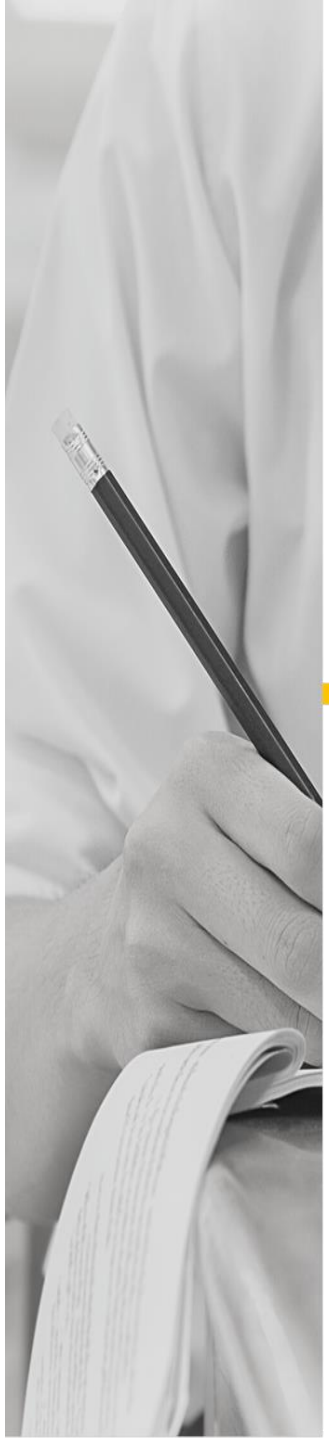

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Subject year: MSc - PHARMA

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TIKRIT UNIVERSITY
COLLEGE OF VET. MEDICINE

FIRST TERM – M.Sc PHARMACOLOGY
ADVANCED PHARMACOLOGY

PROF DR HUSAMULDEEN ALNAJAR

Cardiovascular System Pharmacology

DRUGS USED IN HYPERTENSION MANAGMENT

Cardiovascular drugs
Antihypertensive Agents

- Hypertension is the most common cardiovascular disease (30% of IRAQI adults) تقرير وزارة الصحة العراقية 2019.
- Hypertension is defined as either a sustained systolic blood pressure (SBP) greater than 140 mm Hg or a sustained diastolic blood pressure (DBP) greater than 90 mm Hg (140/90).
- Hypertension is classified into four categories for the purpose of treatment management.

TABLE 11–1 Classification of hypertension on the basis of blood pressure.

Systolic/Diastolic Pressure (mm Hg)	Category
< 120/80	Normal
120–135/80–89	Prehypertension
≥ 140/90	Hypertension
140–159/90–99	Stage 1
≥ 160/100	Stage 2

- **Etiology of Hypertension:**

There are 2 basic types of hypertension:

1. **Essential (Primary) hypertension:**

- Unknown cause (multifactorial; genetic, psychological stress, environmental and dietary)
- Symptomatic treatment, i.e. reduce blood pressure. No real cure yet.

- **Secondary hypertension:**

- Result from an identifiable **disease**:
  Kidney disease, renal artery constriction
  Adrenal gland disease e.g. Cushing's disease, Pheochromocytoma, Primary aldosteronism, Thyroid or parathyroid disease.
- **Drugs:**
  Vasoconstrictors, e.g. phenylephrine.
  Volume expanders, e.g. glucocorticoids, NSAIDs and oral contraceptives, chronic steroid therapy.
- It is often curable.

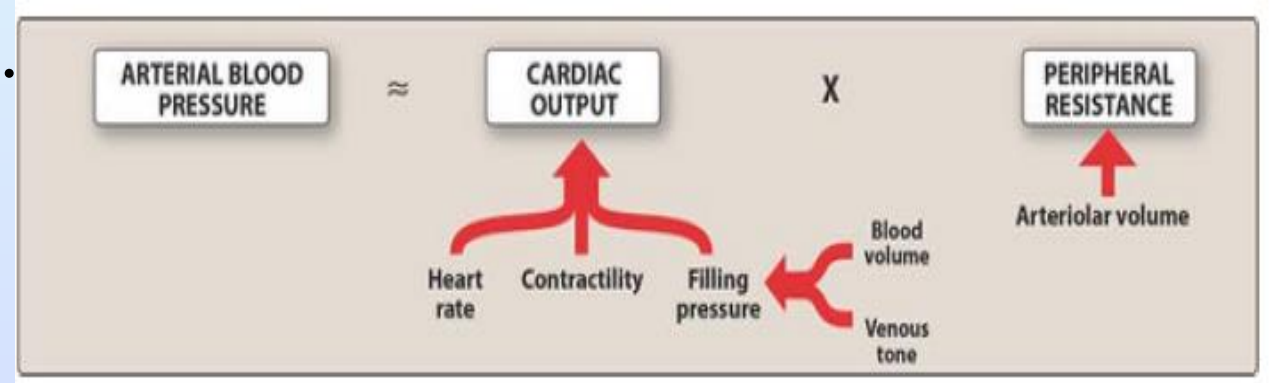
Risk Factors

- Obesity
- Dyslipidemia
- Diabetes
- Cigarette smoking
- Stress
- Lack of exercise
- Diet (excess dietary salt)
- Alcohol intake
- Family history of CVD.

- **Complications**
- **Chronic hypertension** can lead to **end-organ damage**:
- **Heart**: congestive heart failure, myocardial infarction
- **Kidney**: chronic kidney disease, kidney failure
- **Brain**: Stroke
- **Eye**: retinal hemorrhage
- The goal in hypertension treatment is to lower BP with minimal serious toxicity in most patients.

Factors that Govern Blood Pressure

- Normal Regulation of Blood Pressure:
- BP=COXPVR.



- Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or peripheral resistance.
- Cardiac output and peripheral resistance are controlled mainly by two overlapping control mechanisms:

1. **The baroreflexes:**
2. **Renin-angiotensin-aldosterone system**

1. **The baroreflexes:**
   Are mediated by the sympathetic nervous system

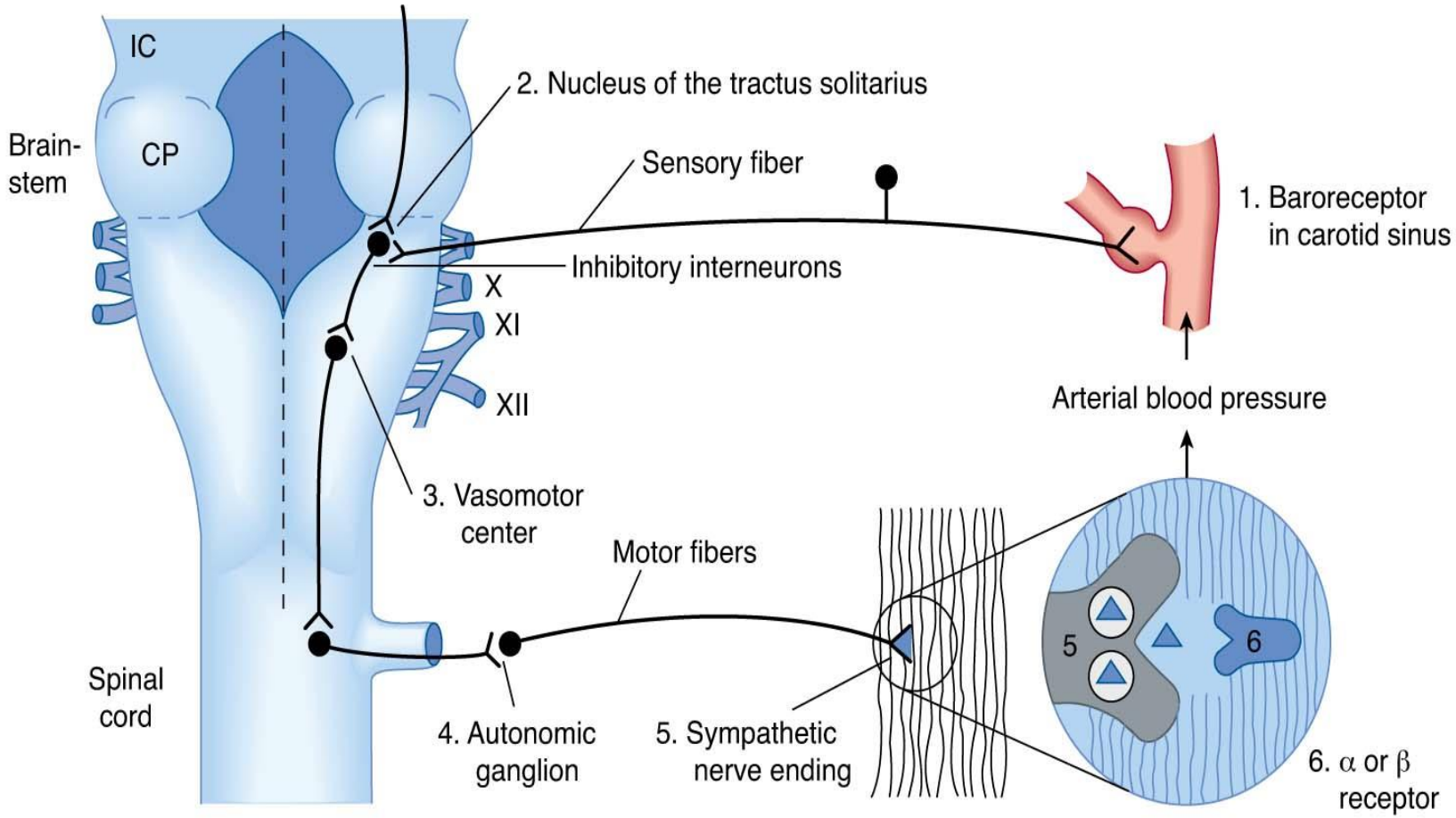


FIGURE 11–2 Baroreceptor reflex arc.

- **Postural Baroreflex:-**
- Baroreflexes are responsible for rapid adjustments in blood pressure (supine to upright position).
- Carotid baroreceptors are stimulated by elevated BP.
- **Baroreceptor activation inhibits central sympathetic discharge**. Conversely reduction in BP results in a reduction in baroreceptor activity.
- The baroreflex acts in response to any event that lowers arterial pressure (vasodilators, hemorrhage or diuretics)

2. Renin-angiotensin-aldosterone system

- Role of the kidney in BP regulation:

- ↓ renal arteriolar pressure → stimulates β_1 → stimulates renin production →↑ angiotensin II which causes:
  1. Direct constriction of blood vessels.
  2. Stimulation of aldosterone synthesis which increased renal sodium retention →↑blood volume and BP.
- Vasopressin (ADH) increases water retention and constricts blood vessels→↑BP.

- Baroreflexes, act in combination with the renin – angiotensin-aldosterone system to regulate BP at four anatomic sites and to maintain normal blood pressure.
  1. Arterioles.
  2. Postcapillary venules (capacitance vessels).
  3. Heart.
  4. Kidney
- All antihypertensive drugs act by interfering with these mechanisms.

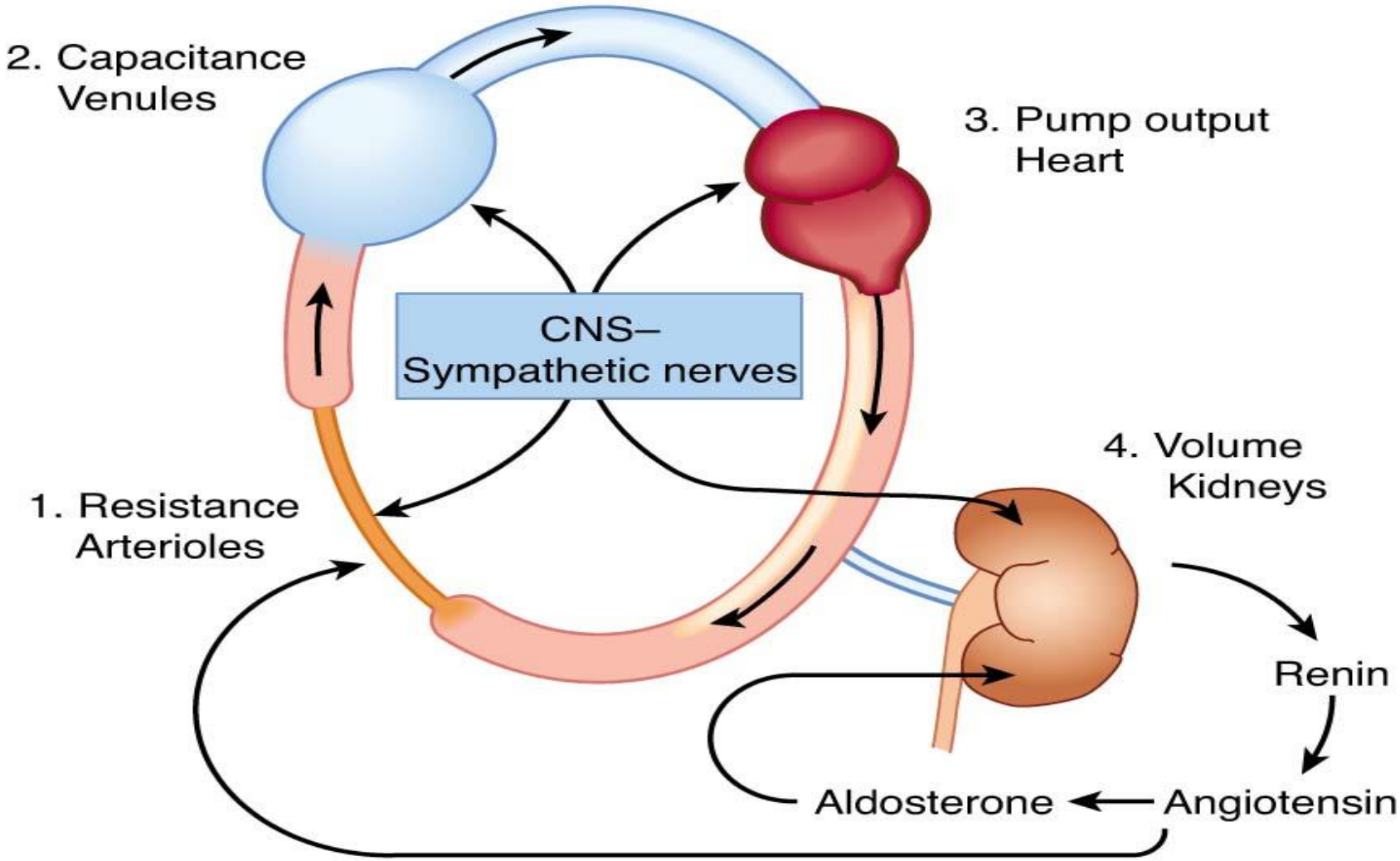


FIGURE 11–1 Anatomic sites of blood pressure control.

- **Classification of antihypertensive agents:-**
- Antihypertensive drugs can be classified according to **mechanism** or the principal regulatory **site** on which they act into:

1. **Diuretics:**

- Lower blood pressure by depleting the body of the sodium and reducing blood volume .

2. **Sympatholetic (sympathoplegic) agents:**

- Act by reducing PVR, inhibiting cardiac function, and increasing venous capacitance.
- they are further subdivided according to their sites of action in the sympathetic pathway.

3. **Vasodilators:**

- Act by dilating resistance vessels.

4. **Agents that block production or action of angiotensin: reduce PVR and blood volume.**

- The combination of antihypertensive drugs with different mechanisms results in increased efficacy and, in some cases, decreased toxicity.

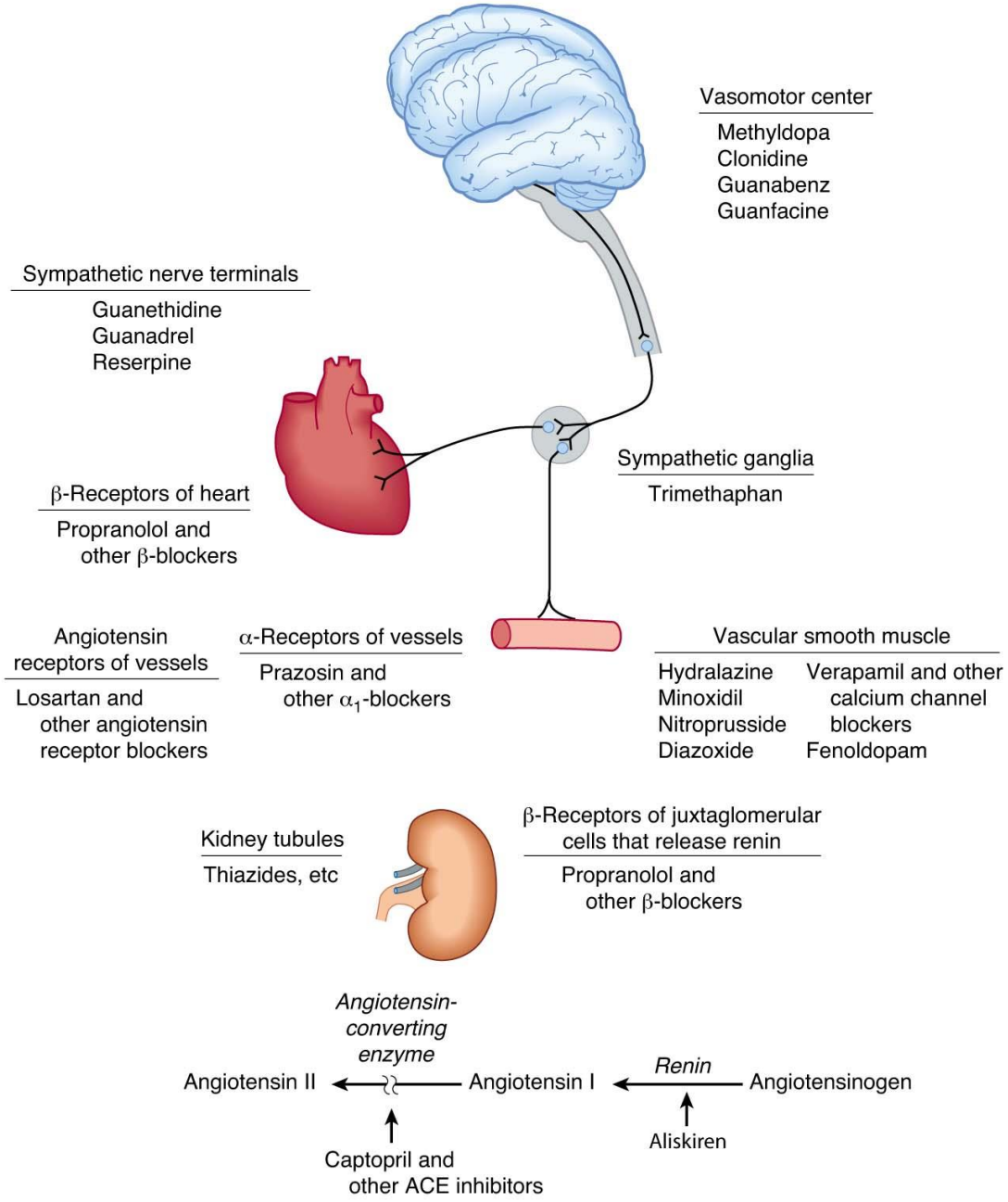


FIGURE 11–3 Sites of action of the major classes of antihypertensive drugs.

- **Diuretics:**

- Diuretics **alone** can adequately control **mild or moderate essential hypertension.**
- In more **severe** hypertension, diuretics are used in **combination** with **sympatholetic and vasodilator** drugs **to control the tendency toward sodium retention** caused by these agents.

- **Selection of diuretics :**

- **Thiazide** diuretics: **mild or moderate hypertension** with normal renal and cardiac function (**1st line of therapy**).
- More powerful diuretics (e.g. **loop diuretics) are necessary in severe hypertension.**

- **Potassium–sparing diuretics** are useful both to avoid excessive hypokalemia, particularly in **patients taking digitalis for CHF**, and to **enhance the natriuretic effects of other diuretics.**

2. **Sympathoplegic Drugs:**

- Used in **moderate** to **severe** hypertension.
- Subdivided into:

A. **Centrally acting sympathoplegic drugs:**

- a-Methyldopa, Clonidine, Guanabenz and Guanafacine
- Reduce sympathetic outflow from vasomotor centers.

- **Methyldopa:**
- **Mechanism of action:**

- Methyldopa is a **prodrug** (L-dopa analog), converted to a-methyldopamine and a-methylnoradrenaline which stimulate the central presynaptic a_2 receptor (**a_2–agonist**) →↓ **sympathetic out flow from CNS.**
- It is primarily used for **hypertension during pregnancy**, and also for **hypertension in renal insufficient patient.**

- **Pharmacokinetics:**

- It has low bioavailability (25%).

- **Toxicity:**

1. CNS effects:

- Sedation (at the onset of treatment), nightmares, mental depression, vertigo, and extrapyramidal signs.

2. Endocine effects:

- ↑prolactin secretion → galactorrhea, gynecomastia and impotence.

3. Prolonged used → pseudo-tolerance due to fluid retention (add diuretic)
4. Dry mouth
5. Hemolytic anemia
6. Hepatotoxicity

- **Clonidine:**
- **Mechanism of action:-**

- Clonidine stimulates the presynaptic a_2 receptors (**a_2 agonist**)→↓**central sympathetic out flow.**

- **Pharmacokinetics:**

- Given **orally** (twice a day) or as single **transdermal batch** every 7 days.

- **Toxicity:**

1. Sedation and mental depression.
2. Dry mouth

4. Abrupt withdrawal of clonidine → **hypertensive crisis, requires gradual tapering of the dose** while other agents are being substituted.

B. Ganglion – Blocking Agents:

- **Trimethaphan**
- Competitively **blocks nicotinic receptors** on postganglionic neurons in **both sympathetic and parasympathetic ganglia.**
- No longer available (due to intolerable **toxicities**).

➢ **Adverse effects** include symathoplegia (**orthostaic hypotension and sexual dysfunction)**, parasympathoplegia (**dry mouth, urinary retention and constipation)**

➢ Trimethaphan is used for **its rapid action** in treating **hypertensive crisis**

C. Adrenergic neuron – blocking agents:

- **Guanethidine, Reserpine, Guanadrel, debrisoquine and Bethanidine**

➢ **Guanethidine:**

➢ **Mechanism of action:**

- It is **transported** across the sympathetic nerve membrane by (**uptake** 1), concentrates in the **vesicles**, where **it replaces N.A**. It causes gradual **depletion of the stored N.A.**

➢ **Toxicity:**

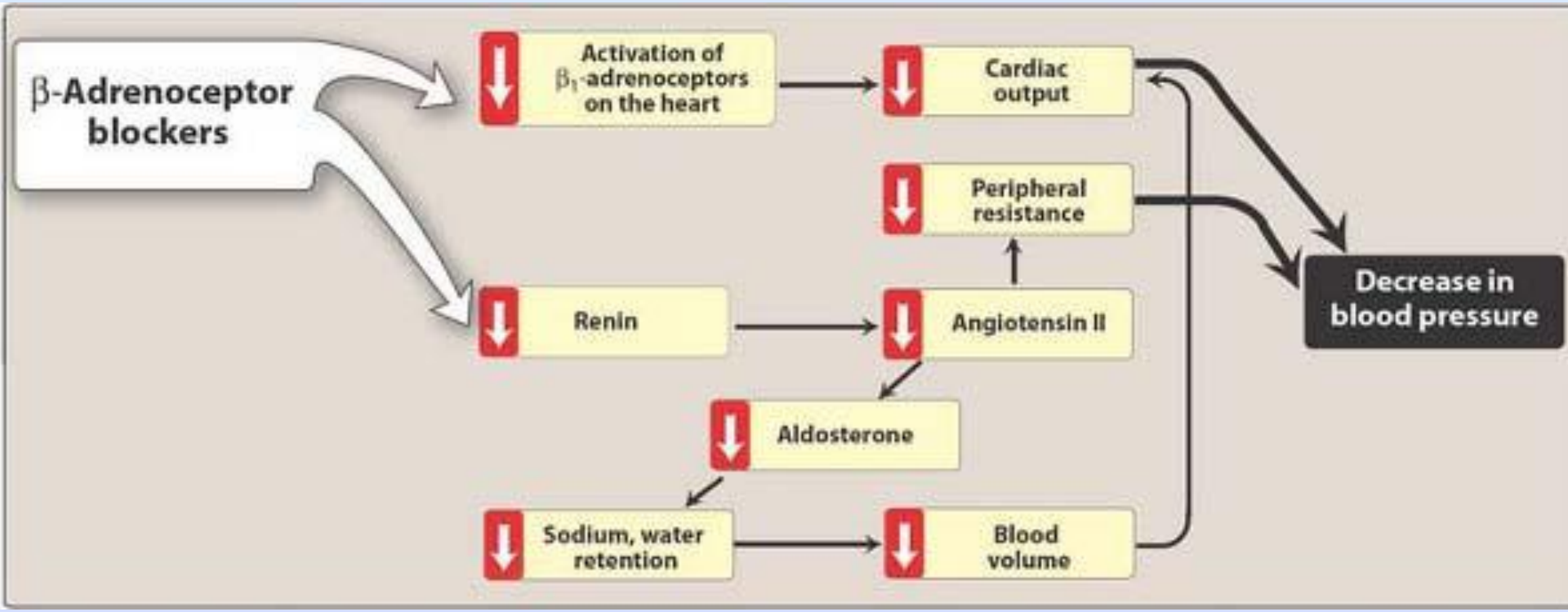
- Postural hypotension and diarrhea.
- **Interaction**: TCA, cocaine, amphetamine (block uptake 1)→↓ hypotensive action of guanethidine.

- **Reserpine:**
- An alkaloid extracted from (Rauwolfia serpentina).
- **Mechanism of action:**
- Inhibits **vesicular uptake and storage of chatecholamines**, resulting in **depletion (central and peripheral) of norepinephrine, dopamine, and serotonin.**
- **Toxicity:**

1. CNS effects: sedation and psychotic depression and parkinsonism symptoms (depletion of cerebral amine stores).
2. Peptic ulcer
3. The use of reserpine has diminished because of its CNS side effects

D. Adrenoceptor antagonist:

- **β-adrenoceptor-blockers:**
- **Propranolol:**
- **Mechanism of action:**
- Is a **non-selective** β-adrenoceptor-blocker.
- It decreases blood pressure primarily as a result of a **decrease** in **cardiac out-put**.
- It **inhibits renin** release (mediated by β1 receptors).
- Is very useful **in mild to moderate hypertension**.
- Is useful in **preventing the reflex tachycardia** that often **results from treatment with direct vasodilators.**


β-Adrenoceptor blockers
Activation of β_1-adrenoceptors on the heart
Cardiac output
Peripheral resistance
Decrease in blood pressure
Renin
Angiotensin II
Aldosterone
Sodium, water retention
Blood volume

- **Toxicity:**

- Toxicities occur in patients with heart failure, asthma, peripheral vascular insufficiency and diabetes

- **Common side effects:**

- Bradycardia , cold extremities, impotence and CNS effects (nightmares, mental depression and insomnia).
- ↑plasma triglycerides and ↓HDL-cholesterol.
- Impair the recovery from hypoglycemia (inhibit glycogenolysis) and mask the symptoms of hypoglycemia in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions.

- **Abrupt withdrawal** of propranolol after prolonged use, may cause a **withdrawal syndrome**, manifested by (nervousness, tachycardia, angina or severe hypertension). It **requires gradual tapering of the dose over 2 weeks**.
- **Nadolol** is a non-selective β-blocker.
- **Metoprolol, Atenolol, Betaxolol, Bisoprolol and Esmolol:**
- Are **β1-selective antagonists**.
- Their relative cardioselectivity may be beneficial in **treating hypertensive patients who are asthmatic, diabetic, or with peripheral vascular disease** (cardioselectivity is not absolute).

- **Pindolol, Acebutolol and Penbutolol:**
- Partial agonist (intrinsic sympathomimetic activity).
- **Decrease BP** by deceasing PVR, and depress CO and HR **less than other β- blockers**.
- This may be beneficial **for patients with chronic heart failure or peripheral vascular disease**
- **Labetalol, Carvedilol:**
- Have combined a and β- blocking activity. Therefore, they are useful in treating hypertension of pheochromocytoma and hypertensive emergencies.
- **Nebivolol** is a β1-selective blocker with vasodilating effect (mediated by NO release)

- β blockers are useful in treating conditions that may coexist with hypertension, such as:
- supraventricular tachyarrhythmia
- previous myocardial infarction
- angina pectoris
- chronic heart failure
- migraine headache.

- **Contraindications:**
- Severe or **chronic obstructive lung disease**, **asthma**, **heart failure**, severe symptomatic occlusive **peripheral vascular disease** or **insulin-dependent diabetes.**

- **Drug Interactions.**
- **Aluminum** salts, **cholestyramine** or **colestipol** **↓absorption of β blockers.**
- **Enzyme inducers** (phenytoin, rifampin, phenobarbital, or smoking) ↓ **β blockers effect**.
- **Enzyme inhibitor** (cimetidine) ↑ **bioavailability** of propranolol and metoprolol
- **β blockers + Ca^{2+} channel blockers** (verapamil) have **additive effects on the cardiac conducting system.**
- **NSAIDs decrease** the **antihypertensive effects of β receptor antagonists**.

- **Selective a_1 Blockers:**
- **Prazosin, terazosin,** and **doxazosin**
- Selectively **block a_1 receptors** in arterioles and venules→ **relaxation** →↓ **arterial blood pressure**.
- **Produce less reflex tachycardia than nonselective a-antagonists** such as phentolamine (do not block a2 receptor that mediates a negative feed inhibition of noradrenaline).
- Are **not** recommended as **monotherapy** for hypertension (**Given in combination with β-blocker and a diuretic**).
- Useful in **hypertensive patients with benign prostatic hyperplasia**, since they improve urinary symptoms.

- **Toxicity:**
- Na^+ and water retention (add diuretic).
- Symptomatic orthostatic hypotension after the first dose (**first-dose phenomenon or syncope**). Therefore, the first dose should be small and administered at bedtime..
- **Nonselective a-blockers:**
- **Phentolamine** and **phenoxybenzamine**
- useful in diagnosis and treatment of **pheochromocytoma**
- **Management of clonidine withdrawal syndrome** (phentolamine + propranolol)

- **Vasodilator drugs:**
- Oral vasodilators: **hydralazine** and **minoxidil** (long-term therapy).
- Parenteral vasodilators: **nitroprusside**, **diazoxide**, and **fenoldopam** (hypertensive emergencies).
- The calcium channel blockers: **nifedipine**, **verapamil** and **diltiazem** (used in both circumstances).
- **Mechanism of action:**
- Relax smooth muscle of arteriole→↓ systemic vascular resistance.
- Sodium nitroprusside also relaxes veins.

TABLE 11–3 Mechanisms of action of vasodilators.

Mechanism	Examples
Release of nitric oxide from drug or endothelium	Nitroprusside, hydralazine, nitrates,[1] histamine, acetylcholine
Reduction of calcium influx	Verapamil, diltiazem, nifedipine
Hyperpolarization of smooth muscle membrane through opening of potassium channels	Minoxidil, diazoxide
Activation of dopamine receptors	Fenoldopam

- Vasodilators → ↓arterial BP→ elicit compensatory responses (activation of sympathetic nervous system as well as renin-angiotensin-aldosterone system).
- Therefore, vasodilators work best in combination with other antihypertensive drugs like diuretic and β-blockers that oppose the compensatory cardiovascular responses.

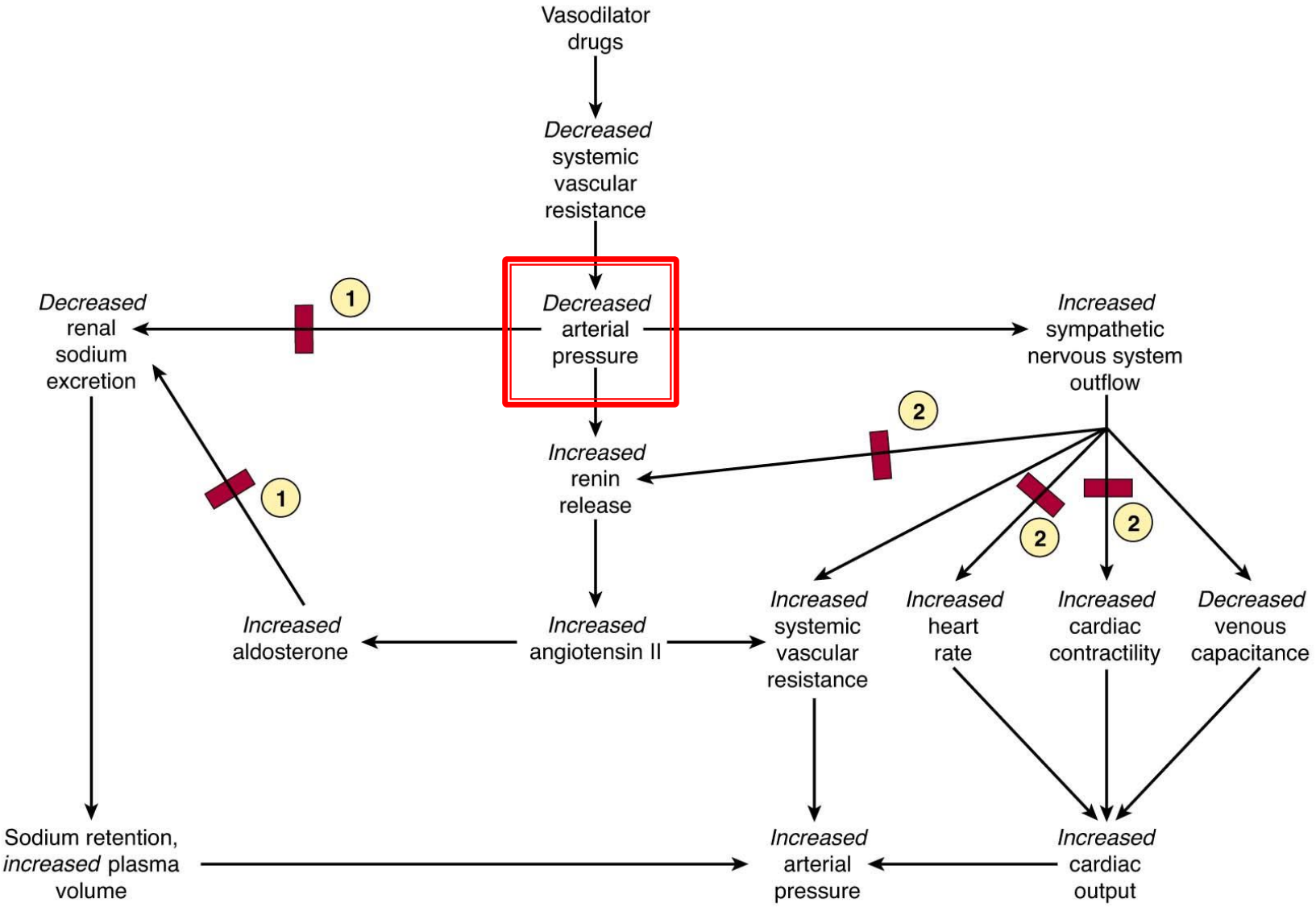


FIGURE 11–4 Compensatory responses to vasodilators; basis for combination therapy with β blockers and diuretics. ① Effect blocked by diuretics. ② Effect blocked by β blockers.

- **Hydralazine:**
- Direct vasodilator (**arterio-dilator, releasing NO**), oral vasodilator.
- Suitable for **moderately sever hypertension**, in **combination** with **β- blockers** (balance reflex tachycardia) and **diuretic** (↓ Na^+ retention).
- As a **monotherapy can be used in pregnancy-induced hypertension.**
- **Side effect:**
- Reflex tachycardia, nausea, sweating, headache, arrhythmia and angina.
- **Lupus erythematosus-like syndrome** most common at **high dose** and in **slow acetylators**.
- **Contraindicated** in hypertensive patients with coronary artery disease because of precipitation of MI due to reflex tachycardia.

- **Sodium Nitroprusside:**
- A potent **parenteral mixed vasodilator** (**arterio-dilator and veno-dilator**).
- Acts by releasing NO (vasodilatation).
- Used for treating **hypertensive crisis** as well as **heart failure**.
- It is metabolized into **cyanide** → **thiocyanate** (less toxic)→ urine.
- **Toxicity:**
- Thiocyanate accumulates after prolong administration especially in patient with renal insufficiency leading to **thiocyanate toxicity** (anorexia, nausea, fatigue, disorientation, and psychosis).
- **Thiocyanate toxicity** can be **treated** by **sodium thiosulfate.**

- **Precautions:**
- Used only by I.V. infusion
- Use fresh solution, and cover with foil (photosensitive)
- Continuous monitoring (prevents thiocyanate toxicity)

- **Minoxidil:**
- **Arterio-dilator**, acts by **opening k-channel**.
- It is used to manage **severe to malignant hypertension resistant to other drugs.**
- Must be **given** concurrently **with a diuretic** to avoid fluid retention and with **β-receptor antagonist** to control reflex tachycardia.
- **Toxicity:**
- Reflex sympathetic stimulation (heart rate, myocardial contractility, and myocardial O_2 consumption)
- Na^+ and water retention (add loop diuretic).
- Hypertrichosis (topical minoxidil is used for alopecia)

- **Diazoxide:**
- It acts by **opening of k-channel.**
- It is a **long-acting, parenteral arteriolar dilator**
- Inhibits **insulin secretion** (**thiazide-like agent**)
- Diazoxide is highly bound to plasma proteins.
- **Uses:**
- Hypertensive emergencies.
- Hypoglycemia due to insulinoma
- **Toxicity:**

1. Hypotension → sympathetic stimulation→ Tachycardia and angina (add β blocker)
2. ↑renin release (add diuretic).
3. Hyperglycemia and hyperuricemia (thiazide-like agent)

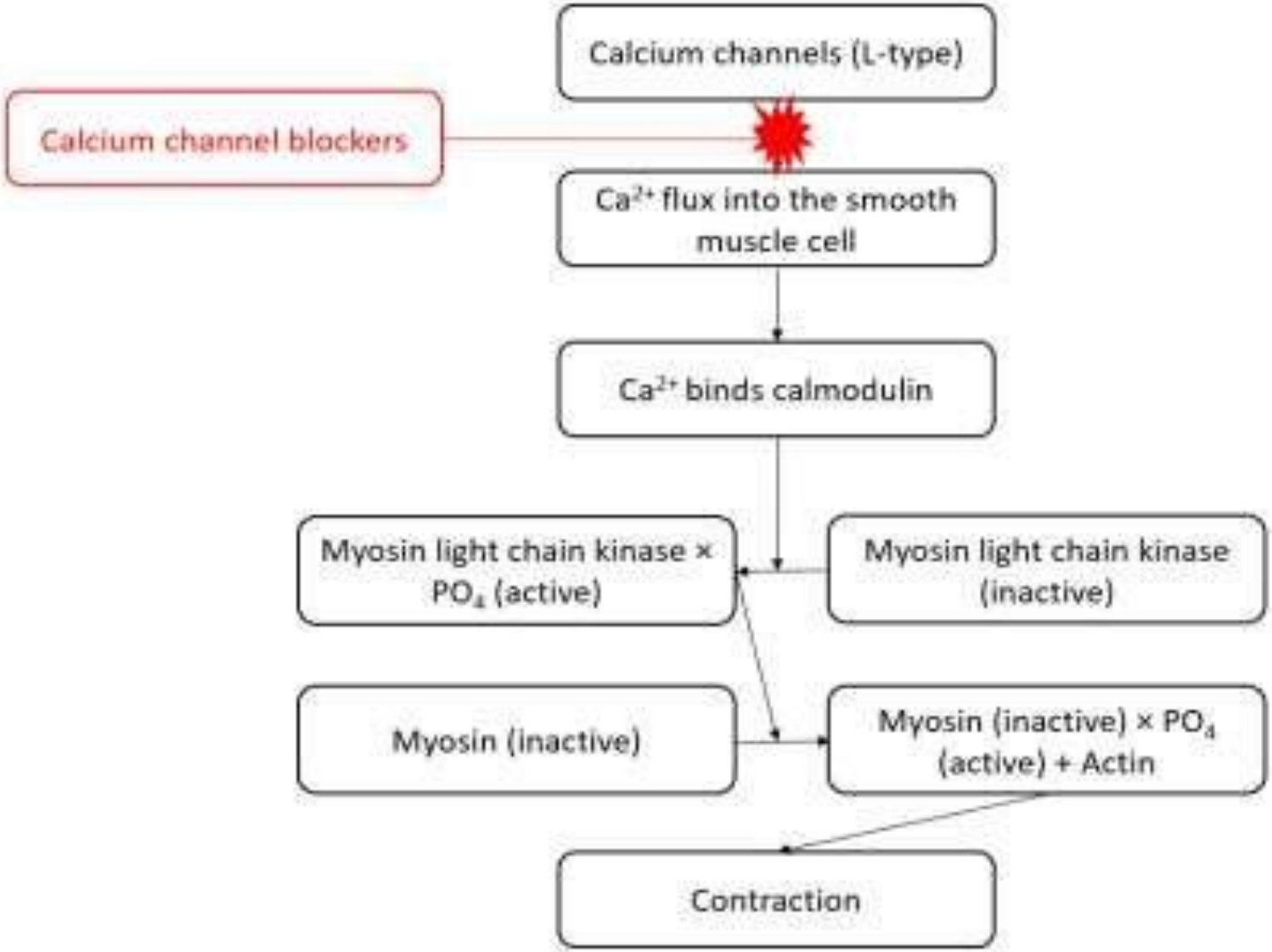
- **Fenoldopam**
- It is dopamine **D_1 receptors agonist → arteriolar dilator and natriuretic.**
- It is used to treat **hypertensive emergencies** (I.V. infusion).
- Particularly beneficial **in patients with renal insufficiency.**
- **Toxicity:**
- Reflex tachycardia, headache and flushing.
- Increases intraocular pressure (**contraindicated** in patient with **glaucoma**).

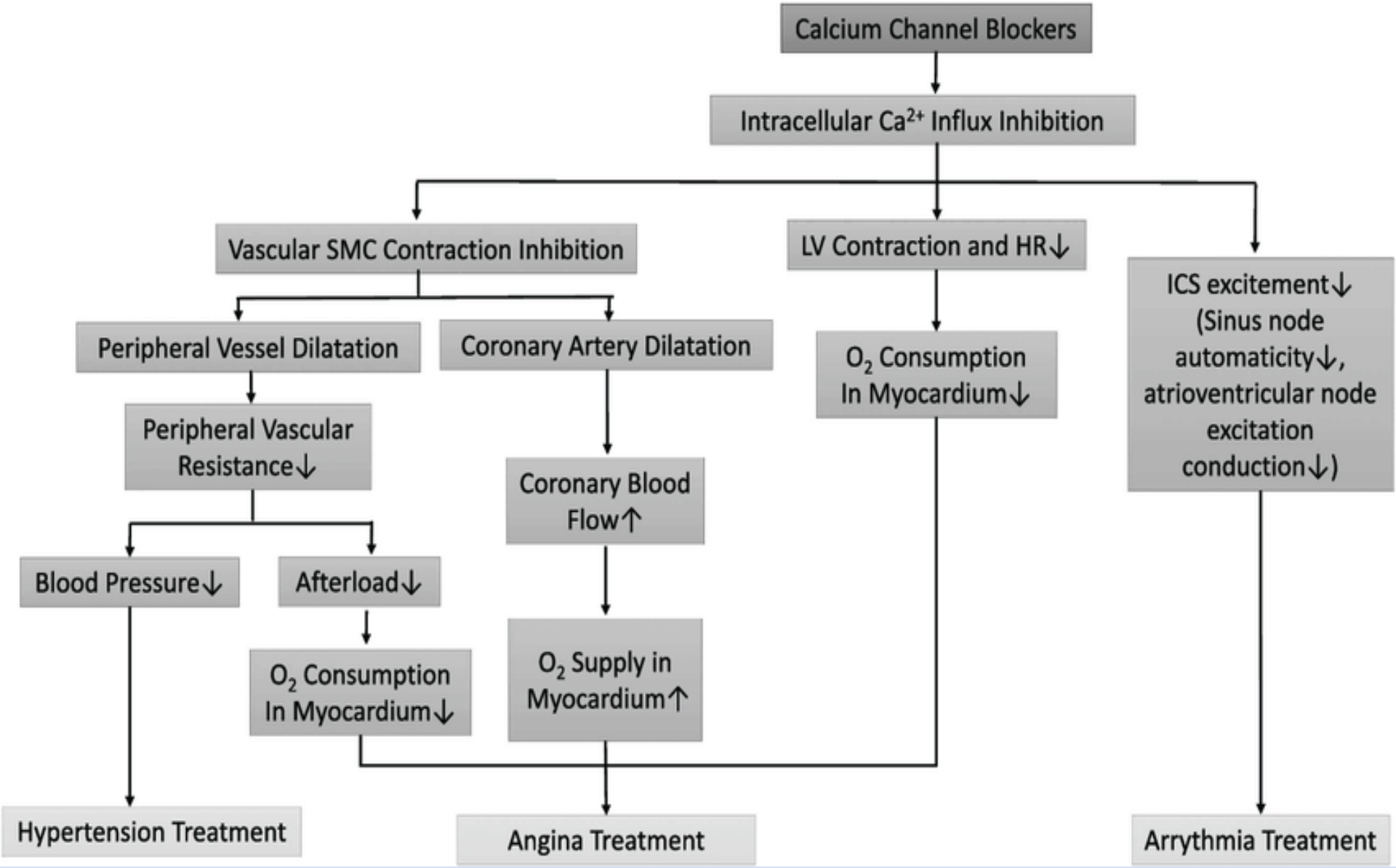
CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are medicines used to lower blood pressure. They stop calcium from entering the cells of the heart and arteries. Calcium causes the heart and arteries to squeeze more strongly. By blocking calcium, calcium channel blockers allow blood vessels to relax and open.

Because muscle contraction is largely dependent upon influx of calcium, its inhibition causes relaxation, particularly in arterial beds. Thus, the major effects of the calcium channel blockers are relaxation of vascular and arterial smooth muscle cells resulting in arterial vasodilation.

There are two distinct chemical classes of CCBs: the dihydropyridines (such as nifedipine and amlodipine) and the non-dihydropyridines (diltiazem and verapamil).


Calcium channels (L-type)
Calcium channel blockers
Ca^{2+} flux into the smooth muscle cell
Ca^{2+} binds calmodulin
Myosin light chain kinase × PO_4 (active)
Myosin light chain kinase (inactive)
Myosin (inactive)
Myosin (inactive) × PO_4 (active) + Actin
Contraction


Calcium Channel Blockers
Intracellular Ca^{2+} Influx Inhibition
Vascular SMC Contraction Inhibition
LV Contraction and HR↓
ICS excitement↓ (Sinus node automaticity↓, atrioventricular node excitation conduction↓)
Peripheral Vessel Dilatation
Coronary Artery Dilatation
O_2 Consumption In Myocardium↓
Peripheral Vascular Resistance↓
Coronary Blood Flow↑
Blood Pressure↓
Afterload↓
O_2 Consumption In Myocardium↓
O_2 Supply in Myocardium↑
Hypertension Treatment
Angina Treatment
Arrythmia Treatment

- **Calcium Channel blockers (CCBs):**
- Have **antihypertensive**, **antianginal** and **antiarrhythmic** effects.
- Examples: **Verapamil, diltiazem,** and the dihydropyridine family **(nifedipine, amlodipine, felodipine, isradipine, nicardipine and nisoldipine).**
- Nifedipine and the other dihydropyridines are more selective as vasodilators and have **less cardiac depressant effect** than verapamil and diltiazem (**arterio-selective**)
- Verapamil is a powerful cardiac depressant (**cardio-selective**)
- Diltiazem has **intermediate actions**.

- **Adverse effects:**

1. Headache and flush
2. Reflex tachycardia → nifedipine
3. Constipation → verapamil
4. Edema → nifedipine

- **Interactions:**

- Verapamil + β blocker → heart block
- Verapamil + digoxin → digoxin toxicity (↓renal excretion of digoxin)
- Nifedipine + nitrates → severe hypotension and tachycardia

Cilnidipine is a recently developed CCB, and possesses both L- and N-type calcium channels blocking activity. Since N-type calcium is distributed along the nerve and in the brain, cilnidipine is anticipated to exert specific action on nerve activity, such as inhibition of the sympathetic nervous system.

Cilnidipine is used in the treatment of Hypertension (high blood pressure), Angina (heart-related chest pain), heart attack and stroke. Cilnidipine is a calcium channel blocker. It lowers blood pressure by relaxing blood vessels, which makes the heart more efficient at pumping blood throughout the body.

cilnidipine being N-type and L-type calcium channel blocker, associated with lower incidence of pedal edema compared to only L-type channel blocked by amlodipine.

Generations of CCBs and Cilnidipine

Generation	Drugs	Plasma NE level	Heart rate	Charact -eristics	Ca 2+ channel blocked
1st generation	Nifedipine	Increased	Increased	Rapid sympathetic activation	L-type
2nd generation	Nicardipine Benitidine	Increased	Increased	Slow acting on L-type Ca^{2+} channels	
3rd generation	Amlodipine Azelnidipine	Increased	Increased	Slow acting on L-type of Ca^{2+} channels	
4th generation	Cilnidipine	No change or decreased	No change or Decreased	L- type and N-type Ca^{2+} channel	L-type and N-type

- **Inhibitors of Angiotensin:**
- Three classes of drugs act specifically on the renin-angiotensin system:
- **ACE inhibitors.**
- **Angiotensin receptor antagonists.**
- **Renin inhibitors**

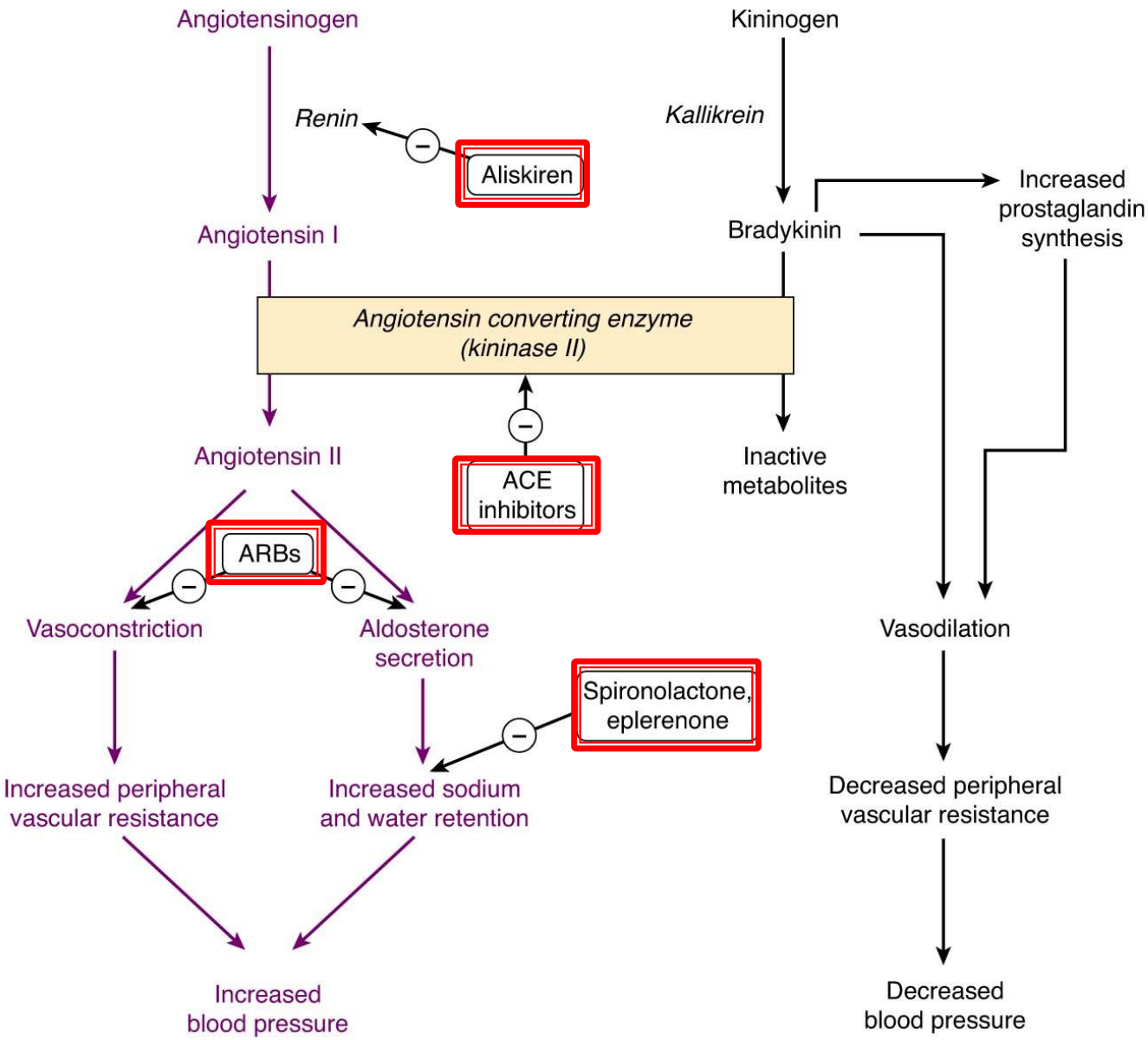


FIGURE 11–5 Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

- **Angiotensin-Converting Enzyme (ACE) Inhibitors:**
- **Examples: Captopril, Enalapril, Lisinopril, Benazepril, Fosinopril, Quinapril and ramipril.**
- **Mechanism of action:**
- Inhibit ACE that converts angiotensin I to angiotensin II and inactivates bradykinin, a potent vasodilator.
- The hypotensive action of ACEIs results from:
- Inhibition of renin-angiotensin system (↓ angiotensin II)
- Stimulaton of kallikrein-kinin system (↑bradykinin, vasodilator)

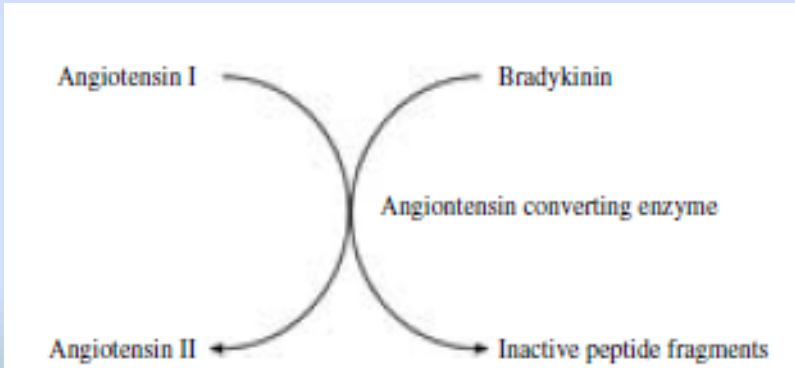


FIGURE 18.4
Interrelationship between the renin–angiotensin system and bradykinin.

- **Clinical uses:**

- Hypertension.
- Heart failure
- Myocardial infarction.
- Useful in slowing the development and progression of diabetic nephropathy
- Useful in slowing the progression of chronic renal disease in patients with hypertension.

- **Toxicity:**
- Dry cough and angioedema (↑bradykinin).
- Hyperkalemia.
- First dose hypotension can occur in hypovolumic patient due to diuretics, salt restriction, or gastrointestinal fluid loss (using **a low dose for initiate therapy**).
- Acute renal failure in patients with bilateral renal artery stenosis →↓GFR

- **Contraindications:**

- During the second and third trimesters of pregnancy (teratogenic).
- In patients with bilateral renal artery stenosis →↓GFR
- Asthmatics

- **Drug interactions:**

- With potassium supplements or potassium-sparing diuretics→ hyperkalemia.
- NSAIDs may impair the hypotensive effects of ACE inhibitors by blocking prostaglandin-mediated Na+/water excretion.

- **Angiotensin Receptor–Blocking Agents (ARBs):**
- Examples: **Losartan, valsartan, candesartan, eprosartan, irbesartan, olmesartan and telmisartan**.
- **Mechanism of action:**
- They block AT_1 receptor.
- They have no effect on bradykinin metabolism (↓ incidence of cough and angioedema).
- **Toxicity:**
- Similar adverse effects but cough and angioedema are less common with ARBs than with ACE inhibitors.

- **Renin inhibitors:**
- **Renin-releases inhibitors:**

- β-blockers: atenolol, propranolol….
- a2-agonists: clonidine and methydopa

- **Renin-receptor blockers:**

- Aliskiren

- **Treatment of hypertension:**

- **Selection** of drugs is dictated by **the level of blood pressure**, the **presence and severity of end organ damage**, and the **presence of other diseases**

1. **Non-pharmacologic therapy:**

- Salt restriction.
- Weight reduction.
- Regular exercise.
- Cessation of smoking and alcohol
- Relaxation

2. **Pharmacologic therapy:**

- **Uncomplicated stage 1 hypertension treatment:**
- Started with monotherapy:
- Thiazides (mainly), β-blockers, ACEI, ARBs or CCB.

➢ **Uncomplicated stage 2 hypertension treatment:**

➢ **Double therapy:**

- Thiazides + β-blockers or Thiazides + ACEIs

➢ **Triple therapy (polypharmacy):**

- Thiazides + β-blockers + vasodilator (ACEI, CCB or hydralazine)