Anti-hypertensive drugs

Definition of Hypertension

❑ Established by the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC8). The last report of the JNC8 was published in 2014.

Hypertension, in people aged 18 years or older, is a medical condition in which the systolic or diastolic blood pressure is higher than the physiological values, monitored over a 6 months period.

❑ The European Society of Hypertension and British Hypertension Society did not adopt the JNC8 definition without comments: they defined the pressure values for physiological and pathological classification of blood pressure.

Blood pressure classification for adults		
	Systolic Blood Pressure	Diastolic Blood Pressure
Normal	< 120 mm Hg	< 80 mm Hg
Pre-hypertension	120 – 139 mm Hg	80 – 89 mm Hg
Stage 1 hypertension	140 – 159 mm Hg	90 – 99 mm Hg
Stage 2 hypertension	> 160 mm Hg	≥ 100 mm Hg

Types of Hypertension

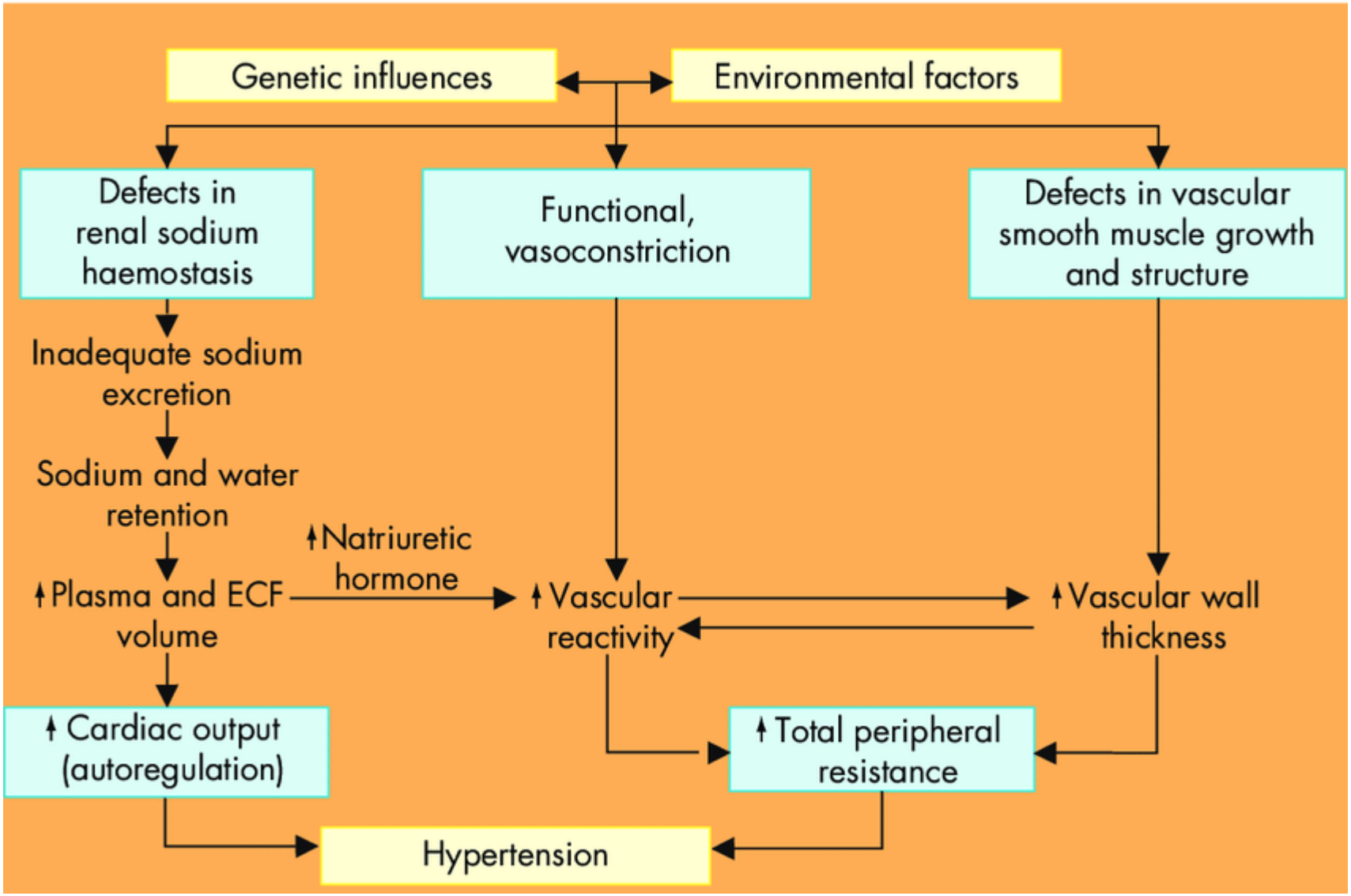
❑ Hypertension can be classified into:

1) **Primary (Essential) Hypertension:** results from a complex interaction of genes and environmental factors.

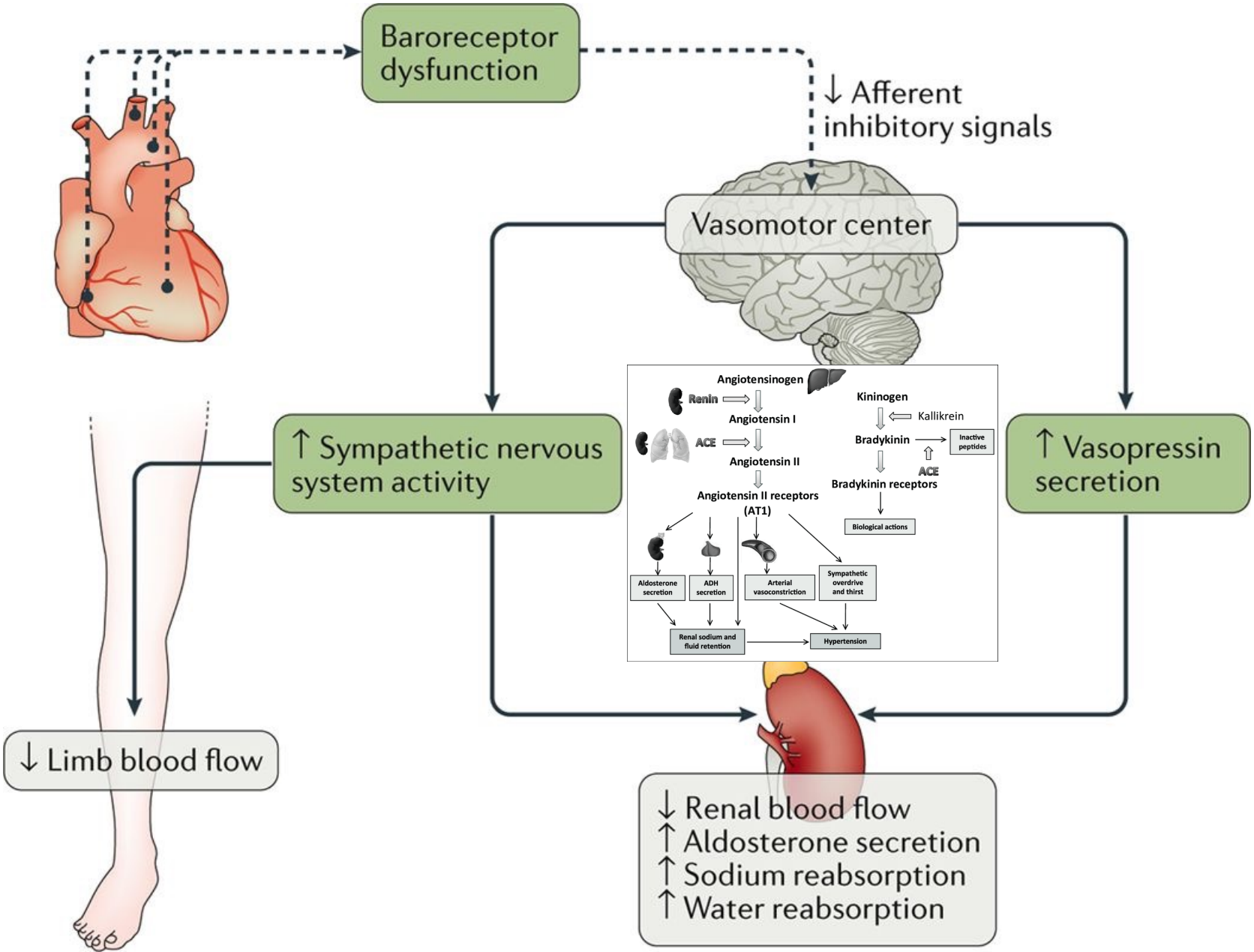
2) **Secondary (Symptomatic) Hypertension:** results from another disease (kidney disease, endocrine conditions, obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive eating of liquorice, drugs, herbal remedies, and psychostimulant abuse such as cocaine and methamphetamine).

A review published in 2018 found that any alcohol increased blood pressure in males while over one or two drinks increased the risk in females (*Roerecke M, et al. "Sex-Specific Associations Between Alcohol Consumption and Incidence of Hypertension: A Systematic Review and Meta-Analysis of Cohort Studies. J Am Heart Assoc. 2018;7(13). pii: e008202*).

The pathophysiology of essential hypertension



Physiological regulation of blood pressure



Why treat hypertension?

To decrease:

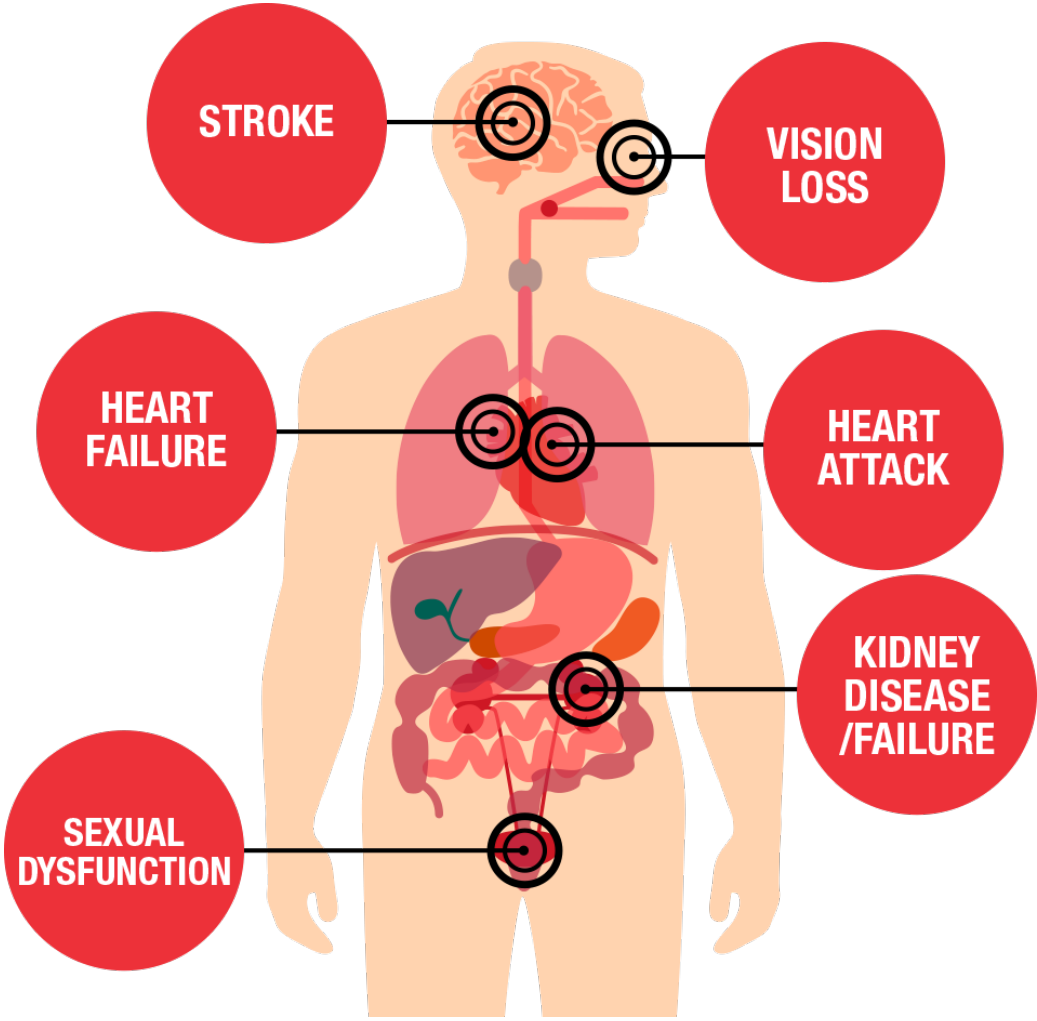
a) Cerebrovascular accidents (35-40%)

b) Coronary events (20-25%)

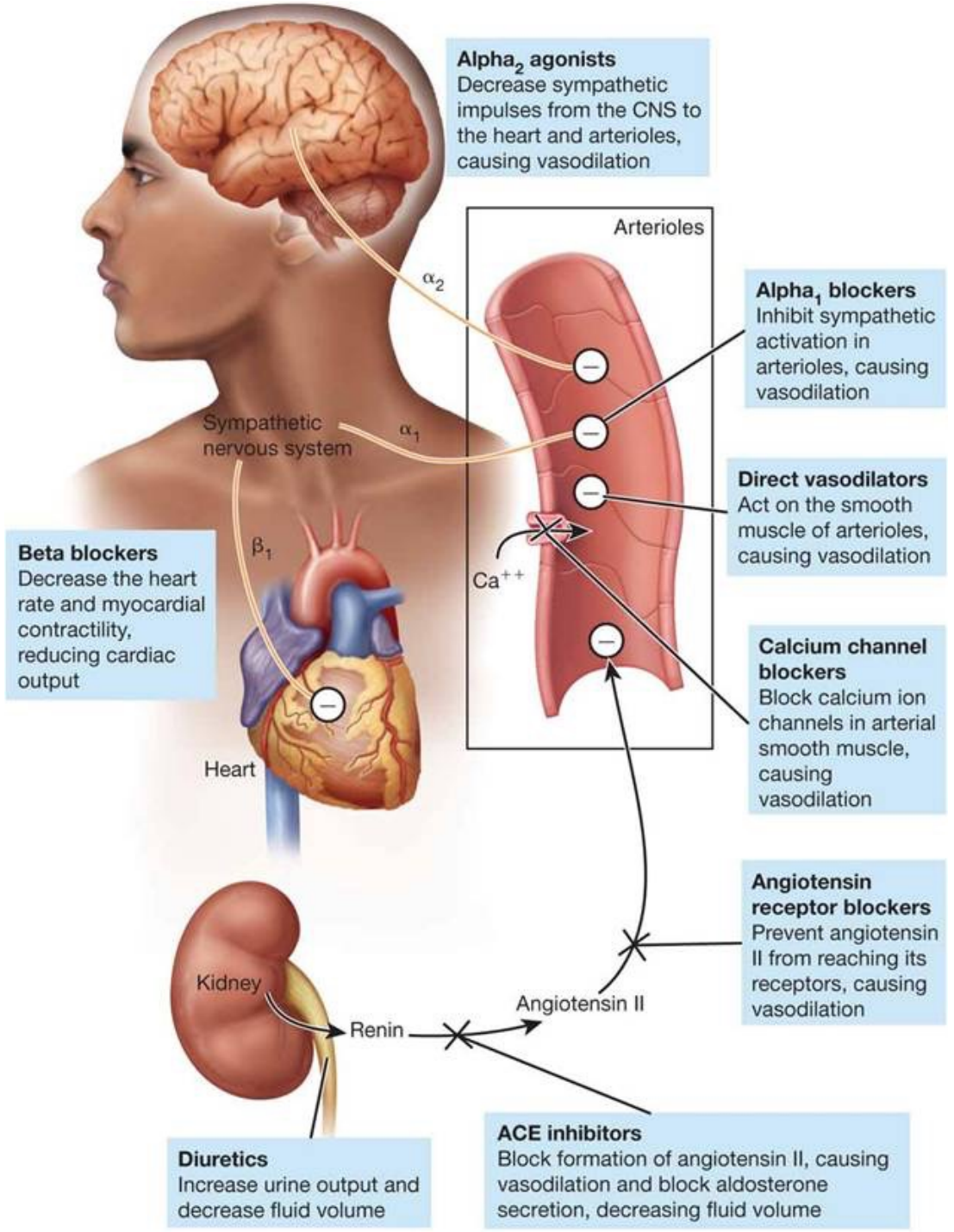
c) Heart failure (50%)

d) Progression to severe hypertension

e) Progression to kidney (~ 6%) and sexual diseases
(erectile dysfunctions ~ 60%)



Targets for anti-hypertensive drugs



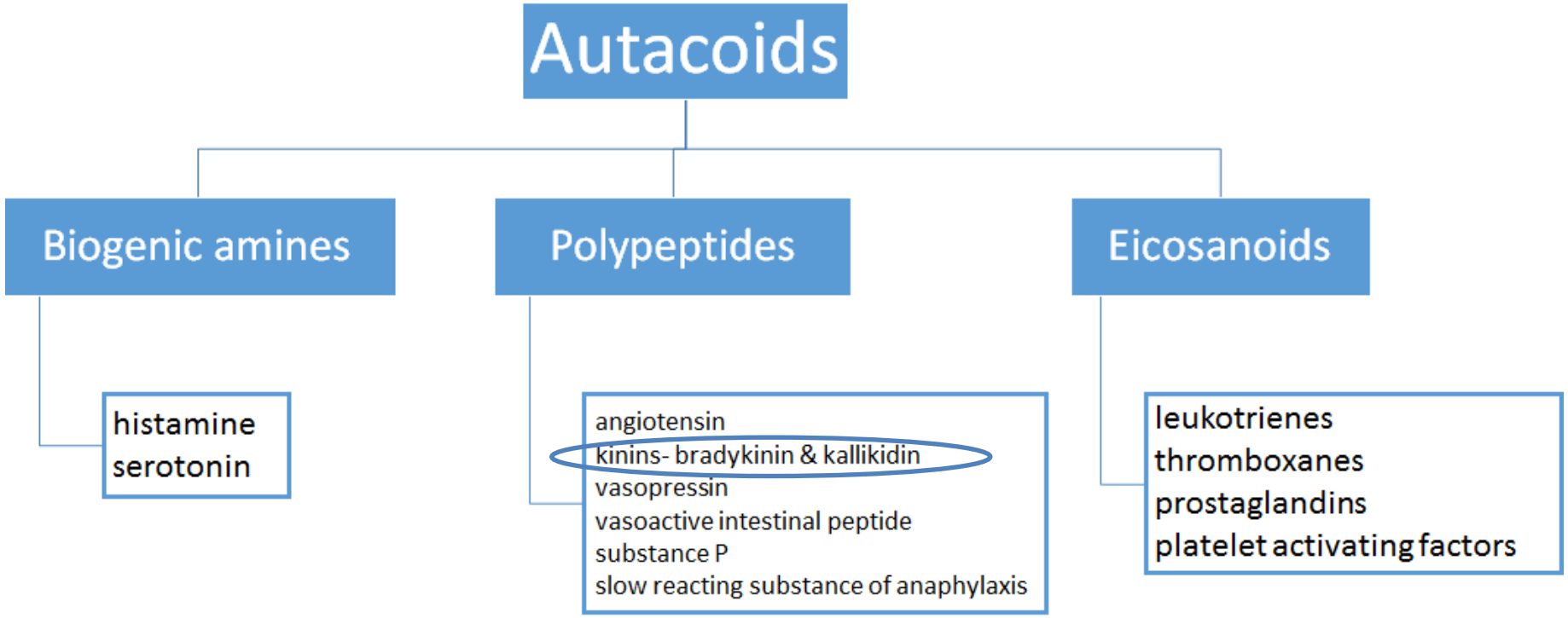
Classes of anti-hypertensive drugs

- ACE inhibitors;
- Angiotensin II type 1 receptor antagonists;
- Ca^{++} channel blockers;
- β-blockers (hypertension with comorbidities);
- Diuretics;
- α1-antagonists;
- Miscellaneous drugs.

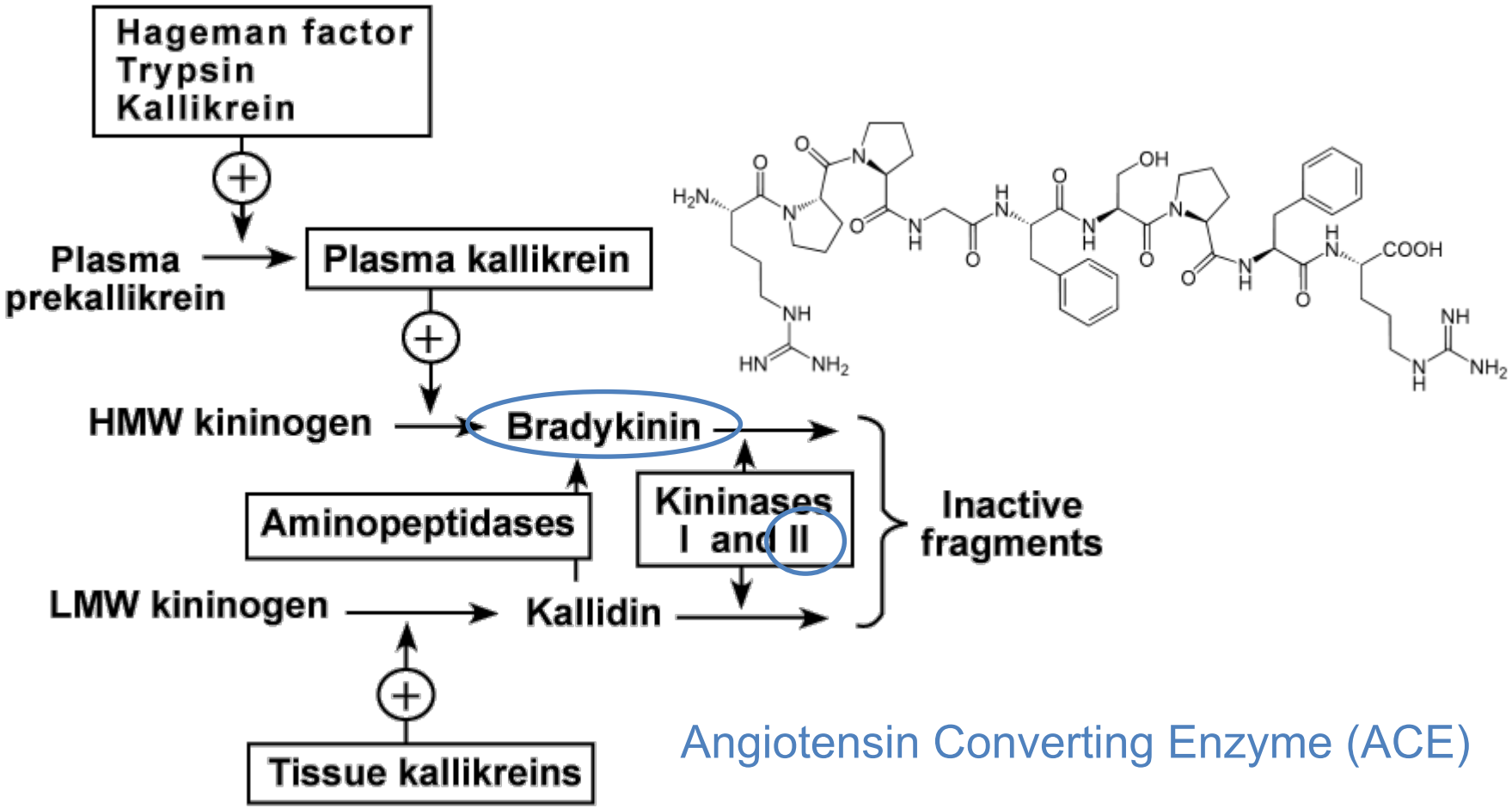
Autacoids

- Autacoids, also known as local hormones, have several biological actions near the site of synthesis.

- Autacoids can be classified basing on their chemical structure into:



The kinin-kallikrein system



Angiotensin Converting Enzyme (ACE)

Bradykinin

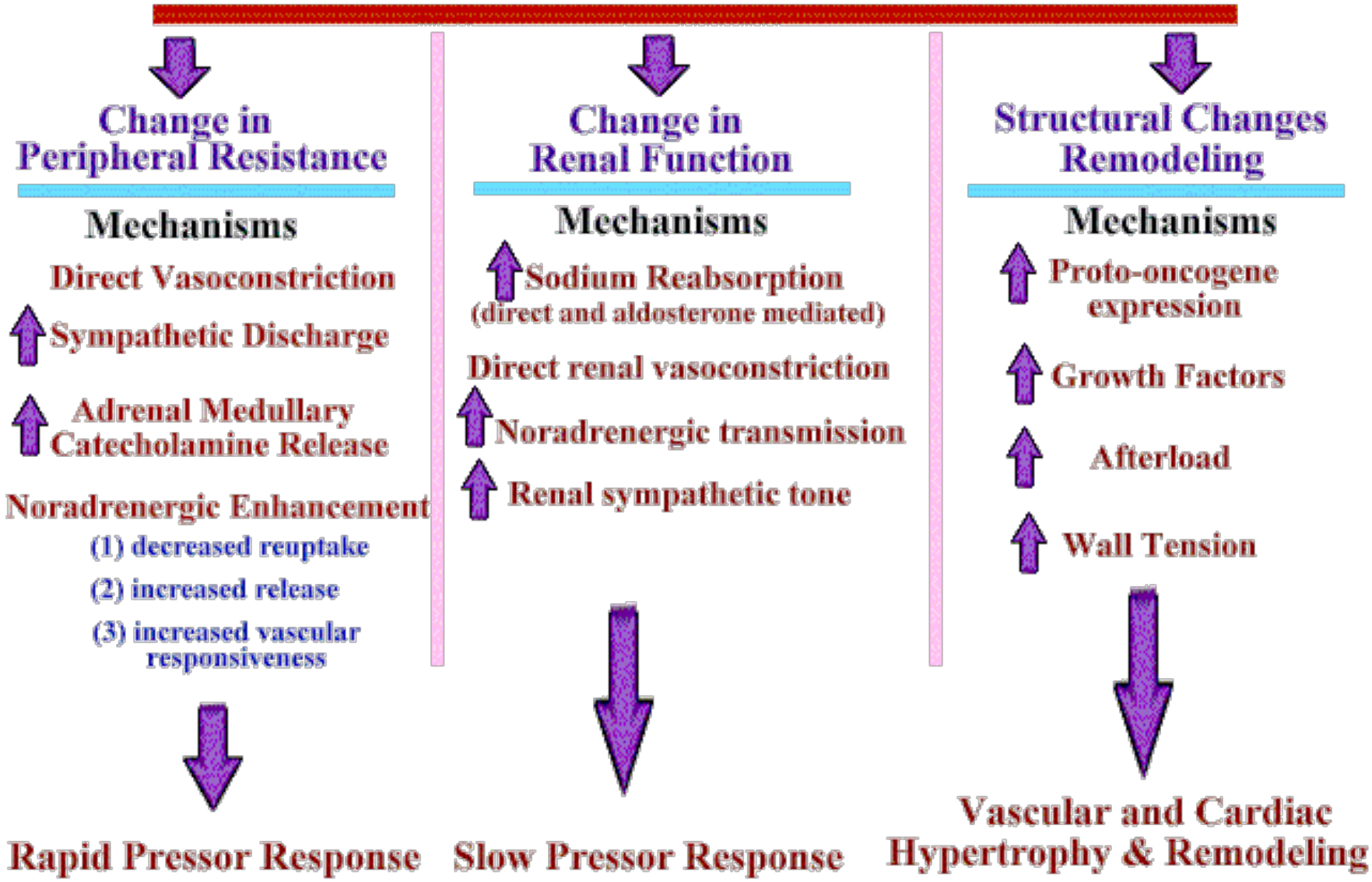
❑ The role of bradykinin in hypertension has been established for more than three decades, with the observations that **urinary kallikrein excretion is significantly reduced in hypertensive patients and hypertensive rats**.

❑ The physiological action of bradykinin in the regulation of systemic blood pressure involves:

1) **vasodilation** in most areas of the circulation,
2) reduction of total **peripheral vascular resistance**,
3) regulation of **Na^+ excretion** from the kidney.

❑ When bradykinin is injected into the renal artery, it causes **diuresis and natriuresis** by increasing renal blood flow. These actions of bradykinin have been attributed to prostaglandin release in the renal circulation. This led to the suggestion that reduced urinary kallikrein excretion might result from a defect in kinin generation in hypertensive situations.

Angiotensin II: Effects



ACE inhibitors

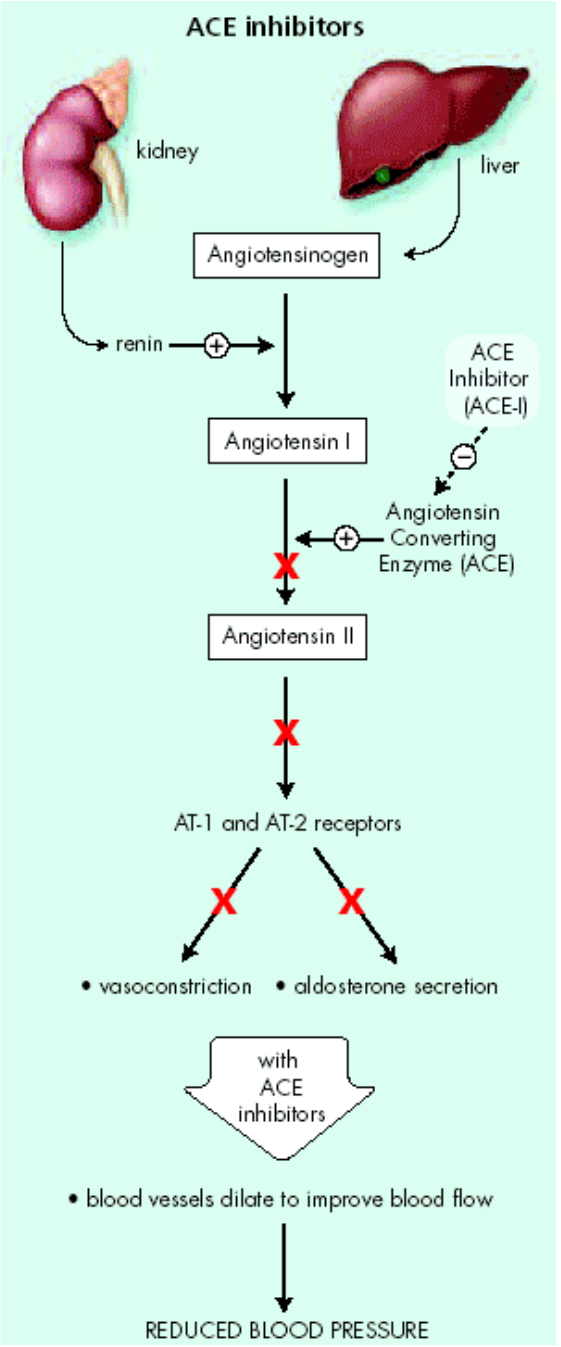
❑ Kininase II (ACE) inhibitors act:
1) inhibiting the biodegradation of bradykinin;
2) blocking the formation of angiotensin II.

❑ ACE inhibitors are currently used in the treatment of both clinical and experimental hypertension.

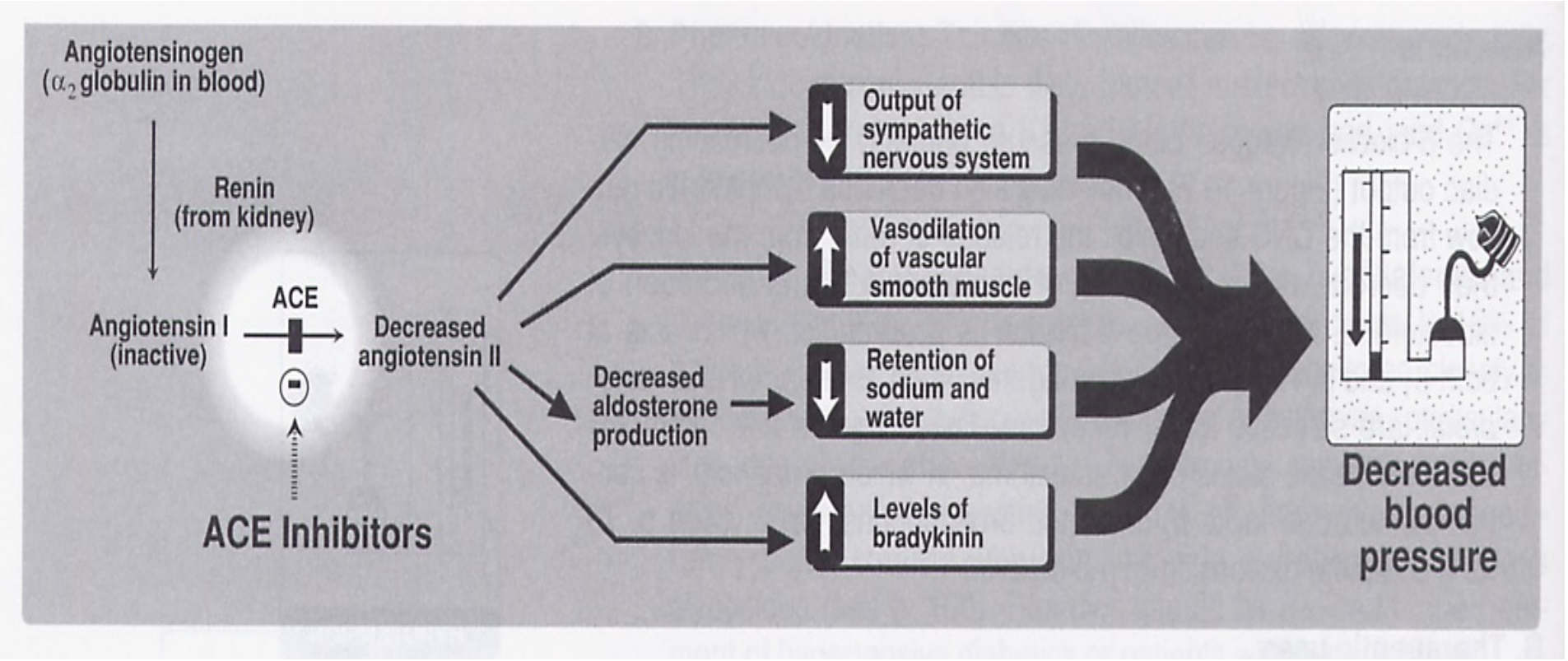
❑ ACE inhibitors pharmacological effects:

1) **relaxation of blood vessels** as well as decrease in blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart;

2) **increasing blood flow**, which helps to decrease the heart work and can help to protect the kidney from the effects of hypertension and diabetes.



Mechanisms of ACE inhibitor-mediated anti-hypertensive effects



ACE inhibitors: an overview

Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril, ramipril.
MECHANISM	Inhibit ACE → ↓ AT II → ↓ GFR by preventing constriction of efferent arterioles. ↑ renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator.
CLINICAL USE	Hypertension, HF (↓ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension.
ADVERSE EFFECTS	Cough, Angioedema (due to ↑ bradykinin; contraindicated in C1 esterase inhibitor deficiency), Teratogen (fetal renal malformations), ↑ Creatinine (↓ GFR), Hyperkalemia, and Hypotension. Used with caution in bilateral renal artery stenosis because ACE inhibitors will further ↓ GFR → renal failure.

Abbreviations: AT II: angiotensin II; GFR: glomerular filtration rate; HF: heart failure

Chemical classification of ACE inhibitors

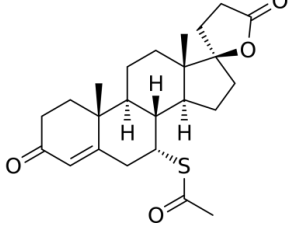
- Peptide structure:

1) Direct-acting ACE inhibitors (Captopril, Lisinopril, Enalapril)
2) Pro-drugs (de-esterified in the liver to active diacid forms).

- Three subgroups:

1) Sulphydryl- containing (Captopril, Zofenopril, Alacepril, Pivalopril);
2) Di-carboxyl-containing (Enalapril, Lisinopril, Quinapril, Ramipril, Perindopril);
3) Phosphorus-containing (Fosinopril).

Captopril

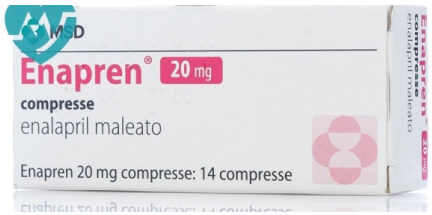


❑ Captopril is the prototype of the sulphydryl-containing ACE inhibitors. In vitro studies suggest that the presence of the sulphydryl group may confer properties other than ACE inhibition to these drugs, such **as free-radical scavenging and effects on prostaglandins**.

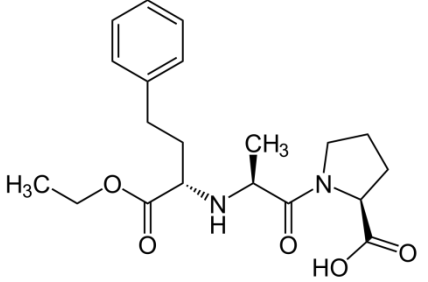
❑ Captopril is indicated in the **initial therapy of hypertension**, for patients with normal renal function or in patients with impaired renal function that do not respond to other drug therapy.

❑ Side effects: **dry cough**, skin rash, angioedema, and dysgeusia (distortion of taste). Proteinuria (1 of 100 patients), neutropenia (less than 1000/mm3) and agranulocytosis may appear after 3-12 weeks of therapy, particularly in patients with autoimmune collagen vascular diseases.

❑ Drug-drug interactions: drugs that increase the level of K+ in the blood (such as Angiotensin II type 1 receptor blockers, birth control pills containing drospirenone).



Enalapril



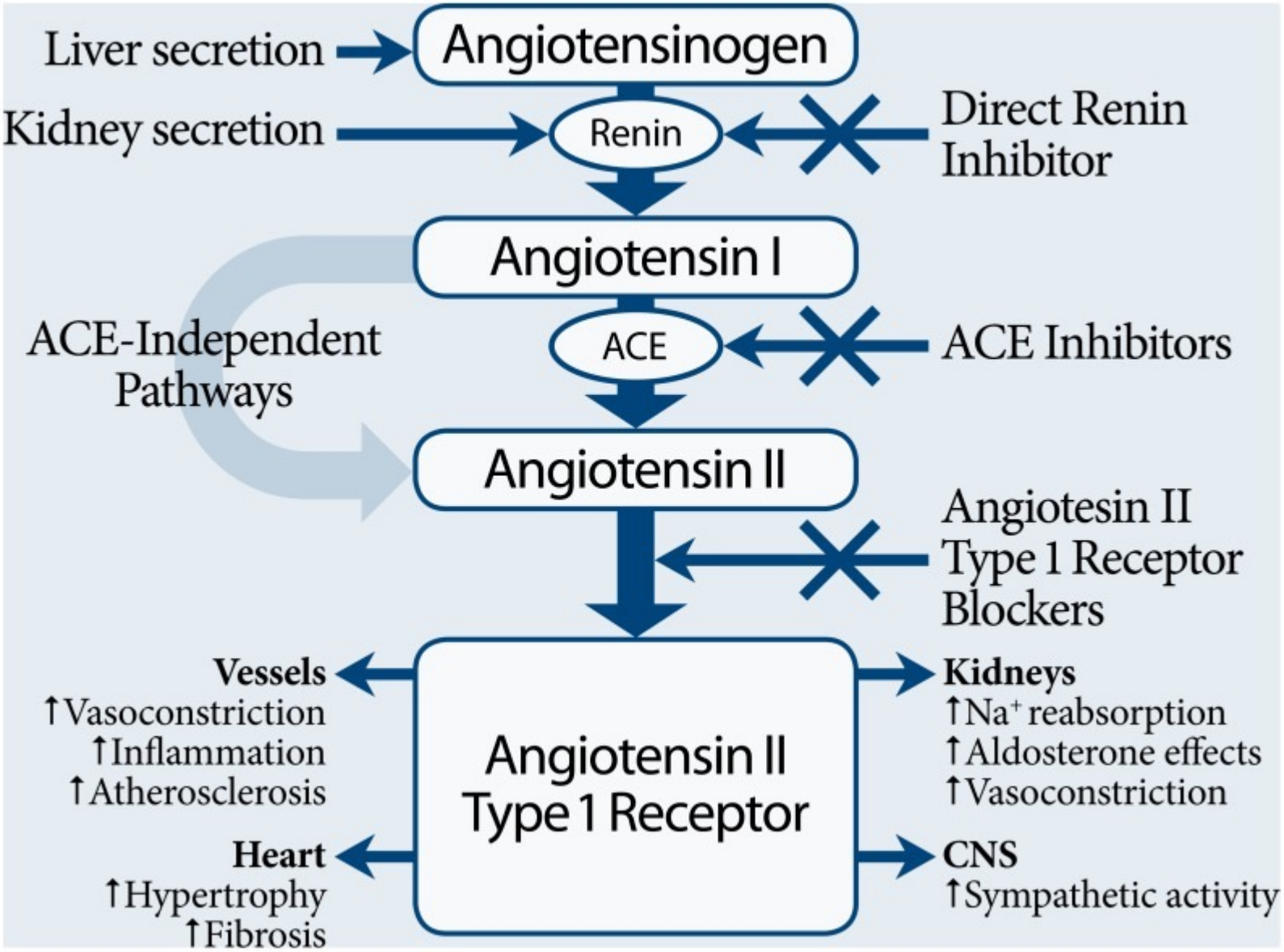
❑ Enalapril is an orally administered prodrug, hydrolyzed to release enalaprilat.

❑ Enalapril has been proven to protect the **function of the kidneys in hypertension, heart failure, and diabetes**, and may be used in the absence of hypertension for its kidney protective effects. Furthermore, enalapril is an emerging treatment for **psychogenic polydipsia**. A double-blind, placebo-controlled trial showed that when used for this purpose, enalapril led to decreased water consumption (determined by urine output and osmolality) in 60% of patients.

❑ Side effects: **dry cough**, skin rash and dysgeusia (distortion of taste). Other adverse effects of enalapril are hypotension, hyperkalemia, angioedema, cholestatic jaundice, and hypersensitivity reaction. The most serious, although rare (0.68%), adverse event is angioedema. The incidence of angioedema is higher in African-American individuals. The involvement of the head and neck can potentially compromise the airway. Angioedema can occur at any point during the treatment, but is most common after the first few doses.

❑ Drug-drug interactions: drugs that may increase the level of K+ in the blood (such as angiotensin II type 1 receptor antagonists, birth control pills containing drospirenone).

Angiotensin II receptor 1 antagonists

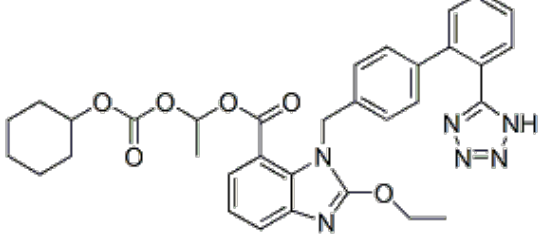


Angiotensin II type 1 receptor antagonists: an overview

Drug	Indications	Possible Side effects	Some Potential interactions	Precautions and Contraindications
Candesartan **Eprosartan** **Telmisartan** **Irbesartan** **Losartan** **Valsartan**	• Hypertension • Intolerance to ACE inhibitor • Post- MI patients (secondary prevention of MI in patients with HF) **Additional** **Irbesartan / Losartan** • HTN plus diabetic nephropathy	• Hypotension • Headache • Dizziness • Lightheadedness • Anemia • Fatigue • Hypoglycemia • Hyperkalemia • Angioedema • ↑ BUN • ↑ Serum creatinine	• Digoxin • Lithium • MAO inhibitors • NSAIDs • Potassium-sparing diuretics	**Precautions:** • Impaired renal/ hepatic function • Unilateral renal artery stenosis • Aortic/ mitral valve stenosis • Should not be used in combination with ACEI unless heart failure with recent hospitalization **Contraindications:** • Hypersensitivity • Pregnancy/ lactation • Bilateral renal artery stenosis

ACEI: Angiotensin-converting enzyme inhibitor; **ARBs:** Angiotensin II receptor blockers; **BUN:** Blood urea nitrogen; **HF:** Heat failure; **HTN:** Hypertension; **MAO:** Monoamine oxidase; **MI:** Myocardial infarction; **NSAIDs:** Nonsteroidal anti-inflammatory drugs

Candesartan cilexetil

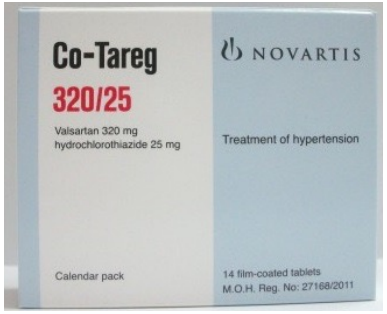


- Candesartan is poorly absorbed after oral administration, therefore Candesartan was esterified.

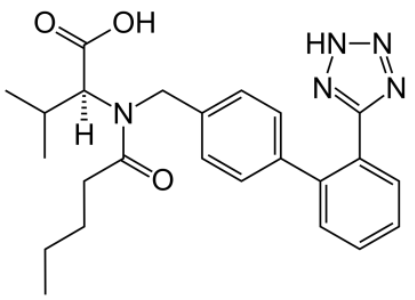
- Candesartan cilexetil finds most significant clinical use in the treatment of **hypertension of all grades**. Candesartan is also approved to treat hypertension in children (1 year or older). Candesartan is also used in preventive treatment of migraine.

- Side effects: The most common adverse effects reported for candesartan are symptomatic hypotension (18.8%), impaired renal function (rise in creatinine, 12.5%), and hyperkalemia (6.3%).

- Drug-drug interactions: NSAIDs, lithium, ACE inhibitors, drugs that increase the K^+ levels.



Valsartan



❑ Valsartan is a diacid that does not require metabolic oxidation to achieve the maximum pharmacologic effect.

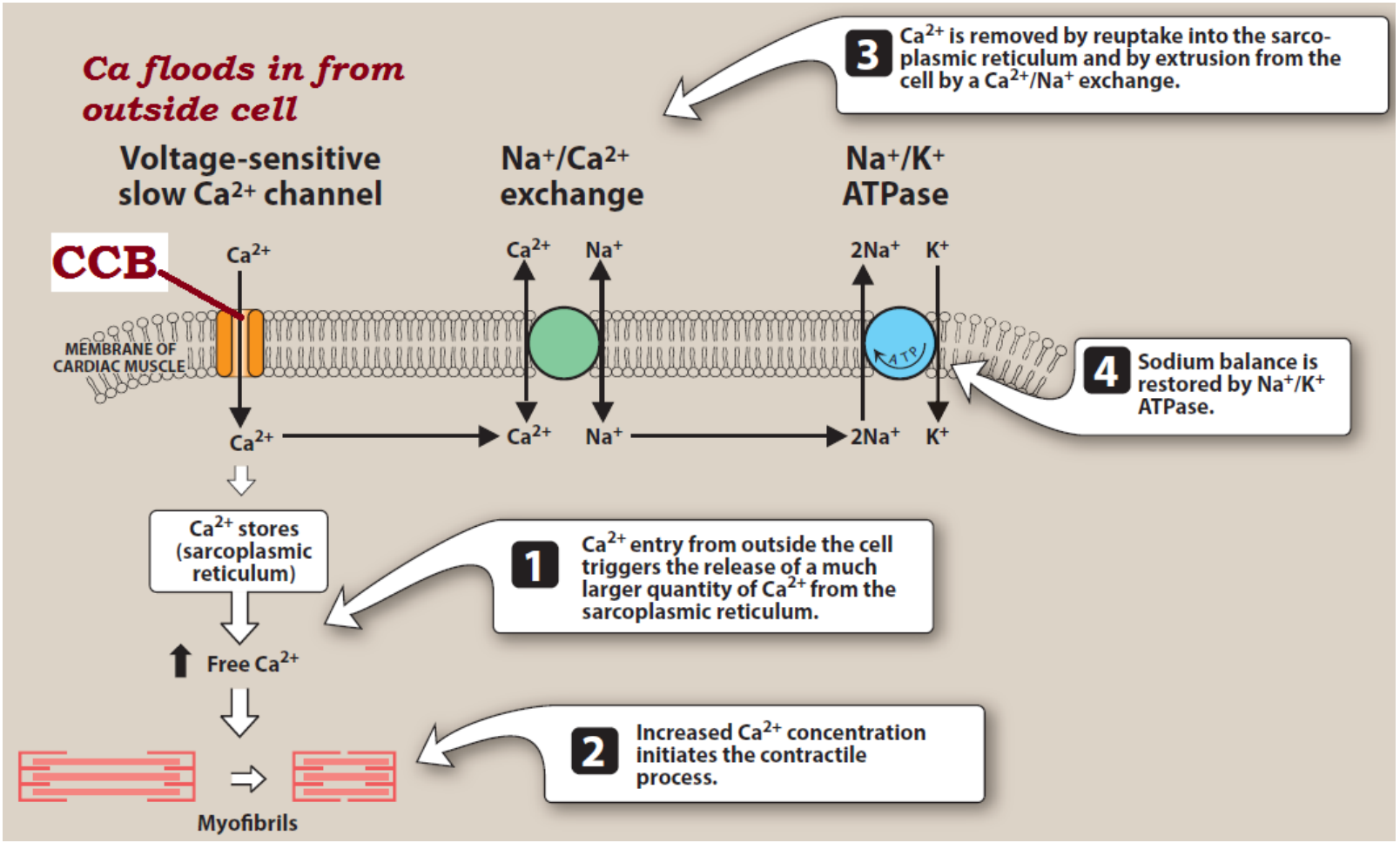
❑ Valsartan is used to treat **hypertension of all grades**. Candesartan is also approved to treat hypertension in children (6 years or older).

❑ Common side effects include headache, hyperkalemia and dizziness. Other serious side effects may include kidney problems, low blood pressure, and angioedema. Use in pregnancy may harm the baby and use when breastfeeding is not recommended.

❑ Drug-drug interactions: Concomitant use of valsartan with other agents that block the renin-angiotensin system or K^+-sparing diuretics may lead to increases in serum K^+ and in heart failure patients to increases in serum creatinine. Other interactions: lithium, NSAIDs.

Ca^{++} channel antagonists

❑ According to recommendations from the JNC8 members, Ca^{++} channel antagonists are a recommended choice for **management of hypertension**, either as monotherapy or as part of anti-hypertensive combination therapy.



Ca^{++} channel antagonists: an overview

❑ Calcium channel blockers are generally classified into three groups:

1) dihydropyridines (amlodipine, clevidipine, nicardipine, nifedipine, bepridil, felodipine, isradipine, and nisoldipine);

2) phenylalkylamines (verapamil);

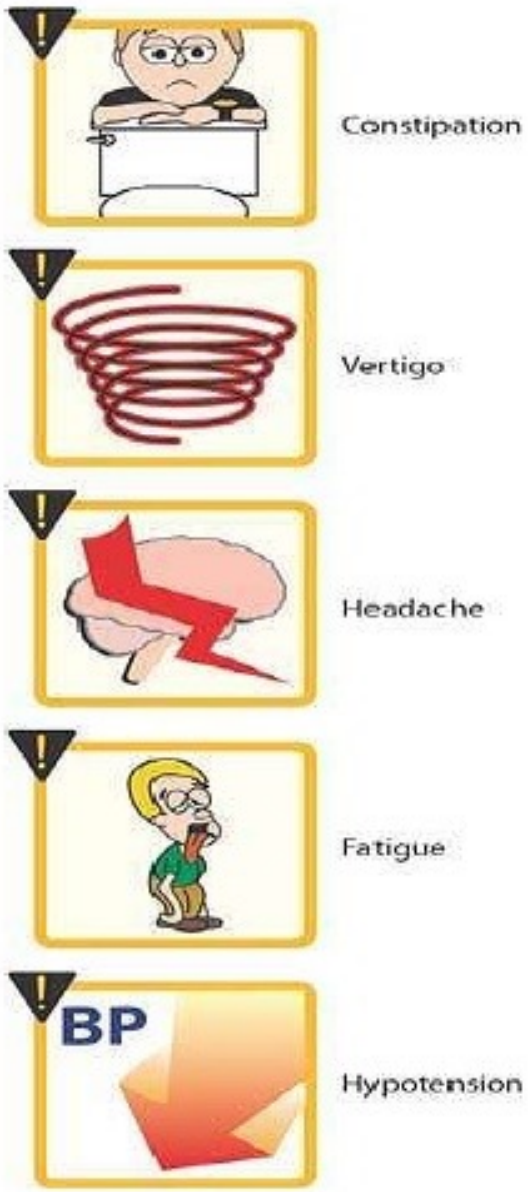
3) benzothiazepines (diltiazem).

Calcium channel blockers	Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart).
MECHANISM	Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility. Vascular smooth muscle—amlodipine = nifedipine > diltiazem > verapamil. Heart—verapamil > diltiazem > amlodipine = nifedipine (verapamil = ventricle).
CLINICAL USE	Dihydropyridines (except nimodipine): hypertension, angina (including Prinzmetal), Raynaud phenomenon. Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm). Nicardipine, clevidipine: hypertensive urgency or emergency. Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.
ADVERSE EFFECTS	Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia, constipation. Dihydropyridine: peripheral edema, flushing, dizziness, gingival hyperplasia.

Therapeutical uses of Ca^{++} channel antagonists

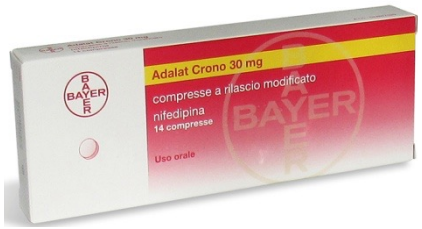
- **angina pectoris** (verapamil, diltiazem),
- **cardiac failure** (verapamil, diltiazem, amlodipine, nisoldipine),
- **dysrrythmias** (verapamil, diltiazem),
- **hypertensions** (dihydropyridines),
- **migraine** (verapamil),
- stroke (nimodipine).

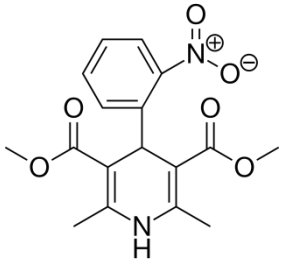
Side effects of Ca^{++} channel antagonists



Adverse Events	Calcium Channel Blockers
Most common	Constipation Dizziness Leg edema Flushing Headache Hypotension Palpitation Weakness
Other significant effects	Myocardial ischemia or infarction due to "coronary steal" hypotension

Nifedipine





- Nifedipine is the prototype of the dihydropyridines.

- Nifedipine is approved for the **long-term treatment of hypertension**. Off-label uses of nifedipine include severe hypertension **during pregnancy and post-partum hypertension**, high pulmonary edema, pulmonary arterial hypertension.

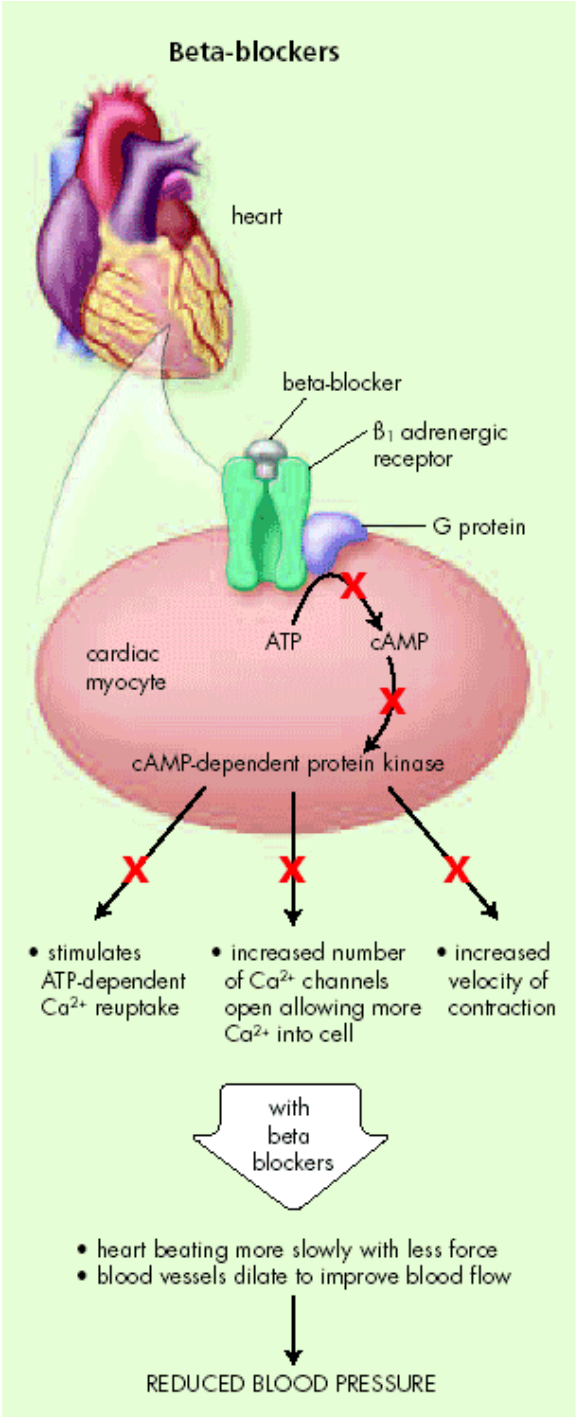
- Adverse effects are present in about **20 to 30% of patients** administered with nifedipine. The most common adverse effects include flushing, peripheral edema, dizziness, headache. These problems are much less frequent in the sustained-release preparations of nifedipine. Abrupt discontinuance of the drug after prolonged use may lead to rebound hypertension or angina.

- Nifedipine **can inhibit the metabolism of drugs that are substrates of CYP3A4**, thereby increasing the exposure to other drugs. CYP3A4 inhibitors that increase the levels of nifedipine when co-administered are: fluconazole, clarithromycin, grapefruit, fluoxetine, saquinavir. Strong CYP3A4 inducers, such as rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine reduce the bioavailability and efficacy of nifedipine.

β-blockers

❑ Two of the major guide-line committees (JNC8 and NICE UK) have **dropped β-blockers as first-line therapy** in the treatment of hypertension.

❑ Moreover, a recent meta-analyses have concluded that β-blockers **are inappropriate first-line agents** in the treatment of hypertension (*Wiysonge CS et al. 2017. "Beta-blockers for hypertension". The Cochrane Database of Systematic Reviews. 1: CD002003*).



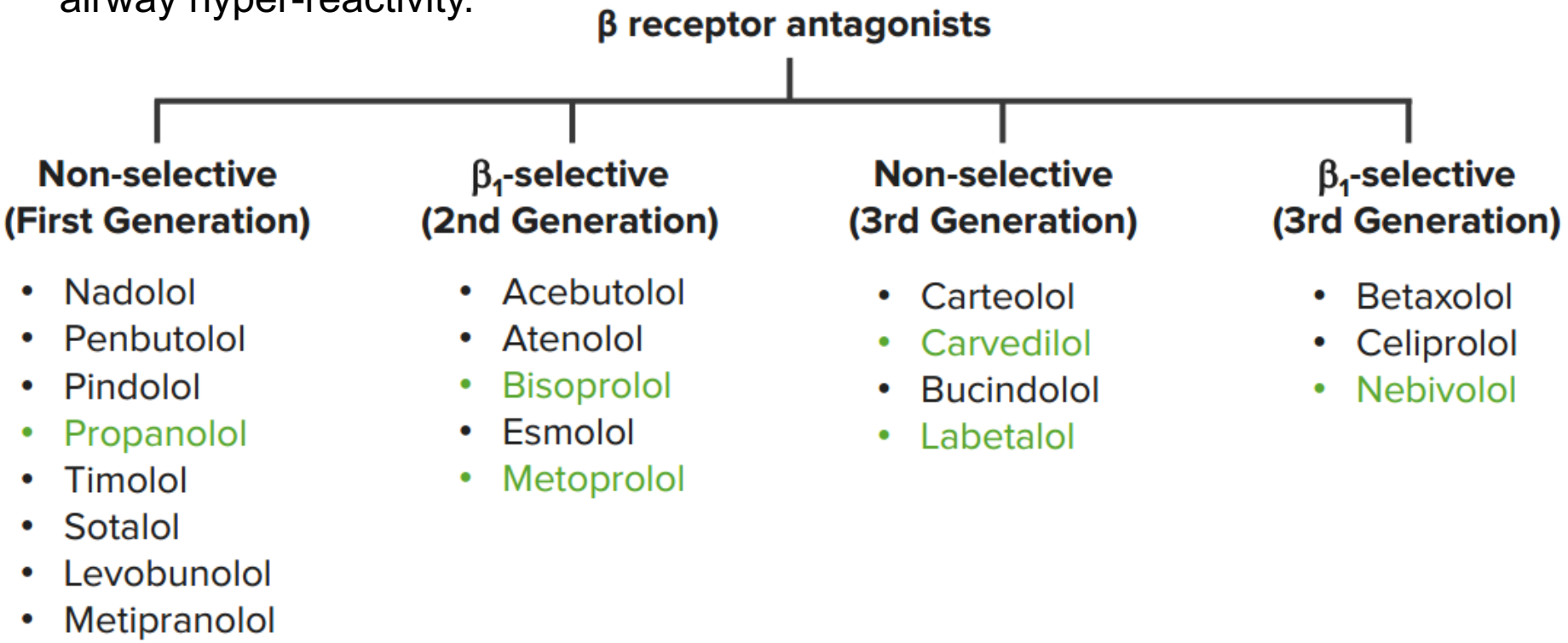
Selected studies on β–blockers in hypertension

Study	Study design	Number of patients	Findings
Srivastava et al[1]	Double-blind prospective trial	20	Treatment benefits versus placebo did not reach statistical significance
Prichard and Gillam[2]	Prospective trial	109	92 of the patients in propranolol group achieved a supine, or standing BP of 100 mm Hg or less
MRC Working Party[14]	Randomized, placebo-controlled, single-blind trial in elderly	4,396 (aged 65-74 years)	Atenolol-treated patients showed no significant reduction in stroke, coronary events, and all CV events
Gupta et al (ASCOT)[17]	Randomized, comparator trial	19,257	Patients assigned to atenolol +/- thiazide developed more NOD
Lindholm et al[22]	Meta-analysis of 7 randomized trials	27,433	β-blockers raised the risk of stroke
Law et al[27]	Meta-analysis of 108 randomized trials	464,000	No significant difference among major antihypertensives
Fretheim et al[28]	Meta-analysis of 25 randomized trials	164,671	β-blockers not superior to other antihypertensives
Mahmud and Feely[41]	Comparator trial of atenolol and nebivolol	40	Nebivolol, but not atenolol, reduced aortic stiffness
Bangalore et al[19]	Comparative meta-analysis of 22 clinical trials	68,222	β-blockers-induced decreased HR increased risk of cardio-vascular events and death
Phillips et al (GEMINI)[45]	Comparative trial of carvedilol and metoprolol	1,235	Carvedilol is better in hypertensive patients with diabetes
Lewin et al[53]	Nebivolol monotherapy in stage II hypertension	290	Nebivolol was significantly effective even in patients with BMI ≥30 Kg/m^2
Zeltner et al[69]	Comparative trial of ramipril vs metoprolol in PCKD	46	No significant difference in proteinuria, renal function, and LVMI in 3 years follow-up
Caglar and Dincer (PROBE)[72]	Comparative trial of nebivolol and ramipril in hypertensive patients with LV hypertrophy	106	Nebivolol significantly reduced LVMI, and at a lower dose
Collier et al (ASCOT-BPLA)[80]	Comparative trial of atenolol and amlodipine in younger and older hypertensive patients	19,257	Amlodipine reduced relative risk of CV events more effectively than atenolol in both older and younger patients
Pareek et al[92]	Comparative trial of metoprolol XL/ amlodipine combination vs losartan/ amlodipine combination	148	Both combinations were equally effective in lowering SBP and DBP

CV - cardiovascular, NOD - newonset diabetes, HR - heart rate, BMI - body mass index, LVMI - left ventricular mass index, PCKD - polycystic kidney disease, SBP - systolic blood pressure, DBP - diastolic blood pressure

β–blockers used in hypertension with comorbidities

- β-blockers are still administered to hypertensive patients who have suffered from myocardial infarction, or other forms of ischemic heart diseases, and other pathologies like diabetes, **but not in hypertensive patients without comorbidities**.
- β-blockers are usually avoided in patients suffering from bronchial asthma, or with airway hyper-reactivity.



Adverse effects of β–blockers

❑ Highly lipophilic β-blockers can easily cross the blood-brain barrier and may cause various CNS manifestations as **insomnia, sleep changes, and nightmares**. Water-soluble β-blockers, for example atenolol, may also cause tiredness and fatigue.

❑ Bradycardia and hypotension are two adverse effects that may commonly occur. Fatigue, dizziness, nausea, and constipation are also widely reported. Some patients report sexual dysfunction and erectile dysfunction.

❑ β-blockers, especially the non-cardioselective blockers, **should not be used in patients with pathologies** such as asthma, diabetes and severe bradycardia (block of the effect of adrenaline).

❑ β-blockers **should not be withdrawn suddenly** because sudden withdrawal may worsen angina and cause heart attacks, serious abnormal heart rhythms, or sudden death.

Interactions of β–blockers with other drugs

β-Blockers may interact with a large number of commonly prescribed drugs, including:

- ❑ anti-hypertensive and anti-anginal drugs,
- ❑ inotropic agents,
- ❑ anti-arrhythmics,
- ❑ NSAIDs,
- ❑ psychotropic drugs,
- ❑ anti-ulcer medications,
- ❑ anesthetics,
- ❑ HMG-CoA reductase inhibitors,
- ❑ warfarin,
- ❑ oral hypoglycemics and rifampicin.

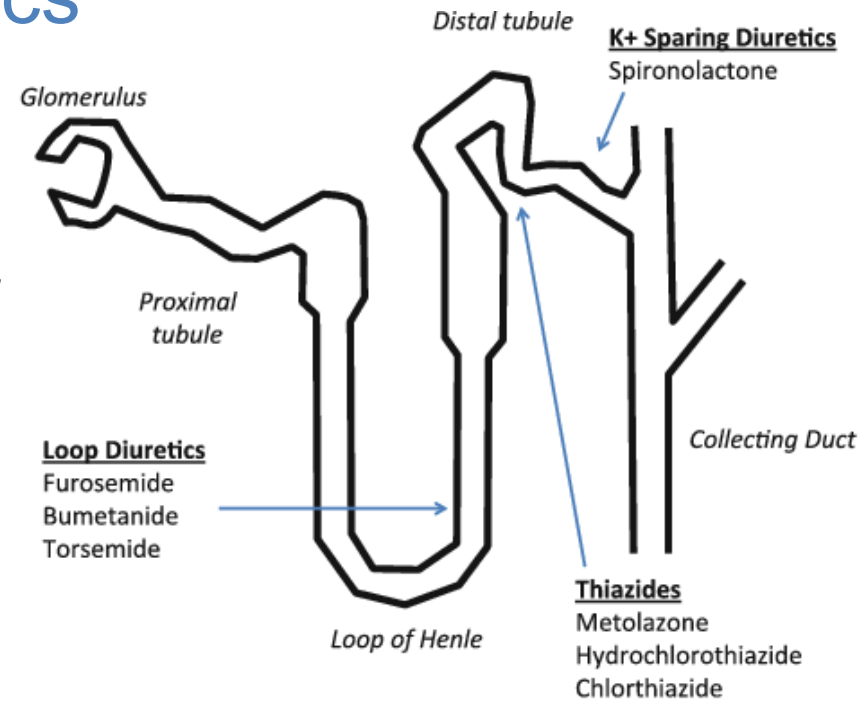
Diuretics

❑ Diuretic drugs are classified according to their predominant site of action:

1) **Loop diuretics** (furosemide, bumetanide, and torsemide) are organic anions acting in the short descending limbs of the loop of Henle.

2) **Thiazides and thiazide-like** drugs are also organic anions that bind the thiazide-sensitive NaCl cotransporter along the distal convoluted tubule.

3) **K^+ -sparing diuretics** include drugs that block apical Na^+ channels (amiloride and triamterene) and those that antagonize mineralocorticoid receptors (spironolactone and eplerenone).



Loop Diuretics: an overview

Drug	Indications	Possible Side effects	Potential Interaction	Precautions and Contraindications
Furosemide	• Peripheral edema • Acute pulmonary edema • Hypertension • Hypercalcemia	• Hypokalemia • Hypochloremia • Hyperuricemia • Metabolic alkalosis • Hyperglycemia	• ACE inhibitors • Allopurinol • Beta 2-agonists • Corticosteroids • Ethacrynic acid • Lithium • MAO inhibitors • Methylphenidate • Phenytoin • Probenecid	**Precautions:** • DM / SLE • Acute MI / arrhythmias • Prostatic hyperplasia/ urinary stricture • Elderly patients **Contraindications:** • Hypersensitivity to the drug • Hypersensitivity to sulfonamides • Anuria • Hepatic coma

ACE inhibitors: Angiotensin-converting enzyme inhibitors; **DM:** Diabetes mellitus; **MAO inhibitors:** Monoamine oxidase inhibitors; **MI:** Myocardial infarction; **SLE:** Systemic lupus erythematosus

Although the FDA approved the use of loop diuretics alone or in combination with other anti-hypertensive medications as an alternative to thiazide diuretics to treat hypertension, JNC-8 published in 2014 and the American College of Cardiology/American Heart Association (ACC/AHA) Task Force Panel Guidelines on hypertension treatment published in 2017 a report that **do not recommend the use of loop diuretic as a first-line medication to treat hypertension**.

Thiazide and thiazide-like diuretics: an overview

Drug	Indications	Possible Side effects	Some Potential Interactions	Precautions and Contraindications
Hydrochlorothiazide **Chlorthalidone** **Indapamide**	• Hypertension • Hypercalcemia • Edema **Additional Chlorthalidone** • Renal tubular acidosis	• Hypokalemia • Hyponatremia • Hyperuricemia • Metabolic alkalosis • Hyperglycemia • Photosensitivity	• Lithium • NSAIDs • Hypoglycemic agents • Corticosteroids	**Precautions:** • Electrolyte abnormalities • Dehydration • DM/ SLE • Elderly patients • Pregnancy/ lactation **Contraindications:** • Hypersensitivity to drug and/or its components • Anuria

DM: Diabetes mellitus; **MI:** Myocardial infarction; **NSAIDs:** Nonsteroidal anti-Inflammatory drugs; **SLE:** Systemic lupus erythematosus

K+-sparing diuretics: an overview

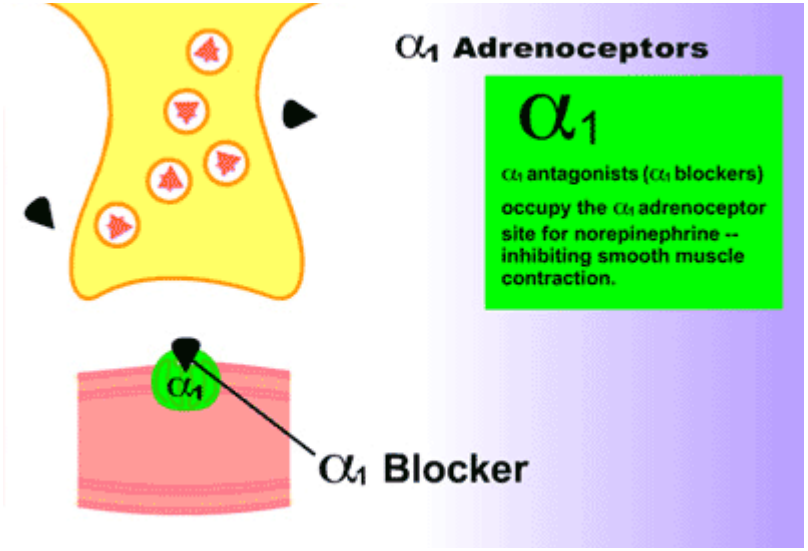
Potassium-sparing diuretics	Spironolactone and eplerenone; Triamterene, and Amiloride.
MECHANISM	Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride act at the same part of the tubule by blocking Na^+ channels in the cortical collecting tubule.
CLINICAL USE	Hyperaldosteronism, K^+ depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen.
ADVERSE EFFECTS	Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects).

Abbreviations: HF: heart failure; nephrogenic DI: nephrogenic diabetes insipidus

K^+-sparing agents **are effective when added to triple hypertension medications regimen but should be used cautiously when added to ACE inhibitors or angiotensin II receptor 1 blockers** due to higher incidence of hyperkalemia. They are effective in treating **chronic heart failure** as they are proven to decrease mortality rates.

α1-antagonists

- α1-antagonists are used as **second line drugs** in the therapy of hypertension.
- This blockade inhibits the smooth muscle contraction and lowers the blood pressure.
- Newer α-antagonists used in treating hypertension are relatively selective α1-adrenoceptor antagonists (e.g., prazosin, terazosin, doxazosin, trimazosin).



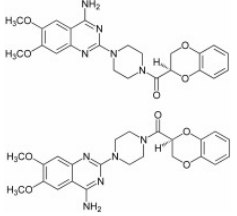
α1-antagonists: an overview

Drug	Indications	Possible Side effects	Some Potential Interactions	Precautions and Contraindications
Selective Alpha-adrenoceptor antagonists				
Prazosin **Terazosin** **Doxazosin**	• Resistant hypertension • Pheochromocytoma • Benign prostatic hyperplasia **Additional Prazosin** • PTSD • Raynaud's syndrome	• Hypotension • Palpitation • Headache • Dizziness • Drowsiness • Weakness	• Amphetamines • PDE-5 inhibitors • Prostacyclin analogues	**Precautions:** • Angina • Cataract surgery • Pregnancy/ lactation **Contraindications:** • Hypersensitivity
Non-selective Alpha-adrenoceptor antagonists				

Phentolamine	• Hypertensive crises due to catecholamine
	• Diagnosis of pheochromocytoma
	• Hypertension due to
	  ◦ Pheochromocytoma
	  ◦ Pralidoxime
		• As Above	• As Above	**Precautions:**
				• Cardiac arrhythmias
				• Peptic ulcer disease
				• Gastritis
				• Pregnancy/ lactation
				Contraindications:
				• Hypersensitivity
				• Renal impairment
				• Coronary or cerebral arteriosclerosis
				• MI (active or history)
				• Concurrent use with PDE-5 inhibitors

MI: Myocardial infarction; **PDE-5 inhibitors:** Phosphodiesterase 5 inhibitors; **PTSD:** Posttraumatic stress disorder

Doxazosin



❑ Doxazosin is a long-acting α1-antagonist structurally related to prazosin and terazosin.

❑ The immediate-release formulation of doxazosin is a **second-line agent for the management of hypertension in patients with concomitant benign prostatic hyperplasia**. Doxazosin has also been used successfully in combination with β-blockers, diuretics, Ca^{++} channel antagonists, and ACE inhibitors in patients with hypertension that is uncontrolled with monotherapy.

❑ The most commonly reported adverse effects are **orthostatic hypotension/syncope**, especially when combined with another anti-hypertensive, nitrates, or a PDE-5 inhibitor.

❑ Doxazosin is a substrate of CYP3A4. Strong CYP3A inhibitors may increase exposure to doxazosin.

Other anti-hypertensive drugs: vasodilators

Drug	Site of action	Mechanism of action
Sodium nitroprusside	Arterioles and veins	Production of nitric oxide
Hydralazine	Arterioles	Stimulation of NO release, Inhibition of Ca++ release from SR
Minoxidil	Arterioles	K+ channel opening
Diazoxide	Arterioles	K+ channel opening

Other anti-hypertensive drugs: adrenergic drugs

Drugs

- Alpha-2 receptor agonists: **clonidine**
- Indirect acting adrenergic drugs: **methyldopa**

Mechanisms of antihypertensive action

a) Alpha-2 receptor agonists:

- Activation of alpha-2 receptors in *Nucleus Tractus Solitarius* and in *rostral ventrolateral medulla* ***(the main mechanism).***
- Activation of peripheral alpha-2 receptors (after high doses).

b) Indirect acting adrenergic drugs:

Methyldopa acts as a false neurotransmitter. It is taken up by the adrenergic neurons where it is transformed into methylnorepinephrine, the alpha-2 receptor agonist, which acts as described above.

The final effect common to all these drugs is a decreased firing of the reticulospinal tract, that is a decrease of central adrenergic tone

Hypertensive emergencies

❑ Hypertensive emergencies are diagnosed when there is a systolic blood pressure higher than 180 mm Hg or a diastolic blood pressure higher than 120 mm Hg

1) with the presence of acute target organ damage;
2) in an otherwise stable person without clinical or laboratory evidence of acute target organ damage.

❑ Patients with hypertensive emergencies include:

- dissecting aortic aneurysm,
- acute pulmonary edema,
- acute myocardial infarction,
- unstable angina pectoris,
- acute renal failure,
- acute intracranial hemorrhage,
- acute ischemic stroke,
- hypertensive encephalopathy,
- peri-operative hypertension,
- sympathomimetic hypertensive crisis caused by use of cocaine, amphetamines, phencyclidine, or monoamine oxidase inhibitors or by abrupt cessation of clonidine or other sympatholytic drugs.

❑ These patients need effective and rapid acting medications administered intravenously to lower the elevated blood pressure safely, protect target organ function, ameliorate symptoms, reduce complications, and improve clinical outcomes

Management of hypertensive emergencies

Drug	Dose	Onset of action	Adverse effects
Diuretics			
Furosemide	20-40 mg i.v. injection in 1–2 min, repeated and higher doses with renal insufficiency	5–15 min	Volume depletion, hypokalemia
Vasodilators			
Sodium nitroprusside	0.25–10 μg/kg/min as i.v. infusion	Within 30 sec	Nausea, vomiting, tachycardia, thiocyanate and cyanide intoxication
Nitroglycerin	5–100 μg/min as i.v. infusion	2–5 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use
Nicardipine	0.5–6 μg/kg/min as i.v. infusion	5–10 min	Headache, flushing, tachycardia, local phlebitis
Hydralazine	10–20 mg i.v. injection	10–20 min	Headache, flushing, tachycardia, worsening of angina
Sympatholytics			
Labetalol	20–80 mg i.v. injection every 10 min; 2 mg/min as i.v. infusion	5–10 min	Nausea, vomiting, bronchospasm, heart block, orthostatic hypotension
Phentolamine	1–10 mg i.v. injection, then 0.5–2 mg/min as i.v. infusion	1–2 min	Headache, flushing, tachycardia

Hypertension and comorbidities

Characteristic (Number and %)	Hypertension	Hypertension and Diabetes mellitus	Hypertension and Hyperlipidemia	Hypertension and Coronary heart disease
Gender				
Male	1146218 (54.00)	209121 (54.44)	108929 (55.63)	163156 (54.44)
Female	976485 (46.00)	174984 (45.56)	86876 (44.37)	136538 (45.56)
Age				
0-44	265554 (12.51)	15222 (3.96)	20557 (10.50)	7444 (2.48)
45-59	653872 (30.80)	100263 (26.10)	62154 (31.74)	56712 (18.92)
60+	1203277 (56.69)	268620 (69.93)	113094 (57.76)	235538 (78.59)

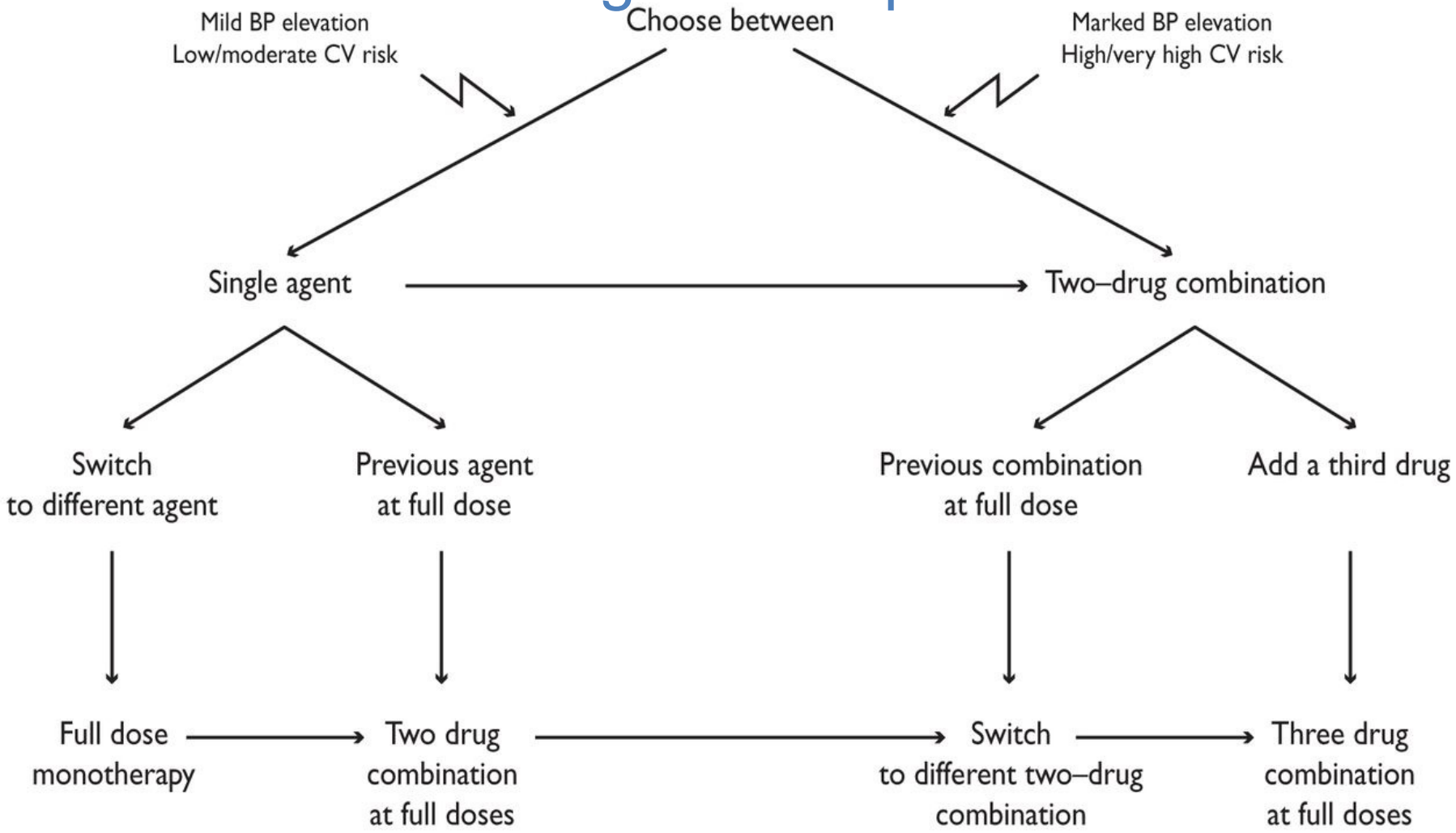
Values in parentheses referred to the percentage of patients in the corresponding group.

Drugs used in hypertension with comorbidities

HTN with:	Suitable Drug(s):
Angina	Beta blockers, CCBS
Diabetes	ACE inhibitors, ARBs
Heart Failure	ACE inhibitors, ARBs, Beta blockers
Post-MI	Beta blockers
BPH	Alpha blockers
Dyslipidemias	Alpha blockers, CCBs, ACE inhibitors/ARBs

Abbreviations: HTN: hypertension; CCBs: Calcium channel blockers; BPH: Benign prostatic hyperplasia; ARBs: Angiotensin receptor blockers; MI: Myocardial infarction.

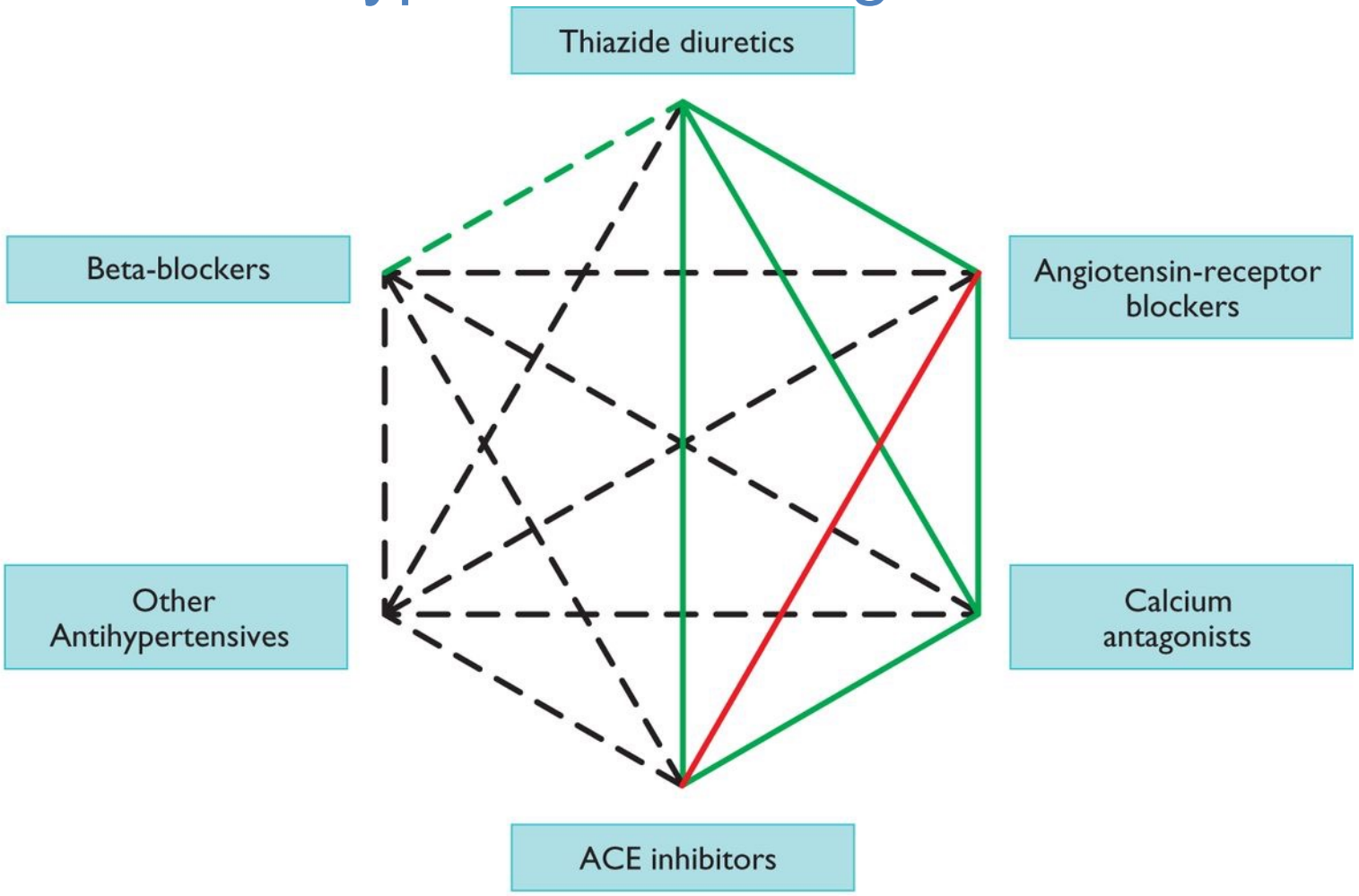
Monotherapy vs. drug combination strategies to achieve target blood pressure



BP = blood pressure; CV = cardiovascular.

Moving from a less intensive to a more intensive therapeutic strategy should be done whenever BP target is not achieved.

Possible combinations of classes of anti-hypertensive drugs.



ACE = angiotensin-converting enzyme.

Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); **black dashed lines**: possible but less well-tested combinations; **red continuous line**: not recommended combination.