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

Antihypertensives Drugs

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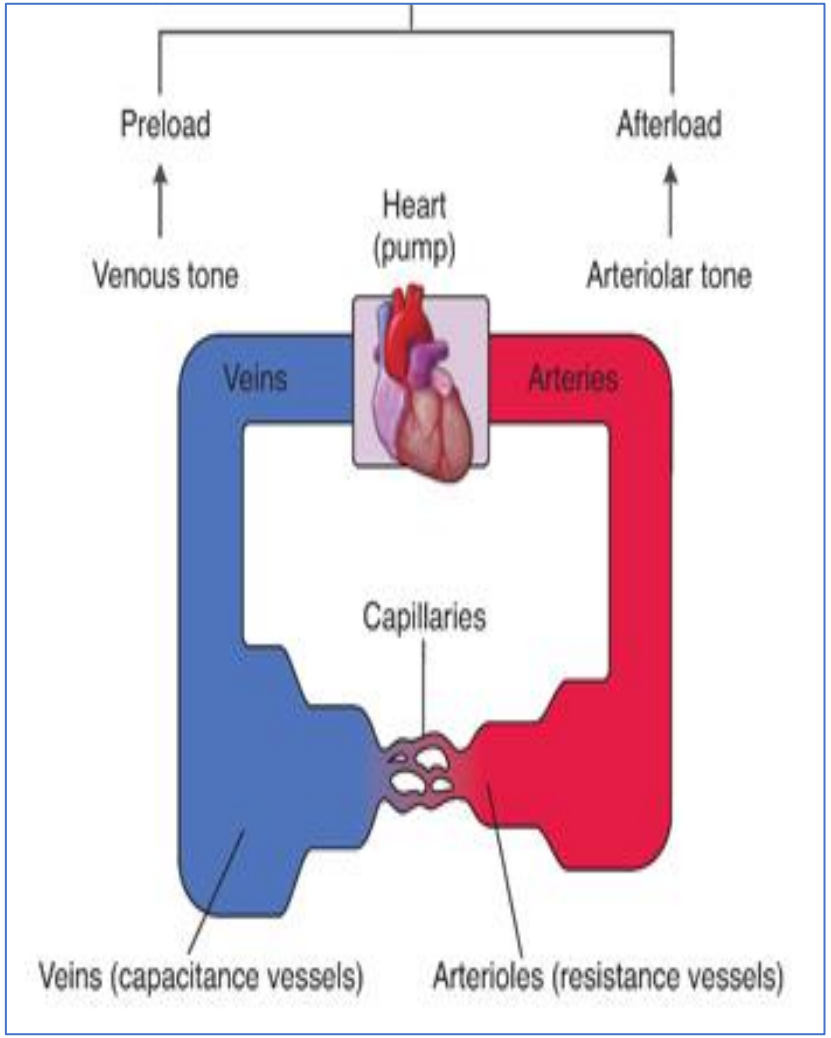
Overview

- Hypertension occurs when **systolic** blood pressure exceeds **130 mm Hg** or **diastolic** blood pressure exceeds **80 mm Hg** on at least two occasions.
- HTN results from **increased peripheral vascular** arteriolar smooth muscle tone, which leads to **increased arteriolar resistance** and **reduced capacitance** of the venous system.
- Elevated blood pressure is a common disorder, affecting approximately **30%** of adults in the United States.
- Although many patients have **no symptoms**, **chronic** HTN can lead to **heart disease** and **stroke**, the top two causes of death in the world.
- Hypertension is also an important **risk factor** in the development of **chronic kidney disease and heart failure**.



Overview

- 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

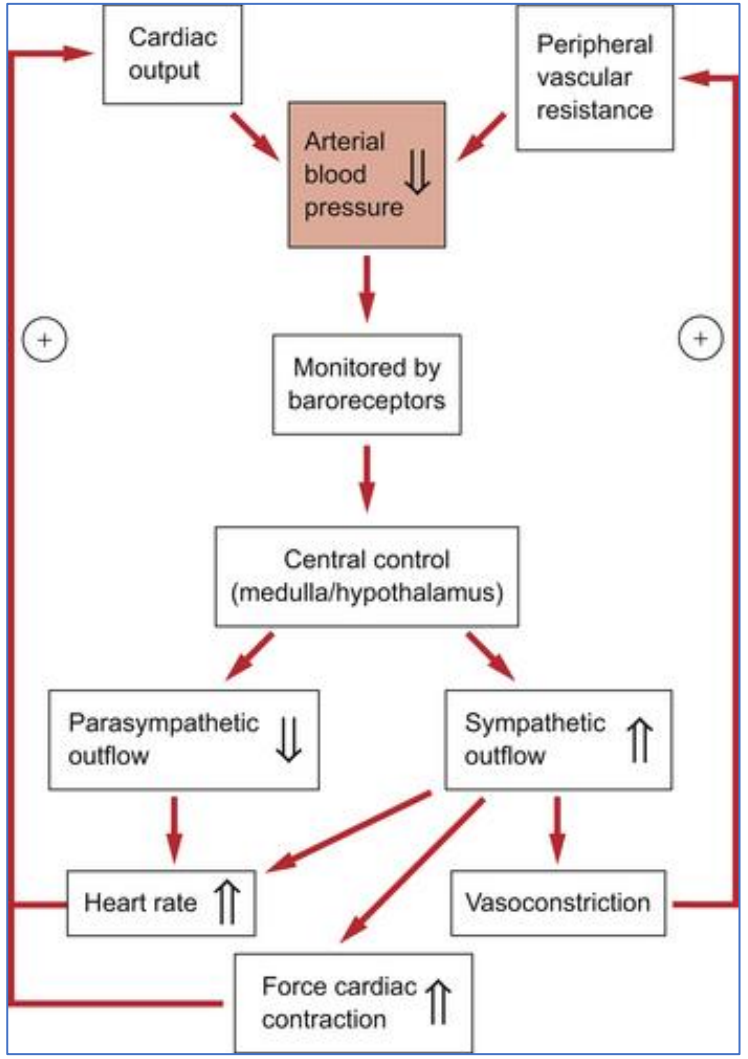
ETIOLOGY OF HYPERTENSION

- Although hypertension may occur **secondary** to other disease processes, more than **90%** of patients have **essential HTN** (HTN with no identifiable cause).
- A **family history** of hypertension increases the likelihood that an individual will develop hypertension.
- The **prevalence** of hypertension **increases** with **age** but decreases with **education** level.
- Non-Hispanic **blacks** have a **higher incidence** of HTN than do both non-Hispanic **whites** and Hispanic **whites**.
- Persons with **diabetes**, **obesity**, or **disability** status are all more likely to have hypertension than those without.
- In addition, **environmental** factors, such as a **stressful** lifestyle, high dietary intake of **sodium**, and **smoking**, may further predispose an individual to HTN.

MECHANISMS FOR CONTROLLING BLOOD PRESSURE

A. Baroreceptors and the sympathetic nervous system

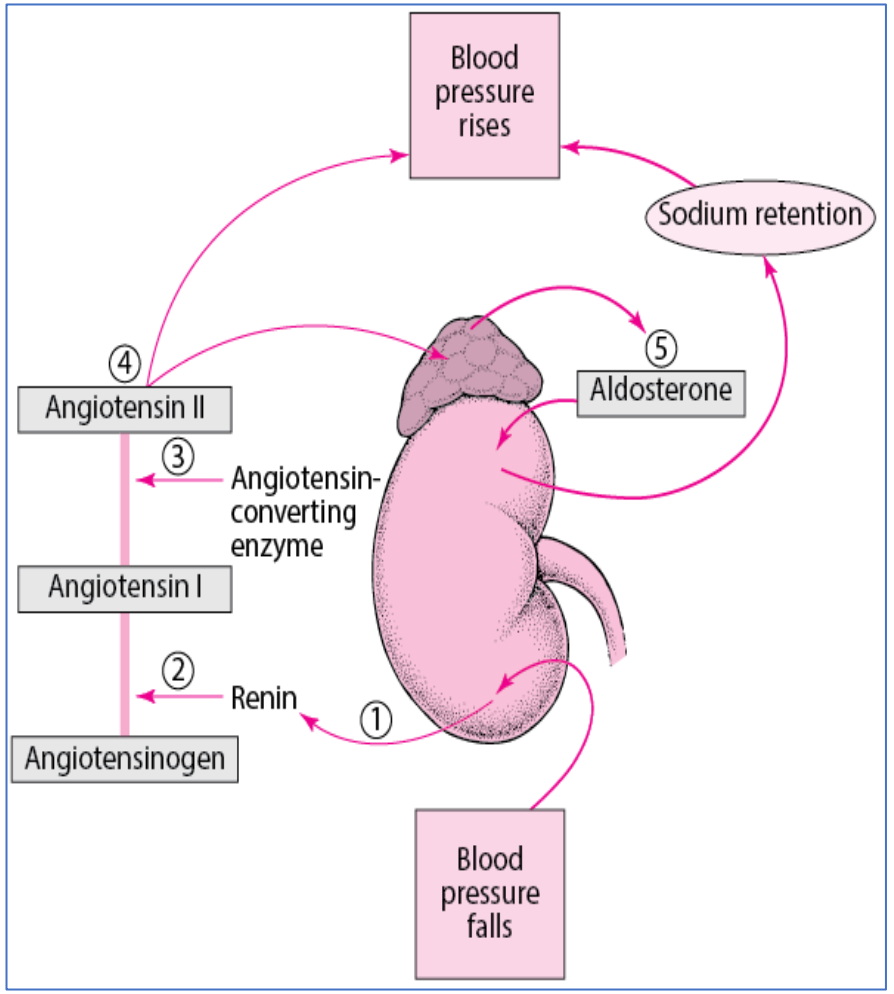
- **Baroreflexes** act by changing the activity of the **sympathetic** nervous system.
- Therefore, they are responsible for the **rapid**, **moment-to moment** regulation of blood pressure.
- A **fall** in blood pressure causes **pressure-sensitive neurons** (baroreceptors in the aortic arch and carotid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



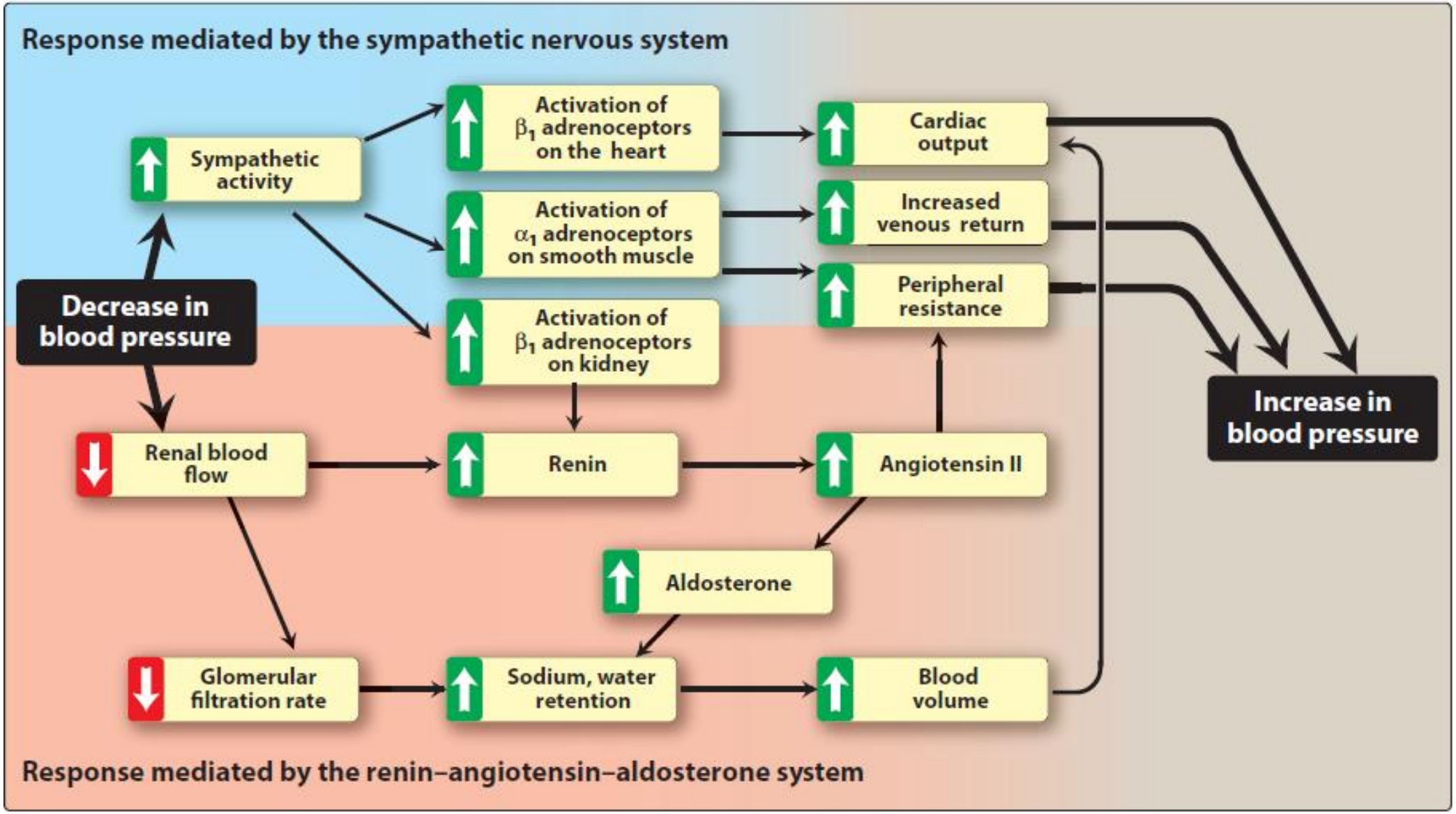
MECHANISMS FOR CONTROLLING BLOOD PRESSURE

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 to 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



TREATMENT STRATEGIES

- The **goal** of antihypertensive therapy is to **reduce cardiovascular and renal morbidity and mortality**.
- **Antihypertensive** therapy is **indicated** in case of **SBP** of **≥150** mm Hg or a **DBP** of **≥90** mm Hg for the general population at 60 years of age or older.
- For most patients, the blood pressure **goal** when treating hypertension is an **SBP < 130 mm Hg** and a **DBP < 80 mm Hg**.
- Current **recommendations** are to initiate therapy with a **thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker**.
- Each of the **antihypertensive** agents are roughly **equally effective** in lowering the BP; however, there is a wide interpatient variability as many patients respond to one drug but not to another, depending in part on patient-specific determinants such as **ethnicity, age, and concomitant diseases**.

TREATMENT STRATEGIES

A. Individualized care

- Hypertension may **coexist** with other diseases that can be **aggravated** by some of the antihypertensive drugs or that may **benefit** from the use of some antihypertensive drugs independent of blood pressure control.
- In addition to the choice of therapy, blood pressure goals may also be **individualized** based on concurrent **disease** states and **age**.
- **Elderly** patients may have **less** stringent goals (**<150/90 mm Hg**).
- In general, a **gradual** reduction in blood pressure is **desirable** in hypertensive patients, particularly in the elderly patients, but the **target** control level should be achieved within a **few weeks** in high-risk patients, such as those with **grade III HTN** and **multiple risk factors**.

TREATMENT STRATEGIES

B. Rational drug combinations

- A fundamental requirement of any useful **combination** is evidence that it lowers blood pressure to a greater extent than **monotherapy** with its individual components.
- The main **objectives** of drug combinations is to:

1. Achieve additional blood pressure reduction by using drugs that act by different mechanisms
2. Minimization of the adverse effects
3. Block-opposing effects on the homeostatic mechanism
4. Block-predictive adverse effects
5. Permits the use of lower dose (less adverse effects)

- Although the blood pressure–reducing ability of antihypertensive drug classes and individual agents varies by only a few mm Hg, the effect of two agents in combination varies considerably.
- Thus, combining an ACE inhibitor and a diuretic produces fully additive blood pressure reduction whereas the same ACE inhibitor added to an ARB results in additional blood pressure reduction of only 2–3 mm Hg.

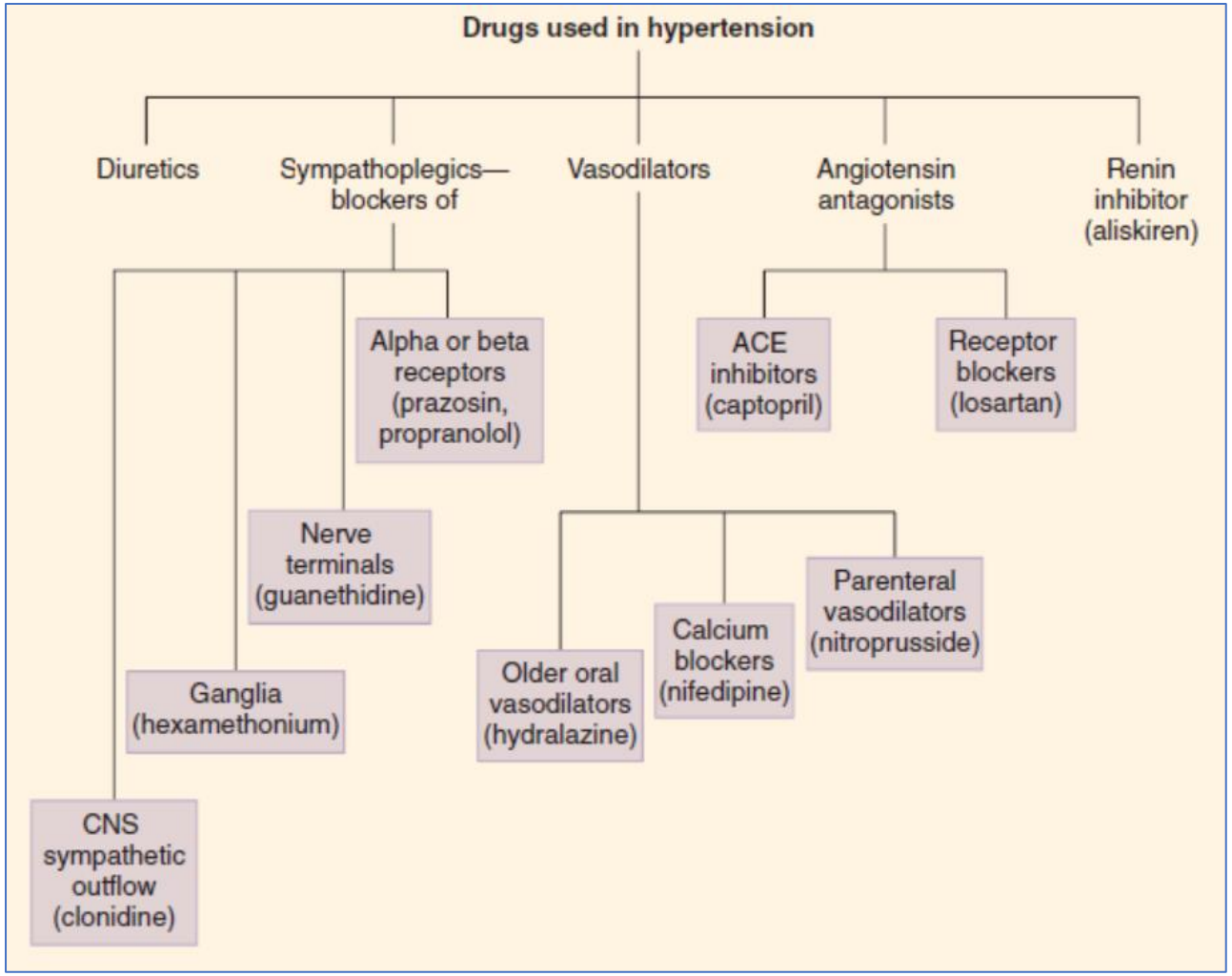
TREATMENT STRATEGIES

C. Patient compliance in antihypertensive therapy

- **Lack** of patient **compliance** is the most common reason for **failure** of antihypertensive therapy.
- The **hypertensive** patient is usually **asymptomatic** and is diagnosed by routine screening before the occurrence of overt end-organ damage.
- Thus, therapy is generally directed at **preventing** future disease sequelae rather than **relieving** current discomfort.
- The **adverse effects** associated with hypertensive therapy may influence the patient more than the future benefits.
- For example, **β-blockers** can cause **sexual dysfunction** in males, which may prompt **discontinuation** of therapy.
- Thus, it is important to **enhance** compliance by selecting a drug regimen that **reduces adverse effects** and also minimizes the **number of doses** required daily.
- Combining two drug classes in a single pill, at a fixed-dose combination, has been shown to improve patient compliance and the number of patients achieving goal blood pressure.

TREATMENT STRATEGIES

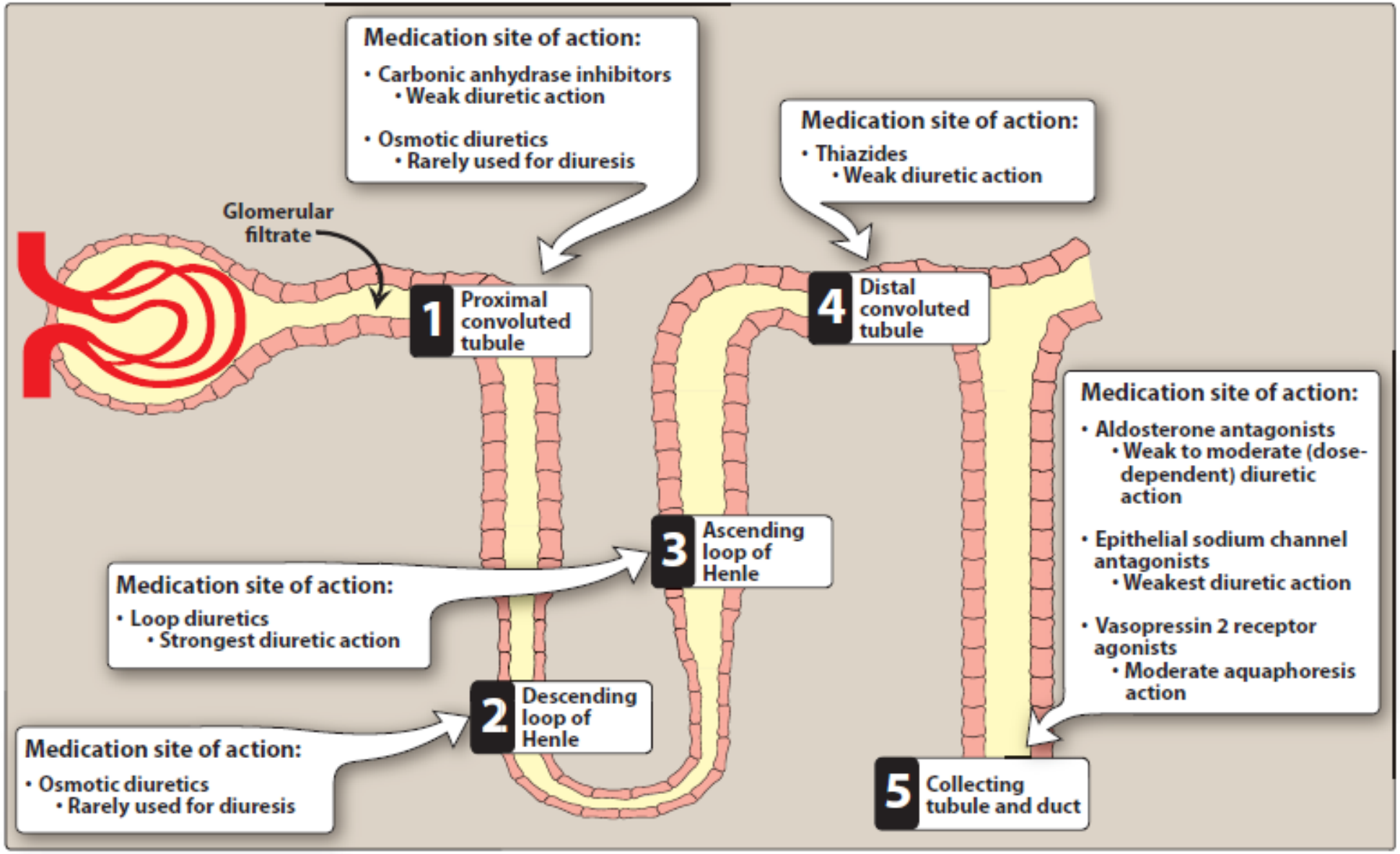
- **Antihypertensive drugs**
  1. **Diuretics**
  2. **β Blockers**
  3. **ACE inhibitors**
  4. **Angiotensin II receptor blockers**
  5. **Renin inhibitor**
  6. **Calcium channel blockers**
  7. **α-adrenoceptor-blocking agents**
  8. **α / β Adrenoceptor-blocking agents**
  9. **Centrally acting adrenergic drugs**
  10. **Vasodilators**



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, and effective in preventing stroke, myocardial infarction, and heart failure.
- Routine serum **electrolyte monitoring** should be done for all patients receiving diuretics.

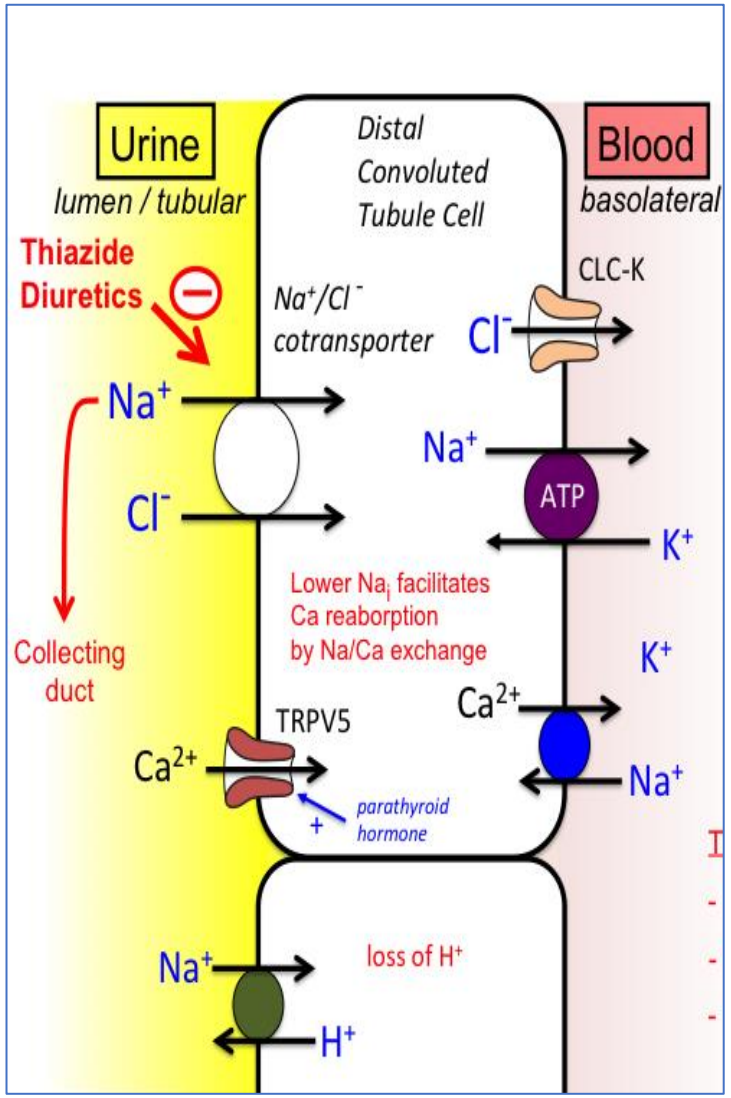
DIURETICS


Medication site of action:
• Carbonic anhydrase inhibitors
• Weak diuretic action
• Osmotic diuretics
• Rarely used for diuresis
Glomerular filtrate
1 Proximal convoluted tubule
Medication site of action:
• Thiazides
• Weak diuretic action
4 Distal convoluted tubule
Medication site of action:
• Aldosterone antagonists
• Weak to moderate (dose-dependent) diuretic action
• Epithelial sodium channel antagonists
• Weakest diuretic action
• Vasopressin 2 receptor agonists
• Moderate aquaphoresis action
Medication site of action:
• Loop diuretics
• Strongest diuretic action
3 Ascending loop of Henle
2 Descending loop of Henle
Medication site of action:
• Osmotic diuretics
• Rarely used for diuresis
5 Collecting tubule and duct

DIURETICS

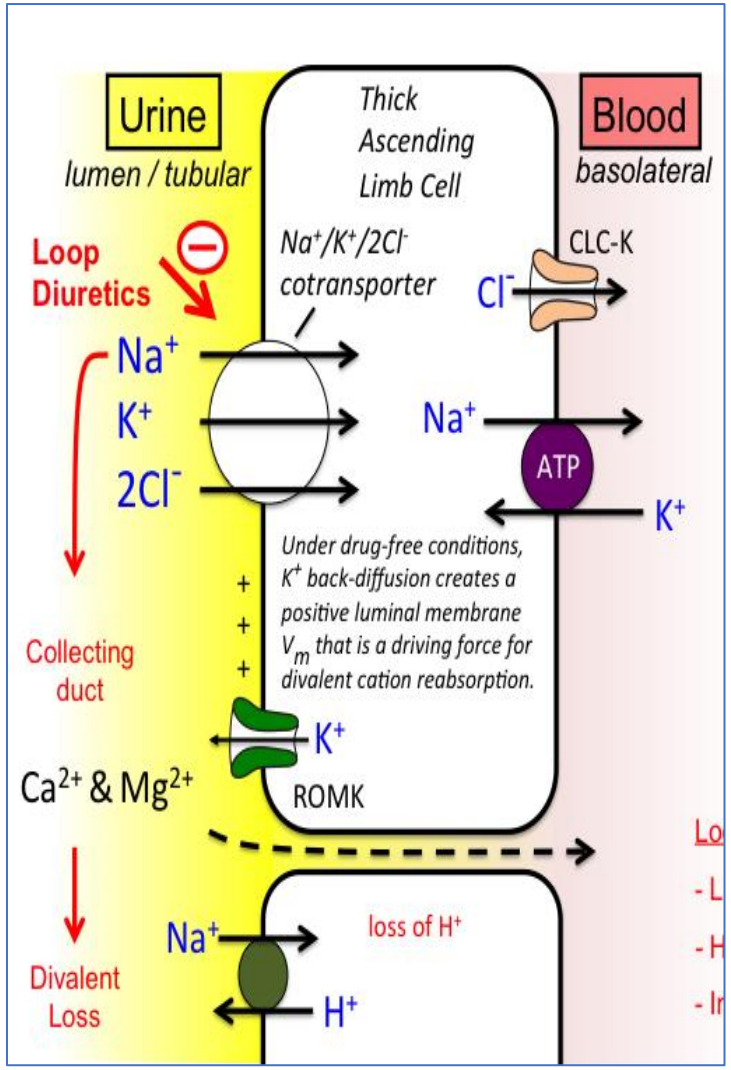
A. Thiazide diuretics

- Thiazide diuretics, such as **hydrochlorothiazide** and **chlorthalidone**, lower blood pressure initially **by increasing sodium and water excretion**.
- This causes a **decrease** in **extracellular volume**, resulting in a decrease in cardiac output and renal blood flow.
- With **long-term treatment**, plasma volume approaches a normal value, but a **hypotensive effect persists** that is related to a decrease **in peripheral resistance**.
- Thiazides are useful in **combination** therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics.
- With the **exception** of **metolazone**, thiazide diuretics are **not effective** in patients with inadequate kidney function (estimated **GFR< 30 mL/min/m2**). Loop diuretics may be required in these patients.
- Thiazide diuretics can induce **hypokalemia**, **hyperuricemia** and, to a lesser extent, **hyperglycemia** in some patients.



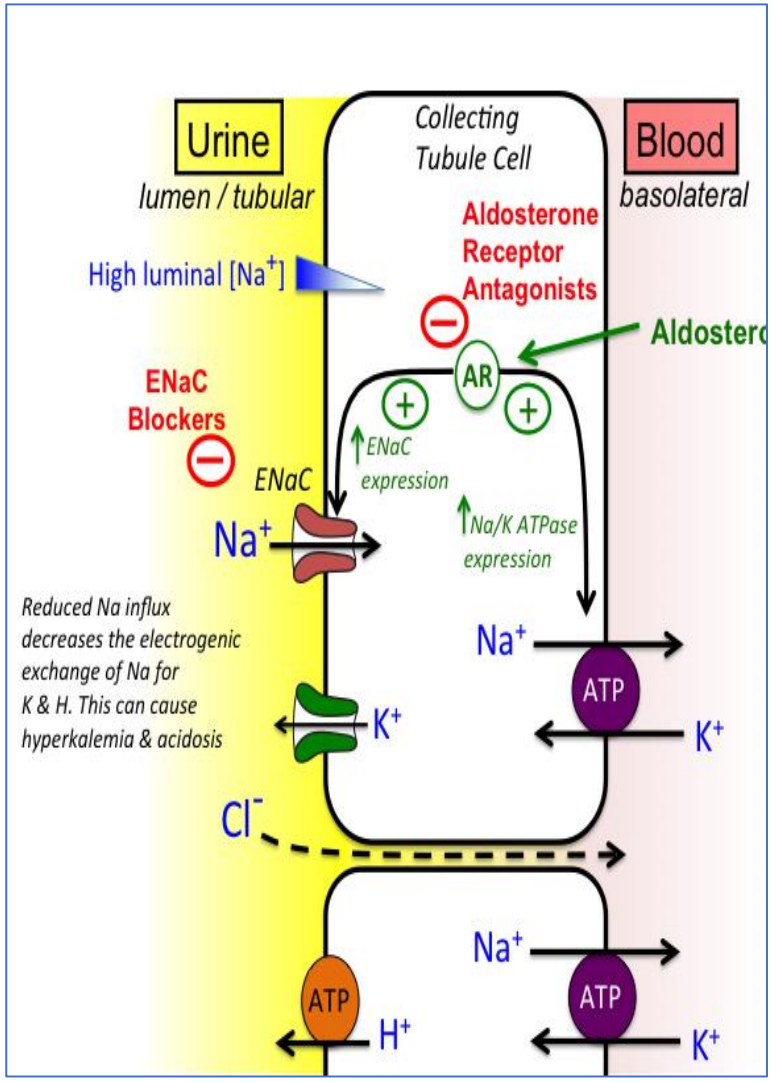
B. Loop diuretics

- The loop diuretics (**furosemide, torsemide, bumetanide, and ethacrynic acid**) act promptly by **blocking sodium and chloride reabsorption** in the kidneys, even in patients with **poor renal function** or those who have **not responded** to thiazide diuretics.
- Loop diuretics cause **decreased renal vascular resistance** and **increased renal blood flow**.
- **Like** thiazides, they can cause **hypokalemia**. However, **unlike** thiazides, loop diuretics increase **the Ca2+ content of urine**, whereas thiazide diuretics decrease it.
- These agents are rarely used alone to treat hypertension, but they are commonly used to manage symptoms of heart failure and edema.

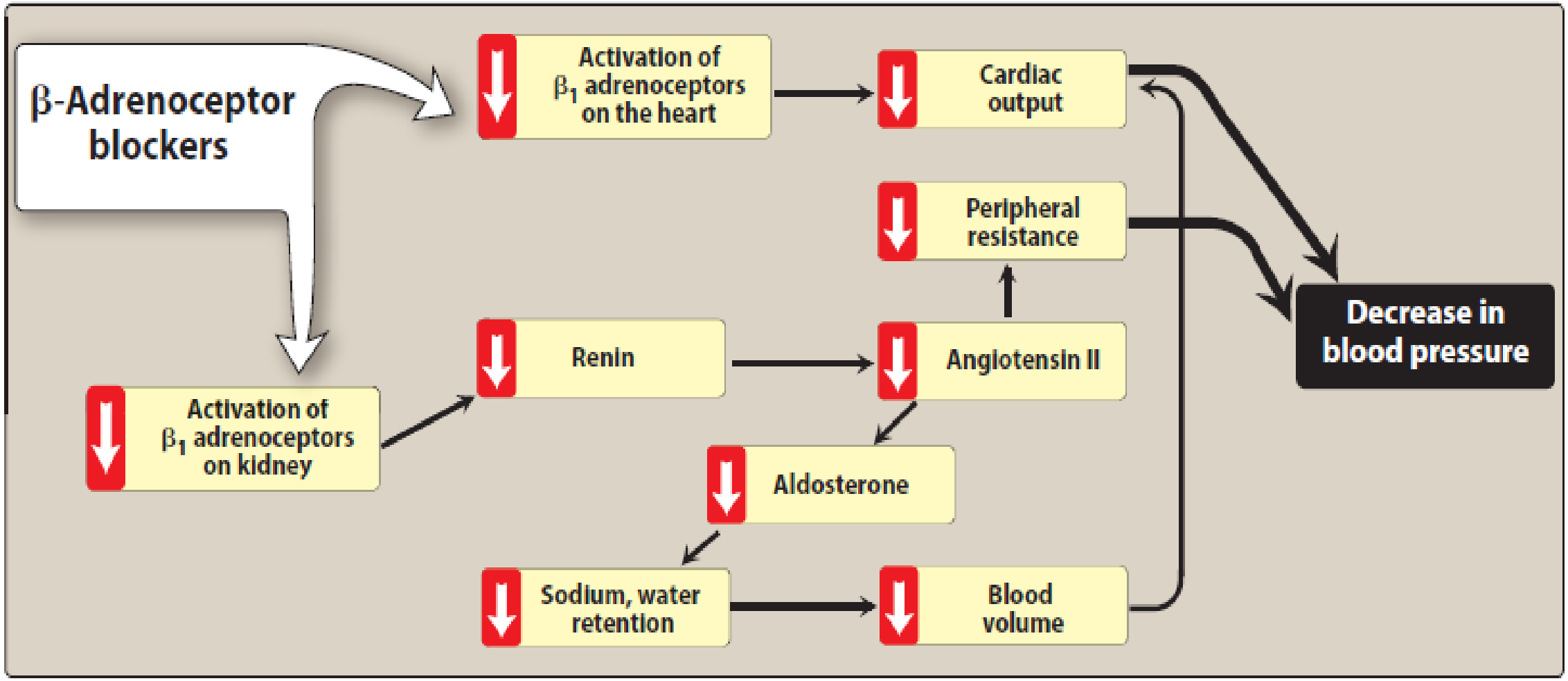


C. Potassium-sparing diuretics

- **Amiloride** and **triamterene** (inhibitors of epithelial sodium transport at the late distal and collecting ducts) as well as **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.



β-ADRENOCEPTOR–BLOCKING AGENTS



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.
- The **selective** β-blockers may be administered **cautiously** to hypertensive patients who also have **asthma**.
- The **nonselective** β-blockers, such as propranolol and 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**.

β-ADRENOCEPTOR–BLOCKING AGENTS

B. Therapeutic uses

- The primary therapeutic benefits of β-blockers are seen in **hypertensive patients** with concomitant heart disease, such as **supraventricular tachyarrhythmia** (for example, atrial fibrillation), **previous MI, angina pectoris,** and **chronic heart failure**.
- Conditions that **discourage** the use of β-blockers include reversible bronchospastic disease such as **asthma**, second- and third-degree **heart block**, and severe **peripheral vascular disease**.

C. Pharmacokinetics

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

β-ADRENOCEPTOR–BLOCKING AGENTS

D. Adverse effects

1. Common effects:

- The β-blockers may cause **bradycardia**, **hypotension**, and CNS side effects such as fatigue, lethargy, and insomnia.
- The β-blockers may decrease **libido** and cause erectile dysfunction, which can severely reduce patient compliance.

2. Alterations in serum lipid patterns:

- Non-cardioselective β-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.

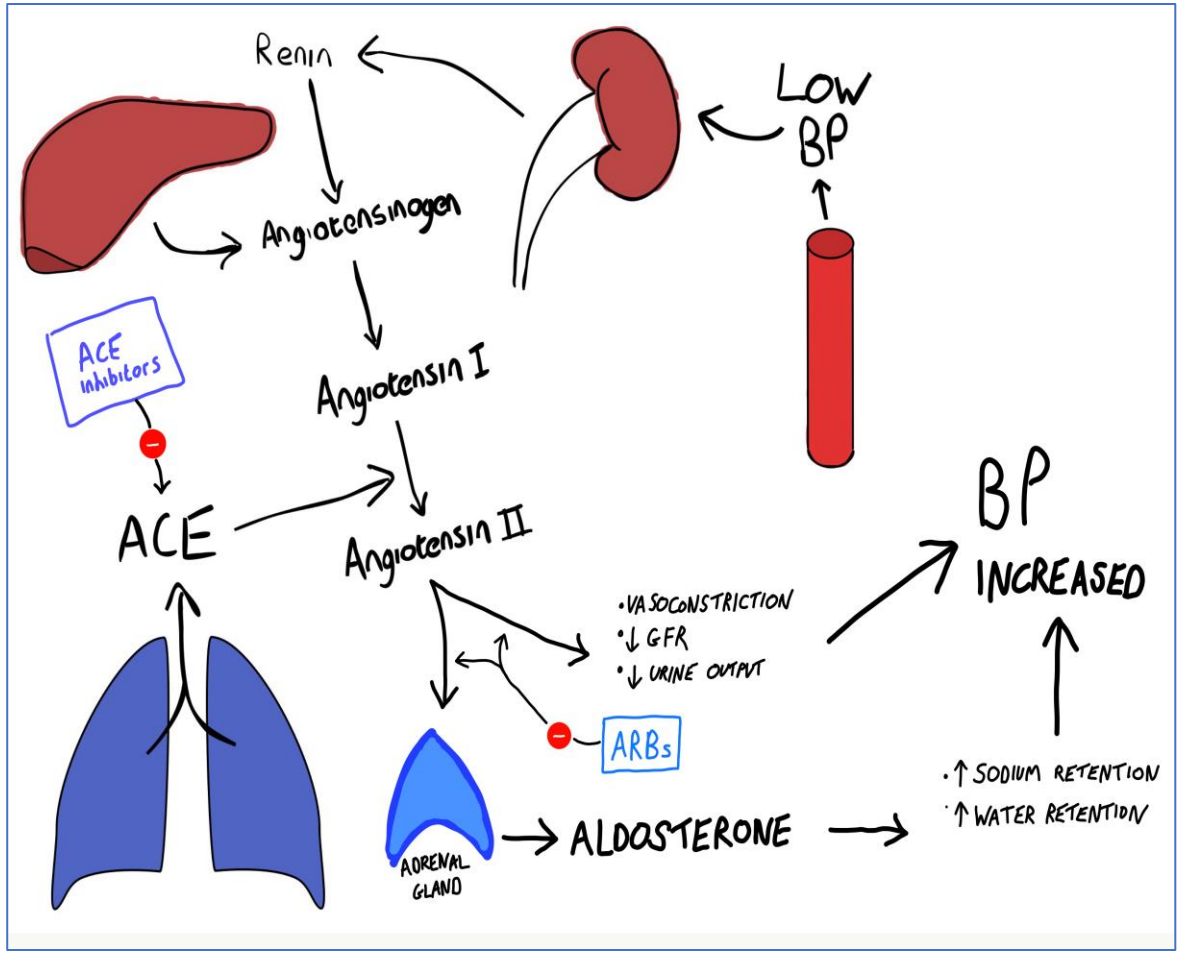
3. Drug withdrawal:

- Abrupt **withdrawal** may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease.
- Therefore, these drugs must be tapered over a **few weeks** in patients with hypertension and ischemic heart disease.

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:

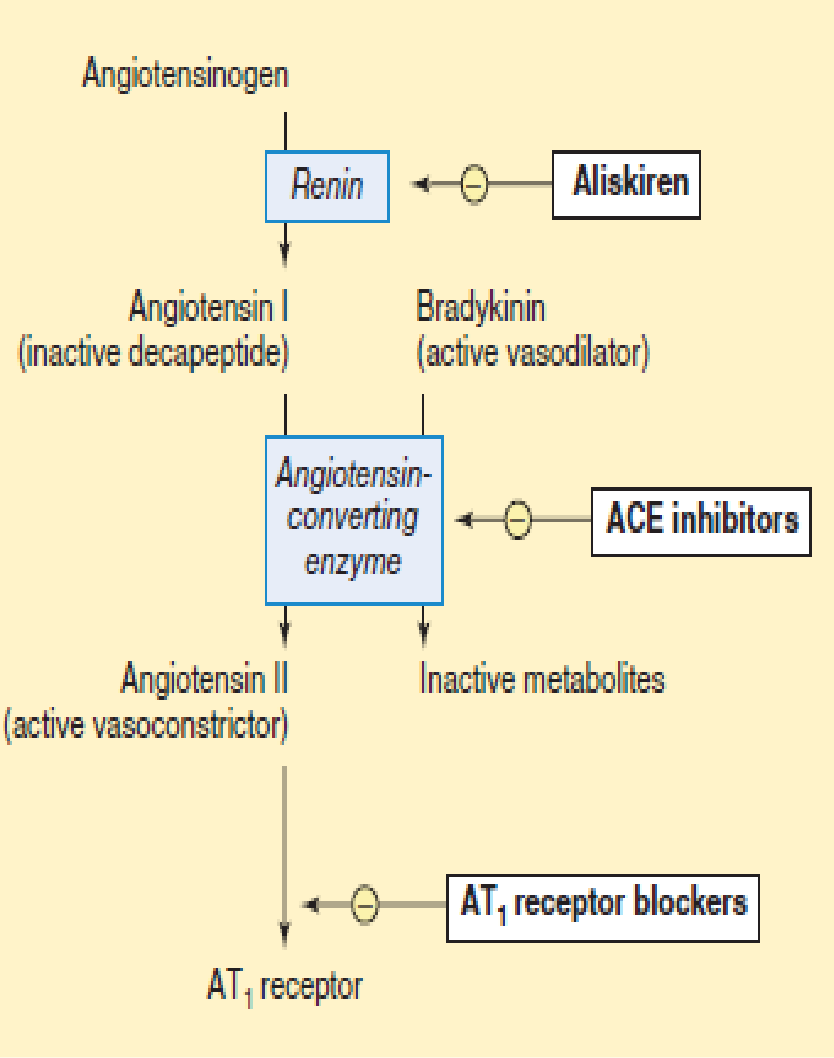
1. High coronary disease risk
2. History of diabetes
3. Stroke, heart failure, & MI
4. Chronic kidney disease



ACE INHIBITORS

A. Actions

- The ACE inhibitors lower blood pressure by **reducing peripheral vascular resistance without** reflexively increasing cardiac output, heart rate, or contractility.
- 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 increases the production of **nitric oxide and prostacyclin** by the blood vessels, which are potent **vasodilators**.
- ACE inhibitors **decrease angiotensin II** and **increase bradykinin levels**.
- **Vasodilation** of both arterioles and veins occurs as a result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin).
- By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of **aldosterone**, resulting in **decreased sodium and water retention**.
- ACE inhibitors reduce **both cardiac preload and afterload**, thereby decreasing cardiac work.



ACE INHIBITORS

B. Therapeutic uses

- Like the ARBs, ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with **diabetic nephropathy**.
- ACE inhibitors are a standard in the care of a patient following **MI** and first-line agents in the treatment of patients with **systolic dysfunction**.
- Chronic treatment with ACE inhibitors achieves sustained blood **pressure reduction**, regression of **left ventricular hypertrophy**, and prevention of **ventricular remodeling** after MI.
- ACE inhibitors are **first-line** drugs for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease.

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, so these agents may be preferred in patients with severe **hepatic impairment**.
- **Fosinopril** is the only ACE inhibitor that is **not** eliminated primarily by the **kidneys** and does **not require** dose adjustment in patients with **renal impairment**.
- **Enalaprilat** is the only drug in this class available **intravenously**.

ACE INHIBITORS

D. Adverse effects

- **Common** side effects include dry cough, rash, fever, altered taste, hypotension (in hypovolemic states), and hyperkalemia.
- The dry cough, which occurs in up to **10% of patients** (more frequently in women), is thought to be due to increased levels of **bradykinin and substance P** in the pulmonary tree and resolves within a few days of **discontinuation**.
- **Angioedema** is a rare but potentially life-threatening reaction that may also be due to increased 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.
- However, an increase in serum creatinine of up **to 30% above baseline is acceptable** and by itself does not warrant discontinuation of treatment.
- ACE inhibitors can induce **fetal malformations** and should not be used by **pregnant** women.

ANGIOTENSIN II RECEPTOR BLOCKERS

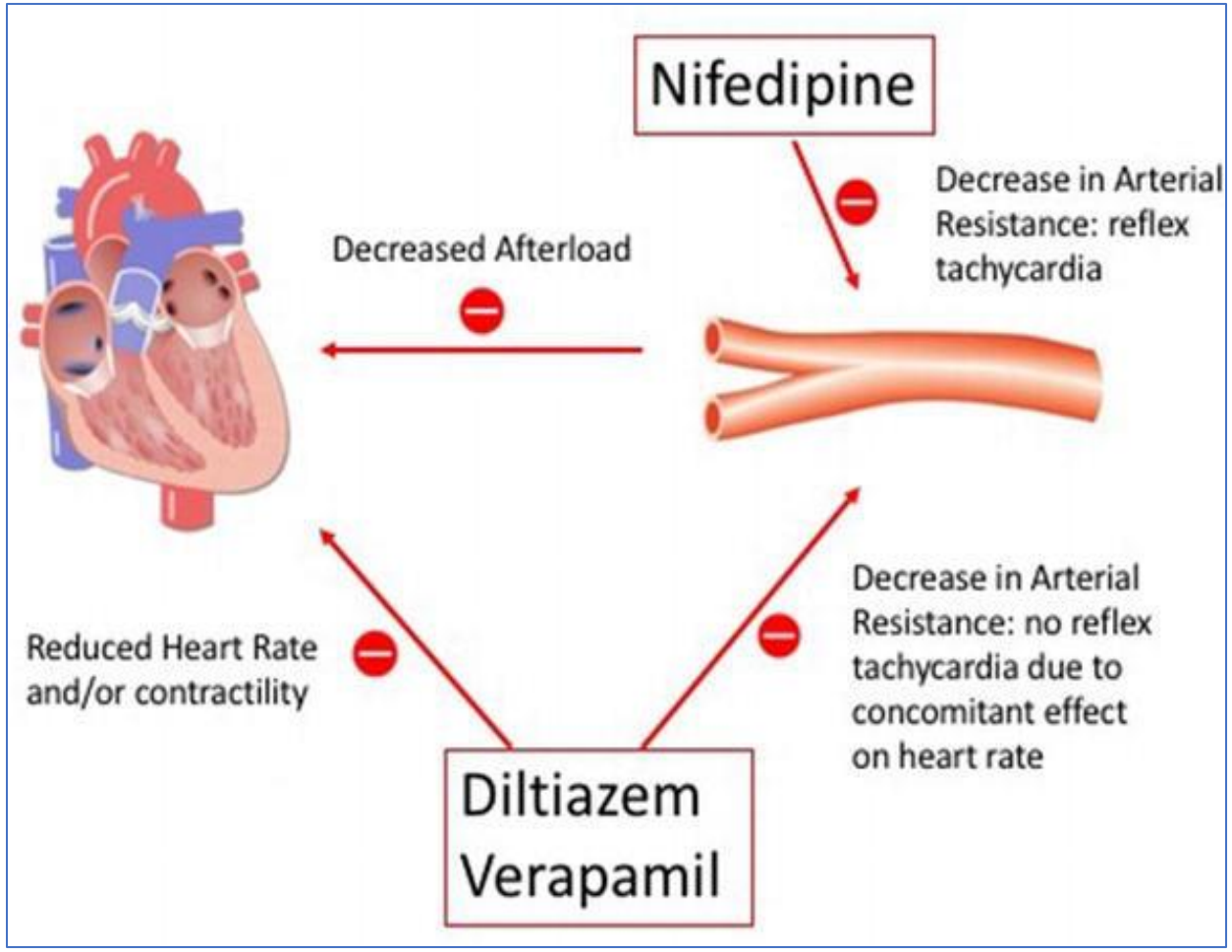
- The ARBs, such as **losartan** and **irbesartan**, are alternatives to the ACE inhibitors.
- These drugs block the **AT1 receptors**, decreasing the activation of AT1 receptors by angiotensin II.
- Their pharmacologic effects are similar to those of ACE inhibitors in that they produce **arteriolar** and **venous** dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention
- 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**
- Adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased.
- ARBs should **not be combined** with an ACE inhibitor for the treatment of hypertension due to similar mechanisms and adverse effects.
- These agents are also **teratogenic** and should not be used by pregnant women.

RENIN INHIBITOR

- A selective renin inhibitor, **aliskiren**, is available for the treatment of hypertension.
- 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**.

CALCIUM CHANNEL BLOCKERS

- Calcium channel blockers are a recommended treatment option in hypertensive patients with **diabetes or angina**.
- **High doses** of short-acting calcium channel blockers should be **avoided** because of the increased risk of **MI** due to excessive vasodilation and marked **reflex cardiac stimulation**.



CALCIUM CHANNEL BLOCKERS

A. Classes of calcium channel blockers

1. Diphenylalkylamines:

- **Verapamil** is the only member of this class that is available.
- Verapamil is the **least selective** of any calcium channel blocker and has significant effects on **both** cardiac and vascular smooth muscle cells.
- It is also used to **treat angina** and **SVT** and to prevent **migraine** and **cluster headaches**.

2. Benzothiazepines:

- **Diltiazem** is the only member of this class that is currently approved.
- Like verapamil, diltiazem affects **both** cardiac and vascular smooth muscle cells, but it has a less pronounced **negative inotropic** effect on the heart compared to that of verapamil.
- Diltiazem has a favorable side effect profile.

CALCIUM CHANNEL BLOCKERS

3. Dihydropyridines:

- This class of CCB includes **nifedipine** (the prototype), **amlodipine**, **felodipine**, **isradipine**, **nicardipine**, and **nisoldipine**.
- These agents differ in pharmacokinetics, approved uses, and drug interactions.
- **All dihydropyridines** have a much greater **affinity** for **vascular calcium channels** than for calcium channels in the heart.
- They are, therefore, particularly beneficial in treating **hypertension**.
- The dihydropyridines have the **advantage** in that they show **little interaction** with other cardiovascular drugs, such as digoxin or warfarin, which are often used concomitantly with CCBs.

CALCIUM CHANNEL BLOCKERS

B. Actions

- The **intracellular** concentration of **calcium** plays an important role in maintaining the **tone** of smooth muscle and in the **contraction** of the myocardium.
- Calcium enters muscle cells through special **voltage-sensitive calcium channels**.
- This triggers **release** of calcium from the **sarcoplasmic reticulum** and **mitochondria**, which further increases the **cytosolic** level of calcium.
- Calcium channel **antagonists** block the **inward** movement of calcium by binding to **L-type calcium channels** in the **heart** and in smooth muscle of the coronary and peripheral **arteriolar vasculature**.
- This causes vascular smooth muscle to **relax**, dilating mainly **arterioles**.
- Calcium channel blockers do **not dilate veins**.

CALCIUM CHANNEL BLOCKERS

C. 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 hypertensive 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**.

D. 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.

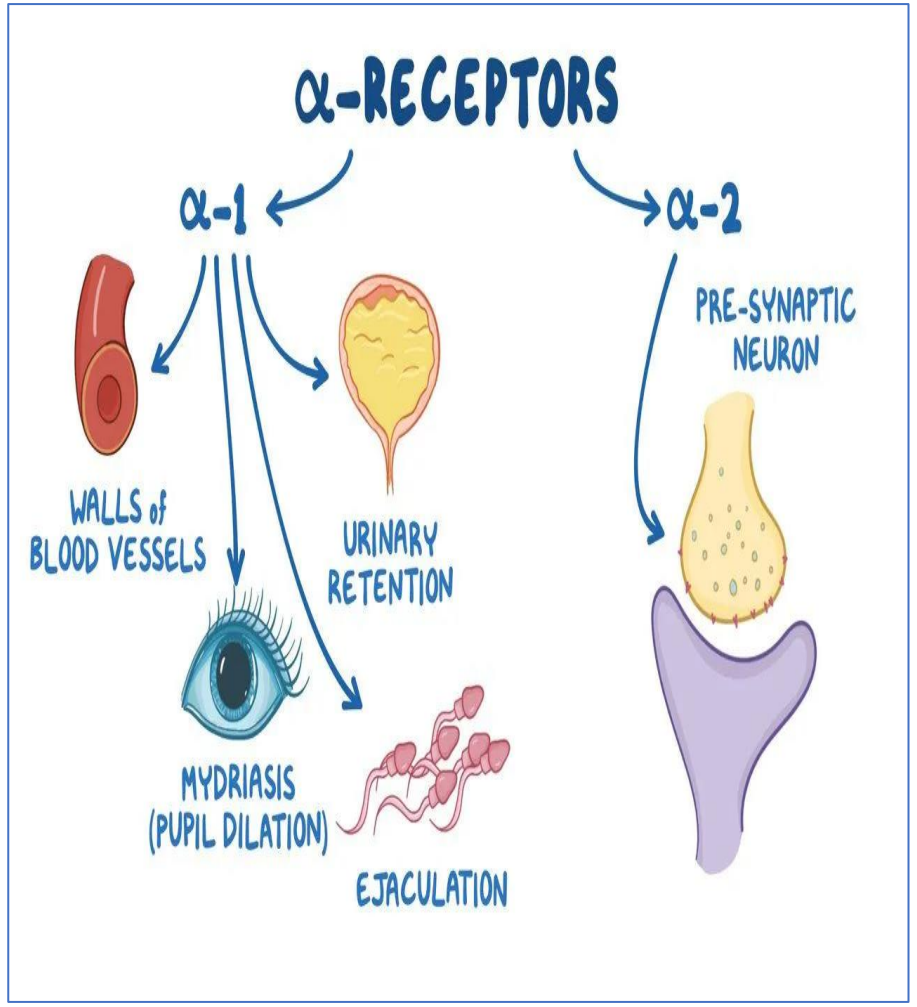
CALCIUM CHANNEL BLOCKERS

E. 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 heart failure or with atrioventricular block due to their **negative inotropic** (force of cardiac muscle contraction) and **dromotropic** (velocity of conduction) 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**.

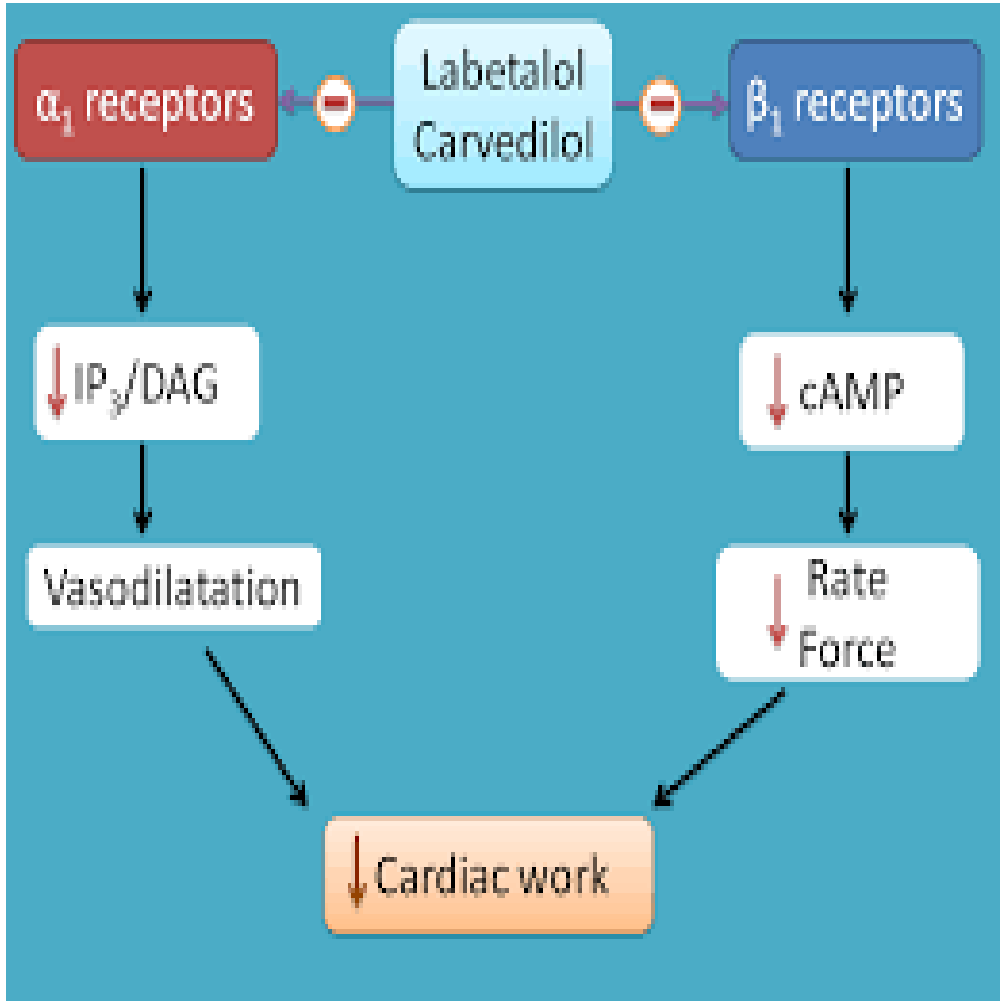
α-ADRENOCEPTOR–BLOCKING AGENTS

- **Prazosin, doxazosin, and terazosin** produce a competitive block of α1-adrenoceptors.
- They **decrease** peripheral vascular resistance and lower arterial blood pressure by causing **relaxation** of **both arterial** and **venous** smooth muscle.
- These drugs cause only **minimal changes** in cardiac output, renal blood flow, and glomerular filtration rate.
- **Reflex tachycardia** and **postural hypotension** often occur at the onset of treatment and with dose increases, requiring slow titration of the drug in divided doses.
- Due to weaker outcome data and their side effect profile, α-blockers are **no longer** recommended **as initial treatment** for hypertension but may be used for refractory cases.



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**.



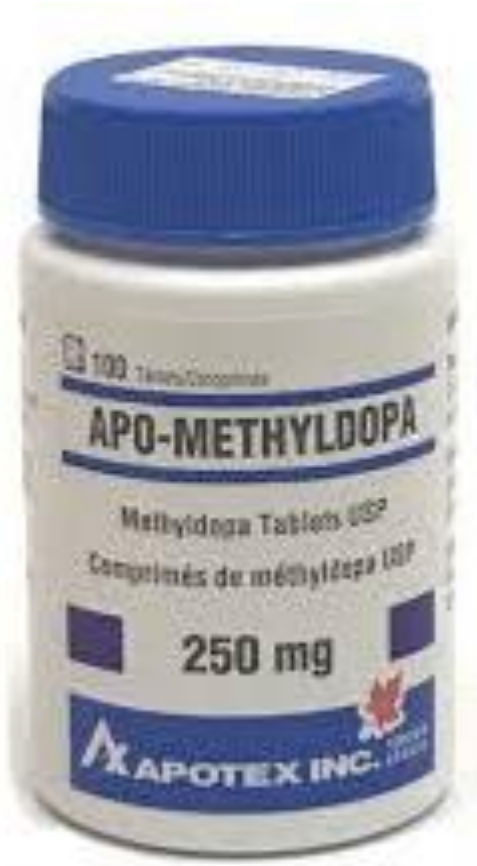
CENTRALLY ACTING ADRENERGIC DRUGS

A. Clonidine

- Clonidine acts **centrally** as an **α2 agonist** to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery.
- This leads to **reduced** total peripheral resistance and **decreased** blood pressure.
- Clonidine is used primarily for the treatment of **hypertension** that has **not responded** adequately to treatment with two or more drugs.
- Clonidine does **not decrease renal blood flow or glomerular filtration** and, therefore, is useful in the treatment of hypertension complicated by **renal disease**.
- Clonidine is absorbed well after **oral** administration and is excreted by the **kidney**. It is also available in a **transdermal patch**.
- Adverse effects include **sedation**, **dry mouth**, and **constipation**.
- **Rebound hypertension** occurs following abrupt withdrawal of clonidine, therefore, it should be withdrawn slowly if discontinuation is required.

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.



VASODILATORS

- The direct-acting smooth muscle relaxants, such as **hydralazine** (release of NO from endothelial cells) and **minoxidil** (potassium **channel opener) 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.

VASODILATORS

- These **undesirable** side effects can be blocked by **concomitant** use of a **diuretic** and a **β-blocker**.
- For example, **hydralazine** is almost always administered in combination with a **β-blocker**, such as propranolol, metoprolol, or atenolol (to balance the reflex tachycardia) and a **diuretic** (to decrease sodium retention).
- Hydralazine is an accepted medication for controlling blood pressure in **pregnancy-induced HTN**.
- Adverse effects of hydralazine include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina. A **lupus-like syndrome** can occur with high dosages, but it is reversible upon discontinuation of the drug.
- Minoxidil treatment causes **hypertrichosis** (the growth of body hair). This drug is used topically to treat male pattern baldness.

HYPERTENSIVE EMERGENCY

- Hypertensive emergency is a **rare** but **life-threatening situation** characterized by severe elevations in **blood pressure** (SBP >180 mm Hg or DBP> 120 mm Hg) with 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 emergencies require **timely** blood pressure reduction with treatment administered **intravenously** to prevent or limit target organ damage.
- A variety of medications are used, including **CCBs** (nicardipine and clevidipine**), nitric oxide vasodilators** (nitroprusside and nitroglycerin), **adrenergic receptor antagonists** (phentolamine, esmolol, and labetalol), the **vasodilator** hydralazine, and the **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 of resistant hypertension are:

1. Poor compliance
2. Excessive ethanol intake
3. Concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome)
4. Concomitant medications (sympathomimetics, nonsteroidal anti-inflammatory drugs, or antidepressant medications)
5. Insufficient dose and/or drugs
6. Use of drugs with similar mechanisms of action

COMBINATION THERAPY

- **Combination** therapy with **separate agents** or a **fixed-dose combination pill** may lower blood pressure **more quickly** with **minimal adverse effects**.
- **Initiating** therapy with **two antihypertensive** drugs should be considered in patients with blood pressures that are more than **20/10 mm Hg** above the goal.
- A variety of **combination** formulations of the various pharmacologic classes are available to increase the ease of patient adherence to treatment regimens that require multiple medications to achieve the blood pressure goal.

Thank You For Your Attention