# PHARMACOLOGY

## Lectures 7&8:
## Antihypertensive Drugs.

- Identify factors that control blood pressure
- Outline the pharmacologic classes of drugs used in treatment of hypertension
- Describe the mechanism of action, therapeutic uses & common adverse effects and contraindications of each class of drugs
- Select the suitable antihypertensive drug to treat a specific patient according to efficacy, safety, suitability & cost

Before studying this lecture we advise you to study physiology “regulation of BP” and revise pharmacology lectures of this block.

PHARMACOLOGY
435

- Important.
- Extra notes.
- Mnemonic.
- Link

# Introduction to hypertension

**High blood pressure (Hypertension)** is a common condition in which the long-term force of the blood against artery walls is high enough that it may eventually cause health problems.

## Epidemiology:

Prevalence: 25-30% of adult population, Only 6% of diagnosed hypertensive patients have goal BP even after correct treatment.

In majority of cases, hypertension persists for years without any symptoms, thus called **"silent killer".** Eventually, it may lead to many complications including end-organ failure* and death (Leading cause).

* **End organ** or target **organ damage** usually refers to **damage** occurring in major **organs** fed by the circulatory system (heart, kidneys, brain, eyes) which can sustain **damage** due to uncontrolled **hypertension**, hypotension, or hypovolemia.

## Classified into 2 types:

1- **Primary** (essential) Hypertension:
mostly no identifiable cause; tends to develop gradually over years.

2- **Secondary** Hypertension:

- secondary to another disease (e.g., Kidney problems, Adrenal gland tumors, Cushing syndrome) it occurs suddenly and causes higher BP than the primary.
- Drug-induced hypertension, caused by a response to medication, as:

➢ Alcohol, cocaine, Antidepressants, Caffeine, Corticosteroids, Cyclosporine, Erythropoietin, Estrogens, Nasal decongestants, **NSAIDs.**

➢ Rebound hypertension occurs when blood pressure rises after you stop taking or lower the dose of a drug (typically a hypertension medication, e.g. **clonidine**).

## Stages of hypertension:

| JNC VII CLASSIFICATION | SYSTOLIC BLOOD PRESSURE (SBP) | | DIASTOLIC BLOOD PRESSURE (DBP) |
|---|---|---|---|
| LOW** | <90 | or | <60 |
| NORMAL | <120 | and | <80 |
| PREHYPERTENSION | 120 – 139 | or | 80 – 89 |
| HIGH: STAGE 1 HYPERTENSION | 140 – 159 | or | 90 – 99 |
| HIGH: STAGE 2 HYPERTENSION | ≥160 | or | ≥100 |
| **Hypertensive emergency** | **> 180** | **or** | **> 120** |

YouTube Video: Factors Affecting Blood Pressure

Figure: Body Response to hypotension

# Management of hypertension

## 1. Lifestyle modification:

Risk factors for hypertension include:

- Old age, Obesity, Tobacco, Lack of physical activity
- Certain chronic conditions (e.g., such as kidney disease and diabetes)
- Increased salt (sodium), Decreased potassium & Vitamin 6 in the diet

Thus patients with hypertension should follow some lifestyle modification, as weight loss, physical activity, sodium reduction and smoking cessation.

## 2. Drug Therapy:

Drug therapy is indicated to achieve target BP = < 140/ 90 mm Hg

* (target BP for diabetics = < 130/80 mm Hg)

| Drug Management of Hypertension: | | |
|---|---|---|
| Classification of Drug | | Examples |
| Diuretics | | Hydrochlorothiazide, Chlorthliazide and chlorthalidone, Furosemide |
| Drugs acting on the renin-angiotensin-aldosterone system (RAAS) | Angiotensin receptor Blockers | **Losartan, valosartan**, Candesatran, Telmisartan & irbesartan |
| | ACE Inhibitor | captopril, lisonopril, enalapril, ramipril |
| Calcium channel blockers | | Verapamil, Diltiazem & Nifedipine |
| Vasodilators | | Hydralazine, Minoxidil, Diazoxide, & Na-nitropruside |
| Drugs acting on sympathetic nervous system | β- Adrenoceptor Blockers | Nadolol, Bisoprolol, Atenolol, metoprolol, propranolol, Labetalol, & carvidalol |
| | α - Adrenoceptor Blockers | **Prazosin, doxazosin** & Terazosin |
| | Centrally acting sympatholytic | Clonidine & α methyl dopa |

**Antihypertensive drugs are used in combinations** for the following reasons:

1. To achieve synergism (improve effects), and thus decrease side effects by decreasing the pharmacological individual dose.
2. Appose side effects for one another.

Note: drugs from the same class or drugs with the same mechanism of action should NOT be combined together, as they may cause resistance and increase side effects.

# Diuretics & ARBs

## Diuretics Drugs:

| Group: | Thiazides | Loop diuretics | Potassium-sparing diuretics |
|---|---|---|---|
| Example | **Hydro-chlorothiazide, Chlorthliazide and chlorthalidone** | **Furosemide** (more potent diuresis but a smaller decrease in PVR) | • Amiloride<br>• Aldosterone antagonists (mainly spironolactone) |
| Uses | Thiazide diuretics can be used as initial drug therapy for Mild to Moderate hypertension | • hypertension with renal impairment<br>• manage symptoms of heart failure and edema. | minimal effect on lowering BP, but used in combination with loop diuretics and thiazides to reduce potassium loss induced by these diuretics |
| Mechanism | **The initial diuresis lasts 4-6 weeks and then replaced by a decrease in PVR.** E.g. thiazide diuretics lower BP 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. With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance. | | |
| Note | Diuretics may be adequate in mild to moderate hypertension, according to ALLHAT, chlorthalidone is superior to an ACE inhibitor, a calcium channel blocker and an alpha1-adrenergic antagonist in preventing one or more cardiovascular events (CVD). | | |

## Angiotensin receptors blockers (ARB):

| | Losartan | Valosartan | Others |
|---|---|---|---|
| Pharmaco-kinetics | Has a Potent active metabolite.<br>Effective Orally once daily (long half life).<br>Do not cross BBB. | No active metabolite | Candesatran, Telmisartan |
| Mechanism of action | • selective block of AT1 receptors, thus decreasing the activation of AT1 receptors by angiotensin II. Blocking the receptor itself, not only the ACE enzyme.<br>• **No effect on bradykinin**, no cough, no angioedema.<br>• Produce more complete inhibition of angiotensin than ACE inhibitors, as there are other enzymes (not only ACE) that can generate angiotensin | | |
| Clinical Uses | 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 | | |
| ADRs | As ACEI except cough and angioedema. (Thus can be used in asthmatic patients) | | |
| Contraindications | Same contraindications as ACEI | | |

# ACE inhibitors

| Captopril | Lisonopril | Enalapril | Ramipril |
|---|---|---|---|

## Mechanism

- ACE inhibitors decrease angiotensin II (vasoconstrictor) and **increase bradykinin** levels (vasodilator) by preventing its degradation by ACE.
- The antihypertensive effect of ACE inhibitors results primarily from vasodilatation (reduction of peripheral resistance) without reflexively increasing cardiac output, heart rate, or contractility.
- a **fall in aldosterone** production may also contribute.

## Pharmaco-kinetics

- Polar, excreted in urine → do not cross BBB
- Rapidly absorbed from GIT after oral administration. Food reduce their bioavailabilitym thus should be taken on empty stomach.
- Have a long half-life and thus given only once daily.
- **Enalapril & Ramipril are prodrugs**, converted to the active metabolite in the liver
- Enalaprilat is the active metabolite of Enalapril, can be given by I.V.. route in hypertensive emergency.
- It takes 2-4 weeks to see the full antihypertensive effect of ACEI

## Clinical use

- Essential hypertension, Particularly effective when hypertension results from excess renin production (renovascular hypertension in white & young patients)
- Hypertension with **chronic renal disease**, ischemic heart disease, diabetes.
- **Treatment of heart failure**, by reducing both cardiac preload and afterload, thereby decreasing cardiac work.

## Adverse Effects

- Acute renal failure, especially in patients with bilateral renal artery stenosis.
  loss of Ag II results in Vasodilation of efferent renal arterioles, which leads to reduce pressure in afferent arterioles and vasoconstriction, thus reducing renal blood flow (especially if already reduced by renal artery stenosis) and thereby reducing GFR.
- **Dry cough** (due to increased bradykinin levels).
- **Angioneurotic edema**, swelling in nose, tongue, throat & larynx (caused by inhibition of bradykinin metabolism which accumulate in bronchial mucosa)
- Severe hypotension in hypovolemic patients (e.g. patients taking diuretics) .
- Renal failure/ agensia (absence of kidneys) in the fetus, which will lead to oligohydramnios (deficiency of amniotic fluid).
- First dose effect (severe hypotension), thus should be given at bed time and start with small dose and increase the dose gradually.
- Hyperkalemia and hyperuricemia (may cause gout)
- **Specific to captopril: skin rash, fever, dysgeusia (loss of taste), Proteinuria and neutropenia.** These effects are due to a sulfhydryl group in the molecule of captopril.

## Contra-indications

- Patients with bilateral renal artery stenosis (to avoid renal failure)
- hypovolemic patients (due to Severe hypotension)
- **Pregnancy** (2nd & 3rd trimester) may lead to fetal hypotension, anuria, renal failure & malformation.
- Potassium-sparing diuretics, because ACEI may cause hyperkalemia.
- NSAISD, because they reduce their hypotensive effects by blocking bradykinin-mediated vasodilatation.

# Calcium channel blockers

| Class: | Dihydropyridine | Non-Dihydropyridine | |
|---|---|---|---|
| Example | Nifedipine ,Nicradipine, amlodipin | Verapmil | Diltiazem |
| Characteristic | act mainly on smooth muscle, thus more selective as vasodilators than cardiac depressants. They are, therefore, particularly beneficial in treating hypertension. | act more on myocardium as cardiac depressant | has intermediate effect in between |
| | | used in the treatment of atrial fibrillation and re-entry Supraventricular arrhythmias | |
| Pharmaco-kinetics | • given orally (onset= 0.5-2h) and I.V. injection for emergency (onset= 1-3min), well absorbed.<br>• CCBs have Short half-life. Sustained-release preparations can permit once-daily dosing, and thus preferred for the treatment of hypertension. | | |
| | verapamil and nifedipine are highly bound to plasma proteins ( more than 90%) | | Diltiazem is less ( 70-80%) |
| | Nifedipine Doesn't have an active metabolite | Verapmil & Diltiazem have active metabolites | |
| Mechanism of action | Block the influx of calcium through calcium channels (Ca is important for muscle contraction) resulting in:<br>1- Peripheral vasodilatation (mainly in arterioles)<br>2- Decrease cardiac contractility. | | |
| Clinical uses | 1-Treatment of chronic hypertension with diabetes or angina<br>2- **Nicardipine can be given by I.V. route & used in hypertensive emergency** | | |
| Adverse effects | Nifedipine: Reflex Tachycardia | Peripheral edema & severe **Constipation** | Peripheral edema (ankle edema) |
| | Headache (due to Hypotension) – Flushing (due to vasodilation) | | |

# Vasodilators

| | Hydralazine | Minoxidil | Diazoxide | Sodium nitropruside |
|---|---|---|---|---|
| **Site of action** | Arteriodilator | | | Arterio & venodilator |
| **Mechanism** | Direct | Opening of potassium channels | | Release of nitric oxide (NO)<br>MNM: Na-nitroprusside release NO |
| **admin.** | Oral | | I.V infusion | |
| **Uses (In combination)** | 1.Moderate-severe hypertension.<br>2. Hypertensive pregnant woman, but not as first-line.<br>3. CHF with rapid fatigue. | 2. correction of baldness, since it causes **Hypertrichosis** (the growth of body hair). | 1.Hpertensive emergency<br>2. Treat **hypoglycemia** due to Insulinoma (tumor of the pancreas that secrete insulin) | 2.Severe heart failure |
| **Adverse effect** | Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema)<br>These ADRs are due to activation of the sympathetic system & the RAAS after vasodilators-induced fall in BP, and thus should be used in combination with a diuretic and a β-blocker. | | | 1. Severe hypotension.<br>2. Headache, palpation (disappear when infusion is stopped)<br>3.Methemoglobin during Infusion<br>4.**Cyanide toxicity** (resulting in metabolic acidosis, arrhythmias, Severe hypotension and death)<br>5. Thiocyanate toxicity |
| **Specific adverse effects** | **lupus erythematosus like syndrome** | Hypertrichosis, thus Contraindicated in females<br>MNM: Minoxidil = used only for men | Hyperglycemia, thus Contraindicated in diabetics<br>MNM: Diazoxide= contraindicated in diabetes. | |

# α and β- Adrenoceptor – blockers

## β- Adrenoceptor – blocking agents

| | Non-cardio selective | cardio selective |
|---|---|---|
| **Drug** | **propanolol** | **Metoprolol , Atenolol,** Bisoprolol |
| **uses** | 1- can be used in mild to moderate hypertension<br>2-In severe cases used in combination with other drugs<br>3-may take 2 weeks to optimal therapeutic response (as ACEI)<br>4-evedance support using it with patient has concomitant coronary artery disease<br>5- When discontinued, ß- blockers should be withdrawn gradually to avoid rebound hypertension (not as severe as clonidine's). | |
| **Mechanism of action** | Decrease blood pressure by:<br>1- Decreasing cardiac output (blocking β1)<br>2- Decreasing renin release (blocking β1)<br>3- Central Mechanism (blocking β-R in CNS) | |
| **Adverse effect** | • Increased triglycerides<br>• Fatigue, Hypoglycemia.<br>• Mask the symptoms of Hypoglycemia in diabetic patients.<br>• Aggravate peripheral arterial disease (as Reynaud's disease)<br>• **Erectile dysfunction** | |

## α-adrenoceptor blockers

| | Prazosin | Doxazosin |
|---|---|---|
| | short-acting, causes first dose hypotension & postural hypotension | **Preferred, because of its long half- life** |
| **Mechanism of action** | • Block α-receptors in arterioles & venules<br>• Reduce pressure by decreasing preload & afterload | |
| **Clinical use** | 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. | |

# Centrally acting sympatholytic drugs

| | Clonidine (Direct α2-agonist) | α methyl dopa (Indirect α2 agonist, converted to methyl norepinephrine) |
|---|---|---|
| Mechanism of action | diminish adrenergic outflow from the C.N.S, & increase parasympathetic outflow to the heart. This leads to reduced total peripheral resistance, and decreased BP. | |
| uses | • hypertension **with renal disease** (it Does not decrease renal blood flow or glomerular filtration)<br>• resistant hypertension<br>(BP that remains elevated despite administration of an optimal three-drug regimen that includes a diuretic, due to drug misuse, drug interaction, compliance, etc.) | Safely used **in hypertension in pregnancy** (first-line) |
| Adverse effect | **Sudden withdrawal of clonidine can lead to rebound hypertension** | |

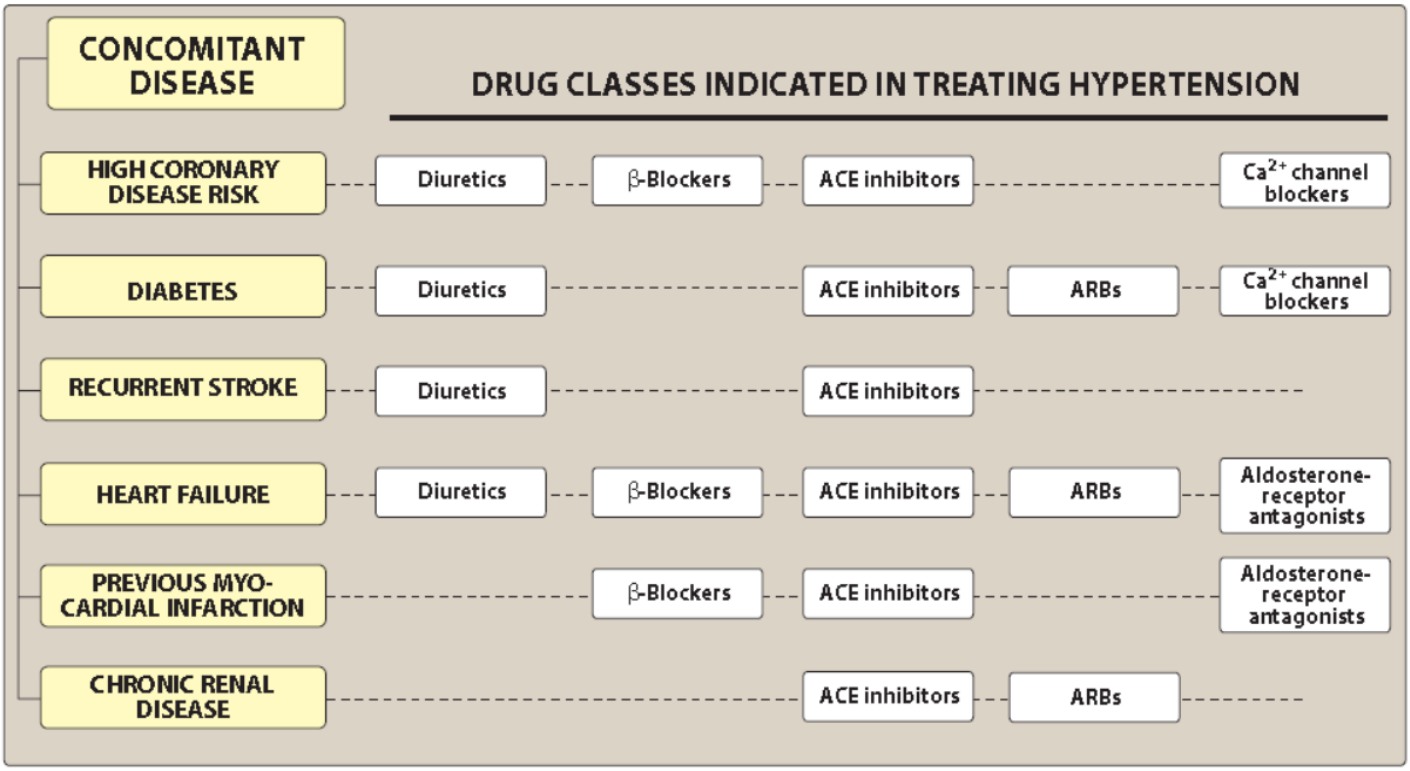


**Figure 17.5**
Treatment of hypertension in patients with concomitant diseases. [Note: Angiotensin receptor blockers (ARBs) are an alternative to angiotensin-converting enzyme (ACE) inhibitors.]

# QUIZ

## THANK YOU FOR CHECKING OUR WORK

### 435 PHARMACOLOGY TEAM

لولوه الصغير
شادن العمران
لمى الزامل
كوثر الموسى
ديمه الراجحي
جواهر الحربي
دلال الحزيمي
رنيم الدبيخي
نورة الصومالي
منيرة السلولي
نورة البصيص

شماء السعد
رهف بن عبّاد
سارة الخليفة
ساره المطوع
فاطمة الدين
آية غانم
أسرار باطرفي
نوف العبدالكريم
وضحى العتيبي
ريما الحيدان

عبدالرحمن السياري
أحمد اليحيى
خالد الزهراني
عبدالله الجنيدل
أحمد المصعبي
عبدالرحمن الزامل
عبدالرحمن الشمري
معاذ باعشن
عبدالعزيز الشعلان
محمد السحيباني
فارس المطيري
فوزان العتيبي
محمد ابونيان
عمر القحطاني
يوسف الصامل

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology.med435@gmail.com

PHARMACOLOGY
435