Drugs affecting the Cardiovascular system (Antihypertensives)

Hypertension (HT) 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.

The mean arterial pressure can be calculated from the following equation:

Mean arterial pressure = Cardiac output (CO) X Peripheral resistance (PR)

According to the above equation a decrease in either CO or PR will decrease blood pressure. Conversely, any increase in blood pressures can be traced back to something can increase one of these two variables.

Hypertension is also an important risk factor in the development of chronic kidney disease, heart failure and stroke specifically when the patient is asymptomatic. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated.

Hypertension is classified into four categories for the purpose of treatment management as demonstrated in table 1.

Table 1: Classification of blood pressure.

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Prehyper-tension	120–139	or	80–89
Stage I	140–159	or	90–99
Stage II	≥160	or	≥100

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).

The main suggested causes for HT are:

1- Family history of hypertension
2- The prevalence of HT increases with age but decreases with education and income level.
3- Ethnicity
4- The prevalence of HT increases in persons with diabetes, obesity, or disability status
5- In addition, environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking, may further predispose an individual to HT.

MECHANISMS FOR CONTROLLINGBLOOD PRESSURE

As mentioned above, arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance. Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping control mechanisms: the baroreflexes and the renin–angiotensin–aldosterone system. So, most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.

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 to send fewer impulses to cardiovascular centres 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 1).

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 β_1-adrenoceptors) by releasing the enzyme renin (figure 1). 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. 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 (AT_1) receptors.

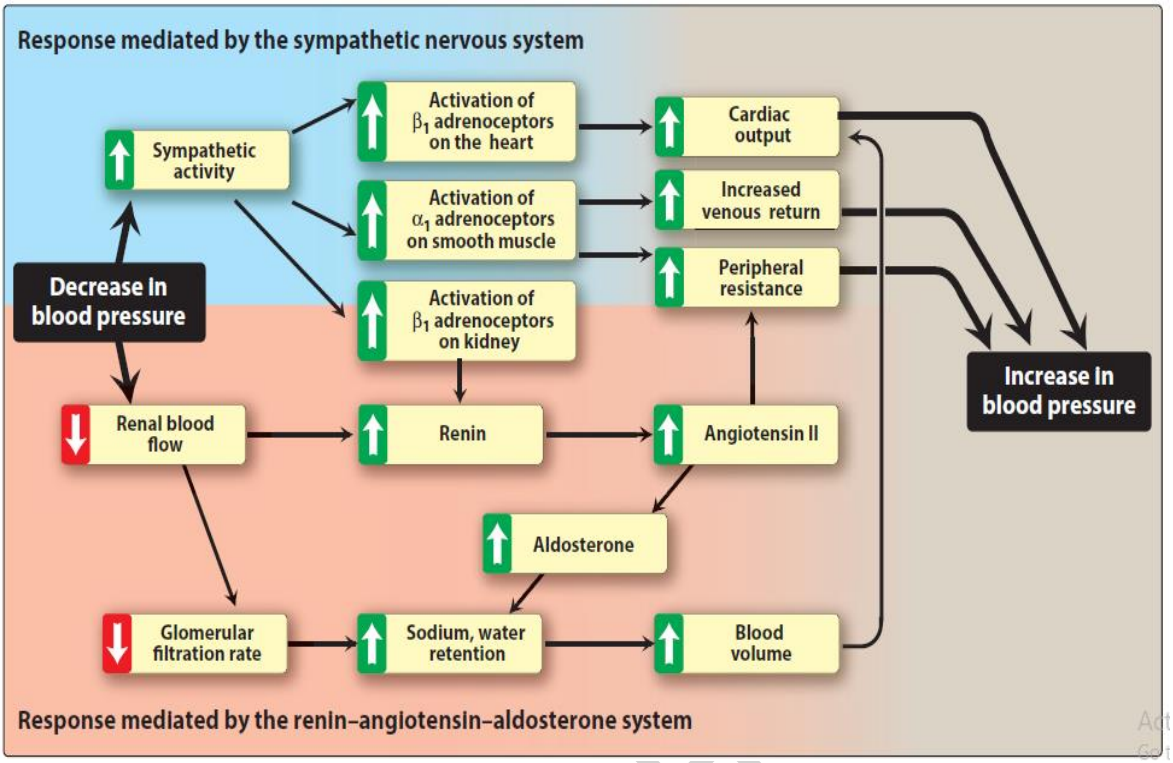

Figure 1: Response of the autonomic nervous system and the renin–angiotensin–aldosterone system to a decrease in blood pressure.

TREATMENT STRATEGIES

- 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 mm Hg. 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.
- The selection of the 2nd drug is based on minimising 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 should be started on two antihypertensives simultaneously.
- It is noteworthy to mention that the HT treatment plan can be (or should be) individualised.
- In addition, the blood pressure goals may also be individualised based on concurrent disease states. For instance, in patients with diabetes, some experts recommend a blood pressure goal of less than 140/80 mm Hg.

TYPES OF ANTIHYPERTENSIVE DRUGS:

1- DIURETICS

There are 3 classes of diuretics, which are:

a- Thiazide diuretics

b- Loop diuretics

c- Potassium-sparing diuretics

Regardless of class, the initial mechanism of action of diuretics is based upon decreasing blood volume leading to decrease in 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.**

a- Thiazide diuretics:

Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone can be used as initial drug therapy for hypertension unless there are compelling reasons to choose another agent.

Mechanism of action:

Thiazide diuretics 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 2). **With long-term treatment**, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance.

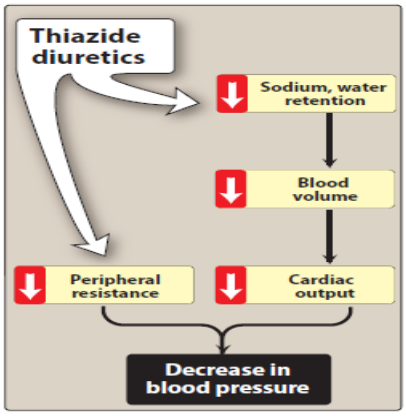

Figure 2: Actions of thiazide diuretics.

Therapeutic uses:

Thiazides are useful in combination therapy with a variety of other antihypertensive agents. With the exception of metolazone, thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate less than 30 mL/min/m^2). Loop diuretics may be required in these patients.

Adverse effects:

Thiazide diuretics can induce hypokalaemia, hyperuricemia and, to a lesser extent, hyperglycaemia in some patients.

b- Loop diuretics (LD)

The loop diuretics (such as furosemide) act 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. LD cause decreased renal vascular resistance and increased renal blood flow.

In comparison to thiazides diuretics:

Like thiazides, LD can cause hypokalaemia. However, **unlike thiazides**, LD 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 oedema.

c- Potassium-sparing diuretics (PSD)

PSD (such as amiloride and spironolactone (aldosterone receptor antagonists) reduce potassium loss in the urine. Aldosterone antagonists (spironolactone) have the additional benefit of diminishing the cardiac remodelling that occurs in heart failure. Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

2- β-ADRENOCEPTOR–BLOCKING AGENTS (β-BLOCKER (BB))

β-Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure. A summary of BB mechanism of action is demonstrated in figure 3. The nonselective β-blockers, such as propranolol and nadolol, are contraindicated in patients with asthma due to their blockade of β_2-mediated bronchodilation. β-Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

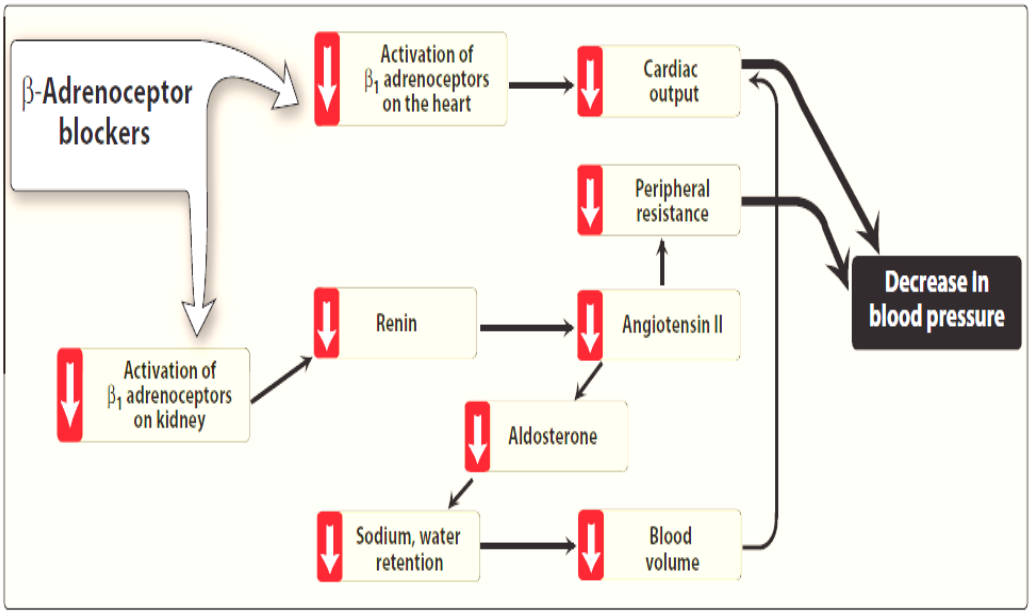

Figure 3: Actions of β-adrenoceptor–blocking agents.

Therapeutic uses

The primary therapeutic benefits of β-blockers are seen in hypertensive patients with concomitant heart disease, such as previous myocardial infarction, angina pectoris, and chronic heart failure. Conditions that discourage the use of β-blockers include reversible bronchospastic disease such as asthma. Oral β-blockers may take several weeks to develop their full effects.

Adverse effects

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.

Alterations in serum lipid patterns: Non-cardioselective β-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.

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.

3- 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.

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 angiotensin converting enzyme (ACE) which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II (figure 4). ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators. ACE inhibitors decrease angiotensin II and increase bradykinin levels.

So, 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). In Addition, ACE inhibitors also decrease the secretion of aldosterone (by reducing circulating angiotensin II levels), resulting in decreased sodium and water retention. Accordingly, ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing cardiac work.

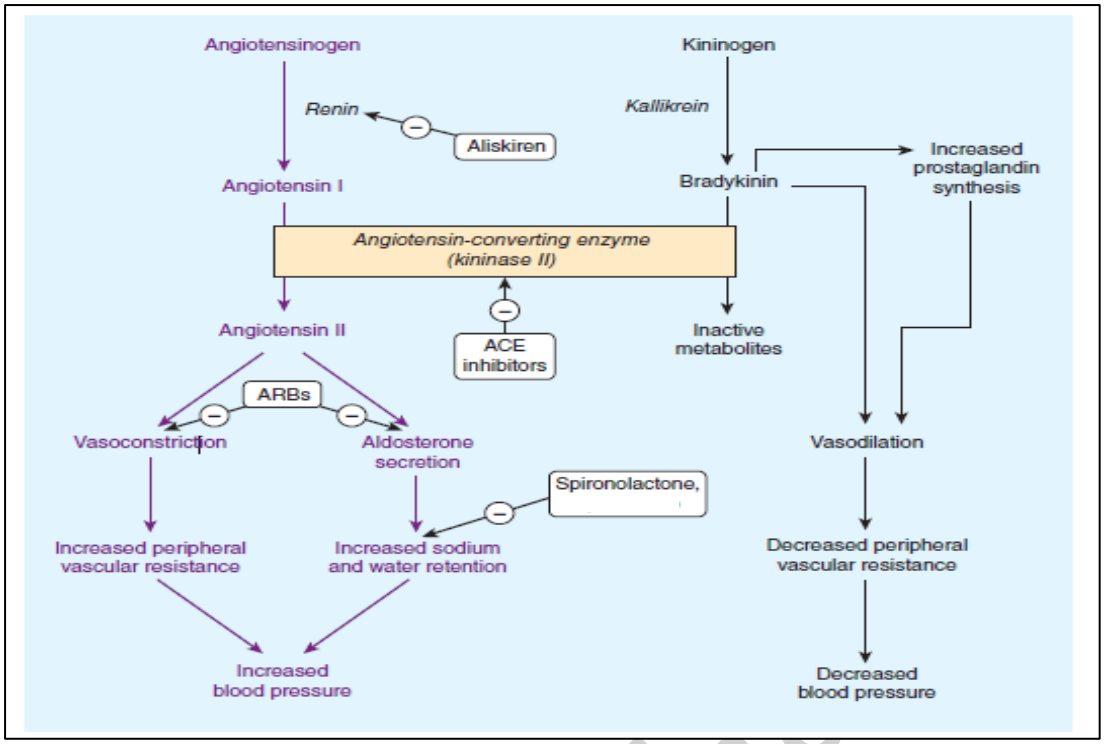

Figure 4: Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

Therapeutic uses

1- ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy. (WHY??)

2- 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.

3- Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodelling after a myocardial infarction.

4- ACE inhibitors are first-line drugs for treating heart failure and hypertensive patients with chronic kidney disease. All of the ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses.

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.

Adverse effects

1- **Common side effects** include dry cough, rash, fever, altered taste, hypotension (in hypovolemic states), and hyperkalaemia. 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.
2- Angioedema is a rare but potentially life-threatening reaction that may also be due to increased levels of bradykinin.
3- 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 hyperkalaemia.
4- Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease.
5- ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

4- ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

- The ARBs, such as losartan and irbesartan, are alternatives to the ACE inhibitors. These drugs 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 (figure 4).
- 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.

5- 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 4).

- 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 diarrhoea, 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.

6- CALCIUM CHANNEL BLOCKERS (CCB)

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.

Classes of calcium channel blockers

The calcium channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications

1. Diphenylalkylamines: Verapamil is the only member of this class and it 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 supraventricular tachyarrhythmias and to prevent migraine and cluster headaches.

2. Benzothiazepines: Diltiazem is the only member of this class that is currently approved in the United States. 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 favourable side effect profile.

3. Dihydropyridines: This class of calcium channel blockers includes many drugs such as the nifedipine (the prototype), amlodipine and felodipine, which 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 calcium channel blockers.

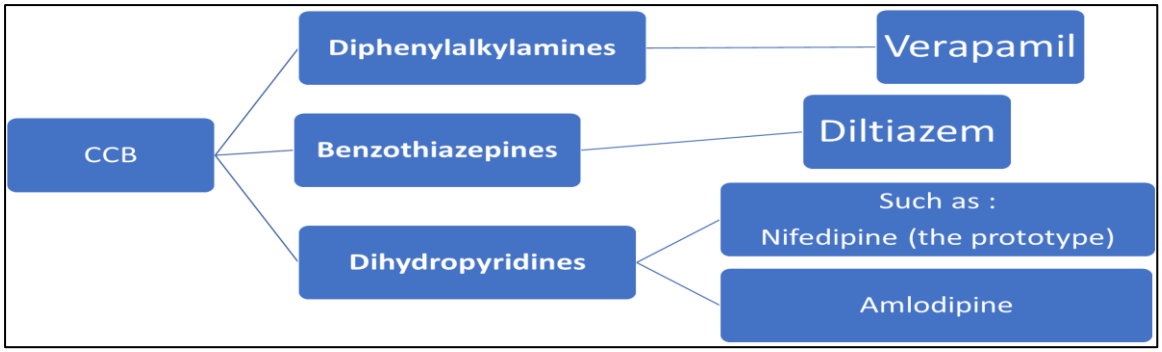

Figure 5: CCB classification.

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 the intracellular release of calcium, 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.

Therapeutic uses

1- 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.
2- All CCBs are useful in the treatment of angina.
3- In addition, diltiazem and verapamil are used in the treatment of atrial fibrillation.

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.

Adverse effects

1- 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.

2- Dizziness, headache and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines. Peripheral oedema is another commonly reported side effect of this class. **Nifedipine and other dihydropyridines may cause gingival hyperplasia.**

7- α-ADRENOCEPTOR–BLOCKING AGENTS

Prazosin, doxazosin, and terazosin 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. Due to weaker outcome data and their side effect profile, α-blockers are no longer recommended as initial treatment for hypertension.

8- α-/β-ADRENOCEPTOR–BLOCKING AGENTS

Labetalol and carvedilol block α_1, β_1, and β_2 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.

9- **CENTRALLY ACTING ADRENERGIC DRUGS**

A. Clonidine

- Clonidine acts centrally as an α_2 agonist to produce inhibition of sympathetic vasomotor centres, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure.
- It does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.
- 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 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.

10- VASODILATORS

1- The direct-acting smooth muscle relaxants, such as hydralazine and minoxidil, are not used as primary drugs to treat hypertension.
2- 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.

3- 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.
4- 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 characterised 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).
- 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 such as calcium channel blockers, adrenergic receptor antagonists (labetalol), the vasodilator and hydralazine.
- 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, excessive ethanol intake, and concomitant conditions (diabetes, obesity).
2- Moreover, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome), concomitant medications (nonsteroidal anti-inflammatory drugs, or antidepressant medications), insufficient dose and/or drugs, and 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 ease of patient adherence to treatment regimens that require multiple medications to achieve the blood pressure goal.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.