

# Antihypertensive Drugs

## Etiology of Hypertension

- A specific cause of hypertension established in only 10–15% of patients.
- Patients in whom no specific cause of hypertension are said to have **essential or primary hypertension**.
- Patients with a specific etiology are said to have **secondary hypertension**.
- Genetic factors, psychological stress, and environmental and dietary factors as contributing to the development of hypertension. The heritability of essential hypertension is estimated to be about 30%.

## Classification of hypertension on the basis of blood pressure



**JNC 7;  
2003**

Systolic/Diastolic Pressure (mm Hg)	Category
< 120/80	Normal
120–135/80–89	Prehypertension
≥ 140/90	Hypertension
140–159/90–99	Stage 1
≥ 160/100	Stage 2

From the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA 2003;289:2560.

## Normal Regulation of Blood Pressure

According to the hydraulic equation, arterial blood pressure (BP) is directly proportionate to the product of the blood flow (cardiac output, CO) and the resistance to passage of blood through precapillary arterioles (peripheral vascular resistance, PVR)

- **BP = CO × PVR**

## Blood pressure is maintained by

- Moment-to-moment regulation of cardiac output and peripheral vascular resistance exerted at three anatomic sites arterioles, postcapillary venules (capacitance vessels), and heart.
- Kidney
- Baroreflexes mediated by autonomic nerves (combination with humoral mechanisms, including the renin-angiotensin-aldosterone system)
- Local release of vasoactive substances

# Antihypertensive agents

- **Diuretics**

- Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide
- High ceiling: Furosemide, etc.
- K<sup>+</sup> Sparing: Spironolactone, Amiloride

- **ACE inhibitors**

- Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril, etc.

- **Angiotensin (AT<sub>1</sub> receptor) blockers:** Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan

- **Direct renin inhibitor:** Aliskiren

- **β Adrenergic blockers:** Propranolol, Metoprolol, Atenolol, etc.

# Antihypertensive agents

- **Calcium channel blockers**
  - Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.
- **$\beta + \alpha$  Adrenergic blockers:** Labetalol, Carvedilol
- **$\alpha$  Adrenergic blockers:** Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine
- **Central sympatholytics:** Clonidine, Methyldopa
- **Vasodilators**
  - Arteriolar: Hydralazine, Minoxidil, Diazoxide
  - Arteriolar + venous: Sodium nitroprusside
- **Others:** Adrenergic neurone blockers (Reserpine, Guanethidine, etc.), Ganglion blockers (Pentolinium, etc.)

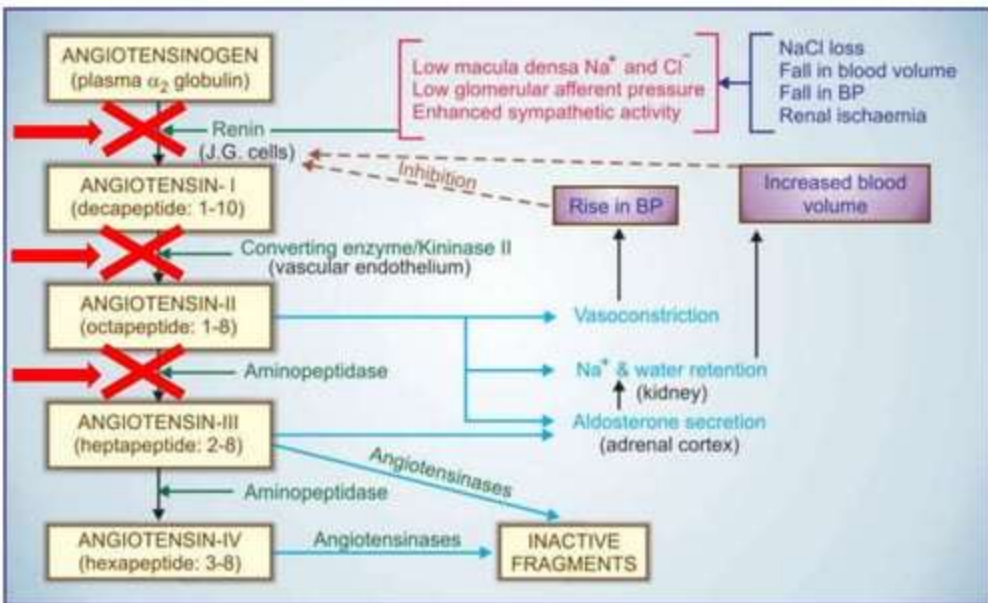
# Diuretics

- **Thiazide diuretics:** Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, lower blood pressure initially by increasing sodium and water excretion. Thiazide diuretics can induce hypokalemia, hyperuricemia and, to a lesser extent, hyperglycemia in some patients.
- **Loop diuretics:** Loop diuretics
  - Inhibitors of epithelial sodium transport at the late distal and collecting ducts (**furosemide**, and **ethacrynic acid**) or antagonizing aldosterone receptor (**spironolactone**, and **eplerenone**) and **reduce potassium loss in the urine**.
  - Aldosterone antagonists have the additional benefit of diminishing the cardiac remodeling that occurs in heart failure.
- **K<sup>+</sup> Sparing:** The loop diuretics act promptly 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



# ACE inhibitors

Renin Inhibitors



ACE Inhibitors

Angiotensin blockers

## ACE inhibitors

- The ACE inhibitors, 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 decrease angiotensin II and increase bradykinin levels. Vasodilation is result of decreased vasoconstriction (**from diminished levels of angiotensin II**) and enhanced vasodilation (**from increased bradykinin**).
- By reducing circulating angiotensin II levels, **ACE inhibitors also decrease the secretion of aldosterone**, resulting in decreased sodium and water retention.

# ACE inhibitors

## Adverse effects of ACE inhibitors:

- The adverse effect profile of all ACE inhibitors is similar. Captopril is well tolerated by most patients, especially if daily dose is kept below 150 mg.
- Hypotension: An initial sharp fall in BP occurs especially in diuretic treated and CHF patients
- Hyperkalaemia
- Cough
- Rashes, urticaria
- Angioedema
- Dysgeusia
- Foetopathic
- Headache, dizziness, nausea and bowel upset
- Granulocytopenia and proteinuria (rare ADR)
- Acute renal failure

# ACE inhibitors

## Advantages of ACE inhibitor:

- Free of postural hypotension, electrolyte disturbances, feeling of weakness and CNS effects
- Safety in asthmatics, diabetics and peripheral vascular disease patients
- Long-term ACE inhibitor therapy has the potential to reduce incidence of type 2 diabetes in high risk subjects
- No rebound hypertension on withdrawal
- No hyperuricaemia, no deleterious effect on plasma lipid profile
- ACE inhibitors are the most effective drugs for preventing sudden cardiac death in post-infarction patients. However, they are less effective for primary prophylaxis of MI and for preventing left ventricular hypertrophy.

## Uses of ACE inhibitors

- **Hypertension:** The ACE inhibitors are first line drugs in all grades of hypertension, but the angiotensin receptor blockers (ARBs) have now surpassed them in popularity.
- **Congestive Heart Failure (CHF):** ACE inhibitors cause both arteriolar and venodilatation in CHF patients; reduce afterload as well as preload.
- **Myocardial infarction:** Long-term ACE inhibitor therapy reduces recurrent MI.
- **Prophylaxis in high cardiovascular risk subjects:** ACE inhibitors are protective in high cardiovascular risk subjects even when there is no associated hypertension or left ventricular dysfunction. ACE inhibitors may improved endothelial function.
- **Diabetic nephropathy:** Prolonged ACE inhibitor therapy has been found to prevent or delay end-stage renal disease in type I as well as type II diabetics.
- **Scleroderma crisis:** The marked rise in BP and deterioration of renal function in scleroderma crisis is mediated by Ang II. ACE inhibitors produce improvement and are life saving in this condition.

## Angiotensin antagonists (ARBs)

- **Angiotensin antagonists:** losartan, candesartan, valsartan, telmisartan, olmesartan and irbesartan.
- Their pharmacologic effects of ARBs are similar to those of ACE inhibitors.
- ARBs 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.**
- ARBs 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.**

## Direct renin inhibitor

- A selective renin inhibitor, aliskiren directly inhibits renin and, thus, **acts earlier** in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs.
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides. **Aliskiren should not be routinely combined with an ACE inhibitor or ARBs.**
- **Aliskiren can cause diarrhea, especially at higher doses, and can also cause cough and angioedema, but probably less often than ACE inhibitors.**
- **Aliskiren is contraindicated during pregnancy.**

## **$\beta$ -adrenergic blockers**

- $\beta$ -adrenergic blockers are mild antihypertensives and do not significantly lower BP in normotensives. In stage 1 cases of hypertensive patients (30 - 40%),  $\beta$ -adrenergic blockers are used alone.



## **$\beta$ -adrenergic blockers**

### **Propranolol**

- Propranolol is a first  $\beta$  blocker showed effective in hypertension and ischemic heart disease.
- Propranolol has now been largely replaced by cardioselective  $\beta$  blockers such as metoprolol and atenolol.
- All  $\beta$ -adrenoceptor-blocking agents are useful for lowering blood pressure in mild to moderate hypertension.
- In severe hypertension,  $\beta$  blockers are especially useful in preventing the reflex tachycardia that often results from treatment with direct vasodilators.

## $\beta$ -adrenergic blockers

### Metoprolol & Atenolol

- Metoprolol and atenolol, which are cardioselective, are the most widely used  $\beta$  blockers in the treatment of hypertension.
- Metoprolol is atenolol is inhibiting stimulation of  $\beta_1$  adrenoceptors.
- Sustained-release metoprolol is effective in reducing mortality from heart failure and is particularly useful in patients with hypertension and heart failure.
- Atenolol is reported to be less effective than metoprolol in preventing the complications of hypertension.

## $\beta$ -adrenergic blockers

### Other beta blockers

- Nadolol and carteolol, nonselective  $\beta$ -receptor antagonists
- Betaxolol and bisoprolol are  $\beta_1$ -selective blockers
- Pindolol, acebutolol, and penbutolol are partial agonists, *ie*,  $\beta$  blockers with some **intrinsic sympathomimetic activity**. These drugs are particularly beneficial for patients with bradyarrhythmias or peripheral vascular disease.

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# $\beta$ -adrenergic blockers

## Other beta blockers

- Labetalol, Carvedilol, & Nebivolol have both  $\beta$ -blocking and vasodilating effects.
- Esmolol is a  **$\beta_1$ -selective blocker** that is rapidly metabolized *via* hydrolysis by red blood cell esterases. Esmolol is used for management of intraoperative and postoperative hypertension, and sometimes for hypertensive emergencies, particularly when hypertension is associated with tachycardia or when there is concern about toxicity such as aggravation of severe heart failure.

## **$\alpha$ -Adrenergic blockers**

### **Prazosin, terazosin, and doxazosin**

- Prazosin is a prototype  $\alpha_1$ -adrenergic blocking agent.
- Terazosin and doxazosin are long-acting congeners of prazosin
- Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels.

### **Other alpha-adrenoceptor blocking agents**

- phentolamine (reversible nonselective  $\alpha$ -adrenergic antagonist) and phenoxybenzamine (non-selective, irreversible alpha blocker) are useful in diagnosis and treatment of pheochromocytoma.

# Centrally acting adrenergic drugs

## Clonidine

- Clonidine acts centrally as an  $\alpha_2$  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. At present, it is occasionally used in combination with a diuretic.

## Methyldopa

- It is an  $\alpha_2$  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.**

## Vasodilators

- **Hydralazine/Dihydralazine** and **minoxidil** 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.
- 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.** This drug is used topically to treat male pattern baldness.



## Treatment of hypertension

- **Hypertensive emergency:** It is rare but life-threatening condition (systolic BP  $>180$  mm Hg or diastolic BP  $>120$  mm Hg with evidence of impending or progressive target organ damage such as stroke, myocardial infarction).
- A variety of medications are used, including calcium channel blockers (nicardipine and clevidipine), nitric oxide vasodilators (nitroprusside and nitroglycerin), adrenergic receptor antagonists (phentolamine, esmolol, and labetalol), the vasodilator hydralazine, and the dopamine agonist fenoldopam.

## Treatment of hypertension

- **Resistant hypertension:** It is defined as blood pressure that remains elevated despite administration of an optimal three-drug regimen that includes a diuretic. The most common causes of resistant hypertension
  - poor compliance
  - excessive ethanol intake
  - concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, metabolic syndrome)
  - concomitant medications (sympathomimetics, nonsteroidal anti-inflammatory drugs, or antidepressant medications)
  - insufficient dose/ drug

# Treatment of hypertension

- **Summary of WHO-ISH and British Hypertension Society (BHS) 2004, guidelines**
  - Except for stage II hypertension, start with a single most appropriate drug
  - Follow A B C D rule (A—ACE inhibitor/ARB; B— $\beta$  blocker; C—CCB, D—diuretic). While A and (in some cases) B are preferred in younger patients (<55 years), C and D are preferred in the older (> 55 years) for the step I or monotherapy.
  - Initiate therapy at low dose; if needed increase dose moderately.
  - If only partial response is obtained, add a drug from another complimentary class or change to low dose combination

# Treatment of hypertension

- **Summary of WHO-ISH and British Hypertension Society (BHS) 2004, guidelines**
  - If no response, change to a drug from another class, or low dose combination from other classes
  - In case of side effect to the initially chosen drug, either substitute with drug of another class or reduce dose
  - Majority of stage II hypertensives are started on a 2 drug combination

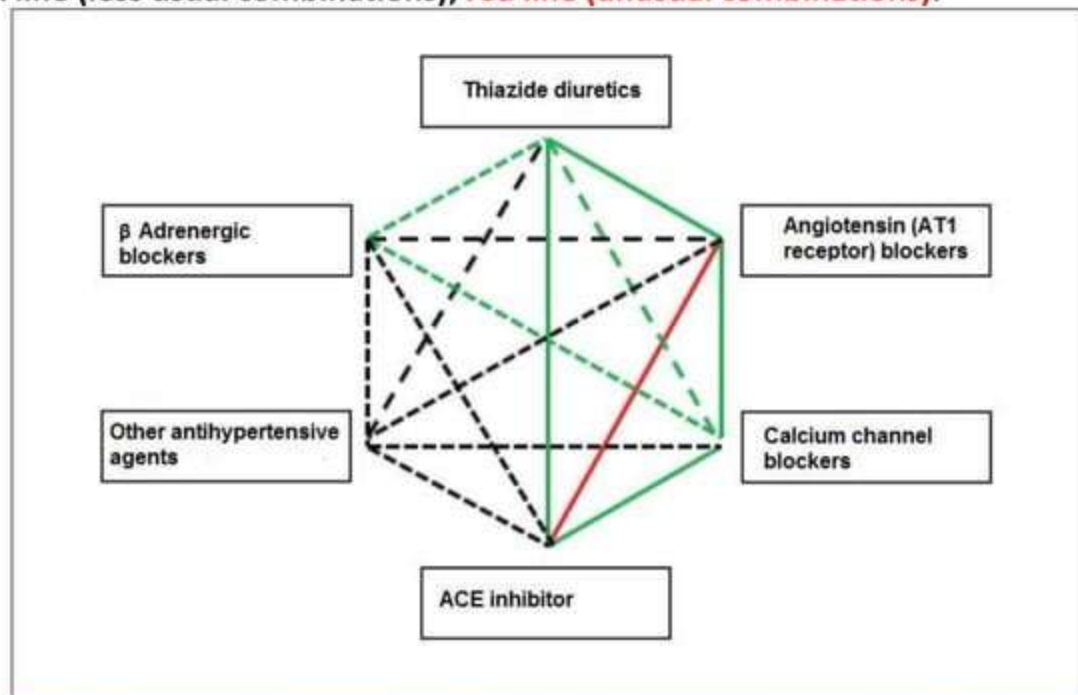
## Combinations to be avoided

Combination	Possible effects
An $\alpha$ or $\beta$ adrenergic blocker with clonidine	Apparent antagonism of clonidine action has been observed.
Hydralazine with a dihydropyridine (DHP) or prazosin	haemodynamic action
Verapamil or diltiazem with $\beta$ blocker	bradycardia, A-V block can
Methyldopa with clonidine or any two drugs of the same class	

## Antihypertensives & pregnancy

Antihypertensives to be avoided during pregnancy	Antihypertensives found safer during pregnancy
<b>ACE inhibitors, ARBs:</b> Risk of foetal damage, growth retardation.	Hydralazine Methyldopa
<b>Diuretics:</b> increase risk of foetal wastage, placental infarcts, miscarriage, stillbirth.	<b>Dihydropyridine CCBs:</b> if used, they should be discontinued before labour as they weaken uterine contractions.
<b>Nonselective <math>\beta</math> blockers:</b> Propranolol cause low birth weight, decreased placental size, neonatal bradycardia and hypoglycaemia.	<b>Cardioselective <math>\beta</math> blockers</b> and those with ISA, e.g. atenolol, metoprolol, pindolol, acebutolol: may be used if no other choice.
<b>Sod. nitroprusside:</b> Contraindicated in eclampsia.	Prazosin and clonidine-provided that postural hypotension can be avoided.

**Possible combination of antihypertensive drugs:** Continuous green line (preferential combinations); dotted green line (acceptable combinations); dotted black line (less usual combinations); **red line (unusual combinations).**



Ref: Póvoa R, Barroso WS, Brandão AA, et al. I brazilian position paper on antihypertensive drug combination. Arq Bras Cardiol. 2014;102(3):203-10.

# Complications of Hypertension

## Brain Stroke

Reduced blood supply to the brain can lead to rapid loss of brain function or stroke.

## Vision Loss

### Hypertensive Retinopathy

High blood pressure can damage blood vessels in the retina, resulting in loss of vision.

## Blood Vessel Damage

### Atherosclerosis

Hypertension is a leading cause of atherosclerosis, the artery-narrowing process that can result in heart attack and stroke.

## Heart Attack

Hypertension causes the heart to pump against high blood pressure, making it work harder than necessary. Over time, this causes the heart muscle to thicken, restricting blood flow which can lead to heart failure.

## Kidney Failure

Damaged blood vessels in the kidneys can't effectively filter your blood, resulting in a dangerous accumulation of fluid and waste.

## Bone Loss

High blood pressure may increase the amount of calcium in your urine. That excessive elimination of calcium may lead to loss of bone density (osteoporosis).



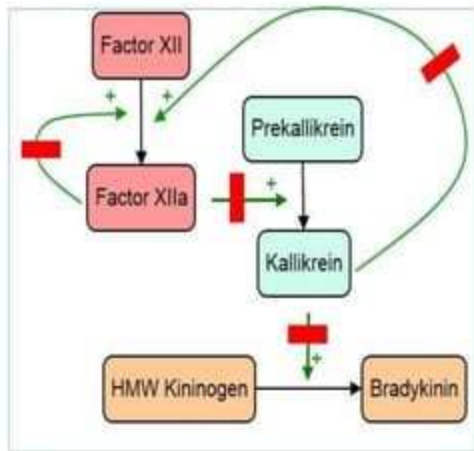
Thank you





## Plasma Kinins (Bradykinin and Kallidin)

- Kinins are generated by proteolytic reactions triggered by tissue injury, inflammation, allergic reaction, etc., and play important mediator roles.
- Kininogens are  $\alpha_2$  globulins present in plasma which also contains inactive kininogenase *prekallikrein*, which is activated by Hageman factor (factor XII) during tissue injury.



### Reference:

Hereditary angioedema. Available in <https://www.immunology.org/public-information/bitesized-immunology/immune-dysfunction/hereditary-angioedema>  
Last accessed on 30/08/2017

## Plasma Kinins (Bradykinin and Kallidin)

Bradykinin and kallidin have similar actions.

- **Cardiovascular system:** Kinins are more potent vasodilators than ACh and histamine. The dilatation is mediated through endothelial NO and PGI<sub>2</sub> generation, and involves mainly the arterioles.
- **Smooth muscle:** Action on other smooth muscles is not prominent, some may be relaxed also. Bradykinin causes marked bronchoconstriction in asthmatic patients.
- **Kidney:** Kinins increase renal blood flow as well as facilitate salt and water excretion by action on tubules.