Antihypertensives

Hypertension is a common cardiovascular disease affecting worldwide population. A persistent and sustained high blood pressure has damaging effects on the heart, brain, kidneys and eyes.

Blood Pressure:

Systolic blood pressure (SBP): It is the maximum pressure recorded during ventricular systole.
Diastolic blood pressure (DBP): It is the minimum pressure recorded during ventricular diastole.

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 these conditions. In addition, environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking, may further predispose an individual to hypertension.

Blood pressure category	**Systolic mm Hg**		**Diastolic mm Hg**
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 crises (consult your doctor immediately)	More than 180	And/ or	More than 120

Treatment Strategies

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. For most patients, the blood pressure goal when treating hypertension is a systolic blood pressure of less than 130 mm Hg and a diastolic blood pressure of less than 80 mm Hg. Current recommendations are to initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker. Patients with 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. Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with minimal adverse effects.

A. 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.

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

II. Loop diuretics: (*furosemide, torsemide, bumetanide*, and *ethacrynic acid*). These drugs have short duration of action; therefore, they are not used in hypertension except in the presence of renal or cardiac failure.

III. Potassium-sparing diuretics: *Amiloride*, *triamterene*, *spironolactone* and *eplerenone* reduce potassium loss in the urine.

Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

B. β-Adrenoceptor–Blocking Agents

β-Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure.

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

C. ACE Inhibitors (Angiotensin Converting Enzyme 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.ACE inhibitors are usually given orally. In hypertensive emergency, *enalaprilat* can be given intravenously.Food reduces the absorption of captopril; hence, it should be given 1 h before meals.

Angiotensin converting enzyme inhibitors:

a. Inhibit the generation of angiotensin II resulting in:

Dilatation of arterioles → ↓peripheral vascular resistance (PVR) → ↓BP. Decrease in aldosterone production → decrease in Na+ and H_2O retention → ↓BP. Decrease in sympathetic nervous system activity.

b. Inhibit the degradation of bradykinin, which is a potent vasodilator.

c. Stimulate synthesis of vasodilating prostaglandins through bradykinin.

All these actions contribute to their antihypertensive effect.

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.

Dry cough which occurs in up to 10% of patients, is due to increased levels of bradykinin and substance P in the pulmonary tree, and it occurs more frequently in women. The cough 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.

ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

D. Angiotensin II Receptor Blockers (ARBs): such as *losartan* and *irbesartan*, 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.

E. 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. 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.

F. Calcium Channel Blockers (CCBs): *Verapamil, diltiazem* and dihydropyridines *(nifedipine, amlodipine, felodipine, nicardipine, isradipine*, etc.) are useful in all grades of hypertension. The antihypertensive effect is mainly due to peripheral vasodilatation.

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.

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 calcium channel blockers.

Nifedipine and other dihydropyridines may cause gingival hyperplasia.

G. α-Adrenoceptors Blocking Agents: *prazosin, doxazosin,* and *terazosin*. These agents 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.

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.

H. α-/β-Adrenoceptor–blocking Agents

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

Carvedilol is indicated in the treatment of heart failure and hypertension.

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

I. Centrally Acting Adrenergic Drugs:

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. Rebound hypertension occurs following abrupt withdrawal of clonidine. The drug should, therefore, be withdrawn slowly if discontinuation is required.

Methyldopa is an α2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. It is mainly used for management of hypertension in pregnancy, where it has a record of safety.

J.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. Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption.
Hydralazine is an accepted medication for controlling blood pressure in pregnancy-induced hypertension. 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 (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.

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.