



DRUGS ACTING ON CARDIO VASCULAR SYSTEM

ANTI-HYPERTENSIVE DRUGS

Subject : Pharmacology-II

Code : BP502TP

Prepared by

Ms. Shweta M. Pandya

Assistant Professor

B.Pharm, M.Pharm

Classification of hypertension on the basis of blood pressure



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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.

Antihypertensive agents

- **Diuretics**

- Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide
- High ceiling: Furosemide, Torsemide, ethacrynic acid.
- K⁺ Sparing: Spironolactone, Amiloride

- **ACE inhibitors**

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

- **Angiotensin (AT₁ receptor) blockers:** Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan

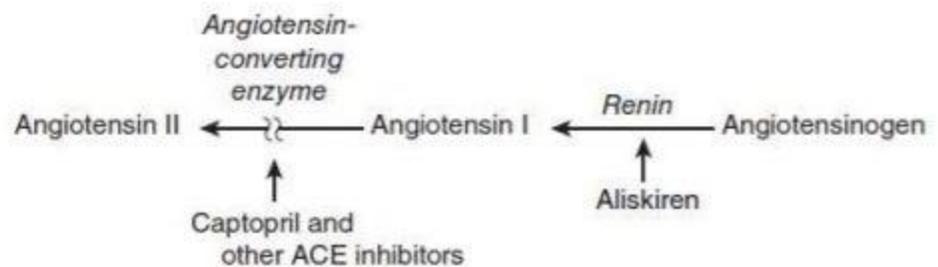
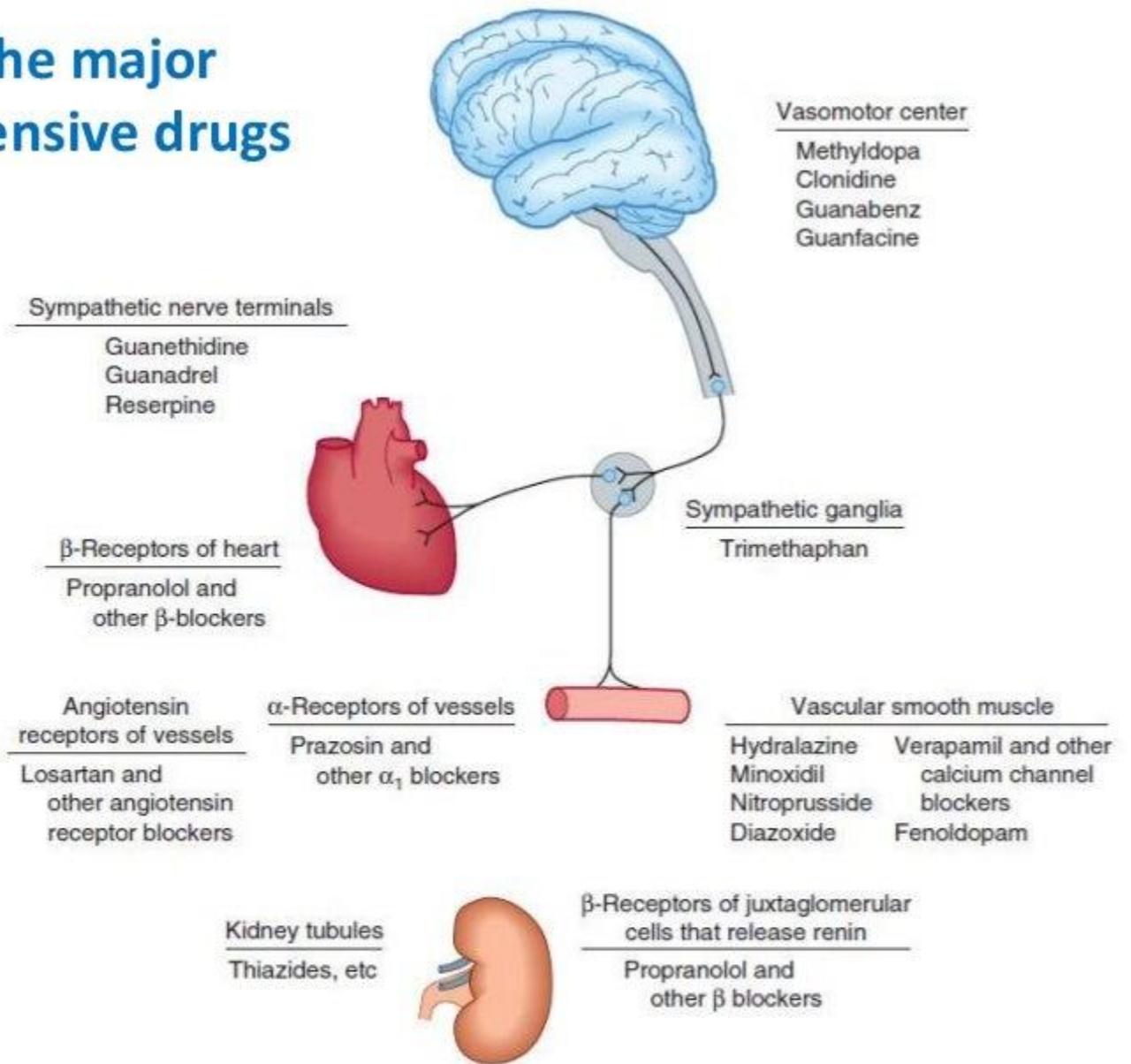
- **Direct renin inhibitor:** Aliskiren

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

Antihypertensive agents

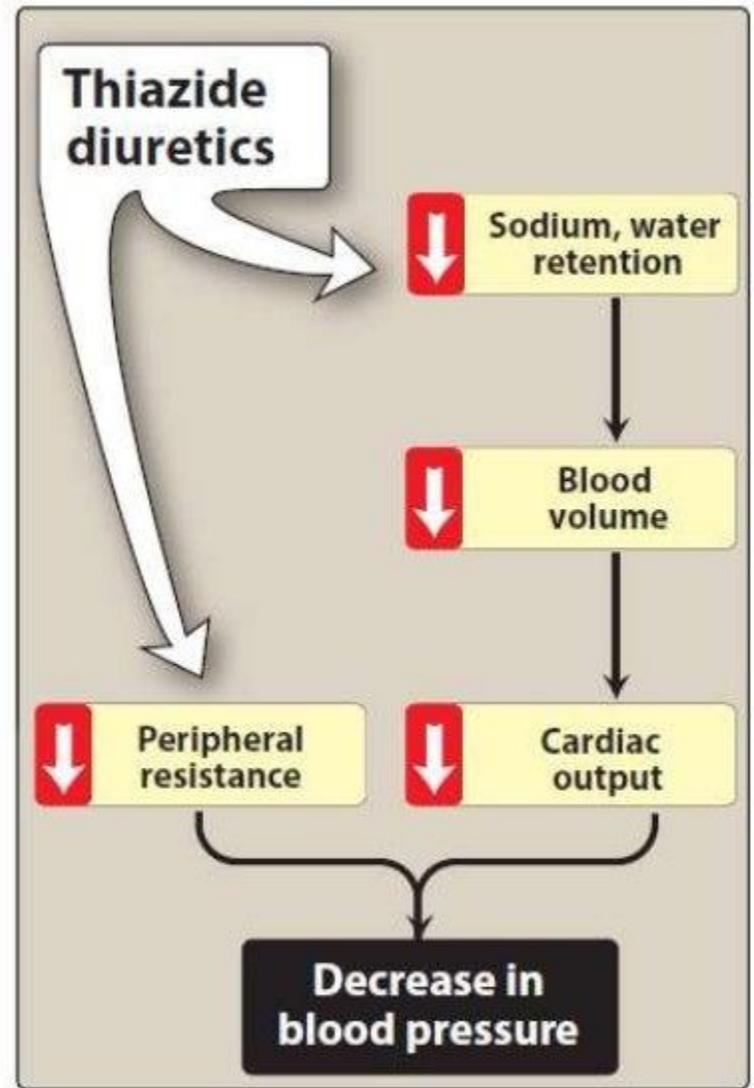
- **Calcium channel blockers**
 - Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.
- **$\beta + \alpha$ Adrenergic blockers:** Labetalol, Carvedilol
- **α Adrenergic blockers:** Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine
- **Central sympatholytics:**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

Sites of action of the major classes of antihypertensive drugs



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.



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.

Diuretics

- *Loop diuretics:*
- 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. Loop diuretics cause decreased renal vascular resistance and increased renal blood flow.

Diuretics

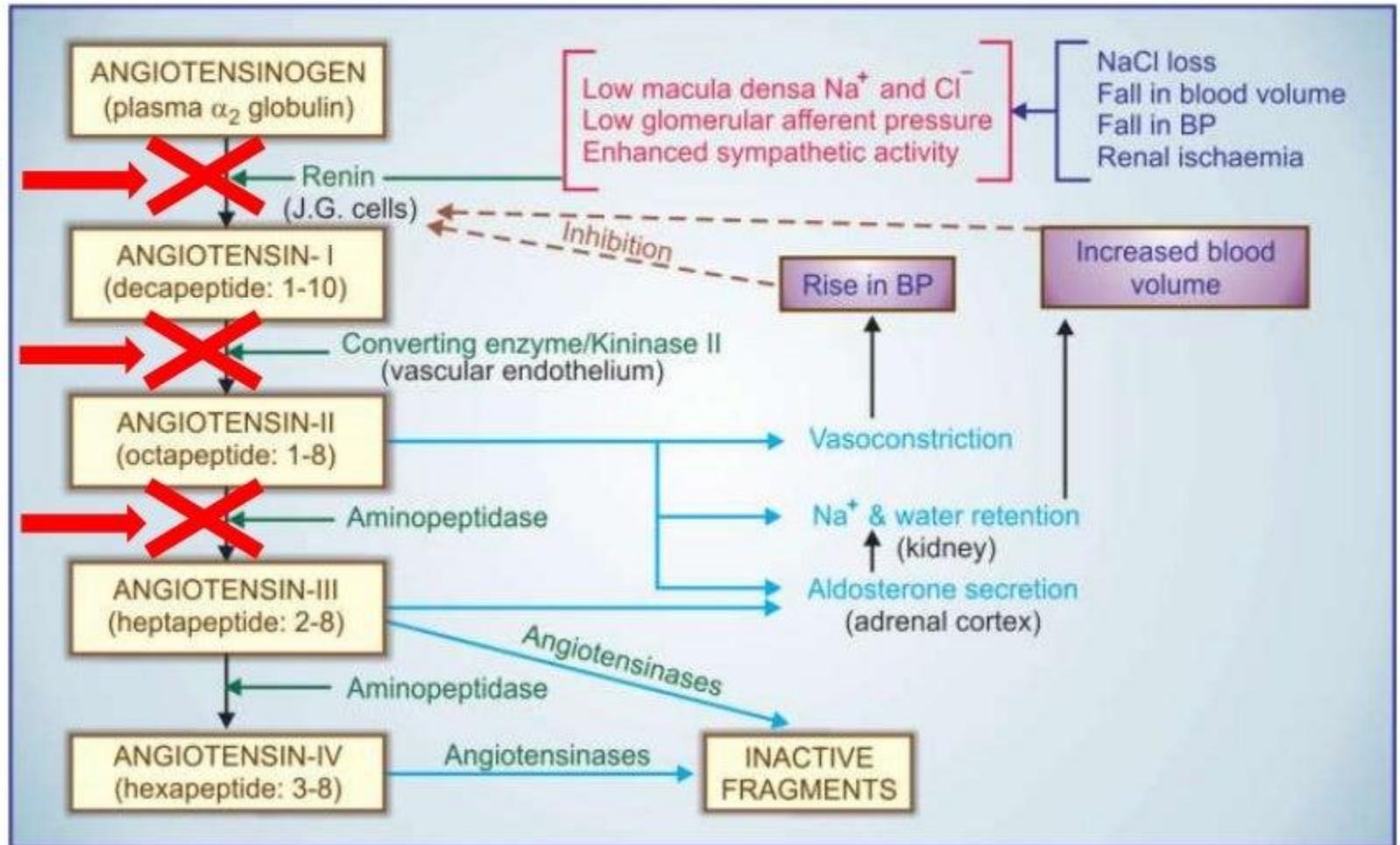
- *K⁺ Sparing:*
- potassium-sparing diuretics (**spironolactone**, and **eplerenone**) are competitive antagonists that either compete with aldosterone, or directly block epithelial sodium channel (**amiloride**).

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

- 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

- 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 **reduce both cardiac preload and afterload**, thereby **decreasing cardiac work**.

ACE inhibitors

Comparative features of some ACE inhibitors

	<i>Captopril</i>	<i>Enalapril</i>	<i>Lisinopril</i>	<i>Fosinopril</i>	<i>Perindopril</i>	<i>Ramipril</i>
1. Chemical nature	Sulfhydryl	Carboxyl	Carboxyl	Phosphinate	Carboxyl	Carboxyl
2. Activity status	Active	Prodrug	Active	Prodrug	Prodrug	Prodrug
3. Bioavailability (as active form)	70%	50%	25%	30%	30–50%	60%
4. Time to peak action	1 hr	4–6 hr	6–8 hr	3–5 hr	6 hr	3–6 hr
5. Elimination $t_{1/2}$ *	2 hr	11 hr	12 hr	12 hr	25–30 hr	8–48 hr
6. Mode of excretion	Renal	Renal	Renal	Renal/hepatic	Renal	Renal
7. Duration of action	6–12 hr	24 hr	≥ 24 hr	24 hr	> 24 hr	>24 hr
8. Daily dose (mg)	25–150	2.5–40	5–40	10–40	2–8	1.25–10

* $t_{1/2}$ including that of active metabolite

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

ACE inhibitors

Adverse effects of ACE inhibitors:

- Dysgeusia/ parageusia
- Foetopathic
- Headache, dizziness, nausea and bowel upset
- Granulocytopenia and proteinuria (rare ADR)
- Acute renal failure

ACE inhibitors

Advantages of ACE inhibitor:

- 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.
- Essential hypertension respond to monotherapy with ACE inhibitors and majority of the rest to their combination with diuretics or beta blockers.

Uses of ACE inhibitors

- **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.

Uses of ACE inhibitors

- **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.
- **Nondiabetic nephropathy:** ACE inhibitors reducing proteinuria by decreasing pressure gradient across glomerular capillaries as well as by altering membrane permeability.
- **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.**

β -adrenergic blockers

Propranolol

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

β -adrenergic blockers

Metoprolol & Atenolol

- Metoprolol and atenolol, which are cardioselective, are the most widely used β blockers in the treatment of hypertension.
- Metoprolol is atenolol is inhibiting stimulation of β_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.**

α -Adrenergic blockers

Prazosin, terazosin, and doxazosin

- Prazosin is a prototype α_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 α -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 α_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 α_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.

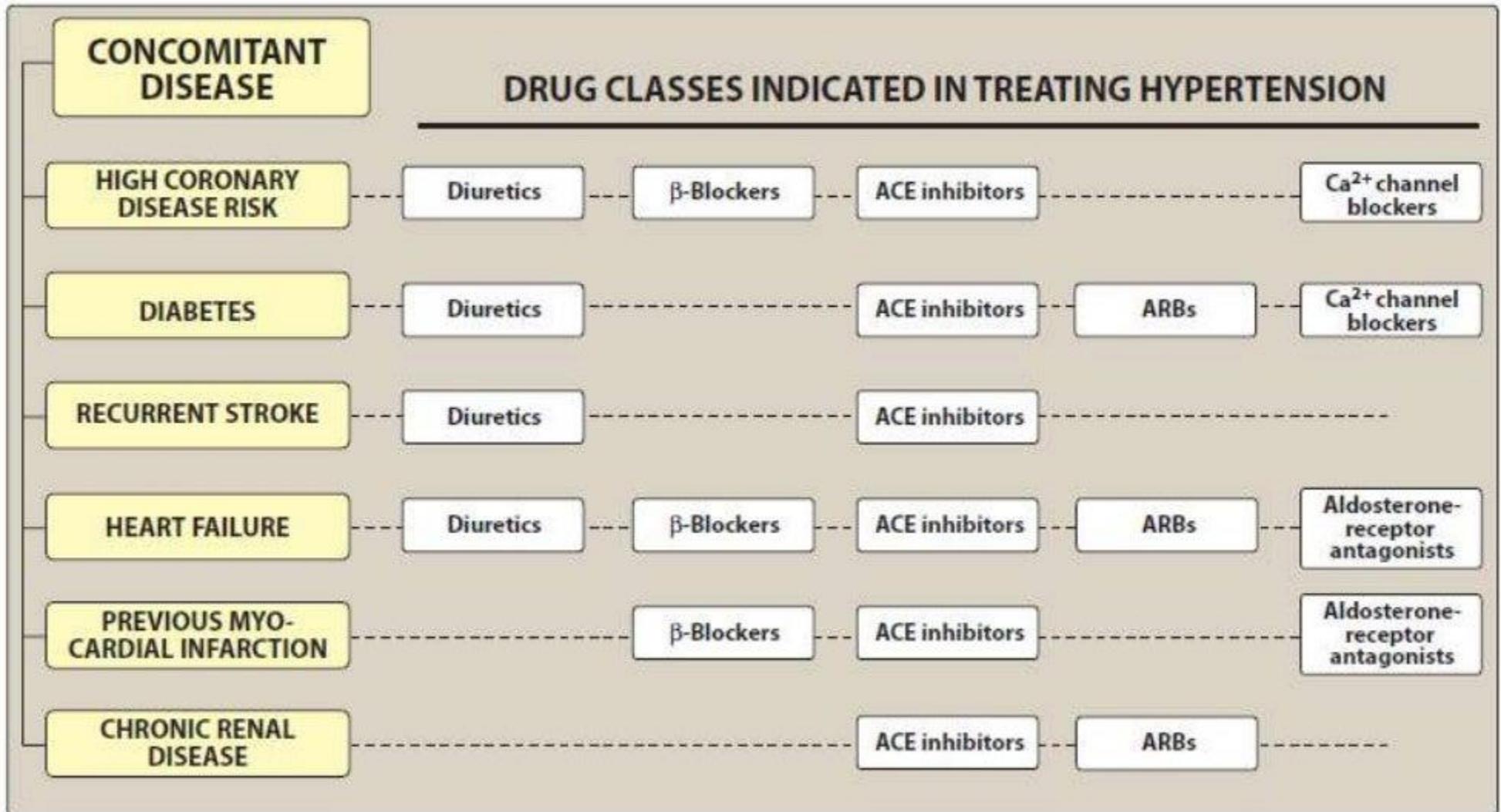
Treatment of hypertension

- **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— β 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

Treatment of hypertension in patients with concomitant diseases



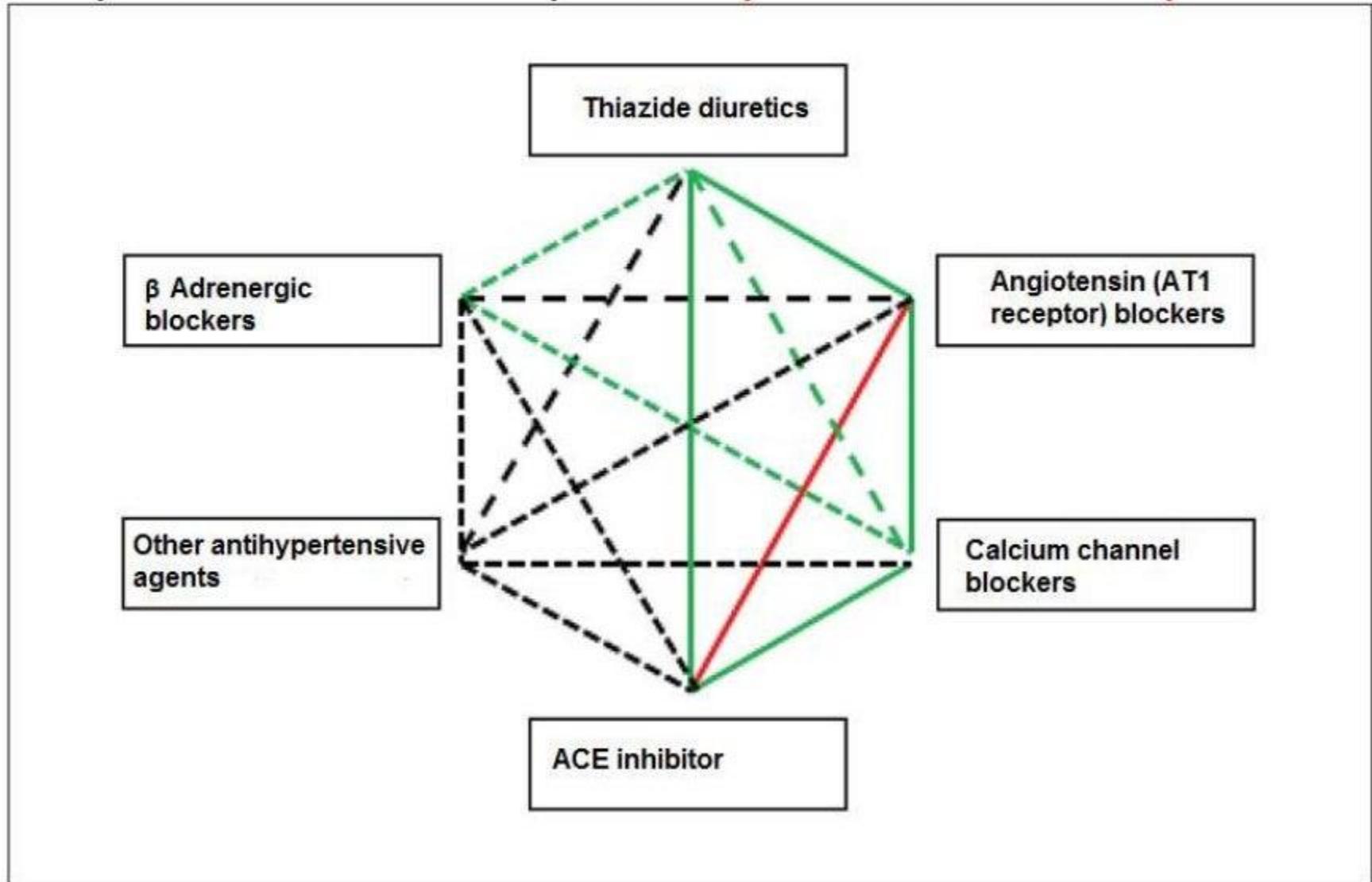
Combinations to be avoided

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

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