Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 1

Antihypertensives Drugs

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Definition

Hypertension occurs when systolic/ diastolic blood pressure exceeds **130/80** mm Hg on at **least two occasions**.

HTN either **primary** (90%) (HTN with no identifiable cause) or **secondary** (10%).

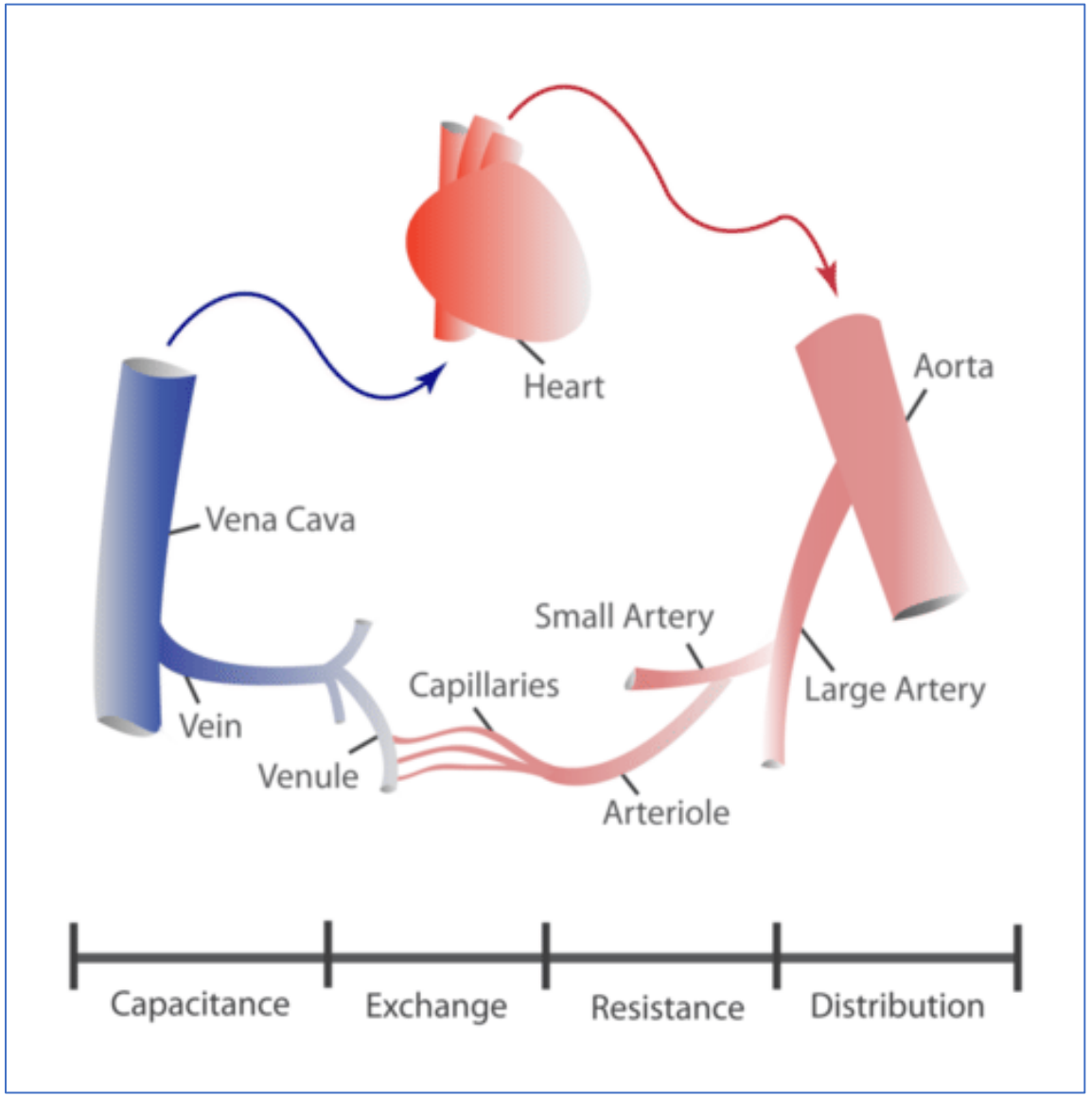
Although many patients have **no symptoms**, chronic hypertension can lead to: **Heart disease, Stroke, &Chronic kidney disease**

Pathophysiology

- Hypertension **results** from **increased** peripheral vascular **smooth muscle tone**, which leads to:

❖ **Increased** resistance of arteries (**↑afterload**)

❖ **Reduced** capacitance of the veins (**↑ preload**)



HTN Classification

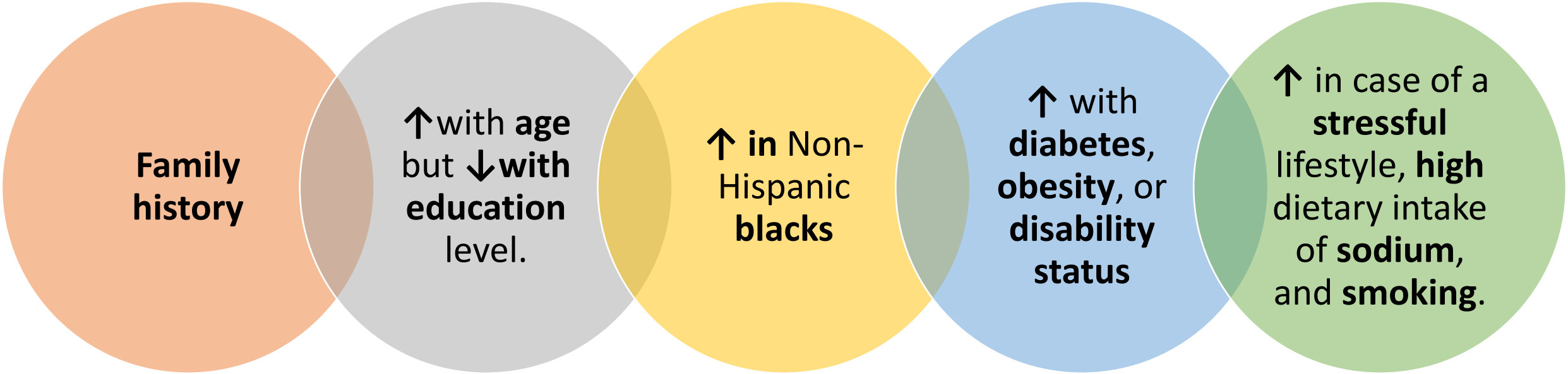
- Hypertension is **classified** into **four** categories for the purpose of treatment management.

Blood Pressure Categories

American Heart Association | American Stroke Association

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

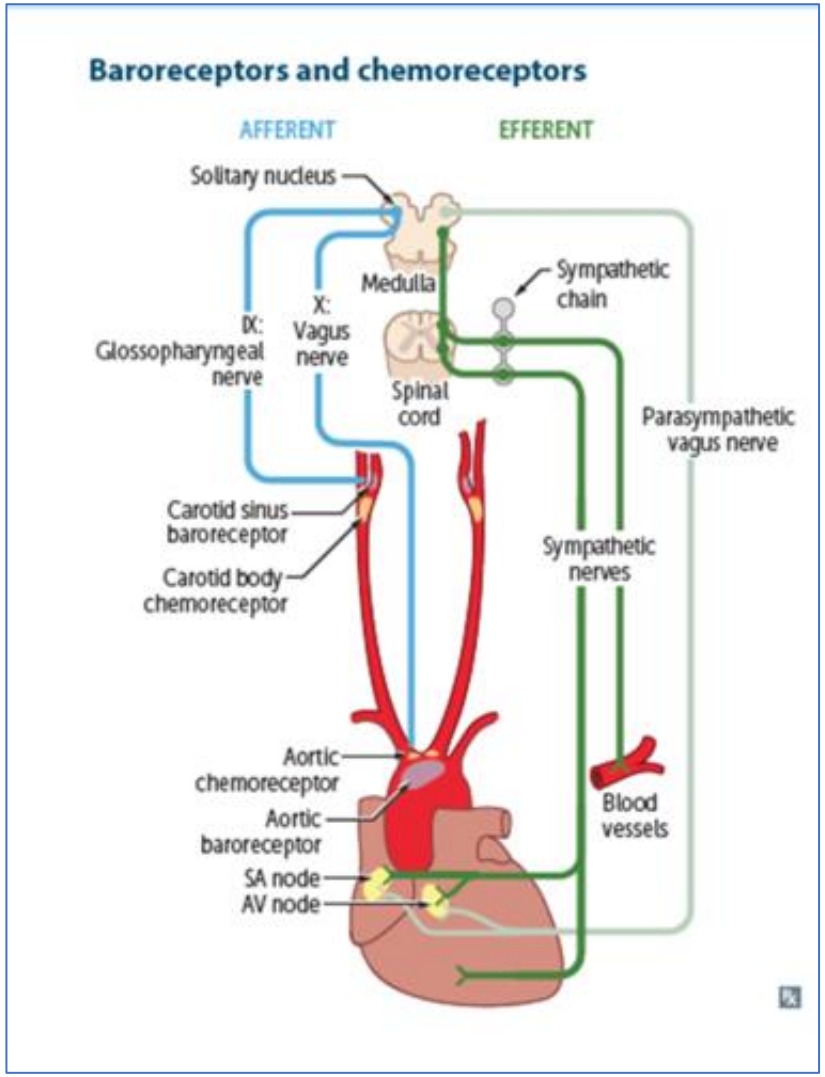
ETIOLOGY OF HYPERTENSION



MECHANISMS FOR CONTROLLING BLOOD PRESSURE

A. Baroreceptors and the sympathetic nervous system

- They are responsible for the **rapid**, **moment-to moment** regulation of blood pressure.
- A **fall** in blood pressure causes **pressure-sensitive neurons** (baroreceptors in the aortic arch and carotid sinuses) to **send** fewer impulses to cardiovascular **centers** in the spinal cord.
- This prompts a **reflex** response of ↑ sympathetic and ↓ parasympathetic output to the heart and vasculature, resulting in **vasoconstriction** and increased **cardiac output**.
- These changes result in a **compensatory** rise in blood pressure.



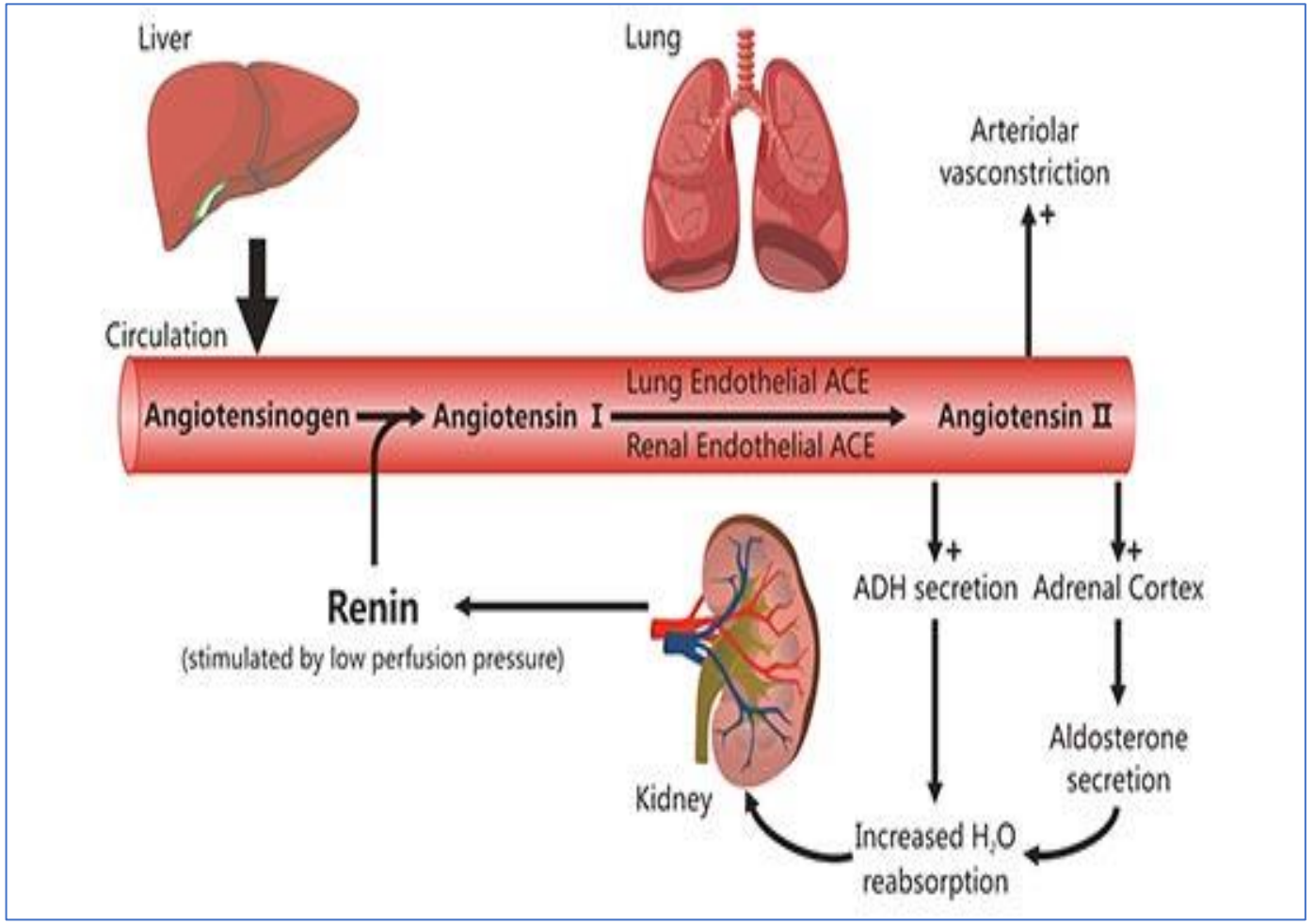
MECHANISMS FOR CONTROLLING BLOOD PRESSURE

B. Renin–angiotensin–aldosterone system

- The kidney provides **long-term control** of blood pressure by altering the **blood volume**.
- Kidneys respond to **reduced arterial pressure** and sympathetic stimulation of **β1-adrenoceptors** by releasing the enzyme **renin**.
- **Low sodium intake** and **greater sodium loss** also increase **renin** release.
- **Renin** converts **angiotensinogen** to **angiotensin** I, which is converted in turn to **angiotensin II**, in the presence of an angiotensin-converting enzyme (**ACE**).
- **Angiotensin II** is a potent circulating **vasoconstrictor**, constricting **both** arterioles and veins, resulting in an increase in **blood pressure**.
- The effects of angiotensin II are mediated by stimulation of **angiotensin II type 1 (AT1) receptors**.

MECHANISMS FOR CONTROLLING BLOOD PRESSURE

B. Renin–angiotensin–aldosterone system



TREATMENT STRATEGIES

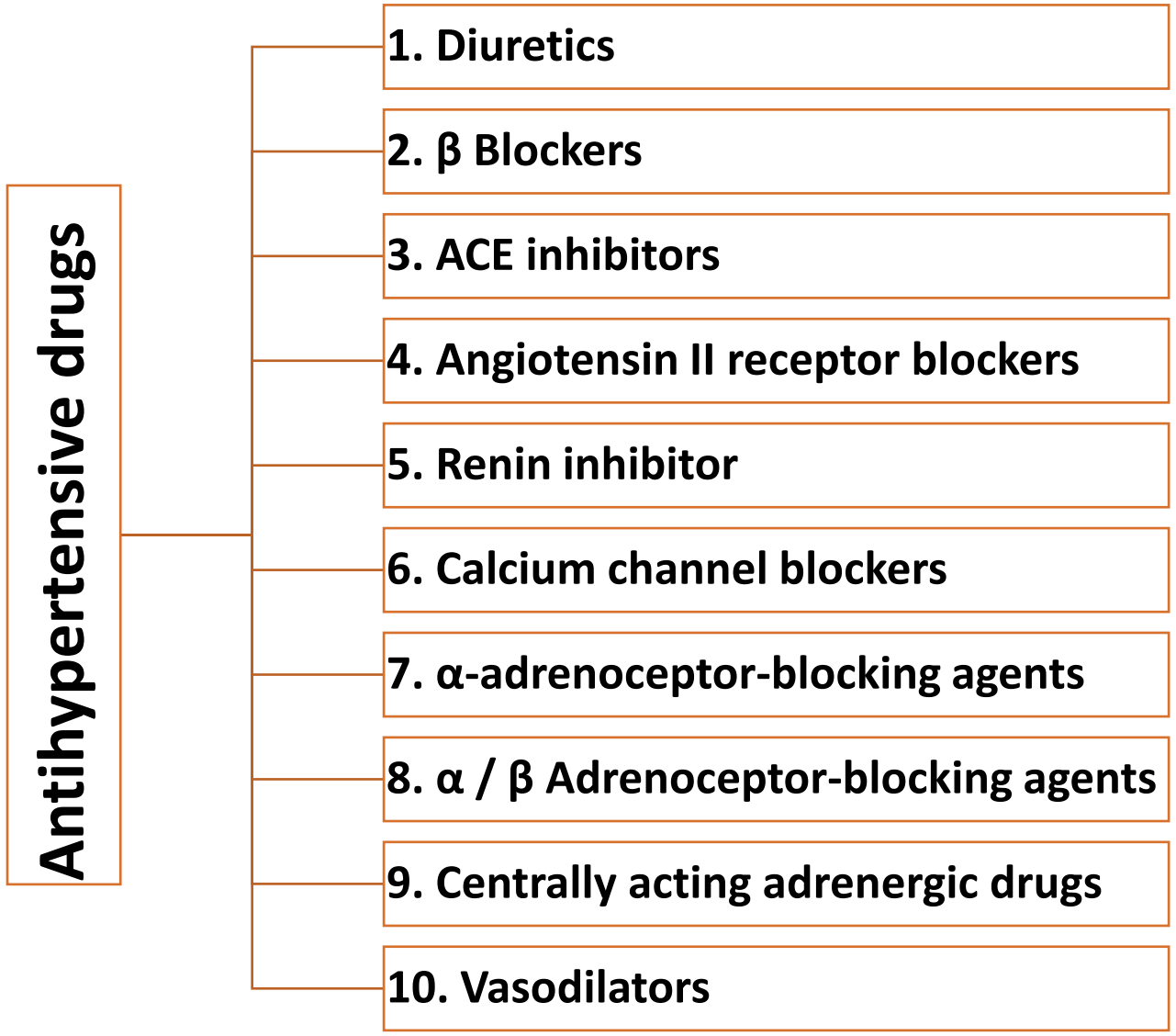
The **goal** of antihypertensive therapy is to get **systolic/ diastolic** blood pressure of **< 130/80** mm Hg to **reduce morbidity and mortality of cardiovascular and renal**.

Depending on the **guideline** and **concomitant** diseases the current recommendations are to **initiate** therapy with a **thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker (CCB)**.

Patients with **systolic** blood pressure **> 20** mm Hg above goal or **diastolic** blood pressure **> 10** mm Hg above goal should be started on **two antihypertensives simultaneously**.

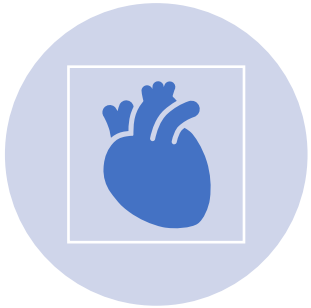
Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure **more quickly** with **minimal** adverse effects.

Antihypertensive Drugs

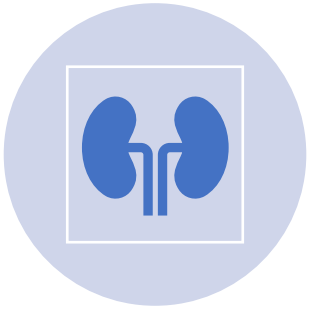


1. DIURETICS

Thiazide diuretics can be used as **initial** drug therapy for hypertension **unless** there are compelling reasons to choose another agent.



Regardless of class, the **initial mechanism** of action of diuretics is based upon **decreasing blood volume**, which ultimately leads to **decreased blood pressure**.

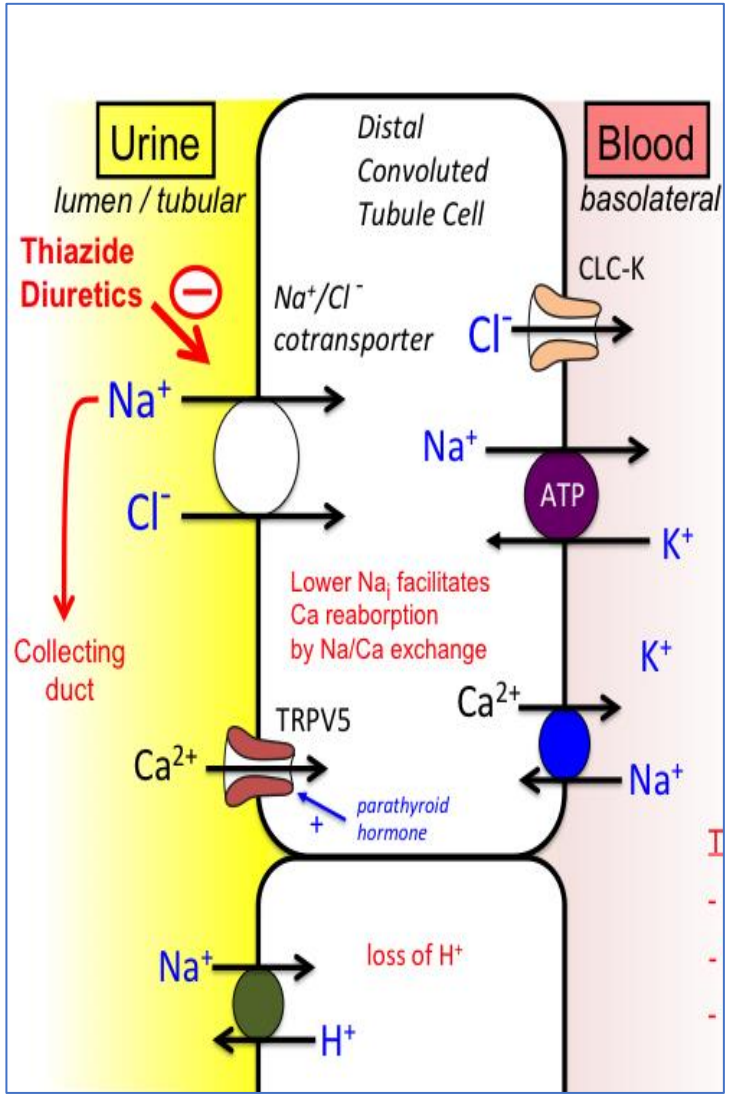


Low-dose diuretic therapy is **safe, inexpensive, & effective**.

Routine serum **electrolyte monitoring** should be done for all patients receiving diuretics.

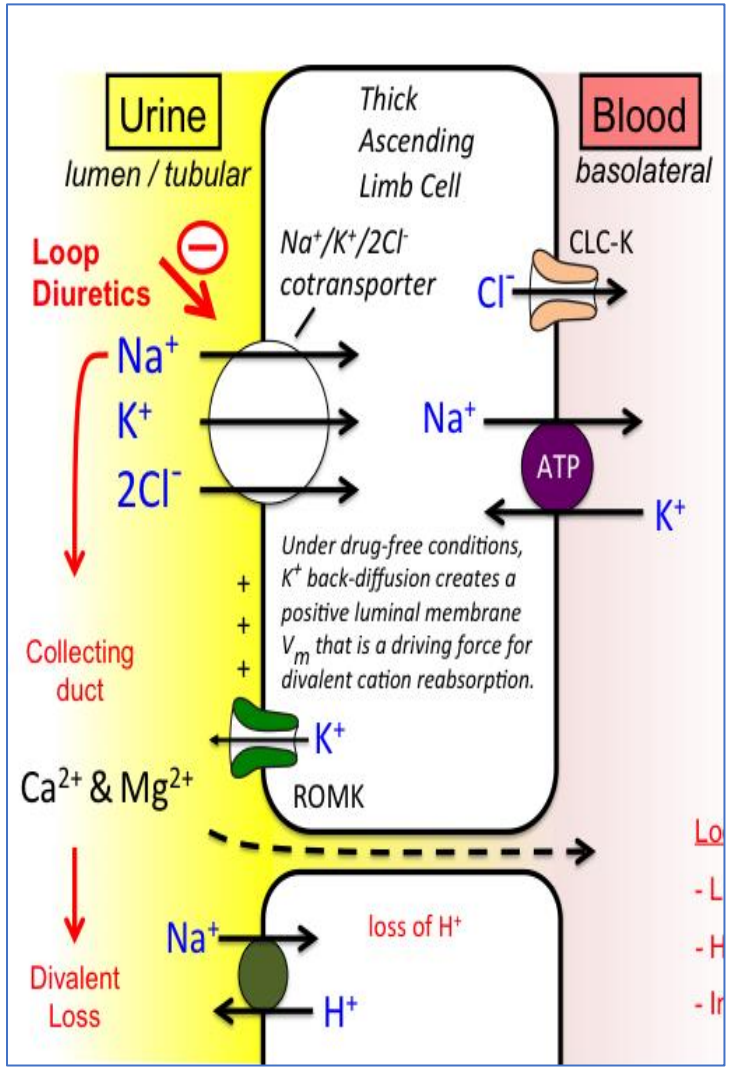
A. Thiazide diuretics

- Such as **hydrochlorothiazide** and **chlorthalidone.**
- **They ↓ BP** initially **by ↑Na and H_2O excretion** →↓ ECV →↓CO & RBF.
- With **long-term treatment**, plasma volume approaches a normal value, but a **hypotensive effect persists** that is related to a **decrease in peripheral resistance**.
- Useful in **combination** therapy with β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics.
- They are **not effective** with inadequate kidney function (**GFR< 30 mL/min/m2**). [**exception** of **metolazone].**
- **Loop** diuretics may be required in these patients.
- Thiazide diuretics can induce **hypokalemia**, **hyperuricemia** and, to a lesser extent, **hyperglycemia** in some patients.



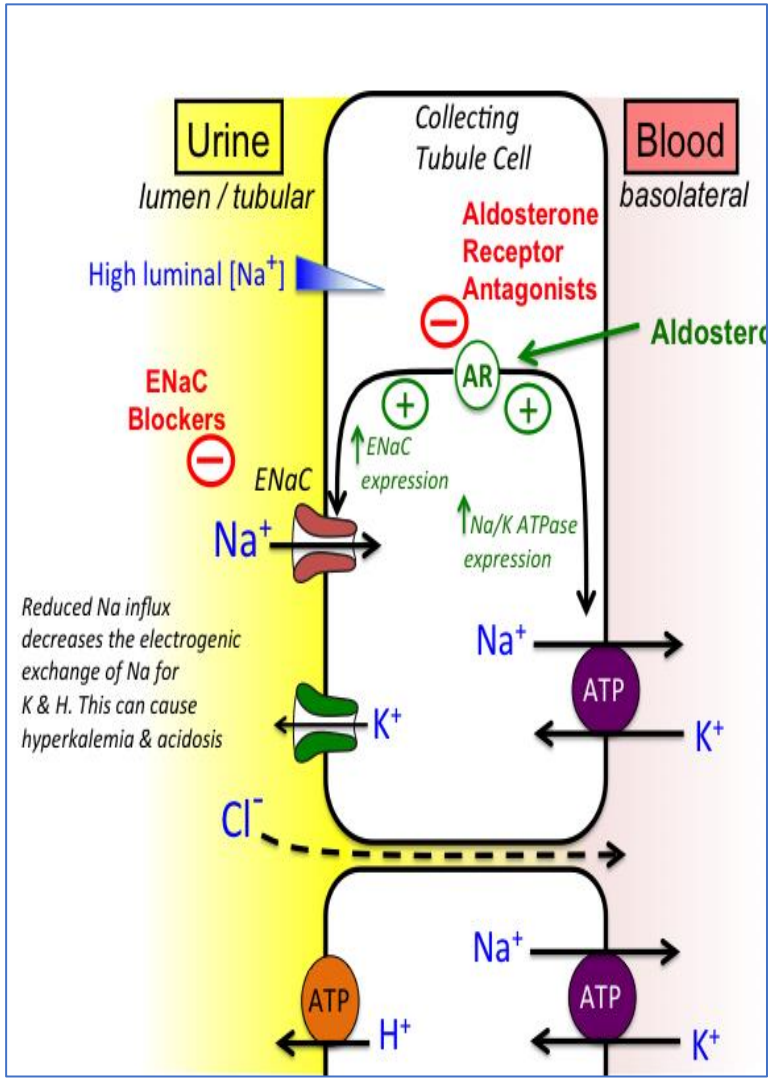
B. Loop diuretics

- **Such as furosemide, torsemide, bumetanide, and ethacrynic acid**
- **They** act promptly by **blocking Na and Cl reabsorption** in the kidneys, even in patients with **poor renal function** or those who have **not responded** to thiazide diuretics.
- Loop diuretics cause ↓ **renal vascular resistance** and ↑ **RBF.**
- **Like** thiazides, they can cause **hypokalemia**. However, **unlike** thiazides, they cause **Hypocalcemia**, whereas thiazide diuretics **Hypercalcemia**.
- These agents are **rarely used alone** to treat **HTN**, but they are **commonly** used to manage symptoms of **HF and edema**.

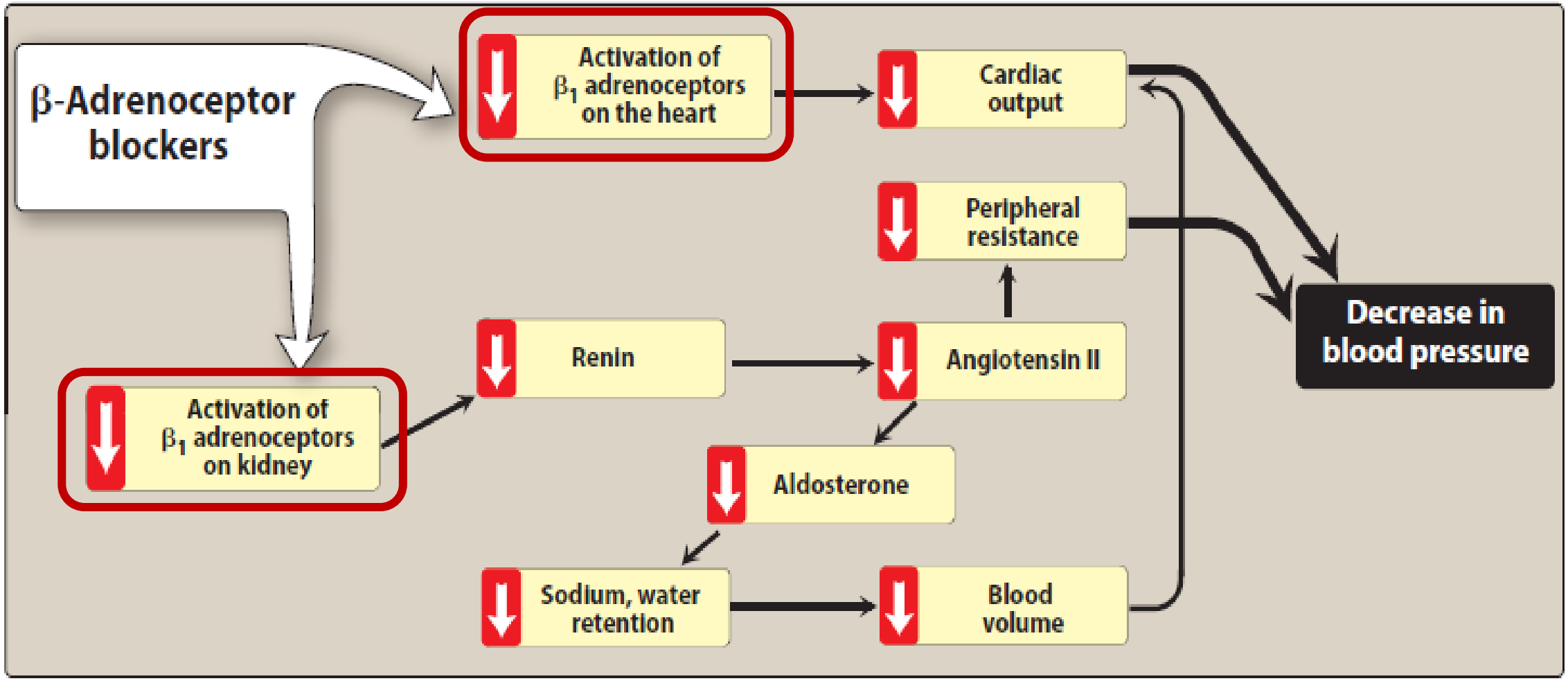


C. Potassium-sparing diuretics

- **Amiloride** and **triamterene** (inhibitors of epithelial sodium transport at the late distal and collecting ducts).
- **Spironolactone** and **eplerenone** (aldosterone receptor antagonists) reduce potassium loss in the urine.
- **Aldosterone antagonists** have the **additional** benefit of diminishing the **cardiac remodeling** that occurs in heart failure.
- Potassium-sparing diuretics are sometimes used in **combination** with **loop diuretics and thiazides** to reduce the amount of **potassium loss** induced by these diuretics.



2. β-ADRENOCEPTOR–BLOCKING AGENTS



2. β-ADRENOCEPTOR–BLOCKING AGENTS

A. Actions

The β-blockers reduce blood pressure primarily by **decreasing cardiac output**.

They may also **decrease sympathetic outflow from CNS** and **inhibit the release of renin** from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone.

The **prototype** β-blocker is **propranolol** which acts at both β1 and β2 receptors.

Selective blockers of β1 receptors, such as **metoprolol** and **atenolol**, are among the most commonly prescribed β-blockers.

Nebivolol is a **selective blocker of β1** receptors, which also increases the production of **nitric oxide**, leading to **vasodilation**.

2. β-ADRENOCEPTOR–BLOCKING AGENTS

- **A. Actions**

The **selective** β-blockers may be administered **cautiously** to hypertensive patients who also have **asthma**.

The **nonselective** β-blockers, such as **propranolol & nadolol**, are **contraindicated** in patients with **asthma** due to their blockade of β2-mediated **bronchodilation**.

β-Blockers should be used **cautiously** in the treatment of patients with **acute heart failure** or **peripheral vascular disease**.

2. β-ADRENOCEPTOR–BLOCKING AGENTS

B. Therapeutic uses

- The **primary therapeutic benefits** of B-blockers are seen in **HTN patients with concomitant heart disease**, such as SVT, previous MI, stable IHD, and chronic HF.
- Conditions that **discourage** the use of B-blockers include reversible bronchospastic disease such as **asthma, second- and third-degree heart block, and severe peripheral vascular disease.**

C. Pharmacokinetics

- The B-blockers are **orally active** for the treatment of **HTN**.
- **Propranolol** undergoes extensive and highly variable **first-pass metabolism**.
- **Oral** B-blockers may take **several weeks** to develop their **full effects**.
- **Esmolol, metoprolol, and propranolol** are available in **IV** formulations.

2. β-ADRENOCEPTOR–BLOCKING AGENTS

D. Adverse effects

- The B-blockers may **decrease libido** and cause **erectile dysfunction**, which can severely reduce patient compliance.
- **Nonselective** B-blockers may **disturb lipid metabolism**, decreasing HDL and increasing TG.

E. Drug withdrawal

- **Abrupt withdrawal** may induce severe HTN, angina, MI, and **even sudden death** in patients with IHD. ??
- Therefore, these drugs **must be** tapered over a **few weeks** in patients with HTN and IHD.

3. ACE INHIBITORS

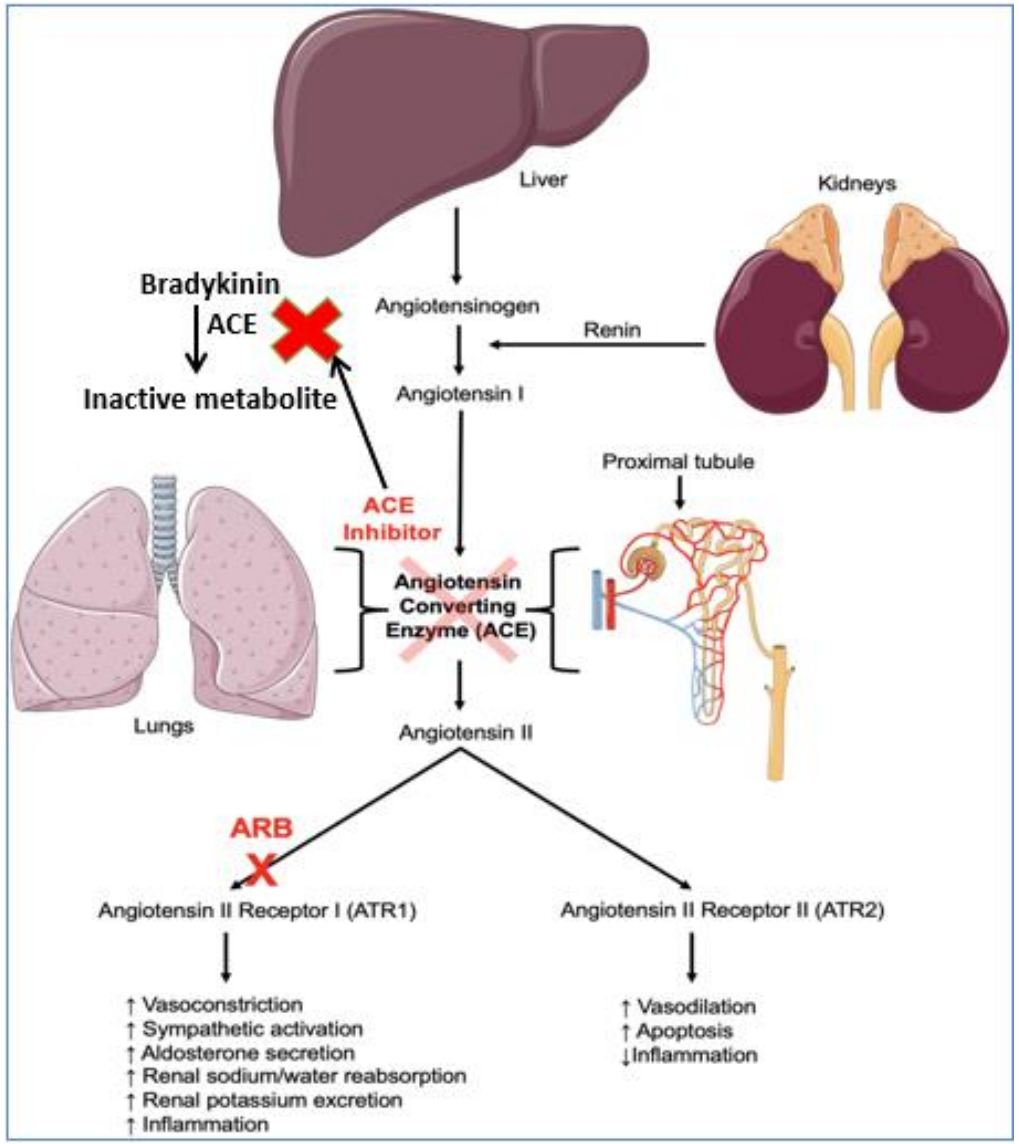
The ACE inhibitors, such as **enalapril** and **lisinopril**, are recommended as **first-line treatment** of HTN in patients with a variety of compelling indications, including:

- **High coronary disease risk**
- **History of diabetes**
- **Stroke, heart failure, & MI**
- **Chronic kidney disease**

3. ACE INHIBITORS

A. Actions

- These drugs **block the enzyme ACE**, which cleaves angiotensin I to form the potent vasoconstrictor **angiotensin II**.
- ACE is also responsible for the **breakdown of bradykinin**, a peptide that ↑ nitric oxide and prostacyclin (**potent vasodilators**).
- By ↓ circulating **angiotensin II** levels, ACE inhibitors also ↓ **the secretion of aldosterone**, resulting in ↓ **Na and water retention**.
- ACE inhibitors **reduce** both cardiac **preload and afterload**, thereby ↓ **workload** on the heart.



3. ACE INHIBITORS

B. Therapeutic uses

- They **slow** the progression of **diabetic nephropathy** and **decrease albuminuria**.
- ACE inhibitors are a **standard** in the care of a patient following **MI.**
- Act as **first-line** agents in the Rx of patients with **HF**, **HTN** patients with **CKD**, and patients at increased risk of **CAD**.
- All of them are **equally effective** in the treatment of **HTN** at **equivalent doses**.

3. ACE INHIBITORS

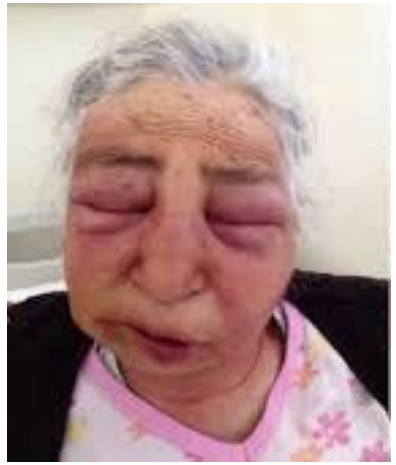
C. Pharmacokinetics

- **All** of the ACE inhibitors are **orally bioavailable** as a drug or prodrug.
- **All but captopril and lisinopril** undergo **hepatic conversion** to **active** metabolites (preferred in severe **hepatic impairment**).
- **Fosinopril** is the **only** ACE inhibitor that is **not** eliminated primarily by the kidneys (does not require dose adjustment in **renal impairment**).
- **Enalaprilat** is the **only** drug in this class available **intravenously**.

3. ACE INHIBITORS

D. Adverse effects

- **The dry cough**, in up to 10% of patients, due to ↑ levels of **bradykinin** and **substance P** in the pulmonary tree, and it occurs more frequently in **women** (resolves by discontinuation).
- **Angioedema** is a **rare** but potentially **life-threatening** reaction that may also be due to ↑ levels of **bradykinin**.
- **Potassium levels** must be monitored while on ACE inhibitors, and potassium supplements and potassium- sparing diuretics should be used with **caution** due to the risk of **hyperkalemia**.
- Serum **creatinine** levels should also be **monitored**, particularly in patients with underlying renal disease.
- ACE inhibitors can induce **fetal malformations** and should not be used by **pregnant women**.



4. ANGIOTENSIN II RECEPTOR BLOCKERS

The ARBs, such as losartan and irbesartan, **block the AT1 receptors** of **angiotensin II.**

Their pharmacologic effects are similar to those of ACE inhibitors.

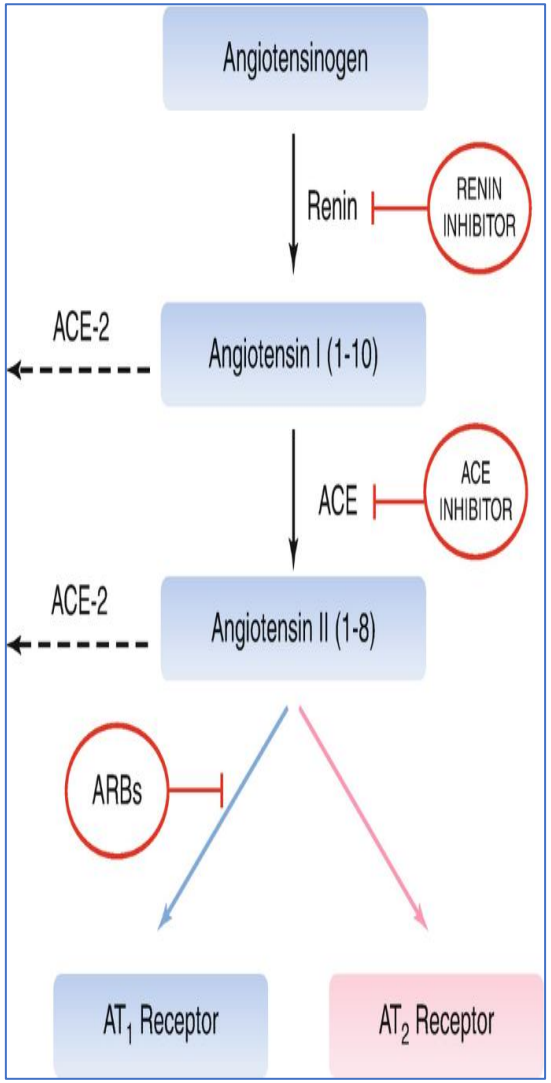
ARBs **do not increase bradykinin levels**.

They may be used as **first-line agents** for the treatment of **hypertension**, especially in patients with a **compelling** indication of **diabetes, heart failure, or chronic kidney disease**.

The risks of **cough and angioedema** are significantly **decreased**.

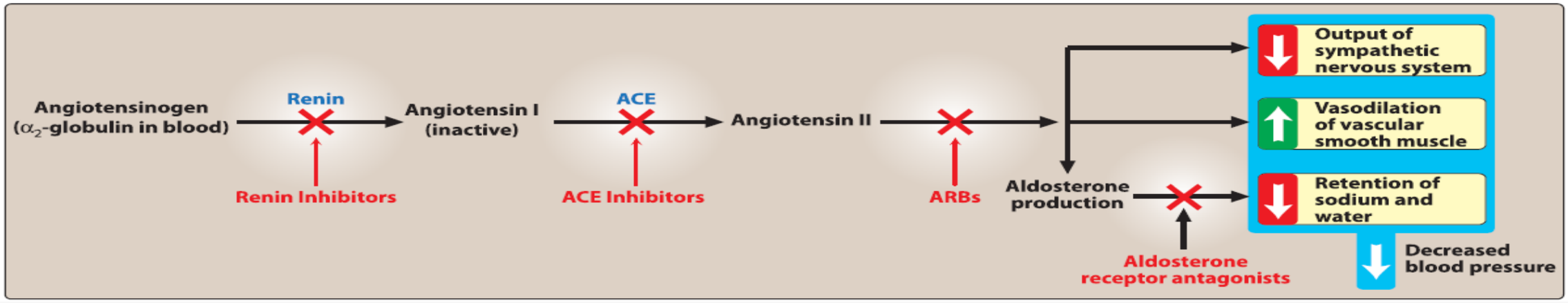
ARBs should **not** be **combined** with an ACE inhibitors.

These agents are also **teratogenic**.



5. RENIN INHIBITOR

- A selective renin inhibitor, **aliskiren**, **directly** inhibits **renin** and, thus, acts earlier in **RAAS** than **ACE inhibitors or ARBs**.
- It lowers blood pressure about as **effectively** as ARBs, ACE inhibitors, and thiazides.
- Aliskiren should **not be routinely combined** with an ACE inhibitor or ARB.
- Aliskiren can cause **diarrhea**, especially at higher doses, and can also cause **cough** and **angioedema**, but probably **less** often than ACE inhibitors.
- As with ACE inhibitors and ARBs, aliskiren is **contraindicated** during **pregnancy**.
- Aliskiren is metabolized by **CYP 3A4** and is subject to many drug **interactions**.



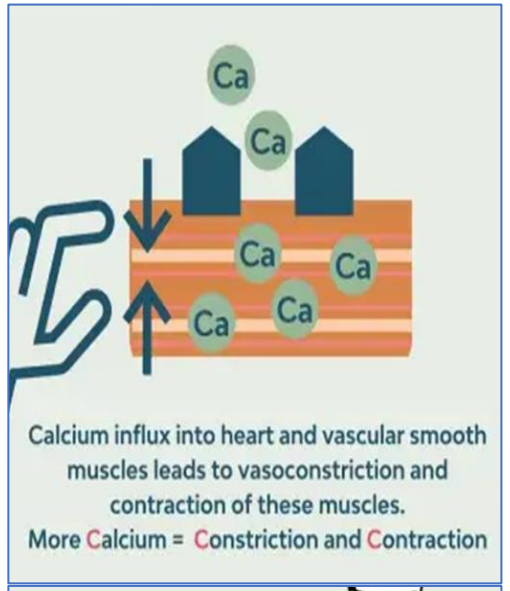
6. CALCIUM CHANNEL BLOCKERS

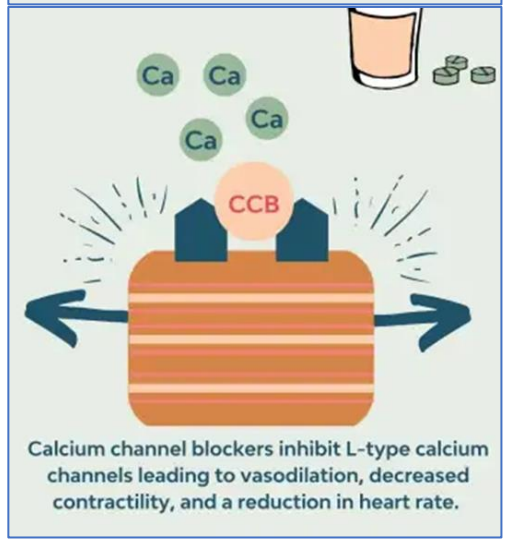
- **CCB** are a recommended:

1. **First-line** treatment option in **black** patients.
2. Useful in HTN patients with **DM** or stable **IHD**.

- **High doses** of short-acting CCB should be **avoided** (risk of MI due to excessive vasodilation and marked **reflex cardiac stimulation**).
- They include:

1. **Diphenylalkylamines**: Verapamil (Cardiac > Vascular SM)
2. **Benzothiazepines**: Diltiazem (Cardiac > Vascular SM)
3. **Dihydropyridines**: Nifedipine, amlodipine, felodipine, isradipine, nicardipine, & nisoldipine (Mainly vascular SM, prefer in HTN, less interaction)

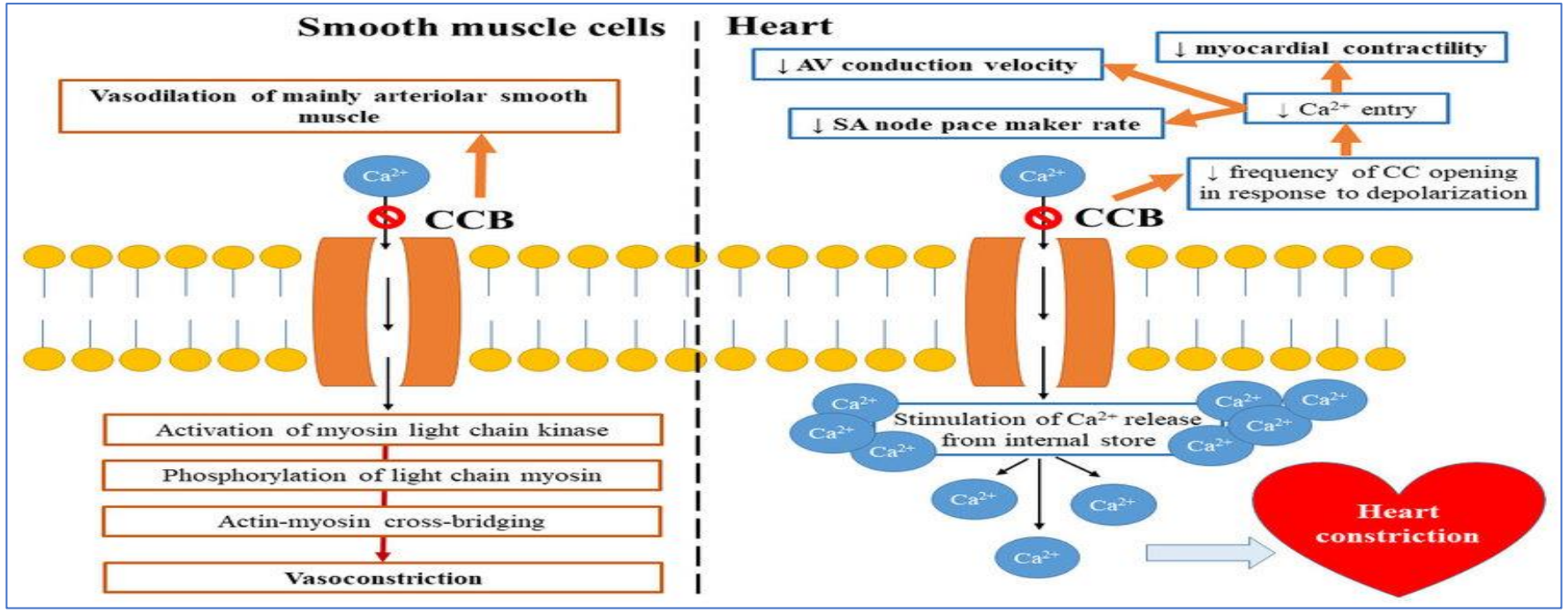




6. CALCIUM CHANNEL BLOCKERS

A. Actions

- CCB **block** the **inward** movement of calcium by binding to **L-type calcium channels** in the **heart** and in **SM** of the coronary and peripheral **arteriolar vasculature**.
- This causes vascular smooth muscle to **relax**, dilating mainly **arterioles**.
- CCBs do **not dilate veins**.



6. CALCIUM CHANNEL BLOCKERS

B. Therapeutic uses

- In the management of **HTN**, CCBs may be used as **initial therapy** or as **add-on therapy**.
- They are useful in the treatment of HTN patients who also have **asthma**, **diabetes**, and/or **peripheral vascular disease**, because, unlike β-blockers, they **do not have** the potential to adversely affect these conditions.
- **All** CCBs are useful in the treatment of **angina**.
- In addition, **diltiazem and verapamil** are used in the treatment of **atrial fibrillation**.

C. Pharmacokinetics

- Most of these agents have **short half-lives** (3 to 8 hours) following an **oral dose**.
- **Sustained-release preparations** are available and permit **once-daily dosing**.
- **Amlodipine** has a very **long half-life (30-50 hr)** and does not require a sustained-release formulation.

6. CALCIUM CHANNEL BLOCKERS

D. Adverse effects

- **First-degree AV block** and **constipation** are common dose-dependent side effects of **verapamil**.
- **Verapamil and diltiazem** should be **avoided** in patients with **HF or AV block**. (**- inotropic & -dromotropic effects**).
- **Dizziness**, **headache**, and a feeling of **fatigue** caused by a decrease in blood pressure are more frequent with **dihydropyridines**.
- **Peripheral edema** is another commonly reported side effect of this class.
- **Nifedipine** and other dihydropyridines may cause **gingival hyperplasia**.

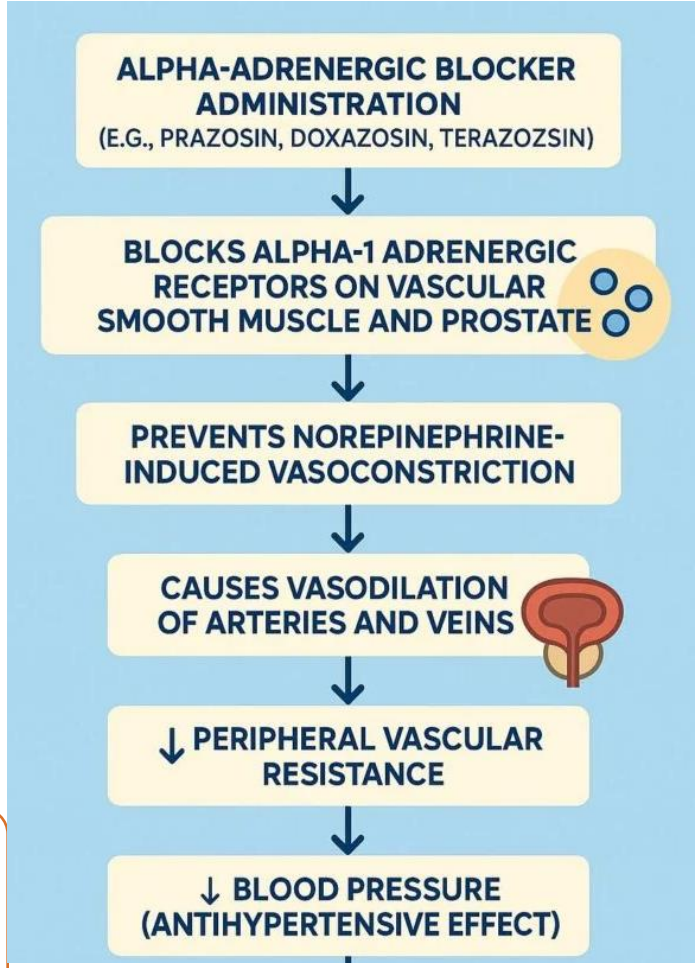
7. α-ADRENOCEPTOR–BLOCKING AGENTS

Prazosin, doxazosin, and terazosin act as competitive **α1-receptors blockers**.

They **decrease** peripheral vascular resistance and lower arterial blood pressure by causing **relaxation** of **both arterial and venous** smooth muscle.

Reflex tachycardia and **postural hypotension** often occur at the onset of Rx and with dose increases, requiring **slow titration** of the drug in **divided doses**.

They are **no longer** recommended **as initial treatment** for HTN but may be used for **refractory cases**. (weaker outcome & side effects)



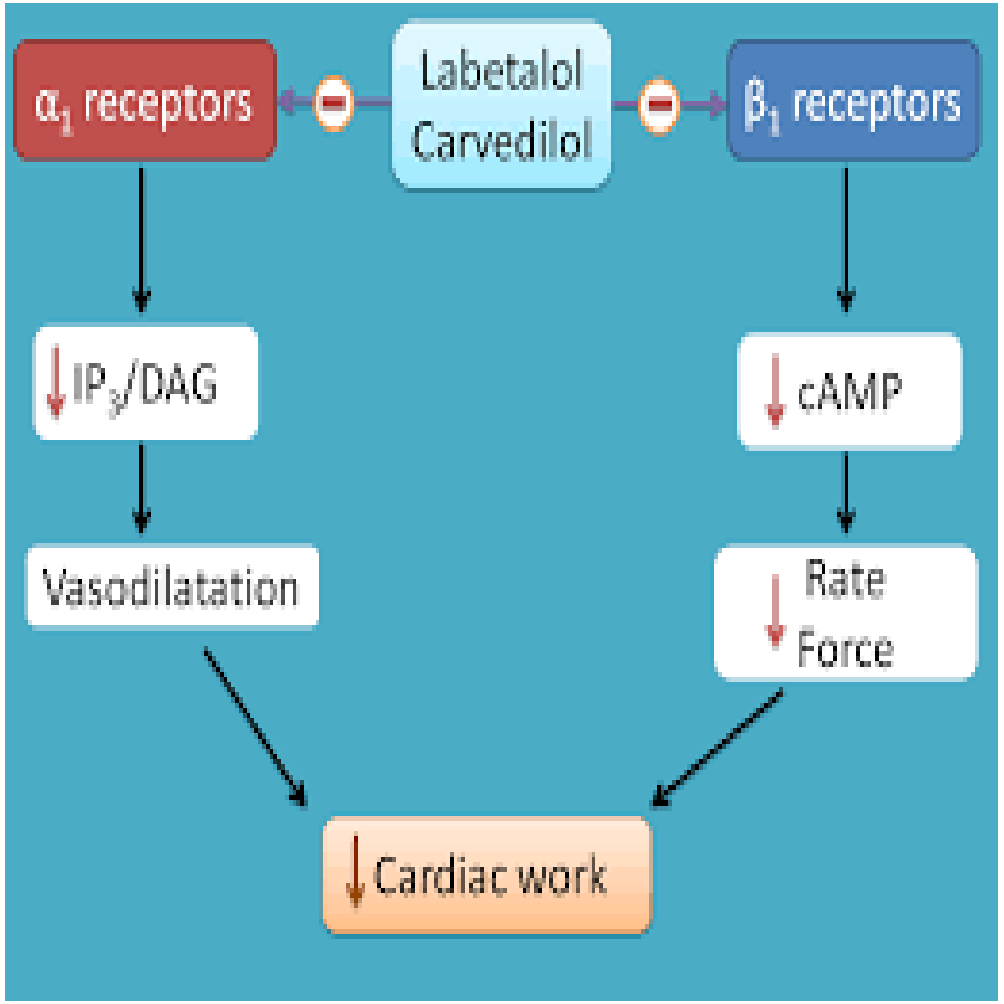
8. α-/β-ADRENOCEPTOR–BLOCKING AGENTS

Labetalol and **carvedilol** block α1, β1, and β2 receptors.

Carvedilol, although an effective antihypertensive, is **mainly** used in the treatment of **heart failure**.

Carvedilol, as well as **metoprolol succinate, and bisoprolol** have been shown to reduce **morbidity and mortality** associated with **heart failure**.

Labetalol is used in the management of **gestational HTN** and **hypertensive emergencies**.



9. CENTRALLY ACTING ADRENERGIC DRUGS

A. Clonidine

It acts **centrally** as an **α2 agonist** to produce **inhibition of sympathetic vasomotor centers**, decreasing sympathetic outflow to the periphery.

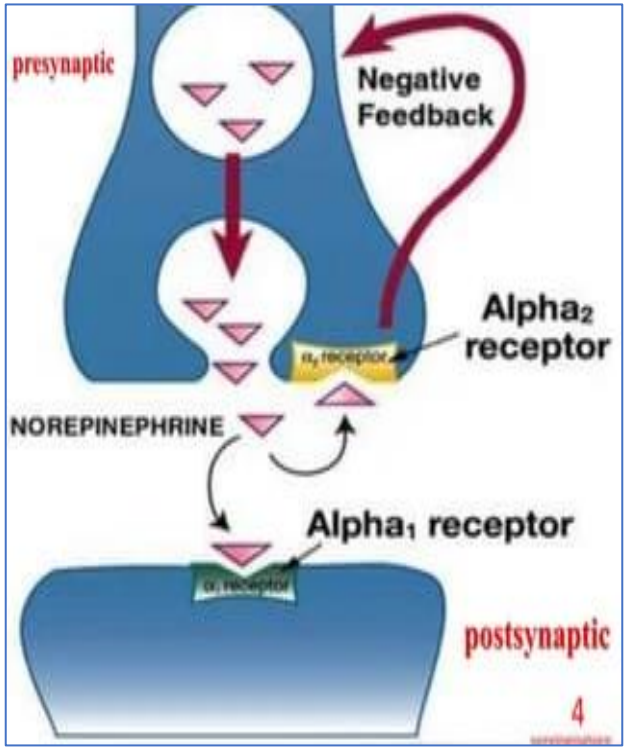
Clonidine is used primarily for the treatment of **HTN** that has **not responded** adequately to treatment with **two or more** drugs.

It does **not decrease renal blood flow or GFR** (useful in the Rx of HTN complicated by **renal disease)**.

It is absorbed well after **oral** administration and is excreted by the **kidney** & also available in a **transdermal patch**.

Adverse effects include **sedation**, **dry mouth**, and **constipation**.

Rebound hypertension (if **abrupt withdrawal -** it should be **withdrawn slowly**).



9. CENTRALLY ACTING ADRENERGIC DRUGS

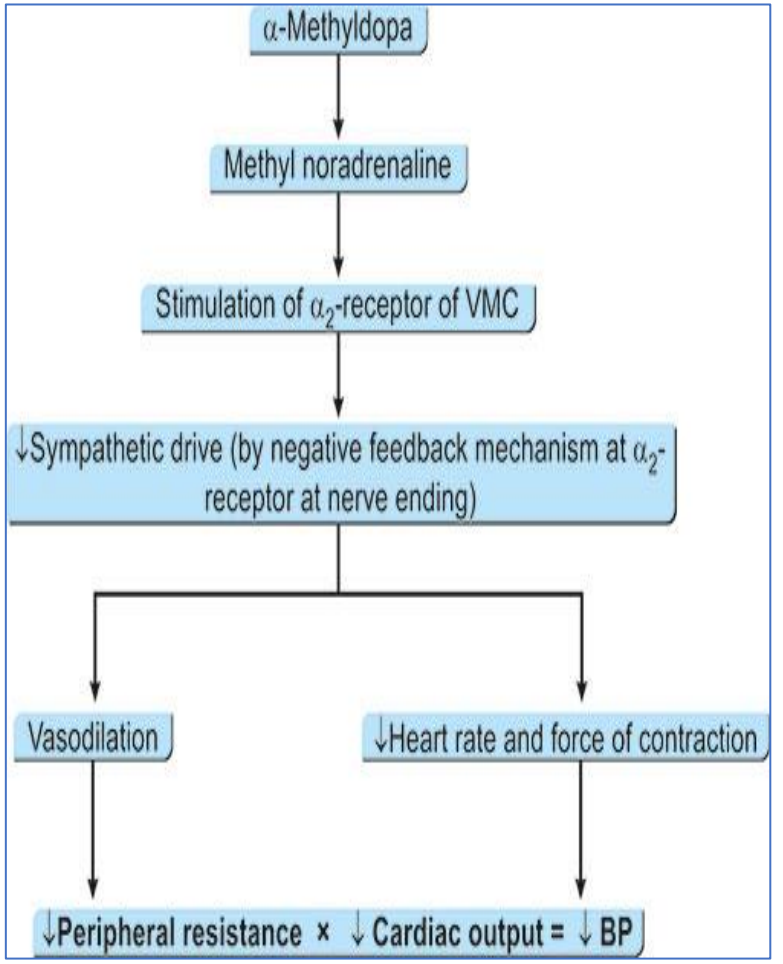
B. Methyldopa

Methyldopa is an **α2 agonist** that is converted to **methylnorepinephrine** centrally to **diminish** adrenergic outflow from the CNS.

The most common side effects of methyldopa are **sedation and drowsiness**.

Its use is **limited** due to **adverse effects** and the need for **multiple daily doses**.

It is mainly used for the management of HTN in **pregnancy**, where it has a record of **safety**.



10. VASODILATORS

The direct-acting smooth muscle relaxants, such as **Hydralazine & Minoxidil** are **not** used as **primary** drugs to treat HTN.

These vasodilators act by producing **relaxation** of vascular smooth muscle, primarily in **arteries** and **arterioles** resulting in **decreased** peripheral resistance and, therefore, blood pressure.

Both agents produce **reflex stimulation of the heart**, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption.

These actions may prompt **angina pectoris**, **MI**, or **HF** in predisposed individuals.

Vasodilators also **increase** plasma **renin** concentration, resulting in **sodium and water retention.**

HYPERTENSIVE EMERGENCY

- Hypertensive emergency is a **rare** but **life-threatening situation** characterized by:

1. Severe elevations in **blood pressure** (SBP/ DBP >180/120 mm Hg)
2. Evidence of impending or progressive **target organ damage** (for example, stroke, myocardial infarction).

- Note: A severe **elevation** in blood pressure **without** evidence of target organ damage is considered a **hypertensive urgency**.

HYPERTENSIVE EMERGENCY

- Hypertensive emergencies require **timely** blood pressure reduction with treatment administered **intravenously** to prevent or limit **target organ** damage.
- A variety of medications are used, including:

1. **CCBs** (nicardipine and clevidipine**)**
2. **Nitric oxide vasodilators** (nitroprusside and nitroglycerin)
3. **Adrenergic receptor antagonists** (phentolamine, esmolol, and labetalol)
4. **Vasodilator** hydralazine
5. **Dopamine agonist** fenoldopam

- Treatment is directed by the **type of target organ damage** present and/or **comorbidities** present.

RESISTANT HYPERTENSION

Resistant hypertension is defined as blood pressure that **remains elevated (above goal)** despite administration of an **optimal three-drug regimen** that includes a **diuretic**.

The most common **causes:**	**Poor compliance**
	Excessive ethanol intake
	Concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome)
	Concomitant medications (sympathomimetics, nonsteroidal anti-inflammatory drugs, or antidepressant medications)
	Insufficient dose and/or drugs
	Use of drugs with similar mechanisms of action

THANK YOU