Drugs affecting the Cardiovascular system (Antihypertensive--Part-1)

Hypertension (HT) occurs when systolic blood pressure exceeds 130 mm Hg or diastolic blood pressure exceeds 80 mm Hg on at least two occasions. 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.

HT 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 HT is diagnosed early and is properly treated.

HT 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
Elevated	120–129	or	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90

ETIOLOGY OF HYPERTENSION

Although HT may occur secondary to other disease processes, more than 90% of patients have essential HT (HT with no identifiable cause).

The main suggested causes for HT are:

1- Family history of HT
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 (RAAS). 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.

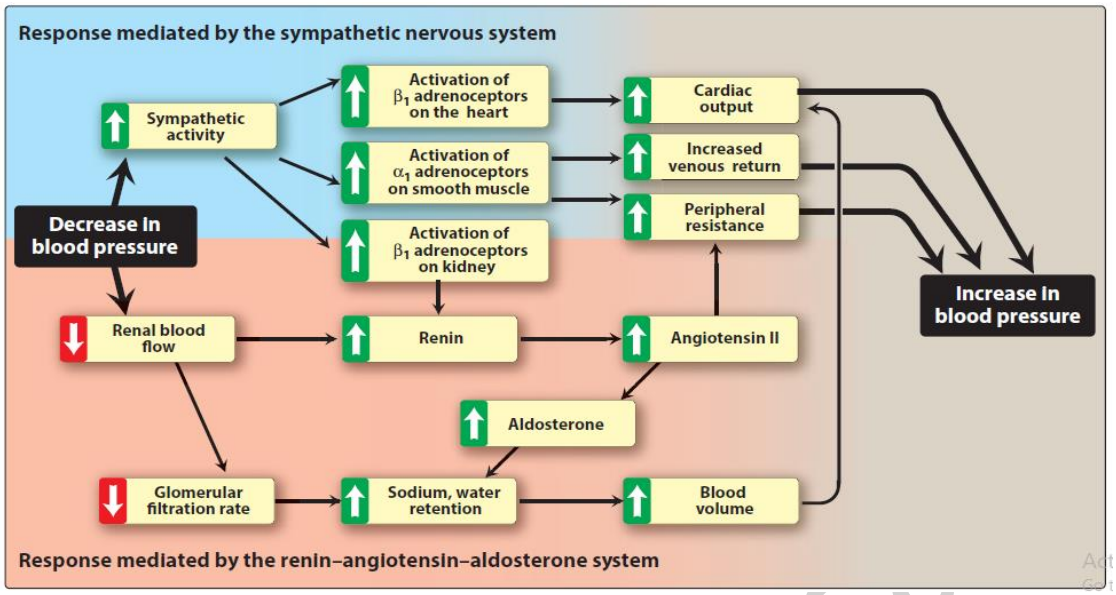

Figure 1: Response of the autonomic nervous system and the renin–angiotensin–aldosterone system to a decrease in blood pressure.

TREATMENT STRATEGIES

- The blood pressure goal when treating HT is **a systolic blood pressure of less than 130 mm Hg and a diastolic blood pressure of less than 80 mm Hg. Mild HT 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 20 mm Hg above goal or diastolic blood pressure more than 10 mm Hg above goal should be started on two antihypertensives simultaneously.
- 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 140/90 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 HT 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.

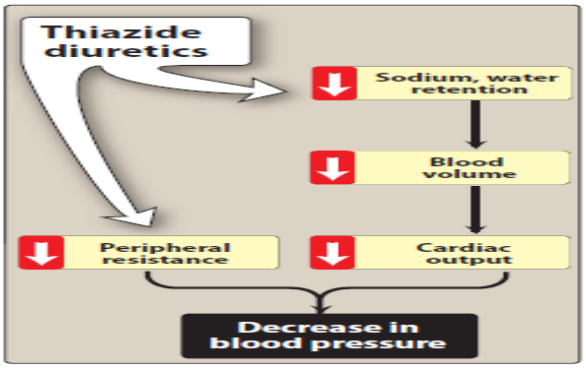

Figure 2: Actions of thiazide diuretics.

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. Thiazides increase serum uric acid by decreasing the amount of acid excreted through competition in the organic acid secretory system. Being insoluble, uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.

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 HT, but they are commonly used to manage symptoms of heart failure and oedema.

In addition, LD can cause hyperuricemia as Loop diuretics compete with uric acid for the renal secretory systems, thus blocking its secretion and, in turn, may cause or exacerbate gouty attacks.

- ✓ Ototoxicity : Reversible or permanent hearing loss may occur with loop diuretics, particularly when infused intravenously at fast rates, at high doses, or when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics)

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.

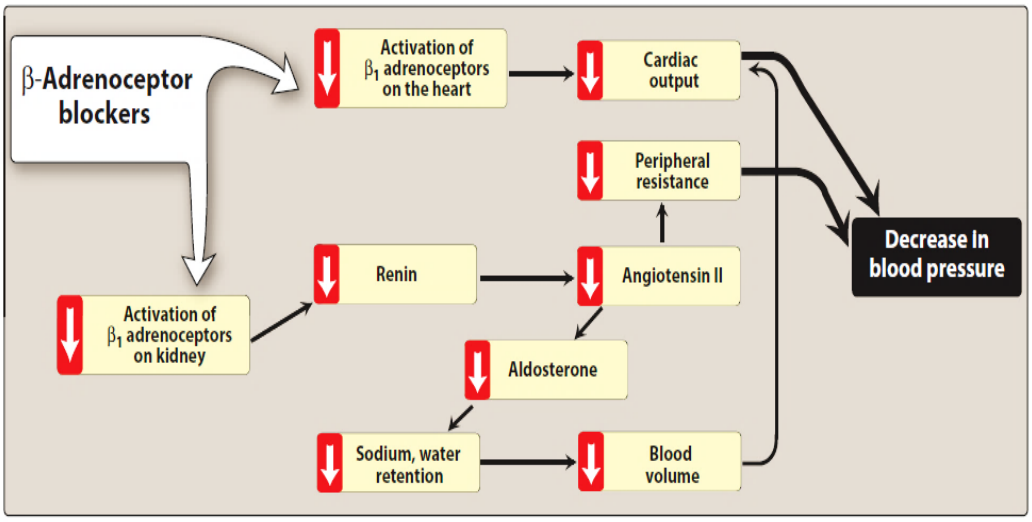

Figure 3: Actions of β-adrenoceptor–blocking agents.

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. Esmolol, metoprolol, and propranolol are available in intravenous formulations.

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 HT and ischemic heart disease.

References:

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