University of Al Qadisiyah  
College of Pharmacy  
Dr. Bassim I Mohammad,  
MBChB, MSc, Ph.D

Cardiovascular Pharmacology  
1. Antihypertensives  
2. Antianginal  
3. Drugs for HF  
4. Antiarythremics  
5. Drugs for Hyperlipoproteiniemia

Hypertension  
Hypertension is currently defined as usual BP of $\geq 140/80$ mmHg.  
- Hypertension may be defined as an abnormal elevation of either SBP or DBP  
- Hypertension is a condition that afflicts almost 1 billion people worldwide and is a leading cause of morbidity and mortality.  
- More than 20% of Americans are hypertensive, and one-third of these Americans are not even aware they are hypertensive. Therefore, this disease is sometimes called the "silent killer"  

Hypertension - Etiology  
- The are two basic types of hypertension:  
  - Primary (essential or idiopathic) hypertension  
  - Secondary hypertension  

Hypertension – Aetiology  
- Primary hypertension: The majority of patients (90-95%) have essential hypertension, which is a form with no identifiable underlying cause.  
- This form of hypertension is commonly treated with drugs in addition to lifestyle changes  
- Secondary hypertension: A smaller number of patients (5-10%) have secondary hypertension that is caused by an identifiable underlying condition.  
- These patients are best treated by controlling or removing the underlying disease or pathology, although they may still require antihypertensive drugs

Causes of 2$^{\text{nd}}$ Hypertension  
Renal or renovascular disease  
- Endocrine disease  
  - Phaeochromocytoma  
  - Cusings syndrome  
  - Conn’s syndrome  
  - Acromegaly and hypo or hyperthyroidism  
- Coarctation of the aorta  
- Pre-eclampsia  
- Stress (equivocal!!)  
- Iatrogenic (steroid, oral contraceptive, NSAIDs)

- Normal $<$120 and $<$80  
- Prehypertensive 120-139 or 80-89  
- Stage 1 Hypertension 140-159 or 90-99  
- Stage 2 Hypertension $>$160 $>$100
Target Organs

1. Stroke
2. LVH, IHD HF
3. Nephropathy
4. Retinopathy

A Significant CV and Renal Disease Risk Factor

1. Stroke
2. CAD
3. CHF LVH
4. Renal disease
5. Peripheral vascular disease
6. \( \uparrow \) Morbidity
7. \( \uparrow \) Disability

Goal of Treatment

1. *To control blood pressure.*
2. *To prevent complications.*
3. Because the majority of patients (with mild-moderate) HT are entirely asymptomatic our primarily goal is to decrease CV risk.
4. The objective of anti-HT therapy is to decrease BP (<140/80 mmHg) or even less in high risk patient like DM.
5. The benefit of treatment is greatest in those with high risk.

Non-Pharmacological Measures

1. Weight reduction (obese patients)
2. Aerobic exercise
3. Diet control
   • low calories, low fat, moderate Na intake
   • High in fruits and vegetables
   • fresh rather than proceed
4. Moderation of alcohol intake (red wine)
5. Cessation of Smoking
   • Independent risk factor
   • Malignant HT via renal artery damage.

What Determines Arterial Pressure?

**Arterial Pressure = Cardiac Output \* Peripheral Resistance**

Cardiac Output affected by (Heart Rate, Filling Pressure, Contractility)
Peripheral Resistance affected by (Arteriolar Radius)
Anti-hypertensive drugs

1. Diuretics
2. Beta Blockers
3. $a_1$-adrenoceptor antagonists ($a_1$-blockers)
4. $a_2$-adrenoceptor agonists
5. Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)
6. Angiotensin Receptor blockers (ARBs)
7. Renin Inhibitors
8. Calcium Channel Blockers (CCBs)
9. Potassium Channel openers
10. Peripheral Vasodilators

Diuretics

- **Diuretics** are basically acting as antihypertensive drugs by increasing Na and H2O renal excretion thereby decreasing the blood volume and CO. This is initial effects, later on diuretics decrease PVR.

- As a class agents diuretics are effective in treating:
  1. Patients with volume dependant form of HT (black, elderly, obese, renal).
  2. HT complicated with HF.
  3. Resistant HT
  4. Renal impairment

Thiazides Diuretics

- Thiazide and thiazide related agents are widely used as monotherapy or in combination with other antihypertensives (B-Blockers, ACEIs or ARBs).
- Low dose thiazide diuretics are effective and safe AntiHT agents in mild-moderate HT (12.5 mg of hydrochloorthiazide, chorthalidone and bendrofluzide).
- Low dose TD are preferred initial therapy for HT especially in elderly, obese and black patients.
- They are more effective in elderly and less effective in younger white.

1. TD are not effective when GFR severely reduced
2. **Advantages of low dose TD:**
   - To minimize the adverse metabolic effects
   - To decrease the risk of impotence
   - To avoid E disturbances
   - To avoid risk of \( \text{RCCa} \) especially in women.

Loop Diuretics

- Loop diuretics are not usually used as AntiHT agent (short acting, required multiple daily dosing).
- However they are indicated in HT emergency, renal insufficiency and when multiple drugs with salt retaining properties are used.
**B-blockers**

1. Propranolol
2. Atenolol
3. Metoprolol.
4. Timolol
5. Nadolol

- Primarily by decreasing HR, stroke volume and so COP followed by reduction in PVR.
- Inhibit renin release from the kidney and so decreasing the formation of Ang II and aldosterone secretion.
- Release of vasodilator PGs.
- Blockage of prejunctional B-receptors.

**Ideal Profile of Anti-HT B-blockers**

- Cardioselective
- Long acting (to prevent BP fluctuation)
- Simple Pks profile (good patient compliance)
- Effective in standard dose
- Has added vasodilating effect
- Has neutral effect on lipids

**B-blocker**

- B-blockers are commonly used as first line therapy for HT especially for young (rather than elderly), white (rather than black) patients or as alternative for diuretics.
- B-blockers are suitable antiHT drugs for patients with increase adrenergic drive and those with renin value.

**Conditions that discourage use of B-blockers**

- Severe COLD
- Chronic sever congestive HF
- Severe occlusive PVDs

These are commonly found in elderly and diabetic patients
\(\alpha\) –blockers:

- Prazocin
- Terazocin
- Doxazocin

- Selective \(\alpha\) -blockers are competitive blockers of \(\alpha_1\)-adrenoceptors and they have direct vasodilating effect (due to PDE inhibition).
- They decrease PVR and so Bp by dilating both arterioles and venules so they reduce preload and after load (balanced vasodilators).
- They are free from metabolic side effects.
- They have no or lesser place in initial monotherapy for HT.
- These drugs are usually combined with B-blocker (to prevent reflex tachycardia) and diuretics (to counter salt and water retention).
- Mild-moderate HT especially those patients with metabolic syndrome and those with BPH
- PVDs
- Refractory HF.

**Side Effects**

- Reflex tachycardia
- First-dose phenomena: brisk sever hypotension after the first or second dose of the drug usually 2 hours after administration. To avoid this phenomenon, we give the dose at bed time or start with small dose and increase it gradually.
- Orthostatic hypotension
- Nasal and conjunctival congestion
- Failure of (or retrograde) ejaculation

**Mixed \(\alpha\) and \(\beta\)-blockers**

- **Labetalol**: Hypertensive emergency and first line therapy for HT in black patients
- **Carbidolol**: Mild-Moderate HF and first line therapy for HT in black patients

**Drugs acting on RAAS**

1. Angiotensin Converting Enzyme Inhibitors (ACEIs)
2. Angiotensin Receptor Blockers (ARBs)
3. Renin Inhibitors
<table>
<thead>
<tr>
<th>ACE Inhibitors</th>
<th>ARBs</th>
<th>Renin Inhibitor</th>
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<tbody>
<tr>
<td>Captopril</td>
<td>Losartan</td>
<td>Aliskiren</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Irbesartan</td>
<td></td>
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<tr>
<td>Lisinopril</td>
<td>Candesartan</td>
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<tr>
<td>Ramipril</td>
<td>Valsartan</td>
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<tr>
<td>Perindopril</td>
<td>Telmisartan</td>
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<tr>
<td>Quinapril</td>
<td>Olmesartan</td>
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**Renin-Angiotensin-Aldosterone (RAA) System**

- Liver secretes angiotensinogen
- Kidneys secrete renin
- Adrenal cortex secretes aldosterone

Angiotensin Converting Enzyme Inhibitor, ACEIs
- Captopril
- Lisinopril
- Enalapril
- Fosinopril
- Zofinopril
ACEIs: Mechanism of Action

Angiotensin I

\[ \text{ACE} \]

Angiotensin II

↑ Sympathetic Output

Constrict Vascular Smooth Muscle

↑ Na⁺/H₂O Retention

Bradykinin

Angiotensinogen

Renin

Angiotensin I

Kininogen

Kalikrein

Bradykinin

Increased prostaglandin synthesis

Convertase Enzyme

1

2

Angiotensin II

Vasoconstriction

Increased peripheral vascular resistance

Aldosterone secretion

Increased sodium and water retention

Increased blood pressure

Increased prostaglandin synthesis

Vasodilation

Decreased peripheral vascular resistance

Decreased blood pressure
**ACEIs: Mechanism of Action**

- Renin is produced by the kidney in response to renal ischemia, hypoxemia and B2-adrenergic stimulation.
- Renin converts angiotensinogen (circulating protein) into Angiotensin-I (Ang I) which is an inert substance.
- Later, Ang-I is converted into Ang-II by the action of ACI (and by Chymases).
- Ang-II is a potent vasoconstrictor causing increase in PVR and stimulate aldosterone release (Na and H2O retention). Further Ang-II causes progressive vascular growth and end-organ damage.
- Action of Ang-II is mediated through specific receptors called Ang receptors (AT1 and AT2).
- AT1 (vasoconstriction, aldosterone release and vascular growth)
- AT2 (antigrowth so has favorable effects)
- ACEIs block the conversion of Ang-I to Ang-II. Further they lead to accumulation of Bradykinin (vasodilator) which is also substrate for ACE.
- Decreased formation of Ang-II (vasodilatation and decrease aldosterone release) and accumulation of Bradykinin (vasodilatation) results in reduction in BP
- Angiotensin II is one of the most potent vasoconstrictors known to man
- Angiotensin II releases aldosterone from the adrenal cortex
- Aldosterone enhances sodium and water retention and potassium loss from the kidney
- Blood volume and BP increase as a result
- Renin release from the juxtaglomerular cell
- Sympathetic nerve stimulation – beta-1 receptor
- Low blood sodium
- Low renal artery pressure
- Renin acts upon angiotensinogen to form angiotensin I
- Angiotensin I is converted to Angiotensin II by a converting enzyme called ACE
- Angiotensin II constricts the renal efferent arteriole more than the afferent arteriole
- It therefore increases or maintains high glomerular filtration pressure
- As mentioned previously, AT-II causes high levels of aldosterone, and therefore leads to water and salt conservation

**Blocking the Renin-Angiotensin System**

- BP decreases MAINLY by lowered TPVR
- Cardiac output is usually NOT significantly affected
- For some reason, reflex sympathetic stimulation DOES NOT OCCUR
- Absence of cardiostimulation makes these drugs safe in patients with ischemia

**ACEIs: Uses**

- Hypertension: as monotherapy or in combination therapy.
- Heart failure
- MI: post MI phase, they prevent vascular and cardiac remodelling.
- Asymptomatic LV dysfunction, they prevent development of overt CHF.

**Side Effects**

- Hypertension: as monotherapy or in combination therapy.
- Heart failure
- MI: post MI phase, they prevent vascular and cardiac remodelling.
- Asymptomatic LV dysfunction, they prevent development of overt CHF.
Calcium Channel Blockers (CCBs)

1. Dihydropyridines (DHP)
2. Non-DHP

<table>
<thead>
<tr>
<th>Dihydropyridines (DHP)</th>
<th>Non-DHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>• Diliazem</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>• Verapamil</td>
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<tr>
<td>Amlodipine</td>
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<td>Felodipine</td>
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<td>Isradipine</td>
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CCBs: Mechanism of Action

- CCBs block the inward movement of the Ca by binding and blocking the L-type voltage gated Ca channels in the heart and smooth muscles (of peripheral arterioles and coronary arteries) causing dilatation and relaxation mainly of the arterioles.
- All CCBs are therefore vasodilators decreasing arteriolar tone and systemic PVR resulting arterial BP (decrease after load).
- In addition CCBs decrease myocardial contractility (-ve inotropic) and the conduction in cardiac muscles (- chronotropic)
- Diliazem and verapamil: primary action on heart
- Dihydropyridines: primary action on arterioles
- Peripheral Effects: Nifedipine > Diliazem > verapamil
- Cardiac Effect: verapamil > Diliazem > Nefidipine

CCBs: PKs

- They are orally active agents; Verapamil and nicardipine are also given by IV route
- Most of them have short half lives
- High plasma protein binding and extensive metabolism
- All CCBs are save in pregnancy and renal failure

CCBs: Uses

1. Hypertension and HT emergencies: CCBs are alternative first line antihypertensive agents and can be used safely in pregnancy, asthma, DM or renal impairment. Nifidipine (SL) and nicardipine (IV) are used in HT emergencies
2. Angina pectoris (stable, unstable and it’s the drug of choice in variant type)
3. As antiarryrthmeic especially verapamil; it is the second choice in treatment or termination of SVT
4. PVDs
5. Subarrchinoid hemorrhage (nimodipine causes cerebral vasodilatation)
6. Although CCBs are contraindicated in HF, amlodipine can be used in the treatment of HF
7. Migraine prophylaxis especially verapamil
8. Tocolytics
CCBs: Side effects
• Headache, flushing of the face and dizziness
• Edema (nifedipine)
• Constipation (verapamil)
• Gingival hyperplasia
• AV block & heart failure (verapamil and diltiazem)
• Drug interactions: beta blockers (verapamil and diltiazem), cimetidine

Centrally Acting Drugs
• Methyldopa
• Clonidine

Direct Vasodilators
• Hydralazine
• Minixidil
• Diazoxid

Hypertensive emergencies
• Sodium Nitroprusside
• GTN
• Diazoxide
• Hydralazine
• Enalaprilat
• Nicardipine
• Esmolol
• Nifedipine – Sublingual
• Fenoldopam