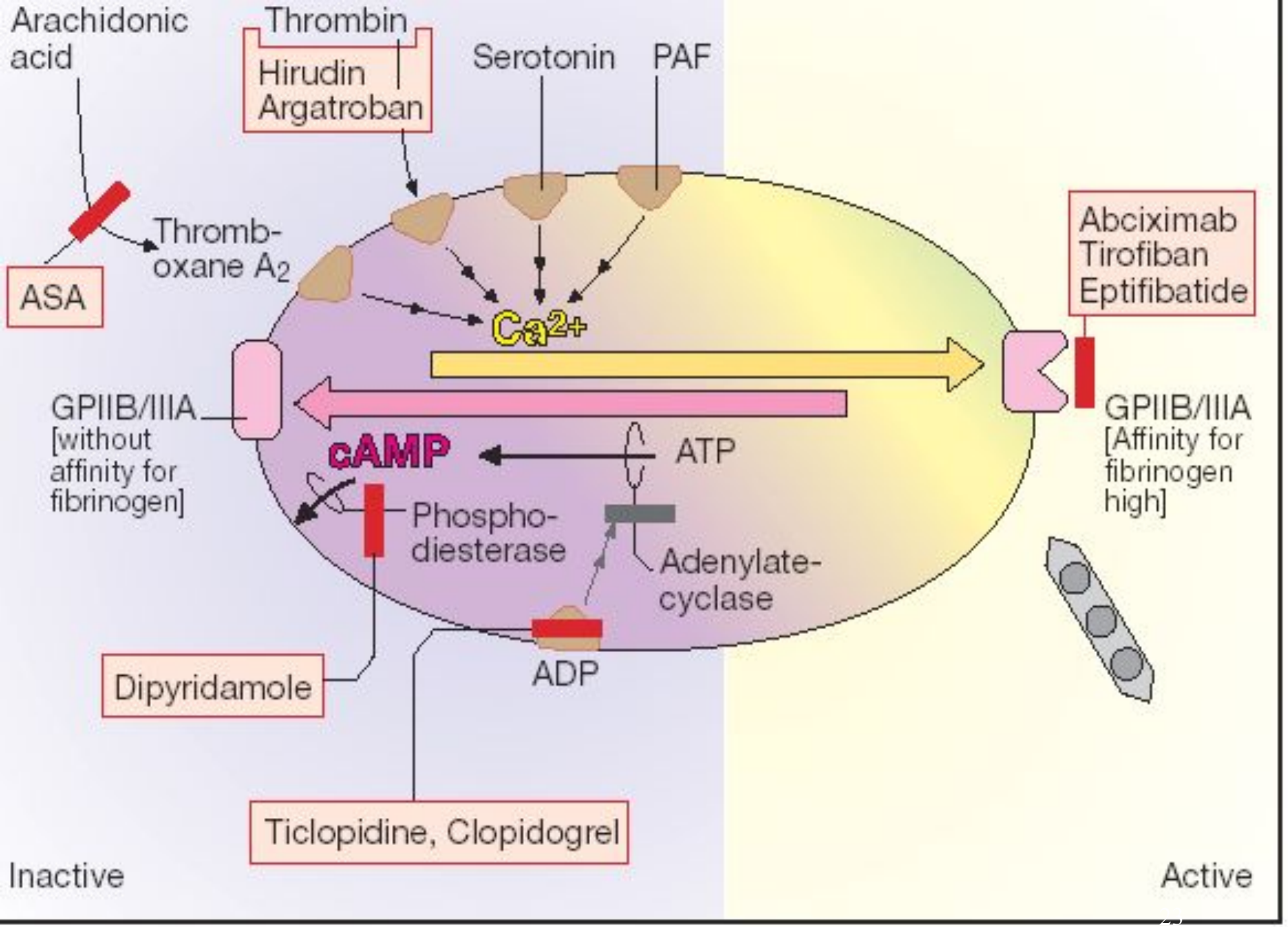
Dipyridamole is a coronary dilator, □ total coronary flow.

It **prevents** uptake and degradation of adenosine – a local mediator involved in autoregulation of coronary flow in response to ischemia.

Ticlopidine (tab. 0.25 g tid) inhibits the ADP pathways to prevent platelet aggregation.

Adverse effects: GIT disorders (in up to 20% of patients), hemorrhage (5%), rash (5%), neutropenia (2%).

Ticlopidine is usually used in patients who cannot tolerate *Aspirin*



.. Inhibitors of platelet aggregation

GPIIb / IIIa antagonists -

a new class of *platelet–inhibiting drugs* that **block**

platelet receptors for **integrin** and other aggregating substances.

Abciximab is a mouse / human chimeric *monoclonal antybody* that blocks GP **IIb / IIIa receptors**.

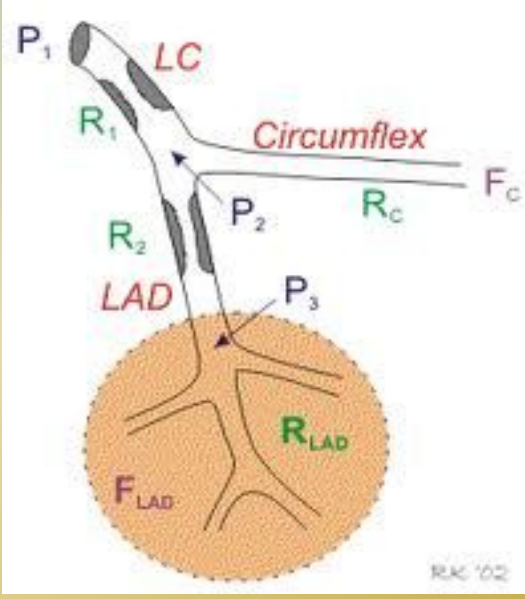
It is used as adjunctive therapy along with *Aspirin* and *Heparin* in patients undergoing high-risk **angioplasty** and **atherectomy**.

The clinical trials demonstrated the efficacy of *Abciximab* as well as its increased bleeding risk versus placebo controls.

Integrelin is a synthetic peptide with high affinity for the *GP IIb / IIIa* integrin receptor protein.

It has undergone successful clinical trial for prevention of thrombosis in **Percutaneous Coronary Angioplasty**.

Coronary steal phenomenon



occurs when two branches from the main coronary vessel have different degrees of obstruction. One branch may be relatively normal and capable of dilating in response to changes in O_2 demand, while the other branch is unable.

If a *powerful arteriolar dilator* (*Acetylcholine, Adenosine, Dipyridamole, Hydralazine*) is administered, the arterioles in the unobstructed vessel will be forced to dilate => ↓ Resistance in the Normal Branch and ↑ Flow through the Adequately Perfused Tissue.

=> ↓Perfusion Pressure in the Main Vessel, ↓ Flow through the Obstructed Brunch and Angina may Worsen.

Drugs for the Treatment of Acute Myocardial Infarction

The major principles treatment of AMI:

- Pain syndrome elimination
- Removal of Disparity between Energetic Demands of Myocardium and Blood Supply
- Struggle with Thrombogenesis
- Electrolytes and acid-base equilibrium correction.

- Neuroleptanalgesia *with*

  Fentanyl 0.005% 2-4 ml

  Droperidol 0.25%-1-4 ml

- is a base of all schemes of anesthesia

at Acute Coronary Syndrome.

- The antiplatelet agent – *Aspirin* - is administered at the first suspected signs of infarction.

Aspirin prevents platelet aggregation and has

an additional beneficial effect on thrombolysis.

Thrombolytic Therapy:

Alteplase or Streptokinase to dissolve the thrombus pharmacologically

- Heparin is given to prevent a possible vascular reocclusion
- Treatment of life-threatening ventricular arrhythmias calls for an antiarrhythmic of

the I class of Na^+channel blockers,

e.g., Lidocaine.

a β-blocker and an ACE inhibitor -

to improve long-term prognosis –

prevention of ventricular enlargement after myocardial infarction

Agents Regulating Cerebral Circulation

I. Agents affecting the platelet aggregation and coagulation

1. Antiaggregants (Antitplatelet Drugs):

Aspirin, Ticlopidine

2. Anticoagulants: Heparin

Low-molecular-weight Heparins:

Enoxaparine, Dalteparine

II. Agents Increasing Cerebral Circulation:

1. Derivatives of purine alkaloids - methylxanthines:

Pentoxifylline

Xantinol nicotinate

Instenon

2. Derivatives of **Vinca alkaloids** - derived from the **Lesser Periwinkle plant** (*Vinca minor*):

Vinpocetin (*Cavinton*)

3.Derivatives of ***Ergot alkaloids***: ("**Rye Ergot Fungus**")

Nicergoline (*Sermion*)

4. Opioid alkaloid of isoquinoline range:

Papaverine hydrochloride

5. Ca^{2+} channel blockers:

Nimodipin, Cinnarisin, Flunarisine

6. GABA and its compounds:

Aminalone, Picamilone

Pentoxiphylline - Tab. 0.1 g, amp. 2% solution 5 ml - a Methylxanthine derivative.

Mechanism of Action:

1). Inhibition of the enzyme **PDE** => accumulation of **cAMP** and ↓intracellular level of **Ca^{2+}** in the smooth muscles

2). Blockade of *Adenosine* receptors

Pharmacological effects: dilation of cerebral vessels, prevention the development of edema of the cerebral tissue.

- Inhibits aggregation of thrombocytes and improves microcirculation in the zone of ischemia.
- Antianginal effect (↑O_2 delivery to heart) is due to coronary arteries dilatation.
- Improves blood oxygenation and prevents storage of cholesterol and atherogenic lipoproteins in vessels wall, improves rheological properties of blood.

Clinical uses: all types of hyperlipidemias, disorders of cerebral and peripheral blood circulation of spastic and atherosclerotic types.

Instenon is a combined drug for the treatment of Ischemic Cerebrovascular Diseases.

It contains: Methylxanthine *Ethophylline*,
Analeptic *Etamivan*
Spasmolytic *Hexobendine*.

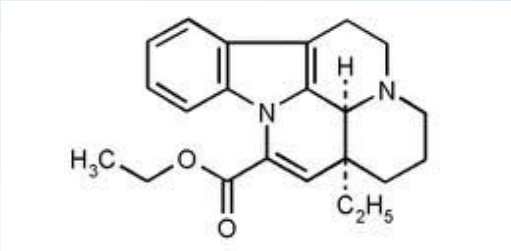
The drug improves cerebral circulation, stimulates the CNS, activates metabolism.

The important role in the mechanism of action of *Instenon* plays inhibiting action of ***Ethophylline*** on *PDE* and as a result accumulation *cAMP* in tissues that induces *slowdown* of actomyosin complex and reduction of smooth muscle contractility.

Vinpocetin (*Cavinton*)

tab. 5 mg, amp. 0.5%-2 ml

is an alkaloid derivative from *Periwinkle* (*Vinca minor*).

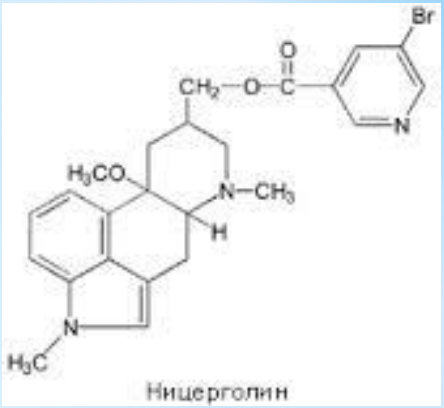


- has spasmolytic properties and acts mainly on cerebral vessels.
- possesses antiplatelet properties and decreases pathologically high blood viscosity.

As a result the microcirculation improves.

Nicergolin (*Sermion*) – *tab. 5 mg, 10 mg;*

vial 4 mg IM



Ницерголин

combines the structures of

Ergot alkaloids (*Rye Ergot Fungus*) and

Nicotinic acid.

It has **α-adrenoblocker** and **spasmolytic activities**.

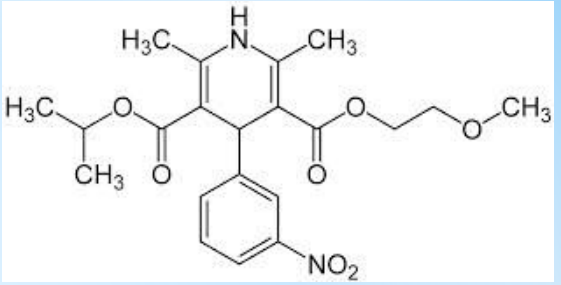
The drug dilates cerebral and peripheral vessels.

<u>Adverse effects</u>: hypotension, dizziness,

reddening of skin, pruritus,

dyspeptic disorders.

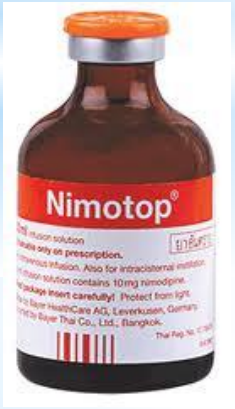
Nimodipine (*Nimotop*)-



a Ca^{2+} channel blocker with mainly influence on cerebral circulation.

It **inhibits Ca^{2+} ion influx** across cardiac and smooth muscle cells, thus decreasing myocardial contractility and oxygen demand, and dilates coronary, cerebral and peripheral arteries and arterioles.

The drug dilates the small cerebral resistance vessels and increases collateral circulation.



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