➢ Antihypertensive drugs

Lecture 8

College of Pharmacy

By:

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➢ Antihypertensive drugs

- Hypertension results from **increased peripheral vascular arteriolar smooth muscle tone**, which **leads to increased arteriolar resistance** and **reduced capacitance of the venous system.**
- **Chronic hypertension** can **lead to heart disease, stroke and chronic kidney disease.**
- Effective pharmacologic lowering of blood pressure **prevents the damage to blood vessels and reduces the morbidity and mortality rate.**

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Elevated	120–129	or	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90

Figure 1: Classification of blood pressure.

DIURETICS

Amiloride MIDAMOR
Bumetanide BUMEX
Chlorthalidone GENERIC ONLY
Eplerenone INSPRA
Ethacrynic acid EDECRIN
Furosemide LASIX
Hydrochlorothiazide MICROZIDE
Indapamide GENERIC ONLY
Metolazone GENERIC ONLY
Spironolactone ALDACTONE
Triamterene DYRENIUM
Torsemide DEMADEX

β-BLOCKERS

Acebutolol GENERIC ONLY
Atenolol TENORMIN
Betaxolol GENERIC ONLY
Bisoprolol GENERIC ONLY
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Pindolol GENERIC ONLY
Propranolol INDERAL LA, INNOPRAN XL

ACE INHIBITORS

Benazepril LOTENSIN
Captopril GENERIC ONLY
Enalapril VASOTEC
Fosinopril GENERIC ONLY
Lisinopril PRINIVIL, ZESTRIL
Moexipril GENERIC ONLY
Quinapril ACCUPRIL
Perindopril GENERIC ONLY
Ramipril ALTACE
Trandolapril GENERIC ONLY

ANGIOTENSIN II RECEPTOR BLOCKERS

Azilsartan EDARBI
Candesartan ATACAND
Eprosartan GENERIC ONLY
Irbesartan AVAPRO
Losartan COZAAR
Olmesartan BENICAR
Telmisartan MICARDIS
Valsartan DIOVAN

RENIN INHIBITORS

Aliskiren TEKTURNA

CALCIUM CHANNEL BLOCKERS

Amlodipine NORVASC
Clevidipine CLEVIPREX
Diltiazem CARDIZEM, CARTIA, TIAZAC
Felodipine GENERIC ONLY
Isradipine GENERIC ONLY
Nicardipine CARDENE
Nifedipine ADALAT, PROCARDIA
Nisoldipine SULAR
Verapamil CALAN, VERELAN

α-BLOCKERS

Doxazosin CARDURA
Prazosin MINIPRESS
Terazosin GENERIC ONLY

OTHERS

Clonidine CATAPRES, DURACLON
Fenoldopam CORLOPAM
Hydralazine GENERIC ONLY
Methyldopa GENERIC ONLY
Minoxidil GENERIC ONLY
Nitroprusside NIPRIDE, NITROPRESS

Figure 2: Summary of antihypertensive drugs. ACE = angiotensin converting enzyme

Mechanisms for Controlling Blood Pressure

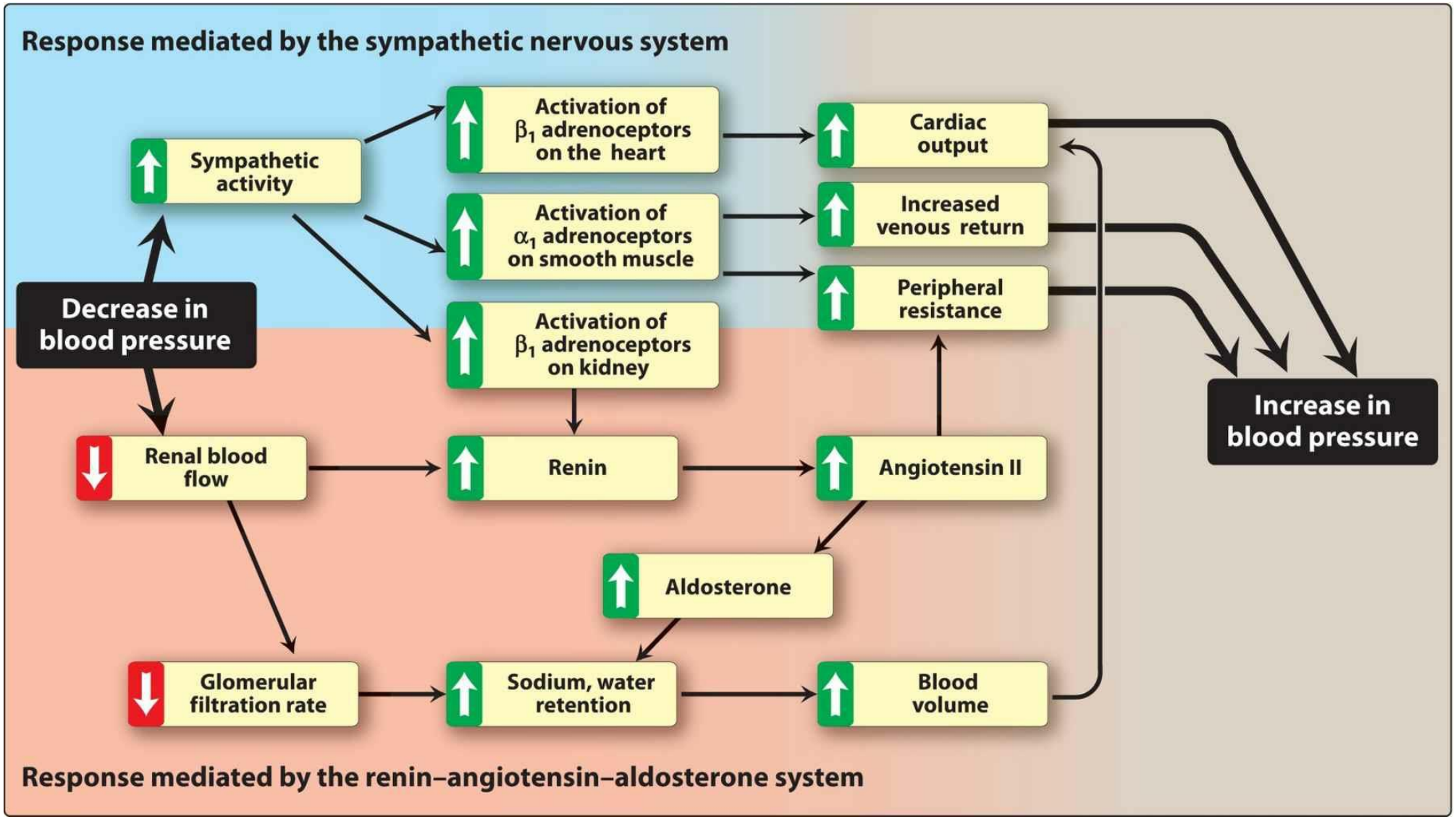

Figure 3: Response of the autonomic nervous system and the renin–angiotensin– aldosterone system to a decrease in blood pressure.

Treatment Strategies

- The goal of antihypertensive therapy is **to reduce cardiovascular** and **renal morbidity and mortality.**
- Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.
- Current recommendations are to initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker.
- If blood pressure is inadequately controlled, a second drug should be added, with the selection based on minimizing the adverse effects of the combined regimen and achieving goal blood pressure.
- Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with minimal adverse effects.

Diuretics

- For all classes of diuretics, the initial mechanism of action is based upon **decreasing blood volume**, which ultimately **leads to decreased blood pressure**.
- Routine serum electrolyte monitoring should be done for all patients receiving diuretics.

A. Thiazide diuretics

- Thiazide diuretics, such as **hydrochlorothiazide and chlorthalidone**.
- 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. Loop diuretics may be required in these patients.
- Thiazide diuretics can induce hypokalemia, hyperuricemia, and, to a lesser extent, hyperglycemia in some patients.

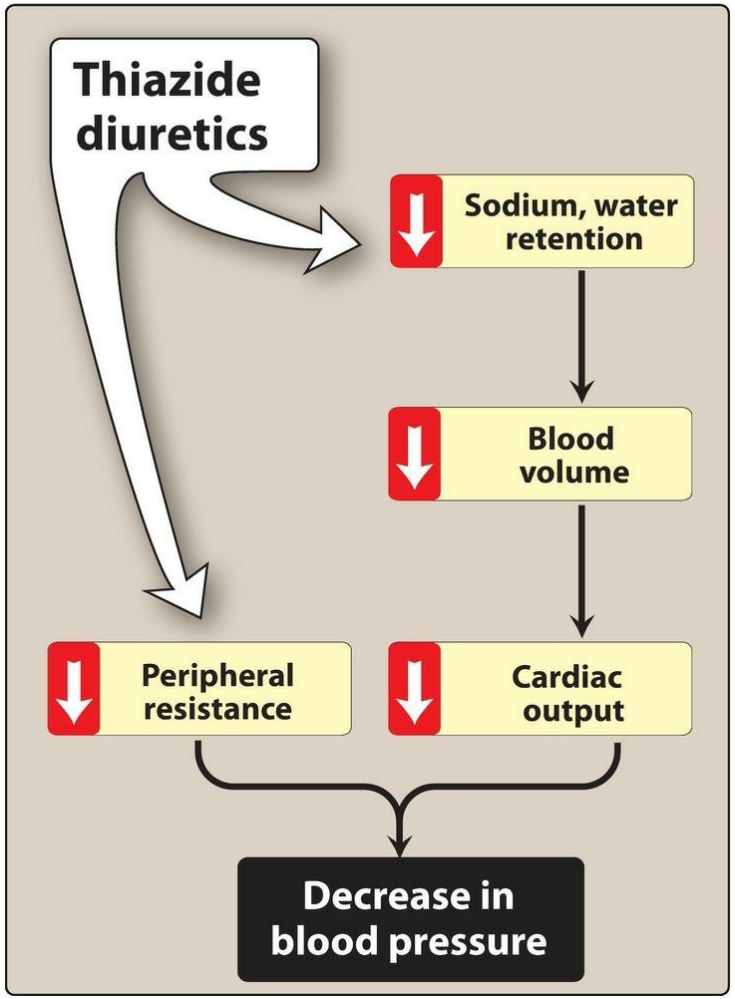

Figure 4: Actions of thiazide diuretics.

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 calcium 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** are **inhibitors of epithelial sodium transport at the late distal and collecting ducts**, and **spironolactone** and **eplerenone** are **aldosterone receptor antagonists**.
- All of these agents **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-Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure (Figure 5).

A. Actions

- The β-blockers **reduce blood pressure primarily** by **decreasing cardiac output** (Figure 16.8). They may also decrease
- sympathetic outflow from the central nervous system (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 β_1 and β_2 receptors.

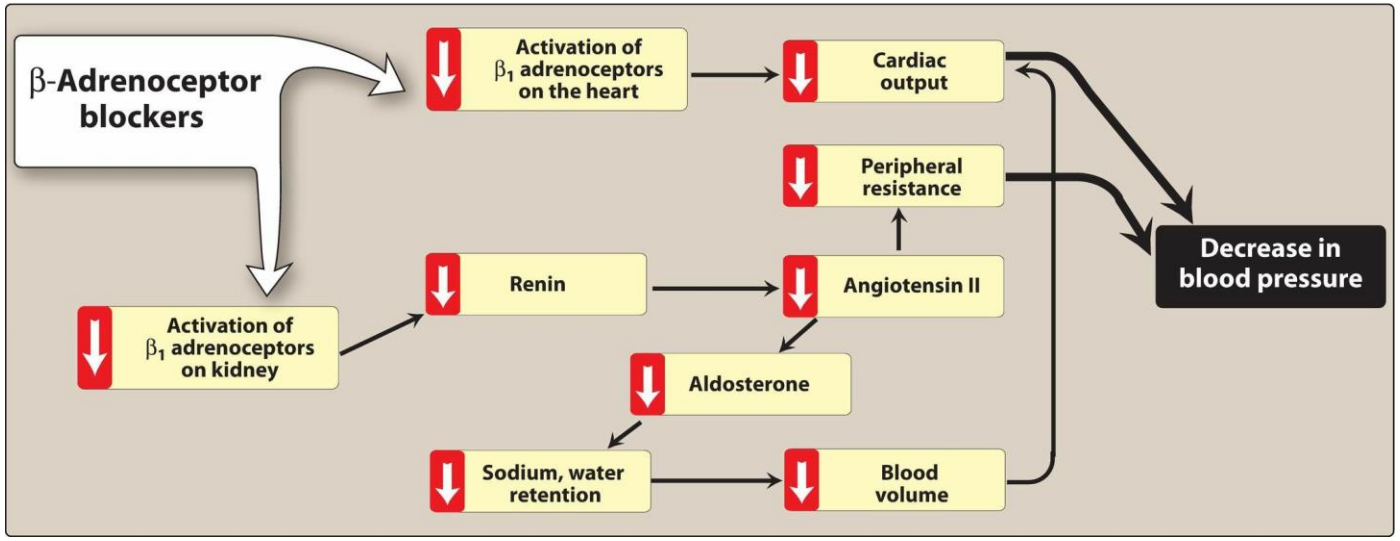

Figure 5: Actions of β-adrenoceptor–blocking agents.

- Selective blockers of β_1 receptors, such as **metoprolol** and **atenolol**, are among the most commonly prescribed β-blockers.
- **Nebivolol** is a selective blocker of β_1 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 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.

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 myocardial infarction, stable ischemic heart disease, 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.**

D. Adverse effects

1. Common effects:

Such as hypotension, bradycardia, fatigue, insomnia; and sexual dysfunction.

2. Alterations in serum lipid patterns

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

3. Drug withdrawal

Abrupt withdrawal may induce severe hypertension, 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.

❖ Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors such as **captopril, enalapril, and lisinopril** are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.

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 (Figure 6).
- ACE is also responsible for the breakdown of **bradykinin**. Both nitric oxide and prostacyclin are potent vasodilators. Vasodilation of both arterioles and veins occurs as a result of decreased vasoconstriction and enhanced vasodilation.
- 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 workload on the heart.

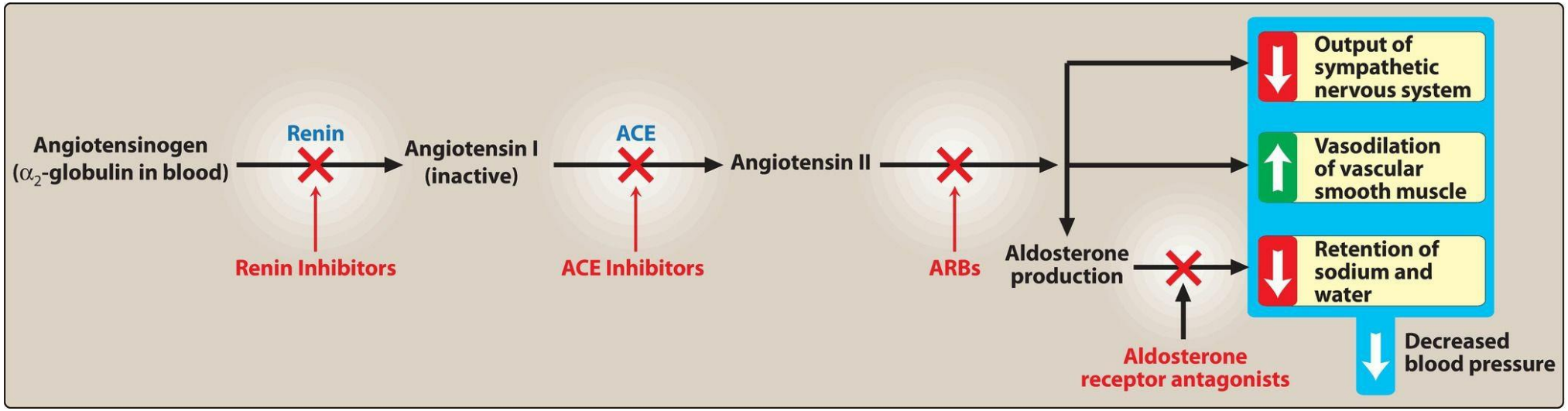

Figure 6: Effects of various drug classes on the renin–angiotensin–aldosterone system. Blue = drug target enzymes; red = drug class.

B. Therapeutic uses

- ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy.
- Beneficial effects on renal function may result from decreasing intraglomerular pressures, due to efferent arteriolar vasodilation.
- ACE inhibitors are a standard in the care of a patient following a myocardial infarction 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 a myocardial infarction.
- 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.

C. Pharmacokinetics

- All of the ACE inhibitors are **orally bioavailable** as a drug or prodrug. A number of these drugs (e.g. **captopril, lisinopril**) are **active per se**, while others (e.g. **enalapril**) are prodrugs and **require metabolic conversion to active metabolites** (e.g**. enalaprilat**).
- **Fosinopril** is the only ACE inhibitor that is not eliminated primarily by the kidneys.
- **Enalaprilat** is the only drug in this class available intravenously.

D. Adverse effects

- The dry cough, which occurs in up to 10% of patients, is thought to be due to increased levels of bradykinin and substance P in the pulmonary tree.
- 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.
- ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

❖ Angiotensin II Receptor Blockers (ARBs)

The ARBs, such as **losartan** and **irbesartan**, **block the AT_1 receptors**, decreasing **the activation of AT_1 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 (See; figure 6).

- 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 the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs** (Figure 6).
- Aliskiren should not be combined with an ACE inhibitor or ARB in the treatment of hypertension.
- Aliskiren can cause diarrhea, especially at higher doses.
- It also causes cough and angioedema but less often than ACE inhibitors.
- As with ACE inhibitors and ARBs, aliskiren is contraindicated during pregnancy.
- Aliskiren is metabolized by CYP3A4 and is subject to many drug interactions.

❖ Calcium Channel Blockers (CCBs)

Calcium channel blockers are used to treat hypertensive patients with diabetes or stable ischemic heart disease. High doses of short-acting calcium channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

A. Classes of calcium channel blockers

The calcium channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications (Figure 7).

B. Actions

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.

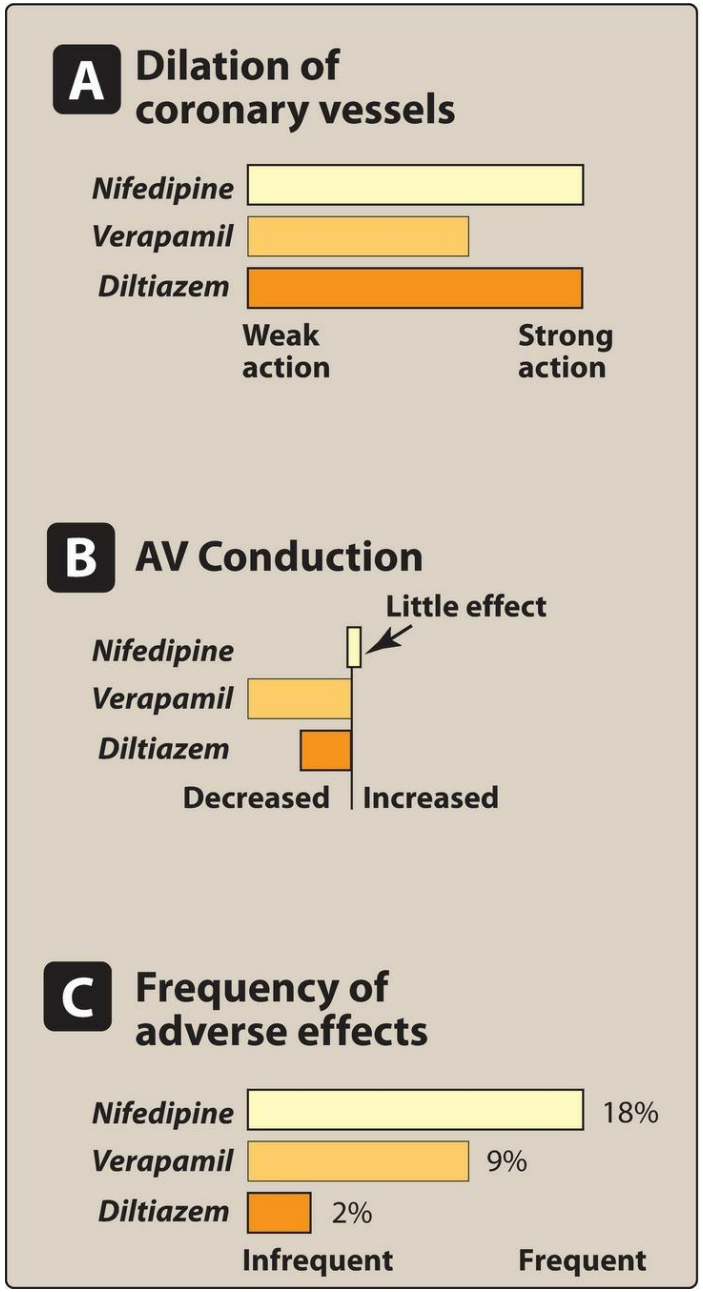

Figure 7: Actions of calcium channel blockers.
AV = atrioventricular.

C. Therapeutic uses

In the management of hypertension, CCBs may be used as an 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 and does not require a sustained-release formulation.

E. Adverse effects

❖ α-ADRENOCEPTOR–BLOCKING AGENTS

- α-Adrenergic blockers used in the treatment of hypertension include **prazosin, doxazosin,** and **terazosin**.
- These **agents produce a competitive block of α_1-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. Therefore, long-term tachycardia does not occur, but salt and water retention does.
- Reflex tachycardia and postural hypotension often occur at the onset of treatment and with dose increases.
- 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.
- Other α_1-blockers with greater selectivity for the prostate are used in the treatment of benign prostatic hyperplasia.

α-/ β-Adrenoceptor–blocking Agents

Labetalol and **carvedilol** **block α_1, β_1, and $\beta_2$receptors**. **Carvedilol** is indicated in the treatment of heart failure and hypertension. **Labetalol** is used in the management of gestational hypertension and hypertensive emergencies.

❖ Centrally Acting Adrenergic Drugs

A. Clonidine

- Clonidine **acts centrally as an α_2 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.
- It is used primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs.
- It does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.
- It is well absorbed after oral administration and is excreted by the kidney. It is also available in a transdermal patch.
- Adverse effects include sedation, dry mouth, hypotension, confusion and constipation. Rebound hypertension occurs following abrupt withdrawal of clonidine.

B. Methyldopa

- Methyldopa is **an α_2 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 management of hypertension in pregnancy, where it has a record of safety.

❖ Vasodilators

- The **direct-acting smooth muscle relaxants**, such as **hydralazine** and **minoxidil**, are not used as primary drugs to treat hypertension.
- These vasodilators act by **producing relaxation of vascular smooth muscle, primarily in arteries and arterioles.** This results in **decreased peripheral resistance** and, therefore, **blood pressure**.
- These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals.
- Vasodilators also increase plasma renin concentration, resulting in sodium and water retention.
- These undesirable side effects can be blocked by concomitant use of a diuretic and a β-blocker.
- Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance.
- Hydralazine is an accepted medication for controlling blood pressure in pregnancy-induced hypertension.
- 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. 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 with evidence of impending or progressive target organ damage.**
- 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 **calcium channel blockers** (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 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 **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 corticosteroids), **insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.**


Thank You!