



Anti-hypertensive Drugs

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Etiology of Hypertension

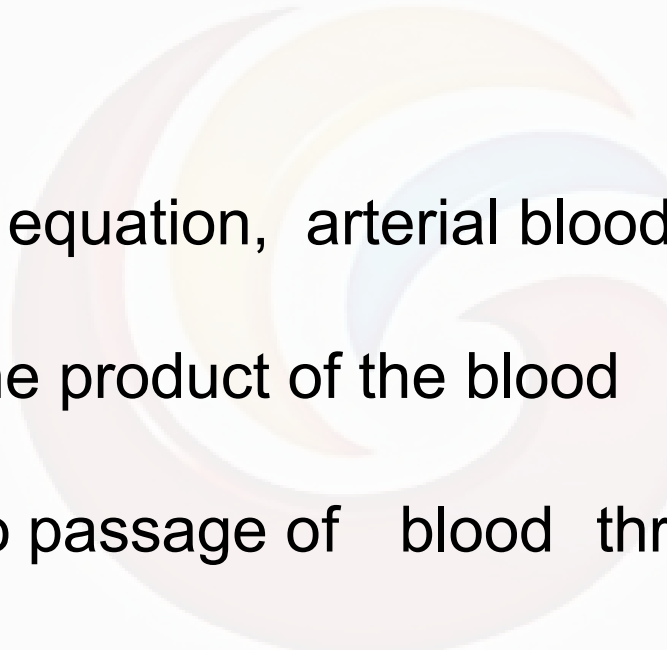
- A specific cause of hypertension established in only 10–15% of patients.
- Patients in whom no specific cause of hypertension are said to have essential or primary hypertension.
- Patients with a specific etiology are said to have secondary hypertension.
- Genetic factors, psychological stress, and 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



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





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)

- **$BP = CO \times PVR$**

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

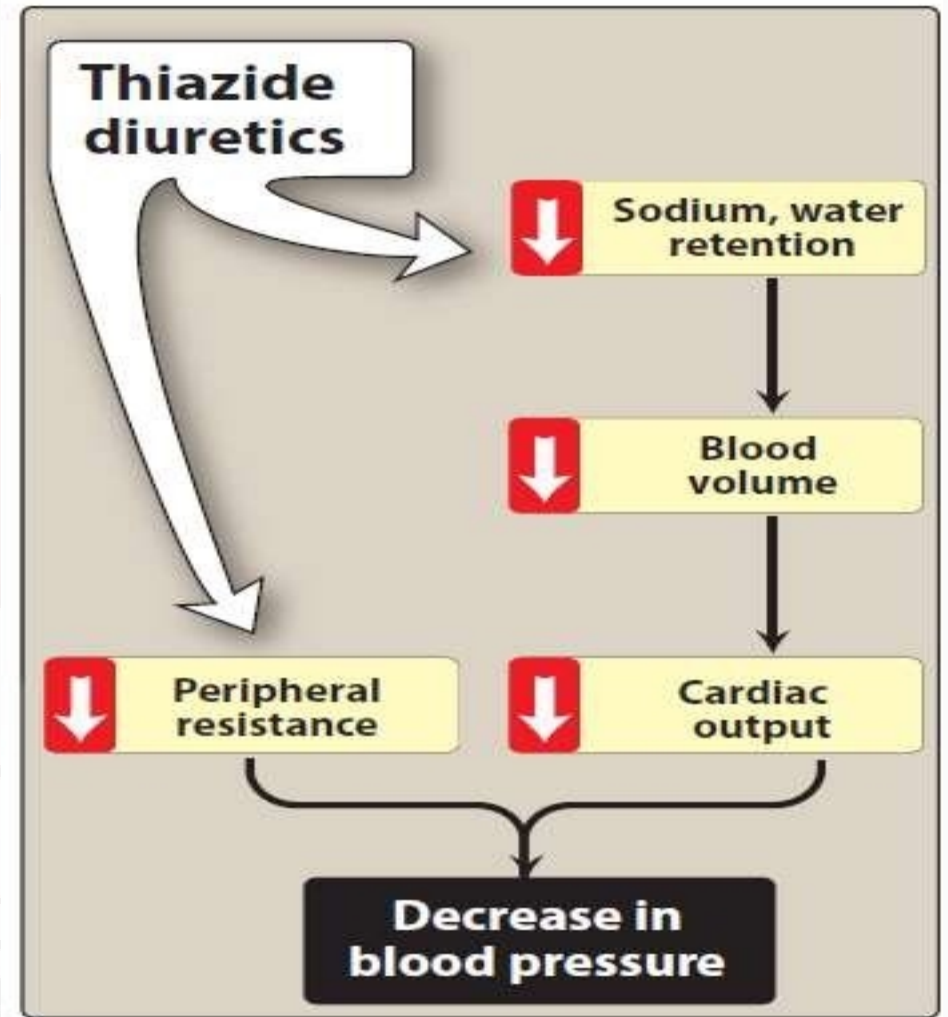
- **β Adrenergic blockers:** Propranolol, Metoprolol, Atenolol, etc.

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.)

Diuretics

- **Thiazide diuretics:** Thiazide 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 patients.



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.

Eg. furosemide, and ethacrynic acid.

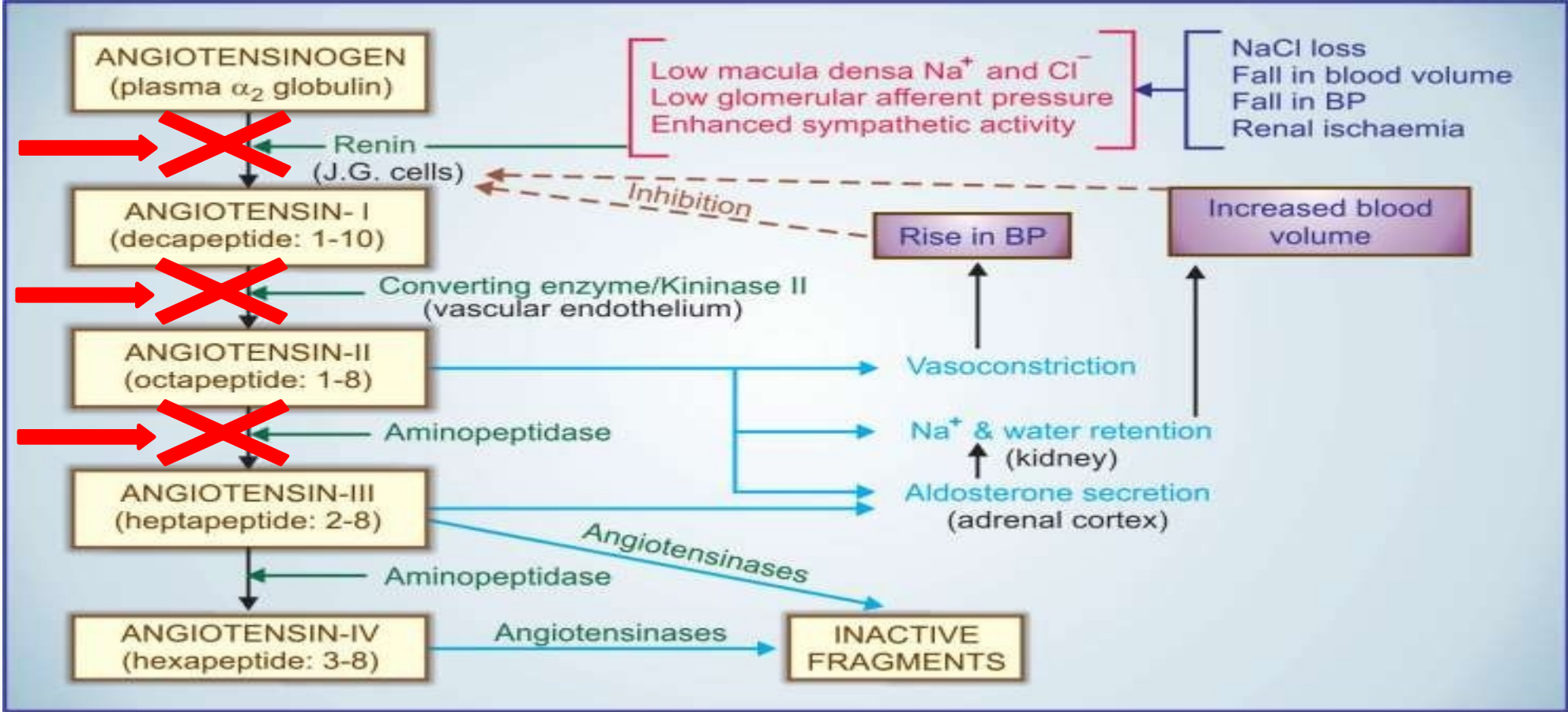
- ***K⁺ Sparing:***
- potassium-sparing diuretics (**spironolactone**, and **eplerenone**) are competitive antagonists that either compete with aldosterone, or directly block epithelial sodium channel (**amiloride**).

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 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.

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
- Foetopathic
- 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.

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

- 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 lowering are useful for blood pressure in mild hypertension. to moderate
- 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 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.

Other beta blockers

- Nadolol and carteolol, nonselective β -receptor antagonists
- Betaxolol and bisoprolol are β_1 -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.

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Other beta blockers

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

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-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

- 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.

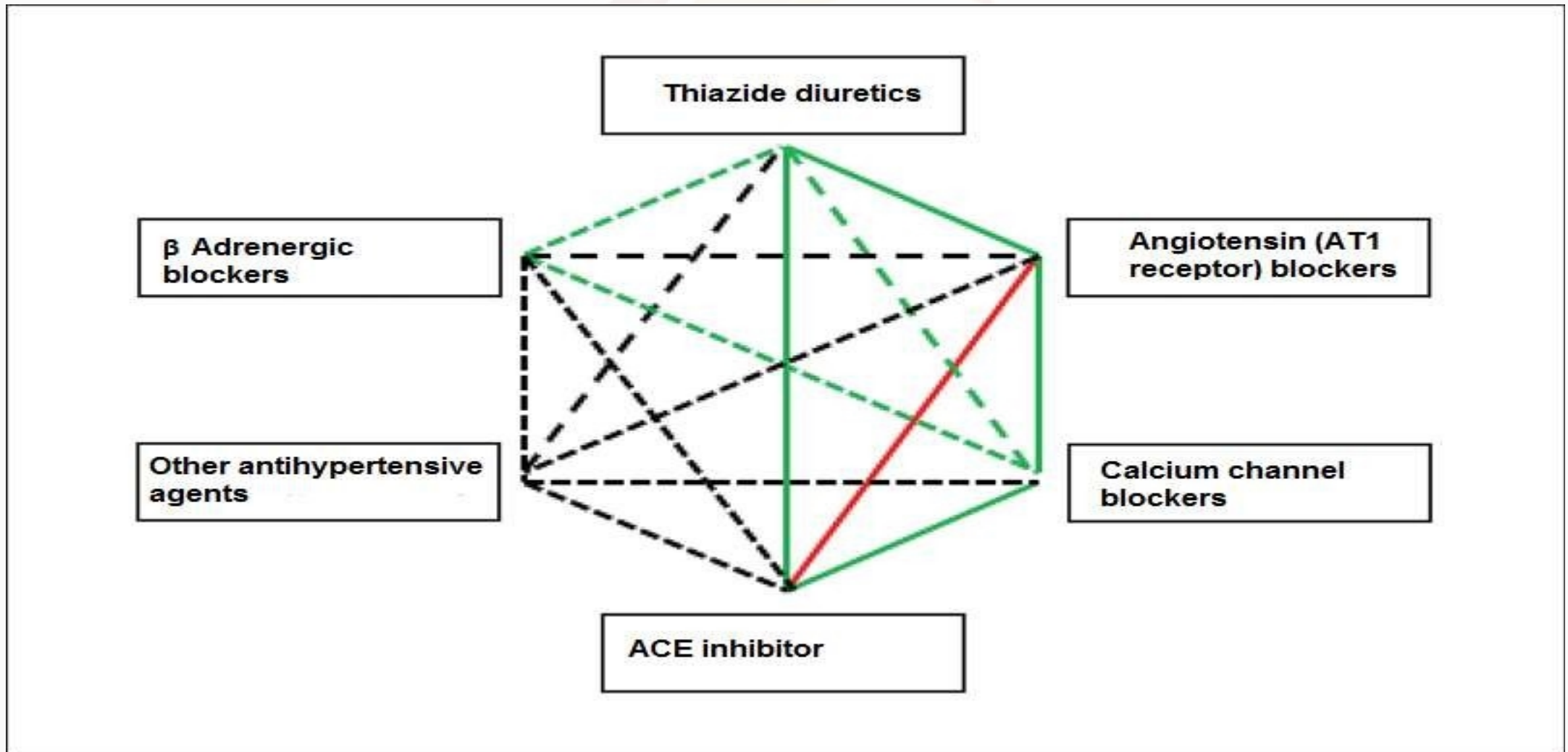
Treatment of hypertension

- **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)

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.**

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).



References

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