Poltava State Medical University
Department of Pharmacology, Clinical pharmacology and Pharmacy

Lecture

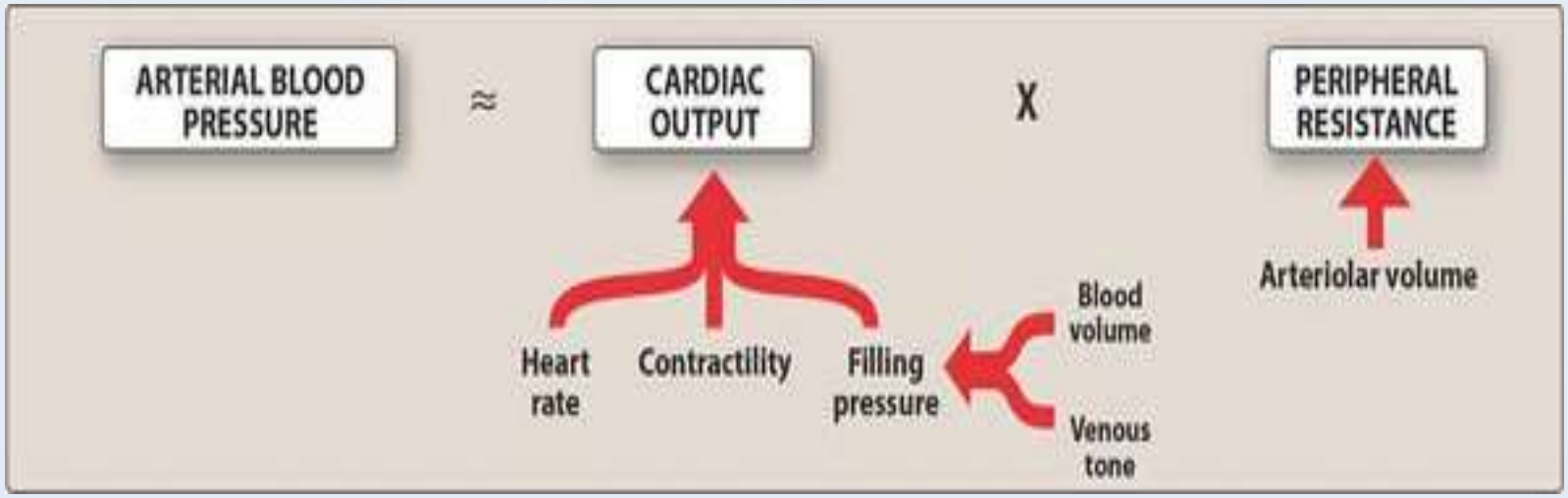
Medicines that affect the cardiovascular system. Antihypertensive drugs

CONTENTS

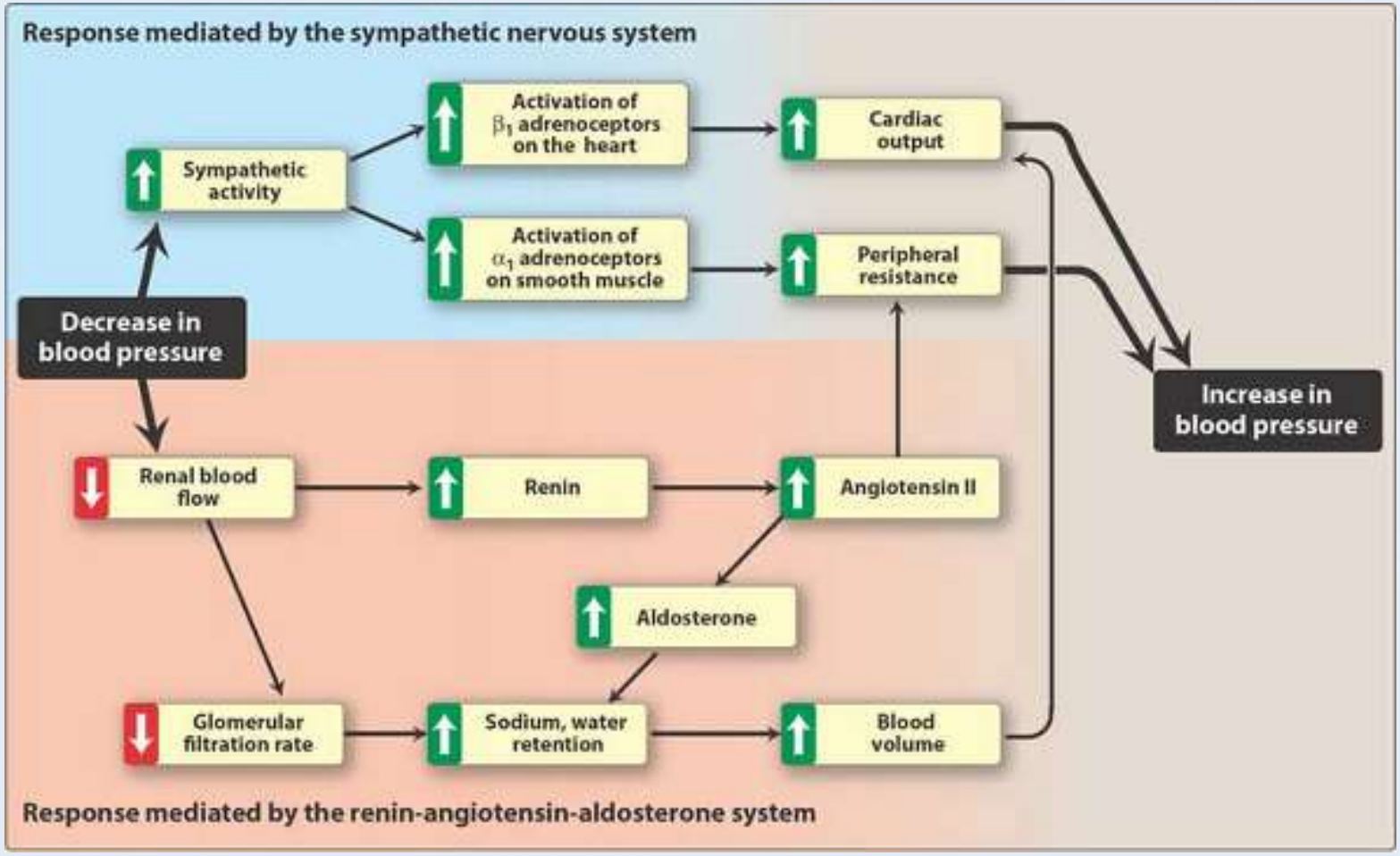
- Blood pressure and its regulation
- Hypertension and its pathogenesis
- Antihyperetensives and their classification
- Neurotropic antihypertensive drugs
- Myotropic vasodilators
- Drugs influencing renin-angiotensin system
- Diuretics
- Drugs for hypertensive emergensy
- Control tasks

ARTERIAL BLOOD PRESSURE

Arterial blood pressure (BP) is a sum of cardiac output and peripheral resistance. Cardiac output depends on heart rate and contractility. Peripheral resistance depends on blood vessels tone and volume of circulating blood.



REGULATION OF BLOOD PRESSURE LEVEL



HYPERTENSION

Hypertension is sustained diastolic blood pressure greater than 90mm Hg accompanied by an elevated systolic blood pressure (more than 140 mm Hg).

Chronic hypertension leads to:

- congestive heart failure
- myocardial infarction
- renal damage
- cerebrovascular accidents.

Main links of pathogenesis of hypertension

Hypertension is a result of disregulation in cardiovascular system and water-electrolytes balance. Its development is connected with:

- Disturbances in ratio between inhibition and stimulation in cortex of brain
- Changes in activity of vasomotor center
- Activation of sympathetic stimulation of the heart and blood vessels
- Changes in blood vessels wall
- Activation of renin-angiotensin system
- Increase in blood volume.

ANTIHYPERTENSIVE DRUGS

Antihypertensive drugs are drugs for the treatment of hypertension.

Treatment strategies:

- mild hypertension can be controlled with one drug
- severe hypertension must be treated with combination of drugs
- drugs for combined therapy of hypertension are selected to minimize side-effects of combined regimen
- ***"first-line" drugs are diuretics, β-adrenoblockers, inhibitors of angiotensin converting enzyme (ACE), calcium channel blockers, α-adrenoblockers.***

ANTIHYPERTENSIVE DRUGS: classification

A. Neurotropic agents

1. Drugs decreasing vasomotor center activity (centrally acting α2-adrenomimetics)

– Clonidine (Clophelinum)
– Methyldopa

2. Anti-adrenergic drugs

a) α-Adrenoblockers
– Prazosin
– Doxazosin

b) β-adrenoblockers
– Metoprolol
– Propranolol (Anaprilinum)

c) α,β-adrenoblockers
– Labetolol
– Carvedilol

d) Adrenergic neuron blocking agents (sympatholytics)
– Reserpine
– Guanethidine

3. M-cholinoblocker
– Platyphylline

B. Myotropic vasodilators

1. Ca++ channel blockers

– Nifedipine
– Verapamil

2. Magnesium salts

– Magnesium sulfate

3.Phosphodiesterase inhibitors

– Papaverine
– Bendazole

4. Potasium channel openers

– Appressin
– Minoxidil
– Diazoxide

5. Other vasodilators

– Sodium nitroprusside

C. Drugs acting on renin-angiotensin system

1. ACE inhibitors

– Captopril
– Enalapril

2. Angiotensin II receptor antagonist

– Losartan

D. Diuretics

– Hydrochlorothiazide
– Furosemide.

NEUROTROPIC DRUGS

DRUGS DECREASING VASOMOTOR CENTER ACTIVITY. CLONIDINE

Pharmacokinetics

- is administered sublingually, orally, IV, IM
- is completely absorbed in the GI tract
- after IV or sublingual administration, begins to act in 5-10 min, after oral administration – in 30-60 min
- penetrates CNS
- is metabolized in the liver and excreted with urine
- acts during 2-12 hrs.

Mechanism of action

- The drug stimulates α2-adrenoceptors in CNS.
- Stimulation of presynaptic α2-adrenoceptors in adrenergic synapsis of vasomotor center results in inhibition of norepinephrine release into synaptic gap and decrease in sympathetic impulsation to peripheral blood vessels.
- That leads to dilation of blood vessels, lowering of BP, and slow heart rate.

Pharmacodynamics

- decrease in BP (antihypertensive action)
- decrease in heart rate and cardiac output
- decrease in renin activity
- sedation
- decrease in pain
- decrease in intra-ocular pressure
- potentiation of other drugs inhibiting CNS.

CLONIDINE

Indications

- Acute hypertension (hypertension crisis)
- Chronic hypertension
- Glaucoma (eye drops)
- Migraine
- Pain syndromes
- Chronic alcoholism
- Potentiation of general anesthesia.

Side effects

- Weakness, somnolence
- Hypotension, postural hypotension
- Transitory elevation of BP after IV or sublingual administration (resulting from stimulation of
- peripheral adrenoceptors)
- Constriction of blood vessels in the brain
- ***Dry mouth***
- Inhibition of gastric secretion
- Constipation
- Retention of sodium and water
- Changes in glucose level in blood
- Abolishing syndrome.

Contraindications

Severe atherosclerosis, job needed quick reaction Should not be given together with alcohol and psychotropic drugs.

METHYLDOPA

- is taken orally, is well absorbed in the GI tract, penetrates CNS, starts to act slowly
- is similar to norepinephrine on chemical structure, that's why acts as "false mediator" in CNS: stimulates α2-adrenocepotors and decreases norepinephrine release in synapses of vasomotor center; by this mechanism it decreases the activity of vasomotor center, inhibits sympathetic impulsation to blood vessels, dilates blood vessels and lowers BP (is centrally acting sympatholytic)
- has antihypertensive action, improves cerebral blood flow, increases lactation
- is used for treatment of hypertension
- has side effects which are similar to the same of clonidine, also may cause muscular and joint pains, rise in body temperature, skin rash, galactorrhea
- is contraindicated to patients suffering from depression, Parkinson's disease, liver diseases.

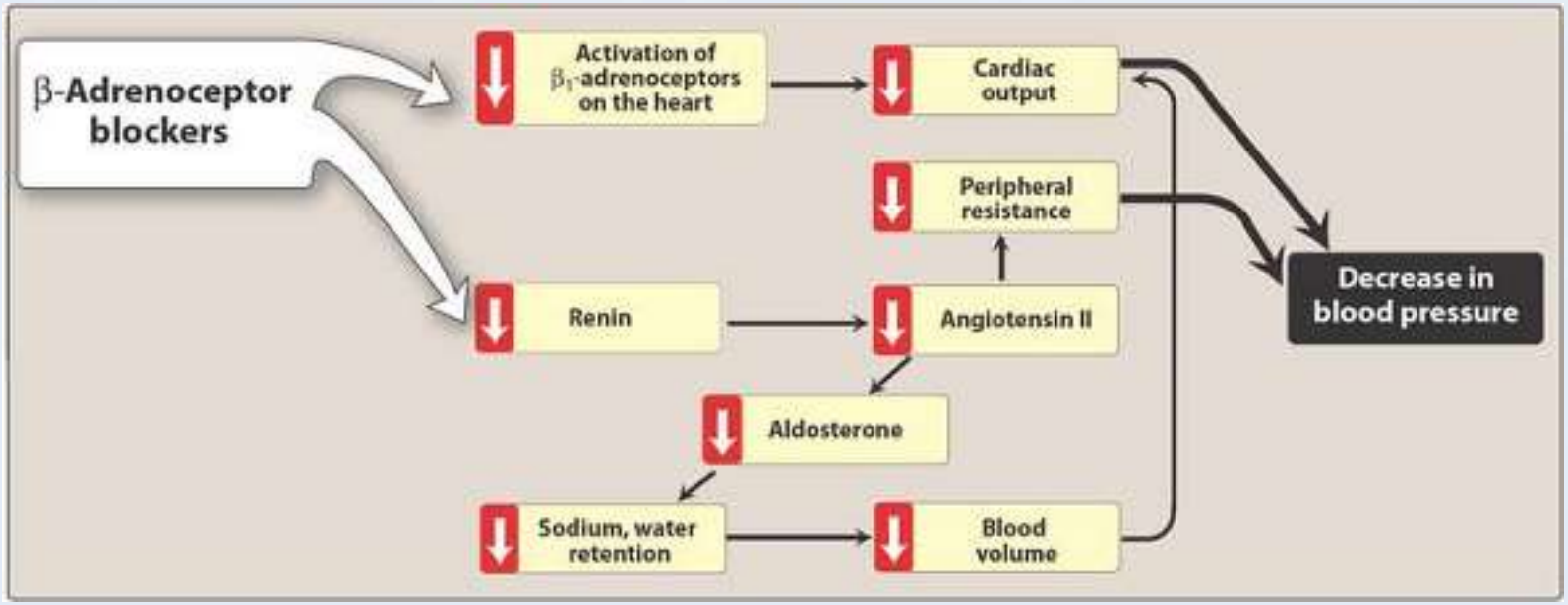
ANTI-ADRENERGIC DRUGS. α-ADRENOBLOCKERS

Prazosin and doxazosin selectively block α1-adrenoceptors, dilate blood vessels, reduce peripheral vascular resistance and decrease BP. They are taken orally for the treatment of mild to moderate chronic hypertension.

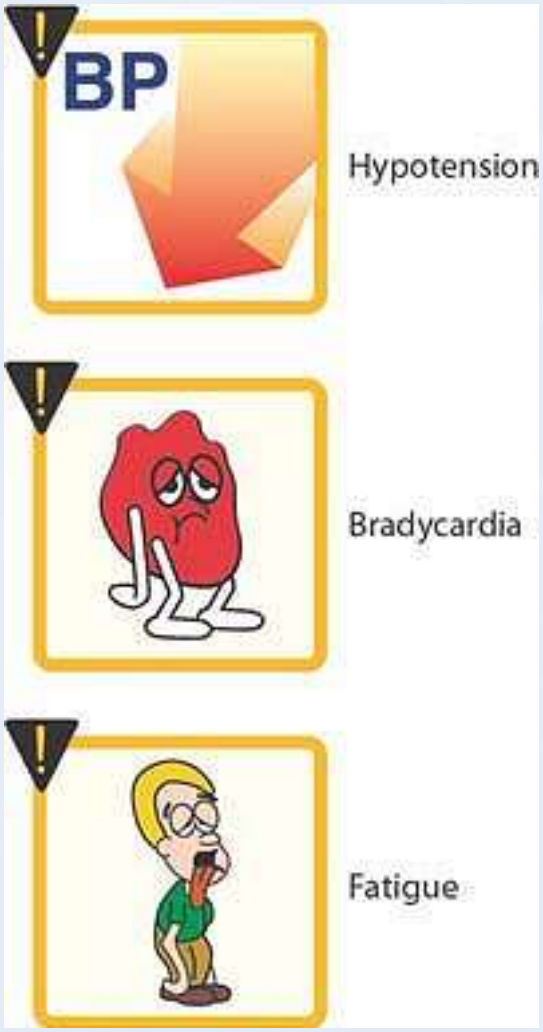
β-ADRENOBLOCKERS

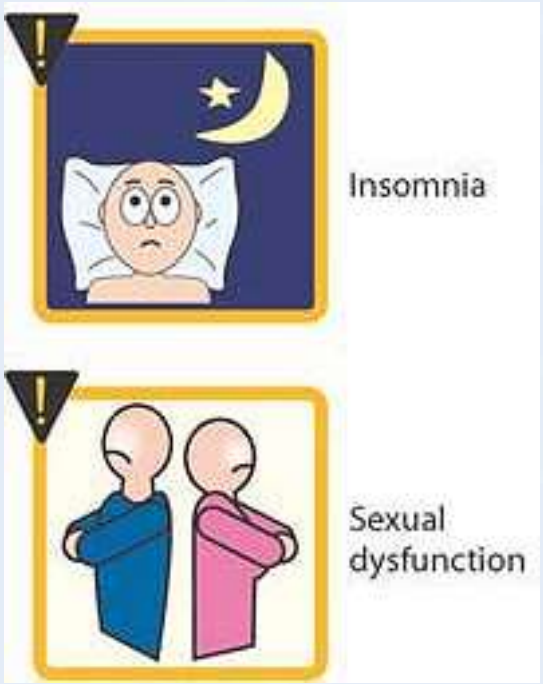
β-adrenoblockers (propranolol) are the "first-line" preparations for chronic hypertension. They are taken orally to control hypertension. Full effect develops in several weeks.

Mechanism of antihypertensive action



β-ADRENOBLOCKERS: side effects





α,β-ADRENOBLOCKERS. SYMPATHOLYTICS

α,β-ADRENOBLOCKERS

Carvedilol is modern preparation which acts both on α- and β-adrenoceptors, but action on β-receptors is more significant. It is an antioxidant, has cardioprotective properties (protects myocardium from hypoxia).

SYMPATHOLYTICS

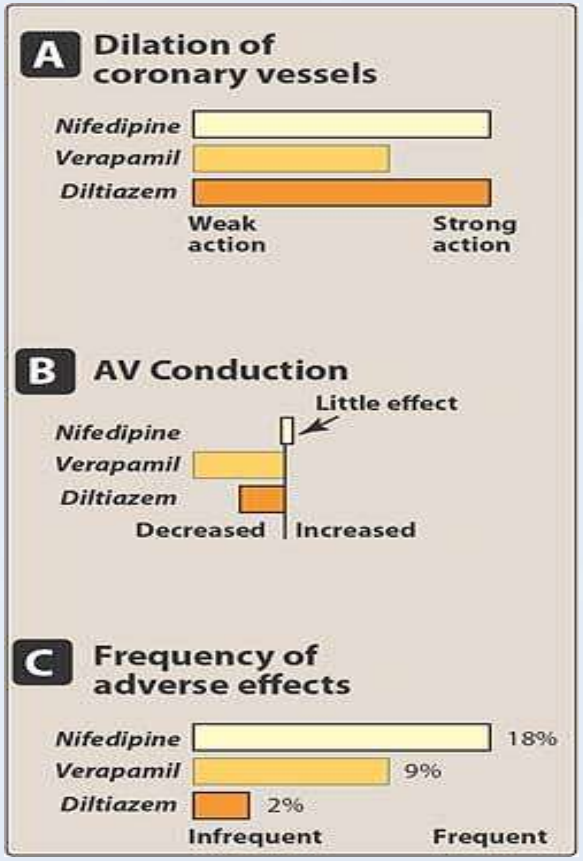
Reserpine acts in peripheral tissues, as well as in CNS (sedative and neuroleptic action); is used for mild forms of hypertension; produces sodium and water retention; is combined with thiazide diuretics; may cause disturbances of sleep, depression, and side-effects connected with prevanence of PANS.

Guanetidine (Octadinum) is potent peripherally acting sympatholytic; is used for severe forms of hypertension; begins to act slowly (in 2-4 days after the start of treatment); may cause postural hypotension, and side effects connected with PANS prevalence in the body (bradycardia, spasm of bronchi, increased activity of the gut, ***enlargement of salivary glands***).

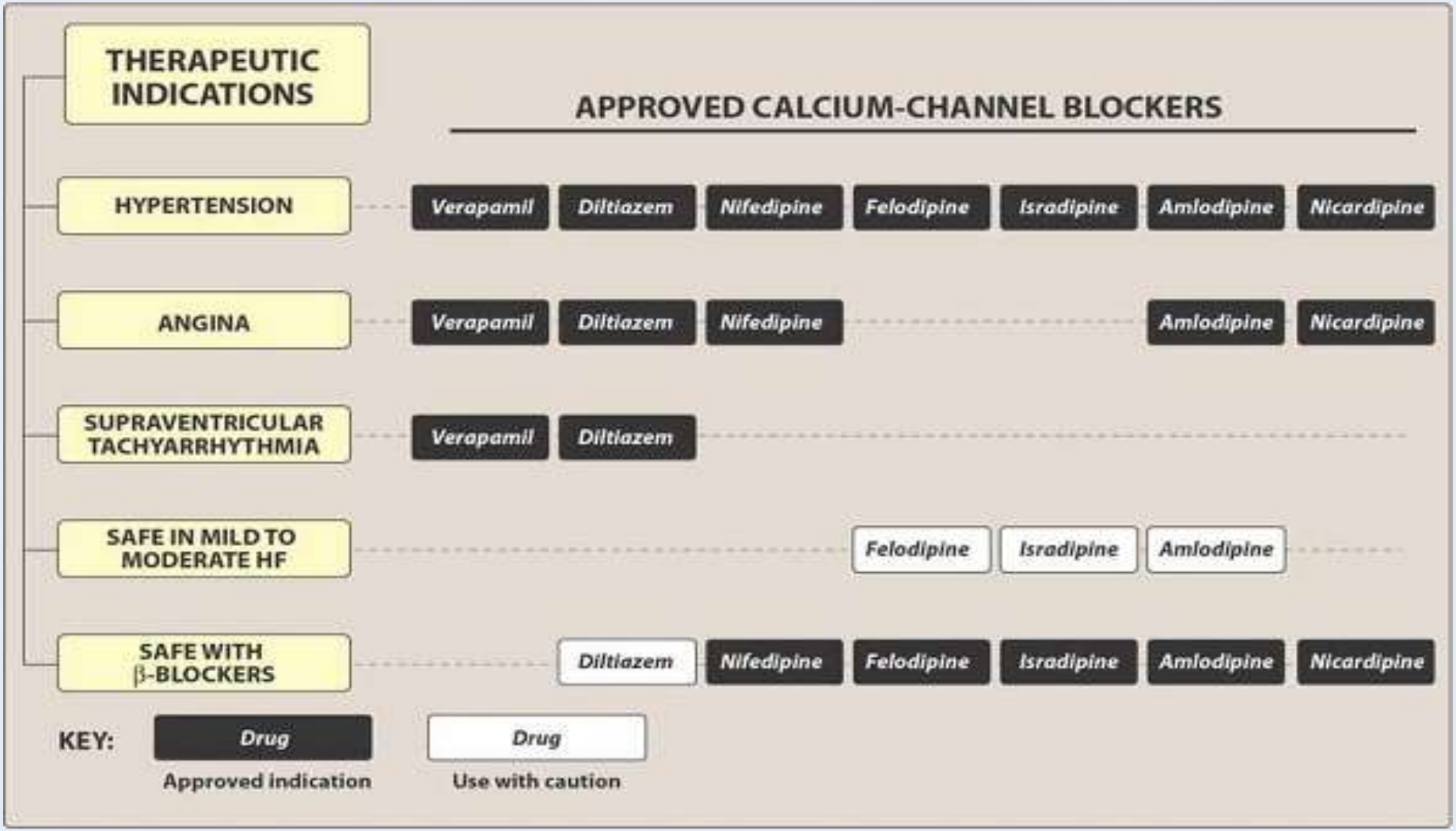
MYOTROPIC VASODILATORS

CALCIUM CHANNEL BLOCKERS

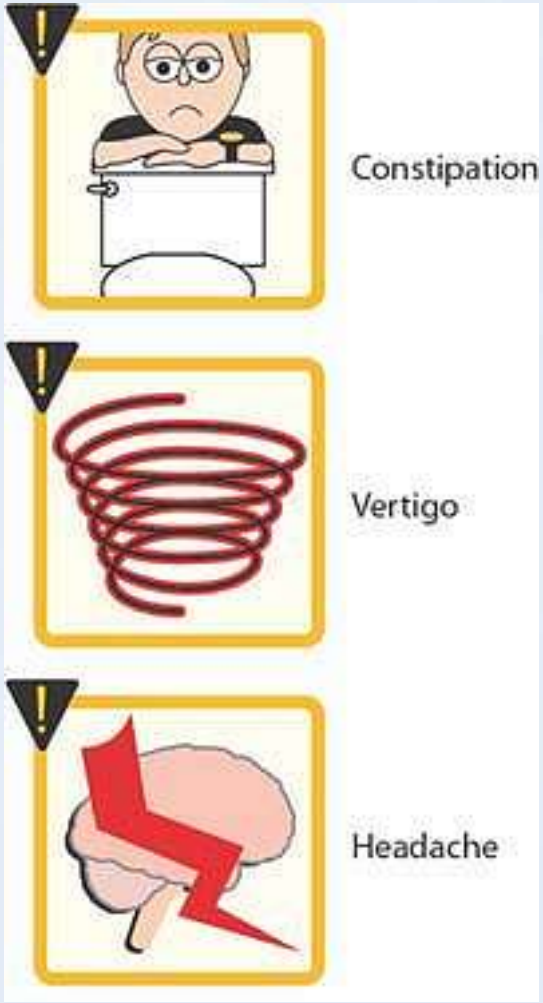
Calcium channel blockers (nifedipine, verapamil, amlodipine, diltiazem) have anti-hypertensive action resulting from dilation of blood vessels and decrease in peripheral vascular resistance. They are suitable for chronic use in hypertension of any severity. The choice of calcium channel blockers is grounded on the effect of the drug on cardiac pacemakers and contractility and coexisting diseases (angina pectoris, bronchial asthma, peripheral vascular diseases).

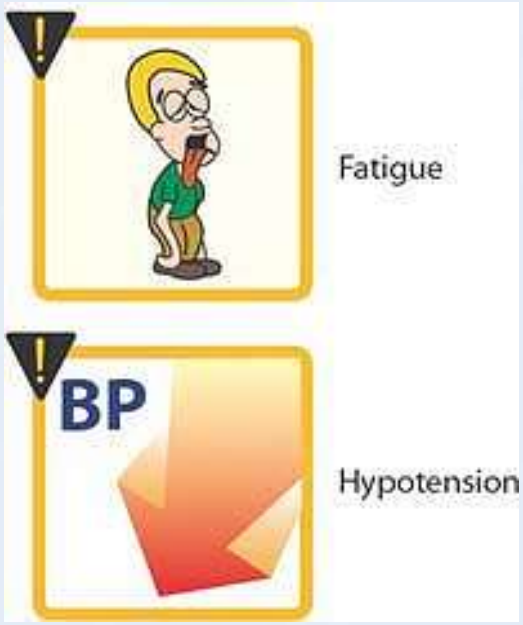


CALCIUM CHANNEL BLOCKERS: clinical use



CALCIUM CHANNEL BLOCKERS: side effects





MAGNESIUM SALTS. MAGNESIUM SULFATE

- is administered IV, IM (after oral administration acts as laxative)
- is an antagonist of calcium ions in cells
- sedative, hypnotic, and narcosis action, inhibition of vasomotor center; anti-seizure action, dilation of blood vessels, and decrease in BP; anti-arrhythmic action, dehydratation of tissues, diuretic action, decrease in intracranial pressure; spasmolytic action; antidote in acute poisonings with compounds of calcium
- is used in hypertensive emergence, chronic hypertension, seizures attack, edema of brain, tachyarrhythmia, myocardial infarction, toxicosis of pregnancy, overdose of calcium preparations
- may cause side effects, such as pain and infiltrate in the site of administration (IM), oppression of respiration (IV). If oppression of respiration is occurred, calcium chloride (IV) and carbogenum (inhalation) should be used.

PDE INHIBITORS. BENDAZOLE (DIBAZOLUM)

- synthetic preparation, imidazole derivative
- is administered IM, IV, orally; acts during 4-6 hrs
- inhibits PDE III and increases the amount of cAMP in cells, that's why produces relaxation of smooth muscles and dilation of blood vessels
- has antihypertensive and spasmolytic actions; stimulates functions of spinal cord; is interferon inductor
- is indicated in hypertensive emergence, mild hypertension, spasms of blood vessels, spasms of smooth muscles in the gut, colic, neurological diseases with lesions of spinal cord, non-specific prophylaxis of viral infections.
- is combined with papaverine to elevate antihypertensive activity.

POTASSIUM CHANNEL OPENERS. APPRESSIN (HYDRALAZIN)

- is administered orally, IM, IV; begins to act slowly (even after IV administration); is well absorbed in the GI tract; is metabolized in the liver by acetylation; the speed of acetylation in one patient differs from the same in another (rapid and slow acetylation); is excreted with urine and feces; acts during 4-12 hrs
- activates K+ channels, causes hyperpolarization and blockage of Ca++channels, relaxes arteriolar smooth muscles and dilates arteriolar vessels; as a result, decreases peripheral vascular resistance and decreases BP
- displays antihypertensive action, increases heart rate and cardiac output (resulting from reflexes, as well as from direct action on β-adrenoceptors in the heart); elevates pressure in lung artery; increases renin secretion
- is used to treat moderate and severe hypertension, CHF
- is combined with β-adrenoblockers and diuretics
- causes side effects, such as weakness, headache, tachycardia, worsen in angina, flushing of skin, sweating, reversible lupus-like syndrome, retention of water and salts.

POTASSIUM CHANNEL OPENERS. DIAZOXIDE AND MINOXIDIL

DIAZOXIDE

- is administered orally, IV; begins to act in 2-5 min after IV administration; has duration of action from 2-4 hrs (IV) to 12 hrs (orally)
- is K+ channel opener, arteriolar vasodilator
- produces decrease in BP; reflexive increase in heart rate; decrease in tone of smooth muscles in the gut and uterus; inhibition of insulin secretion, decrease in renal filtration and ureic acid excretion
- is used to treat hypertensive emergence and chronic hypertension
- may cause tachycardia, worsening in angina pectoris and diabetes, uricosaemia, constipation.

MINOXIDIL

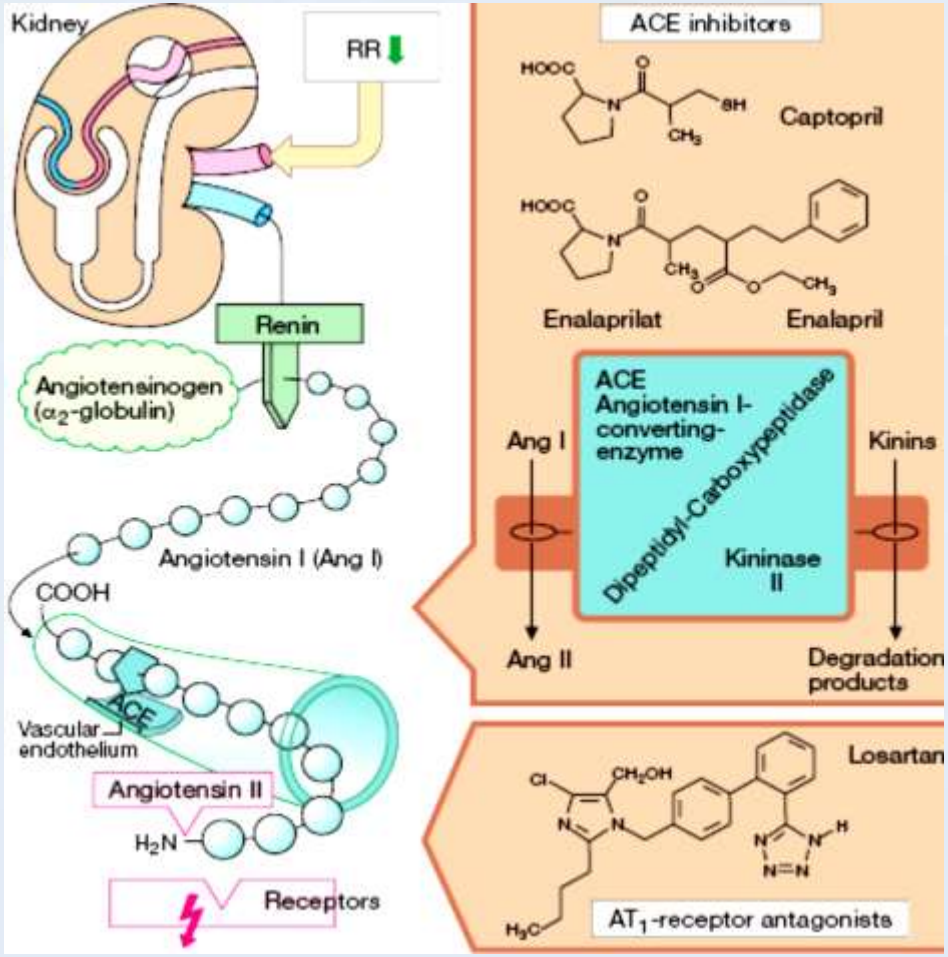
- is K+ channel opener, arteriolar vasodilator
- is more potent than hydralazin
- is used for severe hypertension, renal failure, alopecia (as ointment)
- may cause hyrsutism as side-effect.

OTHER VASODILATORS. SODIUM NITROPRUSSIDE

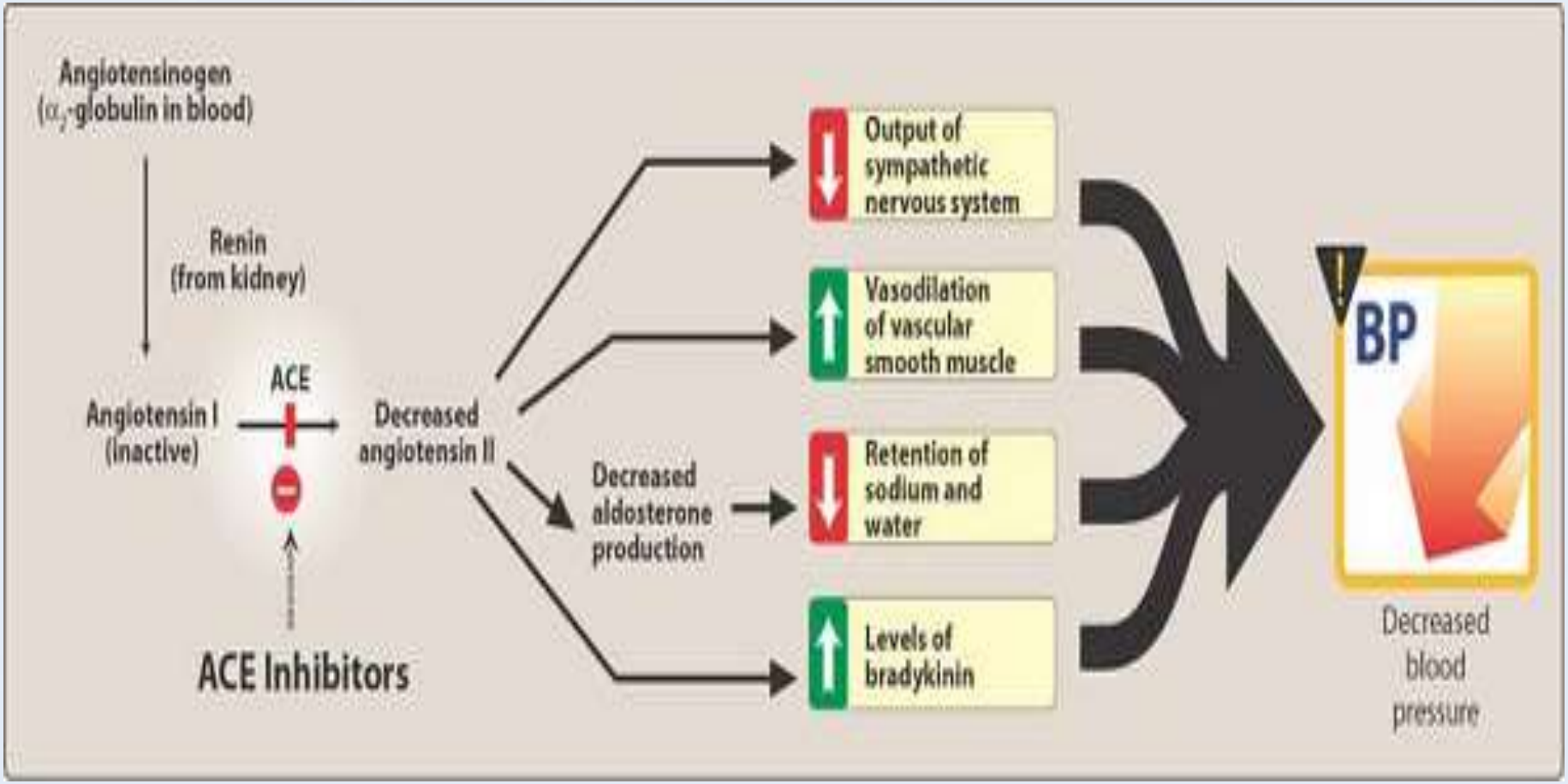
- is administered by IV infusion; begins to act within 1 min; stops to act in 5 min after the end of IV infusion
- contains group NO binding with Fe, that's why mechanism of action is the same as mechanism of nitroglycerine; exceeds nitroglycerine's potency in 1000 times; is arteriolar and venous vasodilator
- decreases BP; decreases the load on myocardium; increases cardiac output under the conditions of heart failure; increases secretion of renin
- is used in hypertensive emergence, acute heart failure, edema of lungs, controlled hypotension in surgeries
- may cause hypotension, nausea, headache, sweating, restlessness, retrosternal pain.

DRUGS ACTING ON RENIN-ANGIOTENSIN SYSTEM

RENIN-ANGIOTENSIN SYSTEM: sites of drugs' action



ACE INHIBITORS: mechanism of action



ACE INHIBITORS: pharmacodynamics and indications

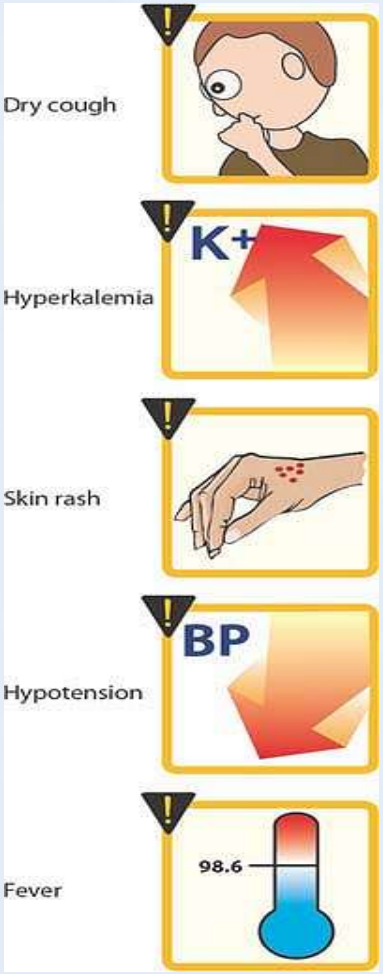
Pharmacodynamics

- vasodilation caused by diminishing of angiotensin II and increase in bradykinin level in blood
- decrease in blood volume resulting from inhibition of secretion of aldosterone and reducing of its action on sodium and water excretion
- decrease in BP resulting from vasodilation and decrease of blood volume
- decrease in load on myocardium
- increase in cardiac output under the conditions of heart failure
- decrease in oxygen demand of myocardium
- reduction of pressure in blood vessels of lungs
- retention of potassium in the organism.

Indications

- Hypertension
- Chronic CHF
- Myocardial infarction.

ACE INHIBITORS: side effects



- Dry cough, spasm of bronchi (resulting from increase in bradykinin level)
- Skin rash
- Fever
- Hypotension
- Hyperkalemia
- Disturbance in renal function
- ***Altered taste (dysgeusia)***.

ACE INHIBITORS: peculiarities of preparations

Captopril is taken orally; reaches peak blood level in 60 min; has duration of action of 6-8 hrs; is eliminated from the body within 24 hrs; the initial dose can be increased in 1- to 2-week intervals.

Enalapril is more potent than captopril; has duration of action which is twice as long as that of captopril; is taken orally once or twice a day.

Lisinopril is the active metabolite of enalapril; is absorbed slowly and has slow onset of action; is taken orally once a day.

ANTAGONISTS OF ANGIOTENSIN RECEPTORS. LOSARTAN

- is taken orally and acts during 6-8 hrs
- blocks angiotensin II receptors, dilates blood vessels, decreases BP and load on myocardium
- is used for monotherapy of hypertension and CHF
- has less side effects than ACE inhibitors, does not cause dry cough and spasm of bronchi.

DIURETICS

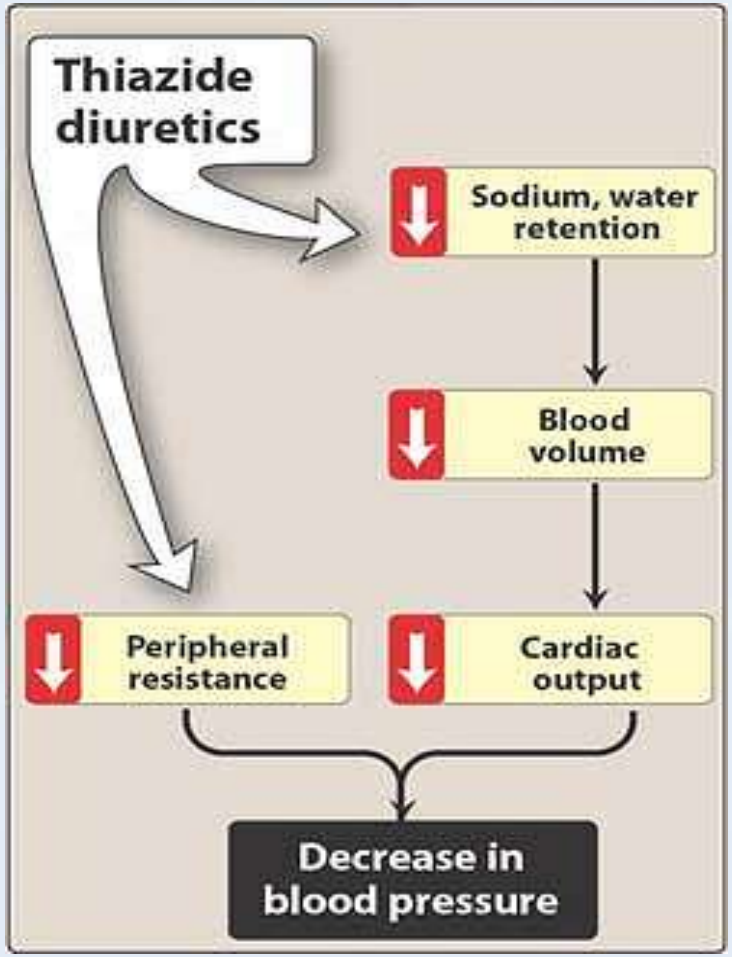
DIURETICS

All oral diuretics are effective in the treatment of hypertension, but the ***thiazides*** (***hydrochlorothiazide, = dichlothiazide***) have found the widest use. They act on cell basal membrane in proximal tubules and decrease reabsorbtion of sodium and chlorides. As a result, they increase sodium, chlorides, potassium, and water excretion with urine, decrease volume of blood and edema of blood vessel wall that leads to decrease in peripheral resistance and lowering of BP.

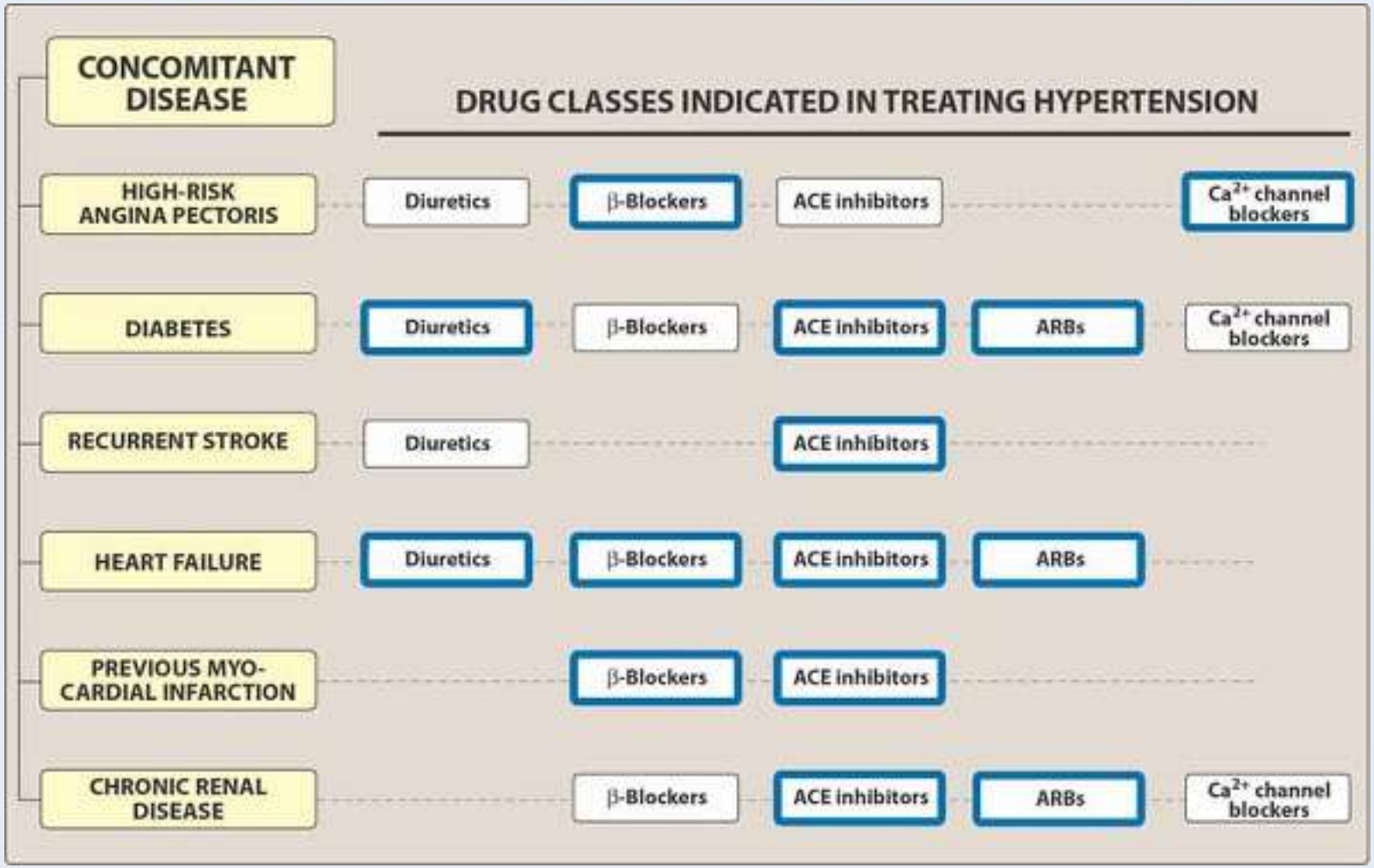
Furosemide is loop diuretic which is used parenterally in hypertensive emergence.

Potassium-sparring diuretics also may be used to treat hypertension. They act in distal tubules, increase excretion of sodium and water, cause the retention of potassium in the body.

DIURETICS: antihypertensive action of thiazides



PHARMACOTHERAPY OF HYPERTENSION WITH CO-EXISTANT DISEASES



DRUGS FOR HYPERTENSION EMERGENCY

For parenteral administration:

- sodium nitroprusside (by IV infusion in severe hypertensive crisis)
- labetalol
- pentamine
- furosemide
- magnesium sulfate
- bendazole and papaverine
- diazoxide

For sublingual administration:

- clonidine
- nifedipine
- captopril.

CONTROL TASKS

- A hypertensive patient has been successfully treated with ACE inhibitor enalopril, but his treatment was complicated by the persistent dry cough. What is the cause of such complication?

  A. A decrease in the renin synthesis B. An inhibition of the angiotensin conversion C. An inhibition of the bradykinin degradation D. An inhibition of angiotensin II receptors

  E. A Blockade of β-adrenoceptors. (C)

- A 50-year-old patient has acute hypertension. Her BP is 190/140 mm Hg. It is accompanied by a severe headache. A centrally-acting α-adrenergic agonist is used for the emergency help. It was administered sublingually and decreased PB in 10 minutes. Which drug was administered to the patient?

A. Papaverine B. Furosemide C. Hexamethonium D. Clonidine

E. Captopril. (D)

CONTROL TASKS

- A patient has moderate essential hypertension. He is treated with a drug suppressing formation of angiotensin II and preventing degradation of bradykinin. Which drug realizes its antihypertensive effect by these mechanisms?

A. Nifedipine B. Reserpine C. Clonidine D. Enalopril

E. Propranolol. (D)

- A patient with an initial form of hypertension informs his physician, that an increase in BP, as a rule, is connected with emotional overstrain and characterized by a rapid enhance of the systolic pressure. He also complains of pain in the heart and tachycardia. Which of the following drugs has to be used in the treatment of this patient?

A. Verapamil B. Nifedipine C. Prazosin D. Doxazosin E. Propranolol.

(E)