Antihypertensive drugs

I-Introduction

Hypertension is defined as either a sustained **systolic blood pressure** of greater than 140 mm Hg or a sustained **diastolic blood pressure** of greater than 90 mm Hg. Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. In most cases, the cause of the increased vascular tone is unknown. Elevated blood pressure is a common disorder, affecting approximately 30% of adults in the United States. Although many patients have no symptoms, chronic hypertension 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. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated. The drugs used in the treatment of hypertension are shown in **(Figure1)**.

Antihypertensive drugs are medications used to treat high blood pressure (hypertension). These drugs work through various mechanisms to lower blood pressure and can be categorized into several classes, including **diuretics**, **beta-blockers**, **ACE inhibitors**, **angiotensin II receptor blockers (ARBs),** and **calcium channel blockers**.

1- Diuretics:

These medications help the body remove excess salt and water, reducing blood volume and thus lowering blood pressure. Examples include thiazide diuretics (like **hydrochlorothiazide**) and loop diuretics (like **furosemide**).

Table 1: Summary of antihypertensive drugs (Diuretics).

Scientific name	Trade name
Amiloride	MIDAMOR
Bumetanide	BUMEX
Chlorthalidone	HYGROTON
Eplerenone	INSPRA
Ethacrynic acid	EDECRIN
Furosemide	LASIX
Hydrochlorothiazide	MICROZIDE
Indapamide	LOZOL
Metolazone	MYKROX, ZAROXOLYN
Spironolactone	ALDACTONE
Triamterene	DYRENIUM
Torsemide	DEMADEX

2- Beta-blockers:

These drugs slow the heart rate and reduce the force of heart contractions, leading to lower blood pressure. Examples include **atenolol** and **metoprolol**.

Table 2: Summary of antihypertensive drugs (Beta-blockers inhibiters).

Scientific name	Trade name
Acebutolol	SECTRAL
Atenolol	TENORMIN
Betaxolol	KERLONE
Bisoprolol	ZEBETA
Carvedilol	COREG, COREG CR
Esmolol	BREVIBLOC
Labetalol	TRANDATE
Metoprolol	LOPRESSOR, TOPROL-XL
Nadolol	CORGARD
Nebivolol	BYSTOLIC
Penbutolol	LEVATOL
Pindolol	VISKEN
Propranolol	INDERAL LA, INNOPRAN XL
Timolol	BLOCADREN

3- ACE Inhibitors:

These medications block the production of a hormone that constricts blood vessels, allowing them to relax and widen. Examples include **lisinopril** and **enalapril**.

Table 3: Summary of antihypertensive drugs (ACE Inhibitors).

ACE INHIBITORS		RENIN INHIBITORS	
Scientific name	**Trade name**	**Scientific name**	**Trade name**
Benazepril	LOTENSIN	Aliskiren	TEKTURNA
Captopril	CAPOTEN		
Enalapril	VASOTEC		
Fosinopril	MONOPRIL		
Lisinopril	PRINIVIL, ZESTRIL		
Moexipril	UNIVASC		
Quinapril	ACCUPRIL		
Perindopril	ACEON		
Ramipril	ALTACE		
Trandolapril	MAVIK		

4- Angiotensin II Receptor Blockers (ARBs):

Similar to ACE inhibitors, ARBs block the action of a hormone that constricts blood vessels. Examples include **losartan** and **valsartan**.

Table 4: Summary of antihypertensive drugs (ARBs).

Scientific name	Trade name
Azilsartan medoxomil	EDARBI
Candesartan	ATACAND
Eprosartan	TEVETEN
Irbesartan	AVAPRO
Losartan	COZAAR
Olmesartan	BENICAR
Telmisartan	MICARDIS

Valsartan	DIOVAN

5- Calcium Channel Blockers:

These drugs prevent calcium from entering muscle cells in the heart and blood vessels, causing them to relax and widen. Examples include **amlodipine** and **diltiazem**.

Table 5: Summary of antihypertensive drugs (Calcium Channel Blockers).

CALCIUM CHANNEL BLOCKERS		α-BLOCKERS		OTHERS	
Scientific name	**Trade name**	**Scientific name**	**Trade name**	**Scientific name**	**Trade name**
Amlodipine	NORVASC	Doxazosin	CARDURA	Clonidine	CATAPRES, DURACLON
Clevidipine	CLEVIPREX	Prazosin	MINIPRESS	Fenoldopam	CORLOPAM
Diltiazem	CARDIZEM, CARTIA, DILACOR	Terazosin	HYTRIN	Hydralazine	APRESOLINE
Felodipine	PLENDIL			Methyldopa	ALDOMET
Isradipine	DYNACIRC CR			Minoxidil	LONITEN
Nicardipine	CARDENE			Nitroprusside	NITROPRESS
Nifedipine	ADALAT, NIFEDIAC, PROCARDIA				
Nisoldipine	SULAR				
Verapamil	CALAN, ISOPTIN, VERELAN				

Combination Therapy:

Many patients require more than one antihypertensive medication to achieve adequate blood pressure control.

Individualized Treatment:

The best choice of medication and dosage depends on various factors, including the patient's age, other medical conditions, and potential side effects.

Hypertension is classified into four categories for the purpose of treatment management (Table 6):

Table 6: Classification of blood pressure.

categories	Systolic (mm Hg)	Diastolic (mm Hg)
Normal	<120	<80
Prehypertension	120 - 139	80 - 89
Stage I	140 - 159	90 - 99
Stage II	≥160	≥100

II. ETIOLOGY OF HYPERTENSION:

Although hypertension may occur secondary to other disease processes, more than 90% of

patients have essential hypertension (hypertension 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 and income level**. 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 hypertension.

III. MECHANISMS FOR CONTROLLING BLOOD PRESSURE:

Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system, particularly the arterial intima (endothelium). **Arterial blood pressure** is directly proportional to cardiac output and peripheral vascular resistance (**Figure 3**). Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping control mechanisms: the baroreflexes and the renin angiotensin–aldosterone system (**Figure 4**). Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.

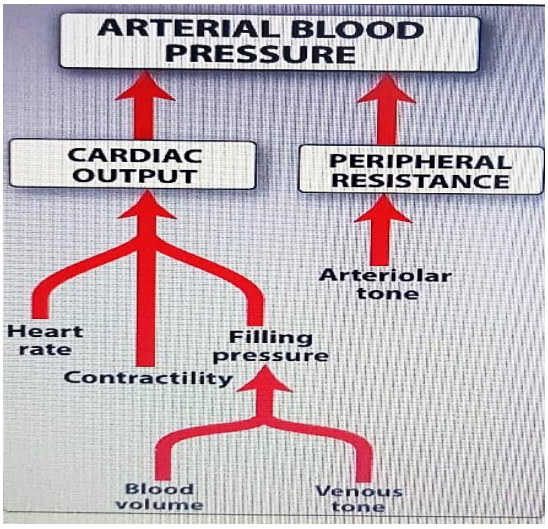

Figure 3: Major factors influencing blood pressure.

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-tomoment regulation of blood pressure. A fall in blood pressure causes pressure-sensitive neurons 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 (**Figure 4**).

B. Renin–angiotensin–aldosterone system:

The kidney provides long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β1 -adrenoceptors) by releasing the enzyme renin (**Figure 4**). 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 angiotensin-converting enzyme (ACE). Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins, resulting in an increase in blood pressure. Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration. Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin II type 1(AT1) receptors.

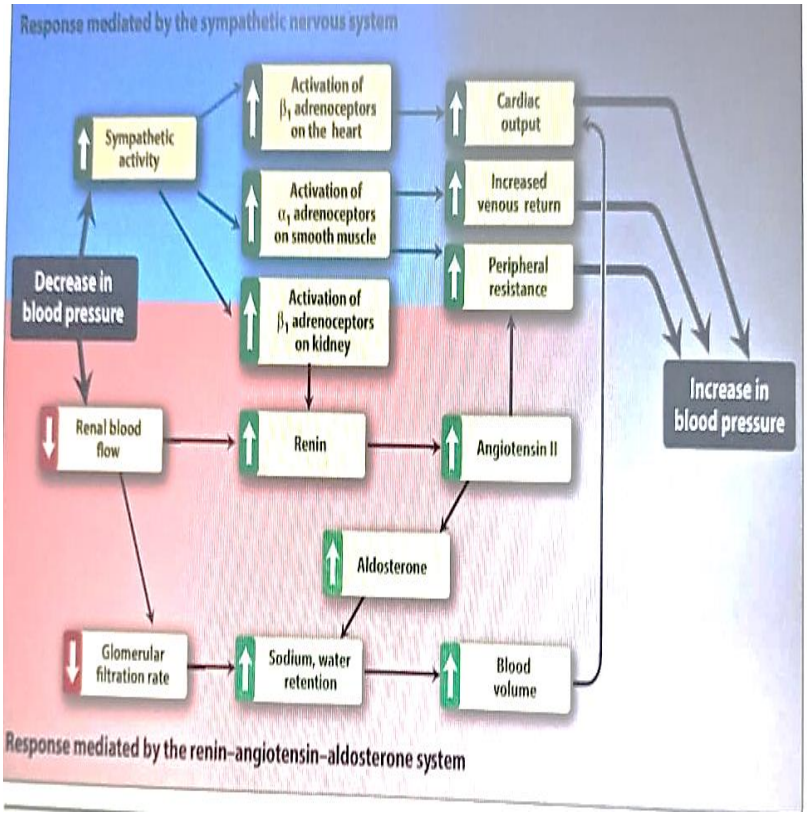

Figure 4 :Response of the autonomic nervous system and the renin–angiotensin–aldosterone system to a decrease in blood pressure.

IV. TREATMENT STRATEGIES:

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. The relationship between blood pressure and the risk of cardiovascular events is continuous, and, thus, lowering of even moderately elevated blood pressure significantly reduces cardiovascular disease. For most patients, the blood pressure goal when treating hypertension is a systolic blood pressure of less than 140 mm Hg and a diastolic blood

pressure of less than 90 mmHg. Mild hypertension can sometimes be controlled with monotherapy, but most patients require more than one drug to achieve blood pressure control. 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. Patients with systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg (or systolic blood pressure greater than 20 mm Hg above goal or diastolic blood pressure more than 10 mm Hg above goal) should be started on two antihypertensives simultaneously.

V. 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.

A- 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 (**Figure 7**). 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.

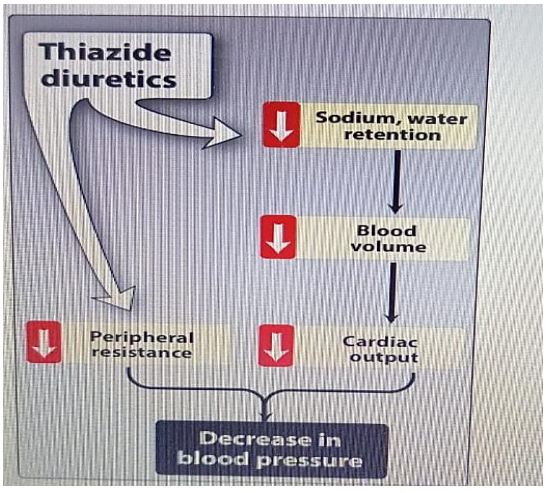

Figure 7: Actions of thiazide diuretics.

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 Ca^{2+} 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.

VI. β-ADRENOCEPTOR–BLOCKING AGENTS:

β-Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure (**Figure 8**).

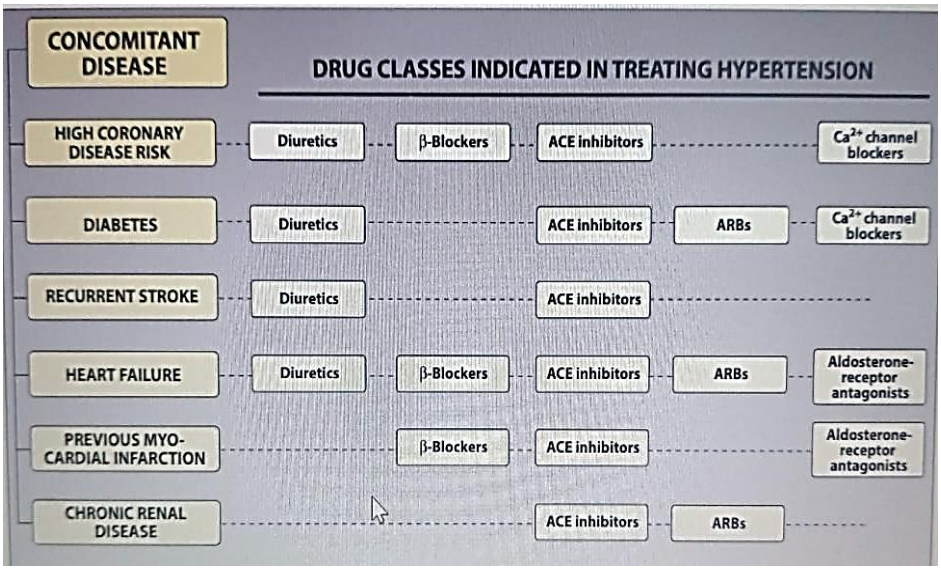

Figure 8: Treatment of hypertension in patients with concomitant diseases. [Note: Angiotensin receptor blockers (ARBs) are an alternative to angiotensin-converting enzyme (ACE) inhibitors.]

A- Actions:

The β-blockers reduce blood pressure primarily by decreasing cardiac output (**Figure 9**). 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

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. for an in-depth discussion of β-blockers.) β-Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

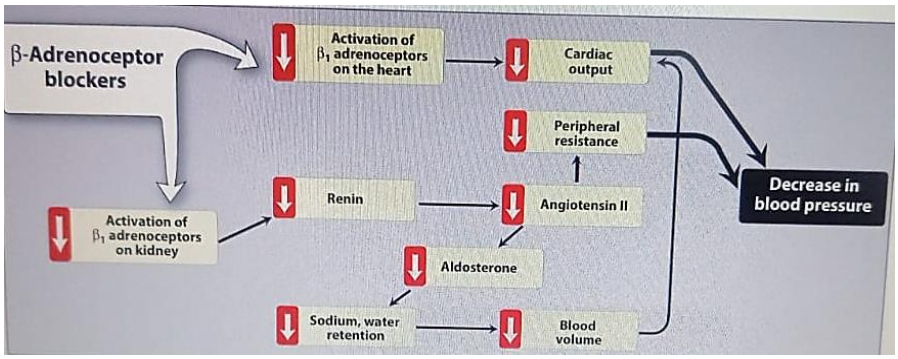

Figure 9: Actions of β-adrenoceptor–blocking agents.

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 myocardial infarction, 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.

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: Noncardioselective 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.

VII. ACE INHIBITORS:

The ACE inhibitors, such as 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 (Figure 8).

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 (**Figure10**). ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and Mprostacyclin by the blood vessels. Both nitric oxide and prostacyclin 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.

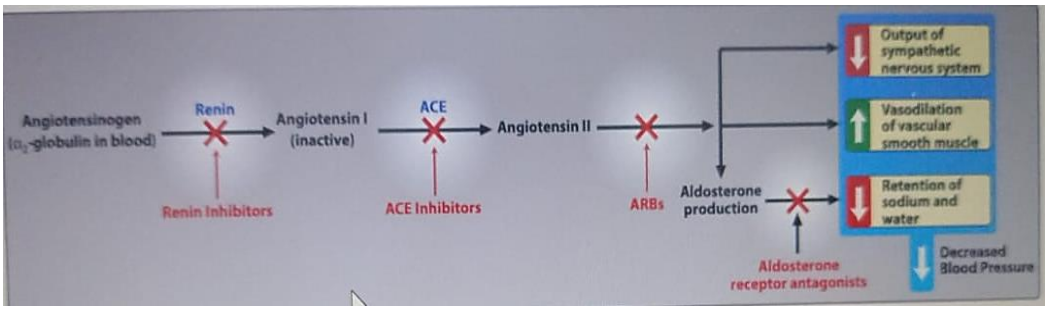

Figure10: Effects of various drug classes on the renin–angiotensin–aldosterone system. Blue = drug target enzymes; red = drug class

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. 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. All of the ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses.

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.

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, 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. The cough occurs more frequently in women. 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.

VIII. ANGIOTENSIN II RECEPTOR BLOCKERS:

The ARBs, such as losartan [LOW-sar-tan] and irbesartan [ir-be-SARtan], are alternatives to the ACE inhibitors. These drugs block the AT1receptors, decreasing the activation of AT1receptors 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 (Figure 17.5). Adverse effects are similar to those of ACE inhibitors. 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.

IX. RENIN INHIBITOR:

A selective renin inhibitor, aliskiren [a-LIS-ke-rin], 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 . 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.

X. 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 increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

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.

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:

First-degree atrioventricular 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.

XI. α-ADRENOCEPTOR–BLOCKING AGENTS:

Prazosin [PRA-zoe-sin], doxazosin [dox-AH-zoe-sin], and terazosin Prazosin [PRA-zoe-sin], doxazosin [dox-AH-zoe-sin], and terazosin [ter-AH-zoe-sin] 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. 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, 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. Other α1-blockers with greater selectivity for prostate muscle are used in the treatment of benign prostatic hyperplasia.

XII. α-/β-ADRENOCEPTOR–BLOCKING AGENTS:

Labetalol [la-BAY-ta-lol] and carvedilol [kar-VE-di-lol] 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 hypertension and hypertensive emergencies.

XIII. CENTRALLY ACTING ADRENERGIC DRUGS:

A. Clonidine: Clonidine [KLON-i-deen] 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. The drug should, therefore, be withdrawn slowly if discontinuation is required.

B. Methyldopa: Methyldopa [meth-ill-DOE-pa] 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 management of hypertension in pregnancy, where it has a record of safety.

XIV.VASODILATORS:

The direct-acting smooth muscle relaxants, such as hydralazine [hyeDRAL-a-zeen] and minoxidil [min-OX-i-dill], 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. 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, 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. 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). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance. Hydralazine is an accepted medication for controlling blood pressure in pregnancyinduced 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 (the growth of body hair). This drug is used topically to treat male pattern baldness.

XV. HYPERTENSIVE EMERGENCY:

Hypertensive emergency is a rare but life-threatening situation characterized by severe elevations in blood pressure (systolic greater than 180 mm Hg or diastolic greater than 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 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 present and/or comorbidities present.

XVI. 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 antidepressant medications), insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.

XVII. 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 ease of patient adherence to treatment regimens that require multiple medications to achieve the blood pressure goal.

Questions:

Choose the ONE best answer: why?

1- A 45-year-old man was just started on therapy for hypertension and developed a persistent, dry cough. Which is most likely responsible for this side effect?

a- Enalapril. d- Losartan. c- Nifedipine. d- Prazosin. e- Propranolol.

Answer:

Correct answer = a. The cough is most likely an adverse effect of the ACE inhibitor enalapril. Losartan is an ARB that has the same beneficial effects as an ACE inhibitor but is less likely to produce a cough. Nifedipine, prazosin, and propranolol do not cause this side effect.

2- Which may cause reflex tachycardia and/or postural hypotension on initial administration?

a. Atenolol. b. Hydrochlorothiazide. c. Metoprolol. d. Prazosin. e. Verapamil

Answer:

Correct answer = d. Prazosin produces first-dose hypotension, presumably by blocking α1 receptors. This effect is minimized by initially giving the drug in small, divided doses. The other agents do not have this adverse effect.

3- Which can precipitate a hypertensive crisis following abrupt cessation of therapy?

a- Clonidine. b- Diltiazem. c- Enalapril. d- Losartan. e- Hydrochlorothiazide.

Answer:

Correct answer = a. Increased sympathetic nervous system activity occurs if clonidine therapy is abruptly stopped after prolonged administration. Uncontrolled elevation in blood pressure can occur. Patients should be slowly weaned from clonidine while other antihypertensive medications are initiated. The other drugs on the list do not produce this phenomenon.

4- A 48-year-old hypertensive patient has been successfully treated with a thiazide diuretic for the last 5 years. Over the last 3 months, his diastolic pressure has steadily increased, and he was started on an additional antihypertensive agent. He complains of several instances of being unable to achieve an erection and not being able to complete three sets of tennis as he once did. Which is the likely second antihypertensive medication?

a- Captopril. b- Losartan. c- Metoprolol. d- Minoxidil. e- Nifedipine.

Answer:

Correct answer = c. The side effect profile of β-blockers, such as metoprolol, is characterized by interference with sexual performance and decreased exercise tolerance. None of the other drugs is likely to produce this combination of side effects.

5- A 40-year-old male has recently been diagnosed with hypertension due to pressure readings of 163/102 and 165/100 mm Hg. He also has diabetes that is well controlled with oral hypoglycemic medications. Which is the best initial treatment regimen for treatment of hypertension in this patient?

a- Felodipine. b- Furosemide. c- Lisinopril. d- Lisinopril and hydrochlorothiazide. e- Metoprolol.

Answer:

Correct answer = d. Because the systolic blood pressure is more than 20 mm Hg above goal (10 mm Hg above goal diastolic), treatment with two different medications is preferred. Because the patient is diabetic, he also has a compelling indication for an ACE inhibitor or ARB.

6- A 60-year-old white female has not reached her blood pressure goal after 1 month of treatment with a low dose of lisinopril. All of the following would be appropriate next steps in the treatment of her hypertension except:

a- Increase dose of lisinopril. b- Add a diuretic medication. c- Add on a calcium channel blocker medication. d- Add on an ARB medication.

Answer:

Correct answer = d. Increasing the dose of lisinopril or adding a second medication from a different class (such as a calcium channel blocker or diuretic) would be appropriate steps to control the blood pressure. Adding an ARB as the second medication is not recommended. ARBs have a similar mechanism of action to ACE inhibitors, and combination therapy may increase the risk of adverse effects.

7- A patient returns to her health care provider for routine monitoring 3 months after her hypertension regimen was modified. Labs reveal elevated serum potassium. Which is likely responsible for this hyperkalemia?

a- Chlorthalidone. b- Clonidine. c- Furosemide. d- Losartan. e- Nifedipine

Answer:

Correct answer = d. Losartan, an ARB, can cause an increase in serum potassium similar to ACE inhibitors. Furosemide and chlorthalidone can cause a decrease in serum potassium. Nifedipine and clonidine do not affect potassium levels.

8- A 58-year-old female reports that she recently stopped taking her blood pressure medications because of swelling in her feet that began shortly after she started treatment. Which is most likely to cause peripheral edema?

a- Atenolol. b- Clonidine. c- Felodipine. d- Hydralazine. e- Prazosin.

Answer:

Correct answer = c. Peripheral edema is one of the most common side effects of calcium channel blockers. None of the other agents commonly cause peripheral edema.

9- Which is an appropriate choice for hypertension treatment during pregnancy?

a- Aliskiren. b- Fosinopril. c- Hydralazine. d- Valsartan.

Answer:

Correct answer = c. Hydralazine is an appropriate choice for a hypertensive pregnant patient. ACE inhibitors, ARBs, and the direct renin inhibitor, aliskiren, are all contraindicated in pregnancy due to their potential for fetal harm.

10- DD is a 50-year-old male with newly diagnosed hypertension. His comorbidities include diabetes and chronic hepatitis C infection with moderate liver impairment. He requires two drugs for initial treatment of his hypertension. Which should be prescribed in combination with a thiazide diuretic?

a- Lisinopril. b- Spironolactone. c- Fosinopril. d- Furosemide. e- Hydralazine.

Answer:

Correct answer = a. Because DD has diabetes, he has a compelling indication for an ACE inhibitor or ARB for the treatment of his hypertension and prevention of diabetic nephropathy. However, most ACE inhibitors undergo hepatic conversion to active metabolites, so his hepatic impairment is of concern. Because lisinopril is one of the two ACE inhibitors that does not undergo hepatic conversion to active metabolites, it is the best choice. Fosinopril is the only ACE inhibitor that is not eliminated primarily by the kidneys but does undergo hepatic conversion. An additional diuretic like spironolactone or furosemide is not indicated. DD does not have a compelling indication for hydralazine.

Reference:

- **Whalen, Karen.** ***Lippincott® illustrated reviews: pharmacology*****. Wolters kluwer india Pvt Ltd, 2018.**