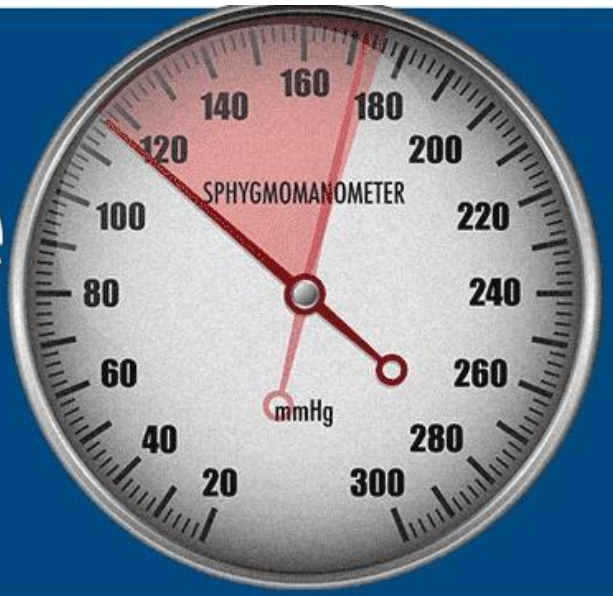
Antihypertensive Drugs



Dr. Mohammad Jadaan

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.

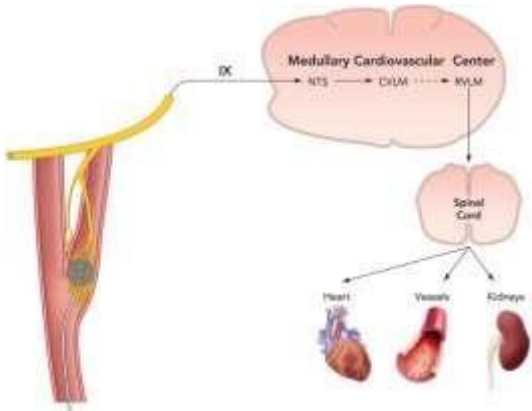
Normal Regulation of Blood Pressure

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** 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, 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.

- **β + α Adrenergic blockers:** Labetalol, Carvedilol
- **α Adrenergic blockers:** Prazosin, Terazosin, Doxazosin,Phentolamine, Phenoxybenzamine

Antihypertensive agents

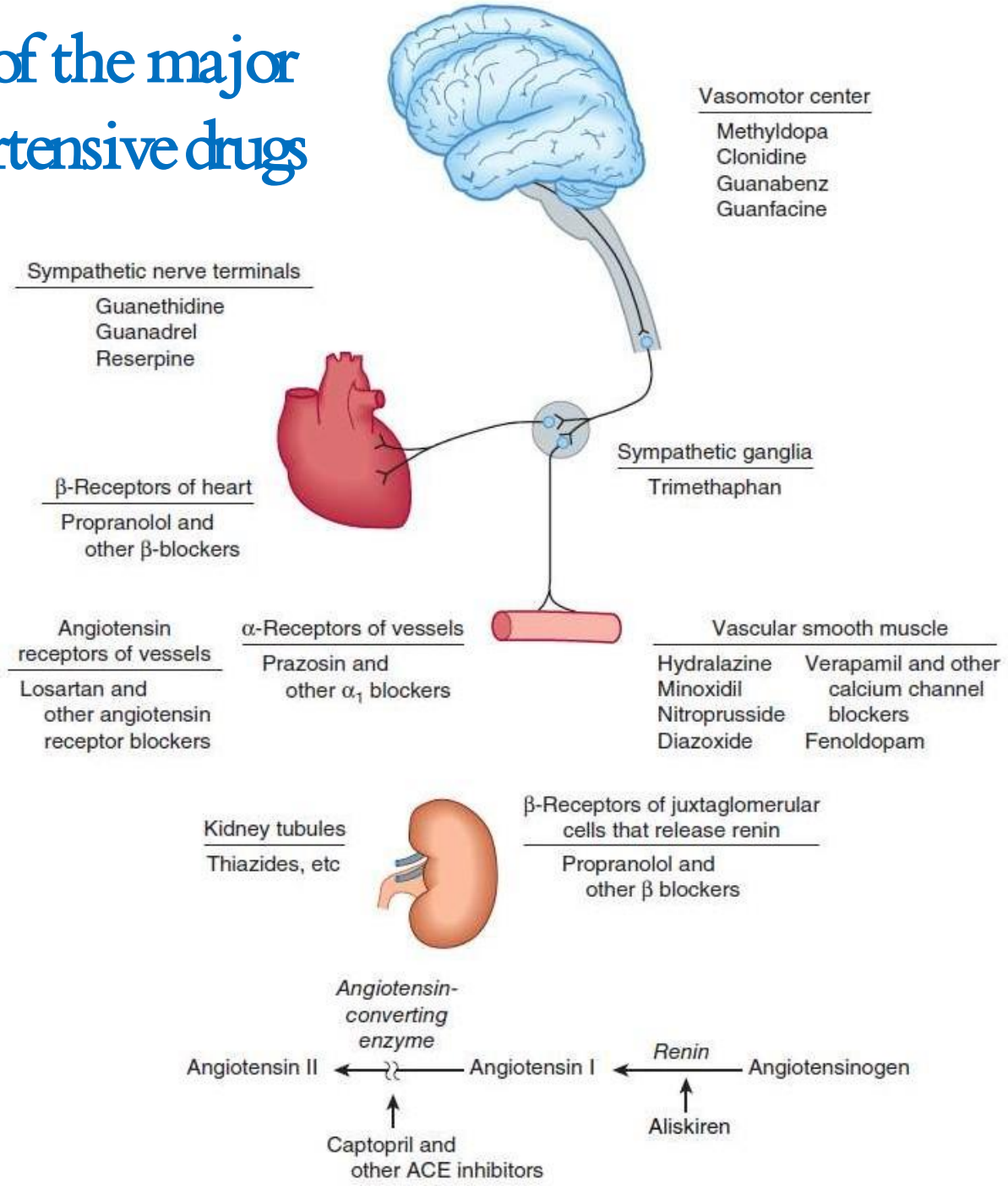
- **Central sympatholytics:** Clonidine, Methyldopa
- **Vasodilators**

– Arteriolar: Hydralazine, Minoxidil, Diazoxide

– Arteriolar + venous: Sodium nitroprusside

- **Others:** Adrenergic neurone blockers (Reserpine, Guanethidine, etc.), Ganglion blockers (Pentolinium, etc.)

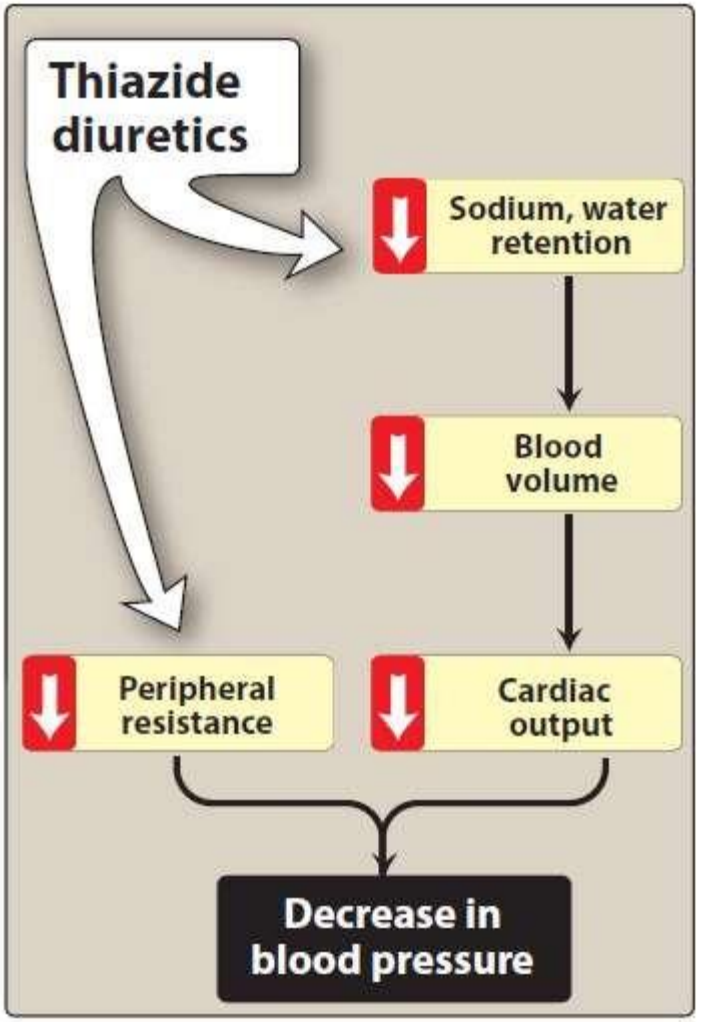
Sites of action of the major classes of antihypertensive drugs



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**) and **reduce potassium loss in the urine**.

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.

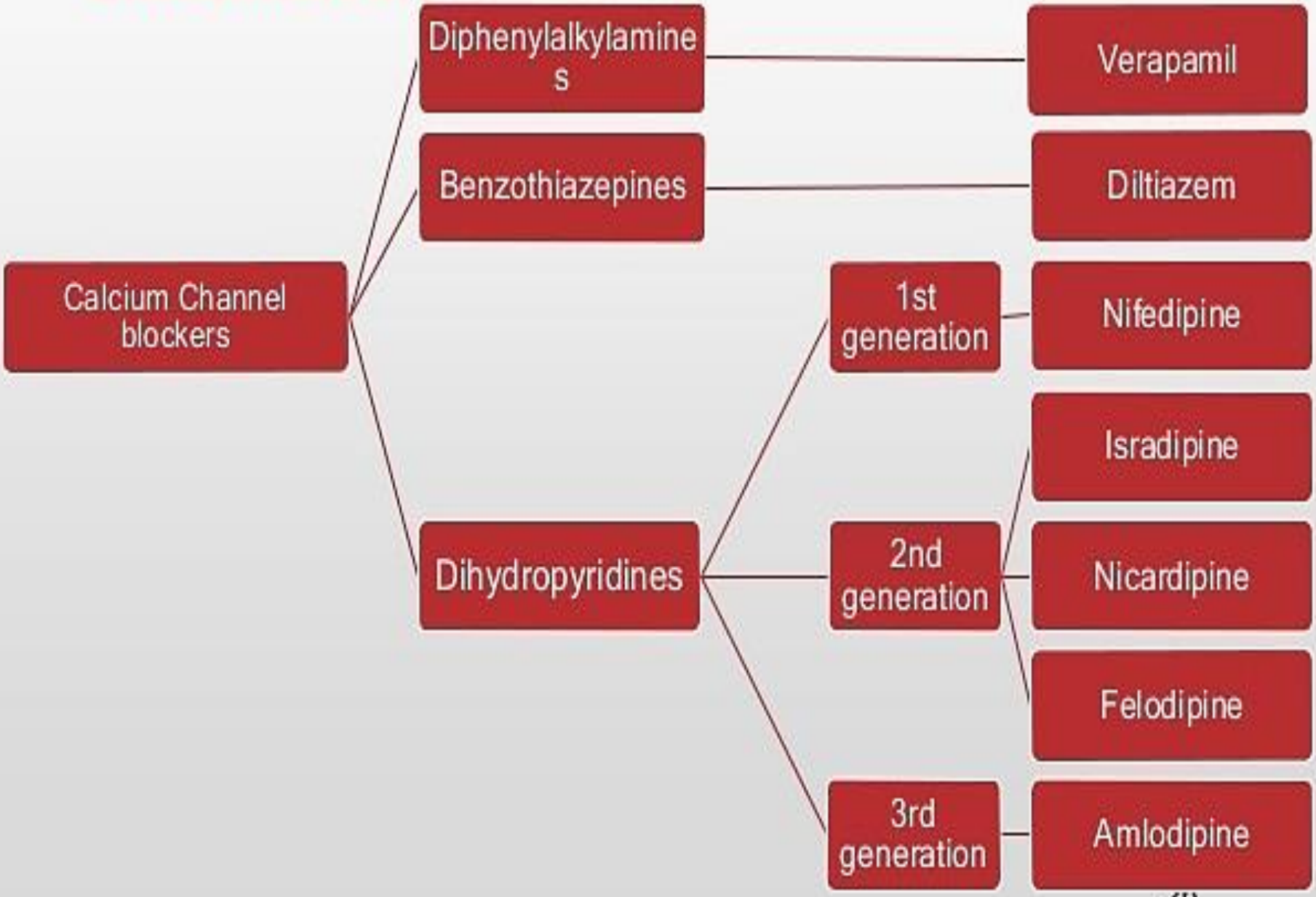
Diuretics

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

Calcium Channel Blockers

Credit: Alex SG/Shutterstock.com

Classification



Mechanism of action

- Three types Ca+ channels in smooth muscles – Voltage sensitive, receptor operated and leak channel
- Voltage sensitive are again 3 types – L-Type, T-Type and N-Type
- Normally, L-Type of channels admit Ca+ and causes depolarization – excitation-contraction coupling through phosphorylation of myosin light chain – contraction of vascular smooth muscle – elevation of BP

Mechanism of action

- CCBs block L-Type channel:
  - Smooth Muscle relaxation
  - Negative ionotropic and chronotropic effects in heart
- DHPs have highest smooth muscle relaxation and vasodilator action followed by verapamil and diltiazem
- Other actions: DHPs have diuretic action

Advantages of Calcium Channel Blockers

- Unlike diuretics no adverse metabolic effects but mild adverse effects like – dizziness, fatigue etc.
- Do not compromise haemodynamics – no impairment of work capacity
- No sedation or CNS effect
- Can be given to asthma, angina and PVD patients
- No renal and male sexual function impairment
- No adverse fetal effects and can be given in pregnancy
- Minimal effect on quality of life

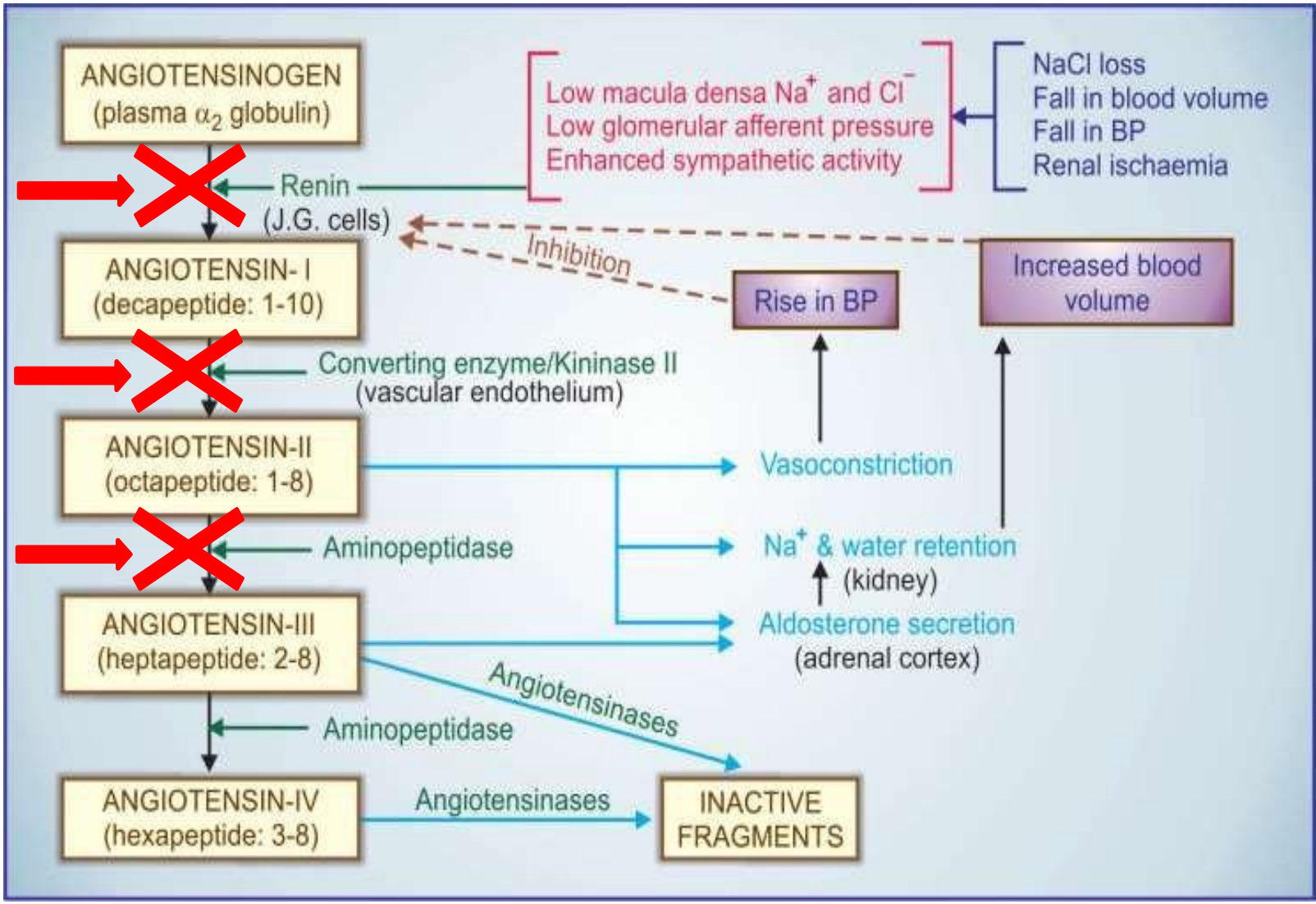
- **Contraindications:**
  - Unstable angina
  - Heart failure
  - Hypotension
  - Post infarct cases
  - Severe aortic stenosis
- **Preparation and dosage:**
  - Amlodipine – 2.5, 5 and 10 mg tablets (5-10 mg OD).
  - Nimodipine – 30 mg tab and 10 mg/50 ml injection.

ACE inhibitors

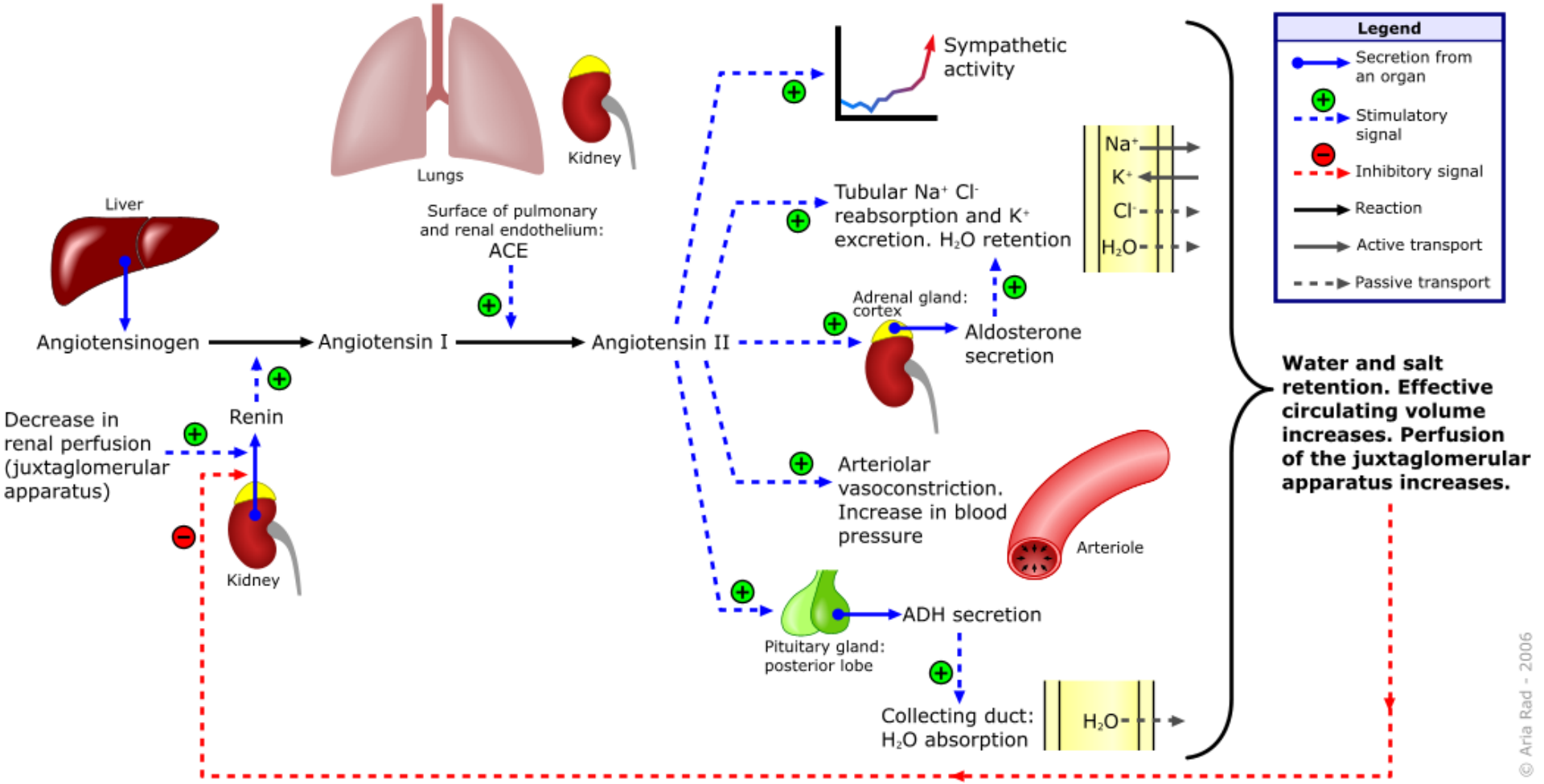
Renin Inhibitors

ACE Inhibitors

Angiotensin blockers



Renin-angiotensin-aldosterone system



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**).

ACE inhibitors

- 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

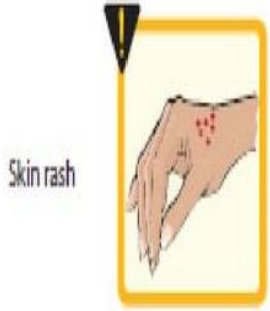
Comparative features of some ACE inhibitors

	Captopril	*Enalapril*	*Lisinopril*	*Fosinopril*	*Perindopril*	*Ramipril*
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 t½*	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

* t½ including that of active metabolite

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



Adverse effects of ACE inhibitors:

- Dysgeusia/ parageusia
- Headache, dizziness, nausea and bowel upset
- Granulocytopenia and proteinuria
- Acute renal failure

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

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

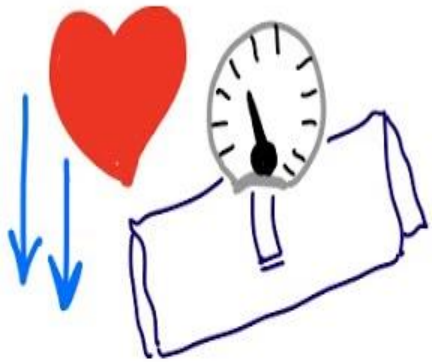
❑ Hypertension:

- ✓ 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.

- **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.
- **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.

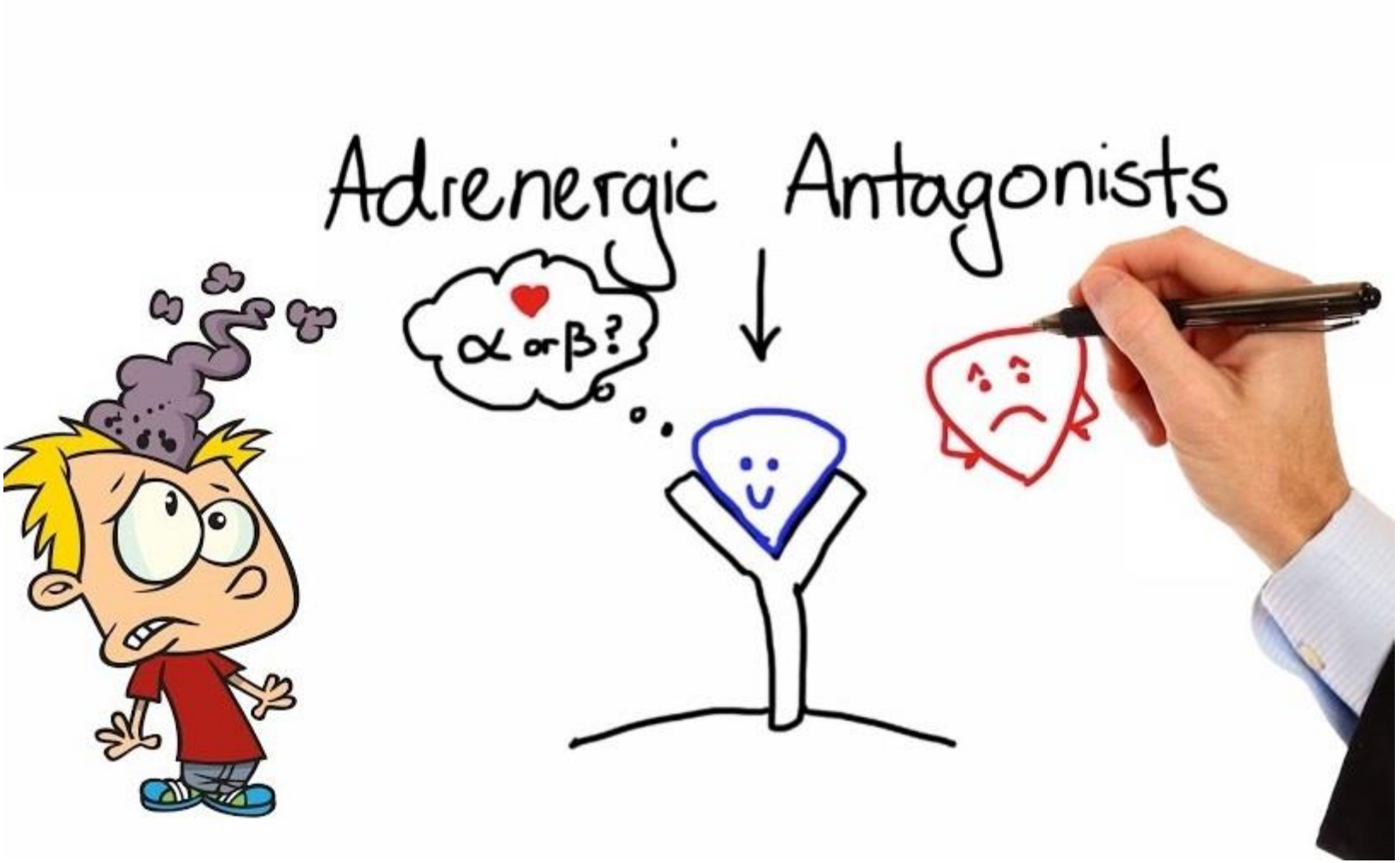
Angiotensin Receptor Blockers (ARBs)



- **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.


Adrenergic Antagonists
α or β?

β-adrenergic blockers

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

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.

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 β1 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.

Other beta blockers

- Nadolol and carteolol, nonselective β-receptor antagonists
- Betaxolol and bisoprolol are β1-selective blockers
- Pindolol, acebutolol, and penbutolol are partial agonists, *ie*, β blockers with some **intrinsic sympathomimetic activity**.
- These drugs are particularly beneficial for patients with bradyarrhythmias or peripheral vascular disease.

- Labetalol, Carvedilol, & Nebivolol have both β blocking and vasodilating effects.
- Esmolol is a β1-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.

α-Adrenergic blockers

Prazosin, terazosin, and doxazosin

- Prazosin is a prototype α1-adrenergic blocking agent.
- Terazosin and doxazosin are long-acting congeners of prazosin
- Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels.

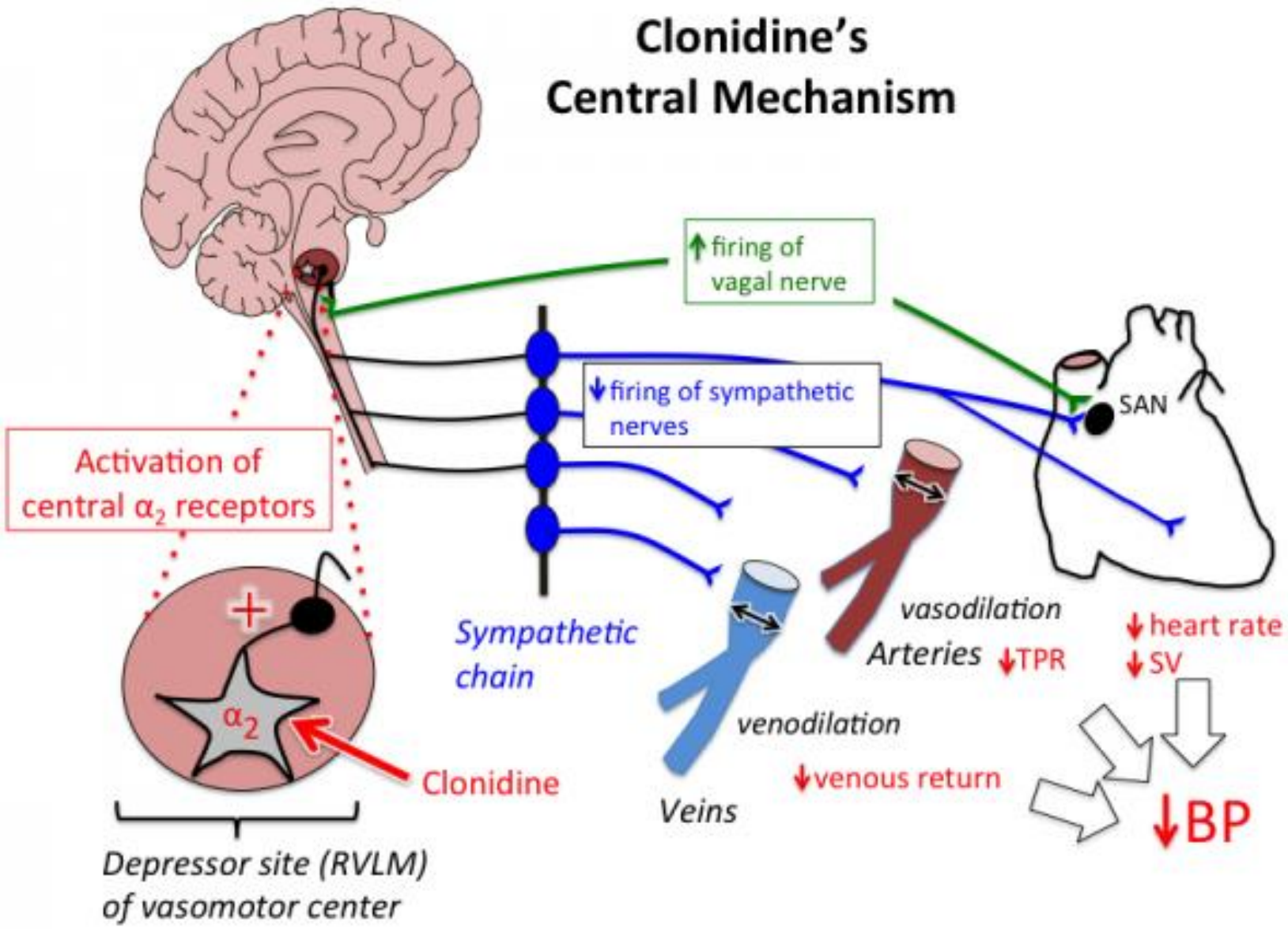
Other alpha-adrenoceptorblocking agents

- 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

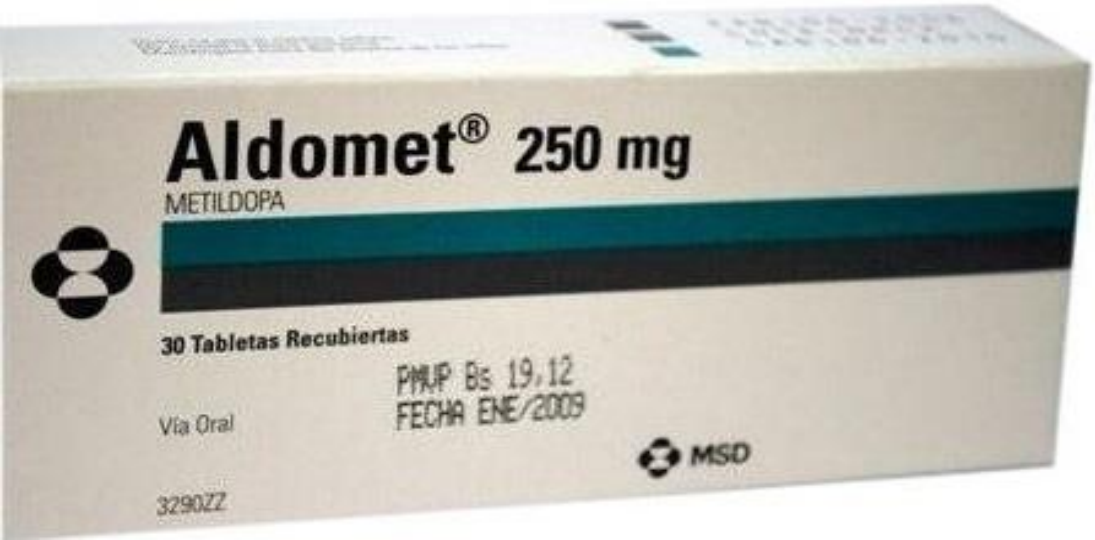
Clonidine

- Acts centrally as an α2 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.


Clonidine's
Central Mechanism
↑firing of
vagal nerve
↓firing of sympathetic
nerves
SAN
Activation of
central α_2 receptors
Sympathetic
chain
vasodilation
Arteries
↓TPR
↓heart rate
↓SV
venodilation
↓venous return
Veins
↓BP
α_2
Clonidine
Depressor site (RVLM)
of vasomotor center

Methyldopa

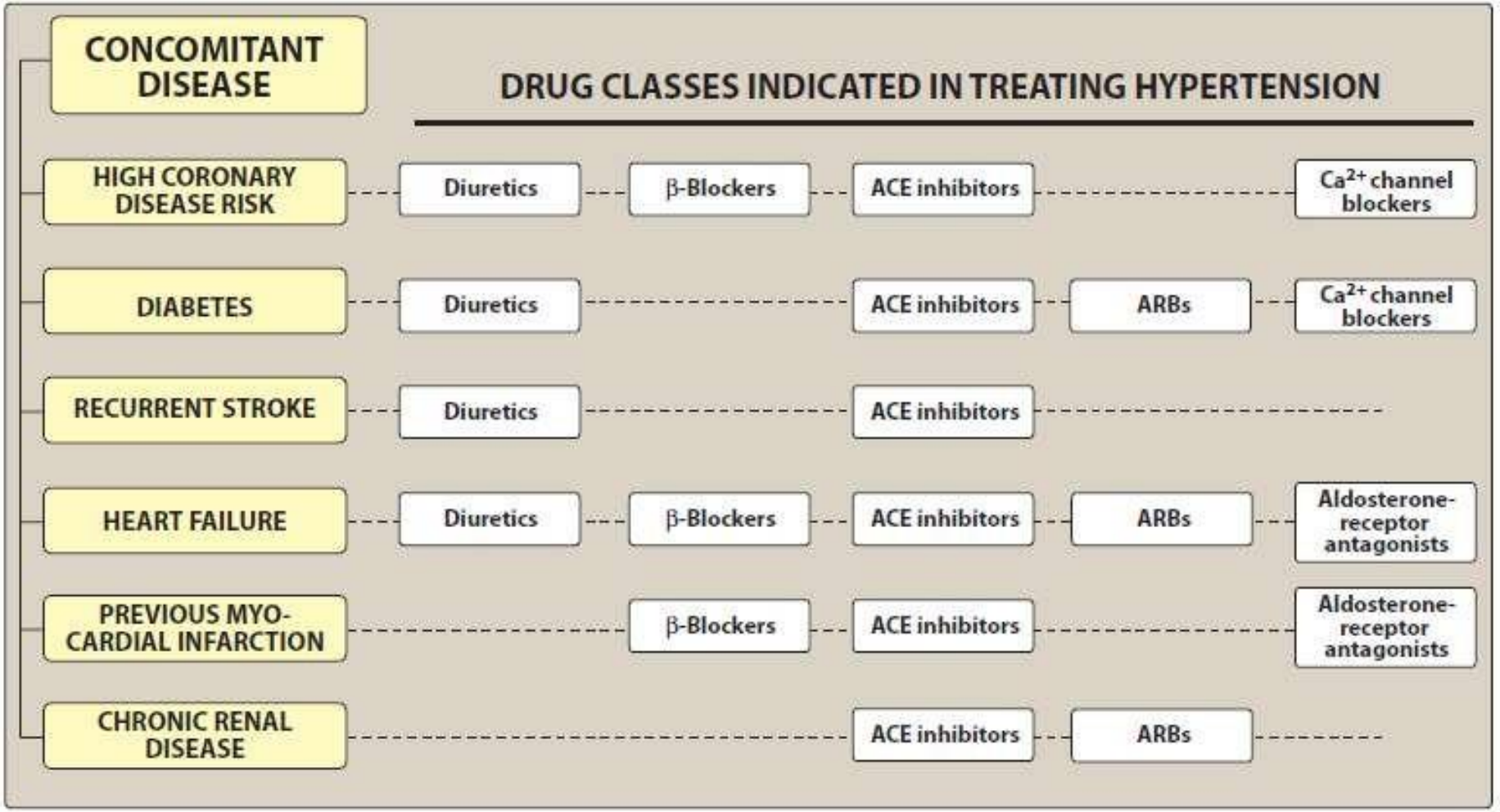
- It is an α_2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS.
- It is mainly used for management of hypertension in pregnancy, where it has a record of safety.



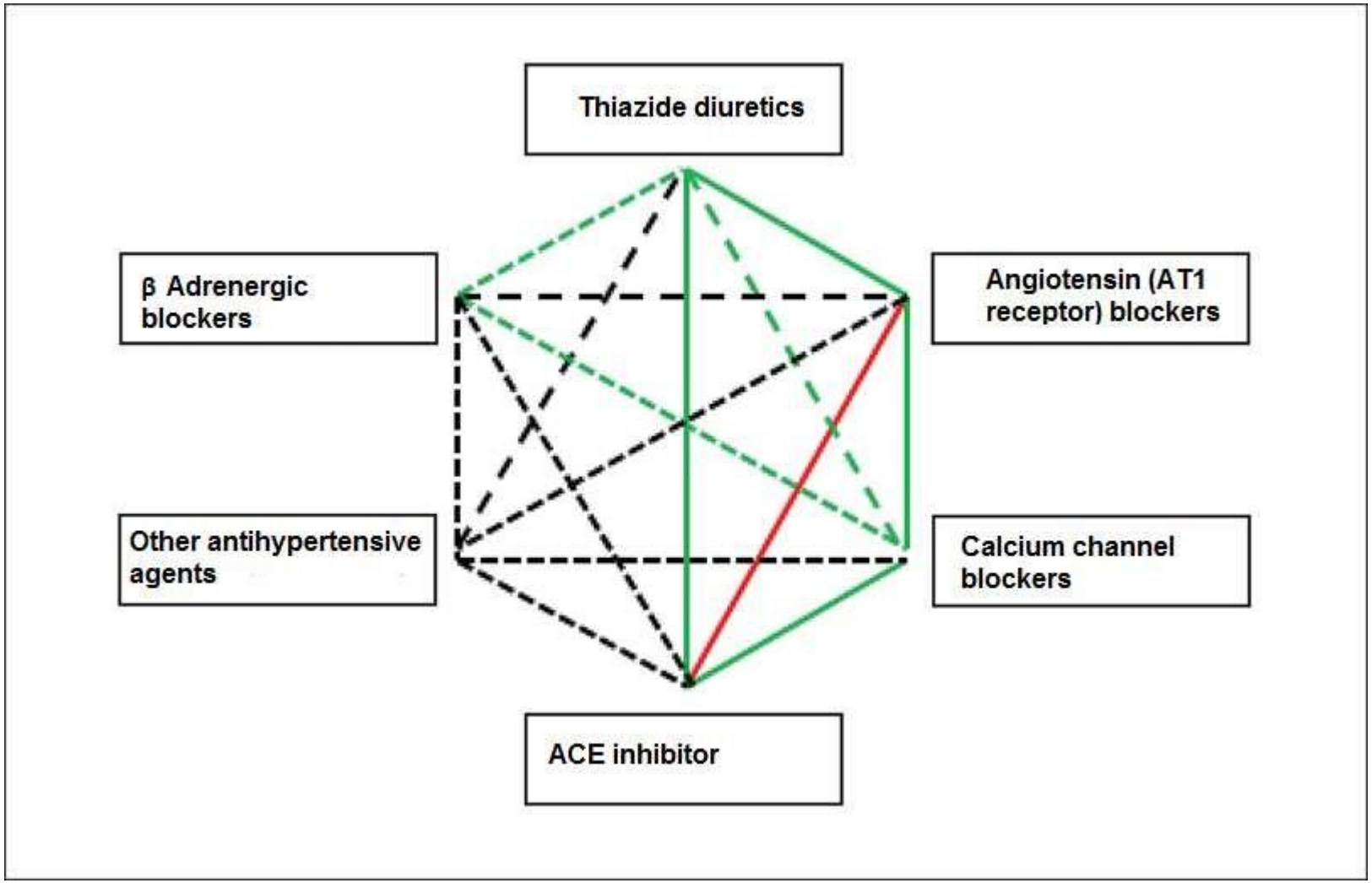
Vasodilators

- 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.
- 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 in patients with concomitant diseases



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).



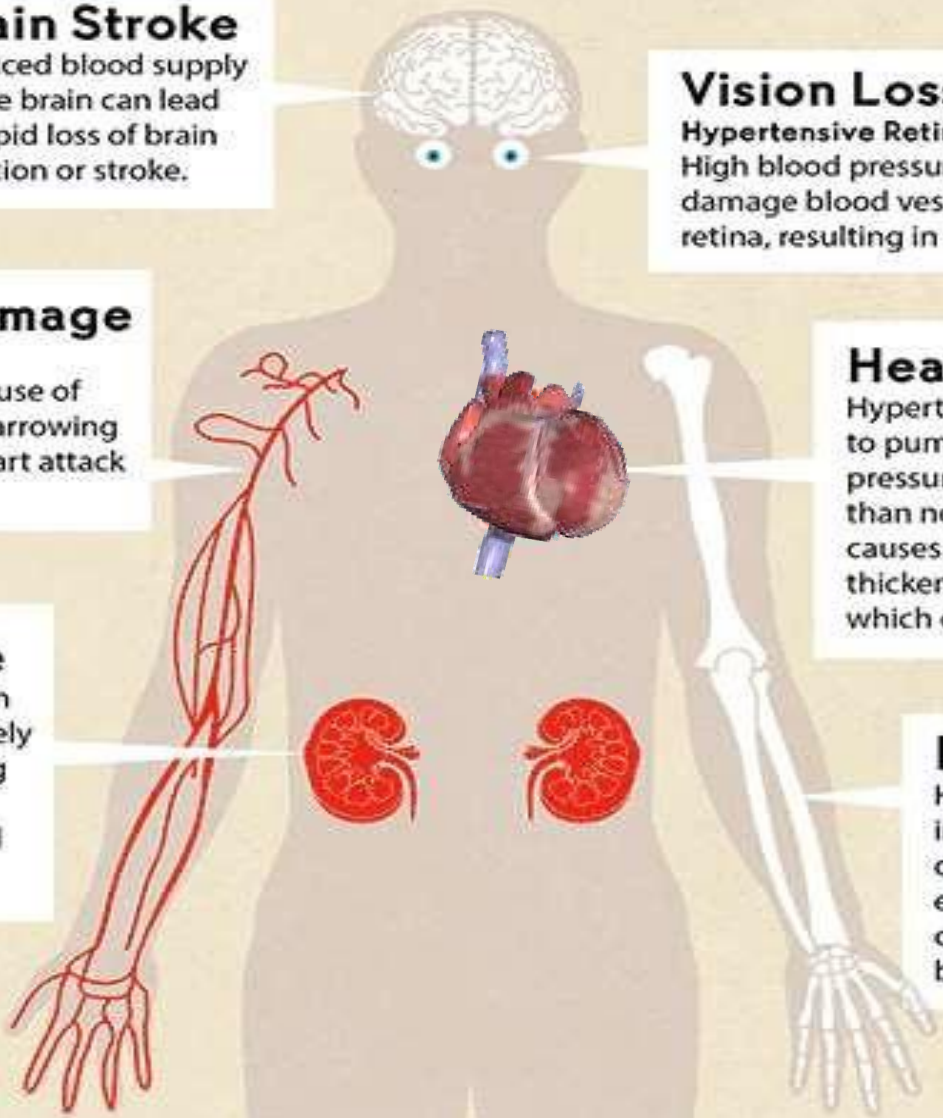
Ref: Póvoa R, Barroso WS, Brandão AA, et al. I brazilian position paper on antihypertensive drug combination. Arq Bras Cardiol. 2014;102(3):203-10.

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).

FASTMED URGENT CARE


Thank
You