Clinical Pharmacology of Antihypertensive

By
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Introduction

- **Hypertension** is a persistent elevation of blood pressure above 140 / 90 mmHg for more than three sitting.
- (0ptimal level <120 / 80 mmHg) .

- **Factors affecting blood pressure:**

1-COP = HR X SV mainly affect SBP.

2-TPR = diameter of arterioles X viscosity of blood affect DBP

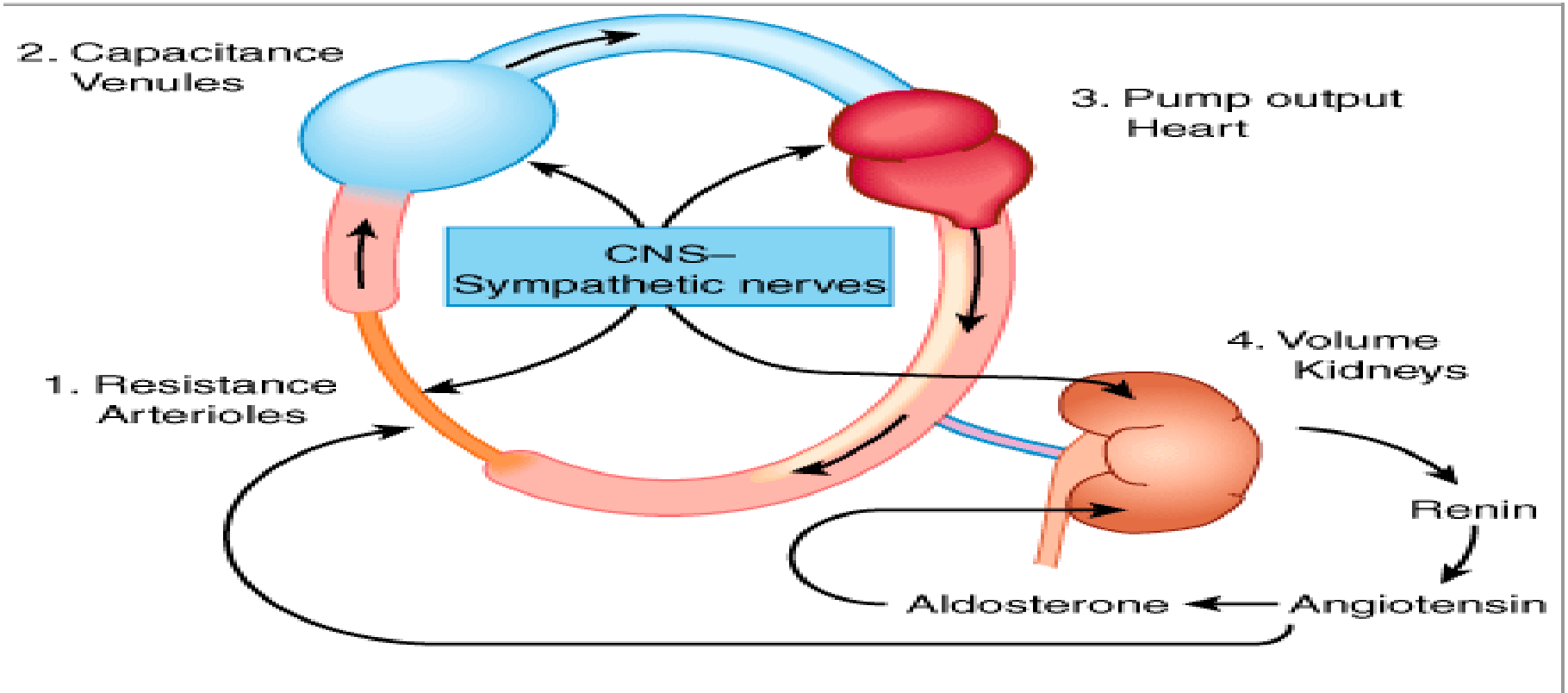
- Each of these factors can be manipulated by drug therapy

Normal Regulation of Blood Pressure

A. Short term regulation: ANS (Sympathy.,parasympath)

B. **Long term regulation**: RAS (kidney)

C. **Local chemical mediators** at the vascular endothelium: NP, , PG, Bradykinin, NO, endothelin, adenosine



Types of hypertension

A. Primary hypertension:

1. Nearly 90% of patients have no specific cause.
2. Elevated blood pressure is usually caused by several abnormalities such as genetic inheritance, psychological stress, dietary factors.
3. Treatment: Such hypertension can be controlled by some combination of antihypertensive drugs and changes in daily habits.

4. LIFE LONG TTT

Pathophysiology of hypertension

1. **Poly genetic factor**
2. **Environmental factors (diet, exercise, obesity, alcohol)**
3. **Activation of sympathetic nervous system**
4. **Activation of RAAS （renin-angiotensin-aldosterone system）→↓ Na excretion**
5. **↑Na^+ in diet**
6. **Dysfunction of vascular endothelium**

B. Secondary hypertension (10% - 15%)

1. **Renal:** RAS, GN, IN, PCD, Ch.P
2. **Endocrine:** Conn's, Cushing, Pheochromocytoma, Acromegaly
3. **Drugs: Corticosteroids, estrogens, NSAIDs, cycolosporines**
4. **Treatment: Curative**

Hypertension Stages

BP Classification	Systolic BP measurement	Diastolic BP Measurement
Normal	< 120mm Hg	**AND** < 80mm Hg
Prehypertension	120 – 139mm Hg	**OR** 80 -89mm Hg
Stage I Hypertension	140 – 159mm Hg	**OR** 90 – 99mm Hg
Stage II Hypertension	160-179 mmHg	**OR** 100-109 mm Hg
Emergency hypertension	180mm Hg	**OR** 110 mm Hg

Hypertension

TOD

- LVH
- Angina or MI
- CHF
- Stroke or TIA
- Nephropathy
- Peripheral arterial disease
- Retinopathy

Risk Factors

- Smoking
- Dyslipidemia
- Diabetes
- Age >60 years
- Gender (men and postmenopausal women)
- Family Hx of CVD

Diagnosis

- Diagnosis is generally based on repeated, reproducible measurements of elevated blood pressure (more than 2) at fixed intervals,
- Do not rely on patient symptoms.
- White coat Hypertension
- Masked hypertension
- Emergency hypertension
- Isolated systolic HT in Elderly

Benefits of Lowering BP

Average Percent Reduction	
35–40%	Stroke incidence
20–25%	Myocardial infarction
50%	Heart failure

The antihypertensive treatment strategies

1. To normalize blood pressure effectively.

2. Controlling hypertension is usually a lifelong treatment (patient compliance)

3. Long-term goal of antihypertensive therapy:

Reduce mortality due to hypertension-induced disease **To prevent target-organ damage to the heart, brain, kidneys and blood vessels, eye.**

Strategy of treatment includes the following:

1-*Evaluation of general condition of the patient*.

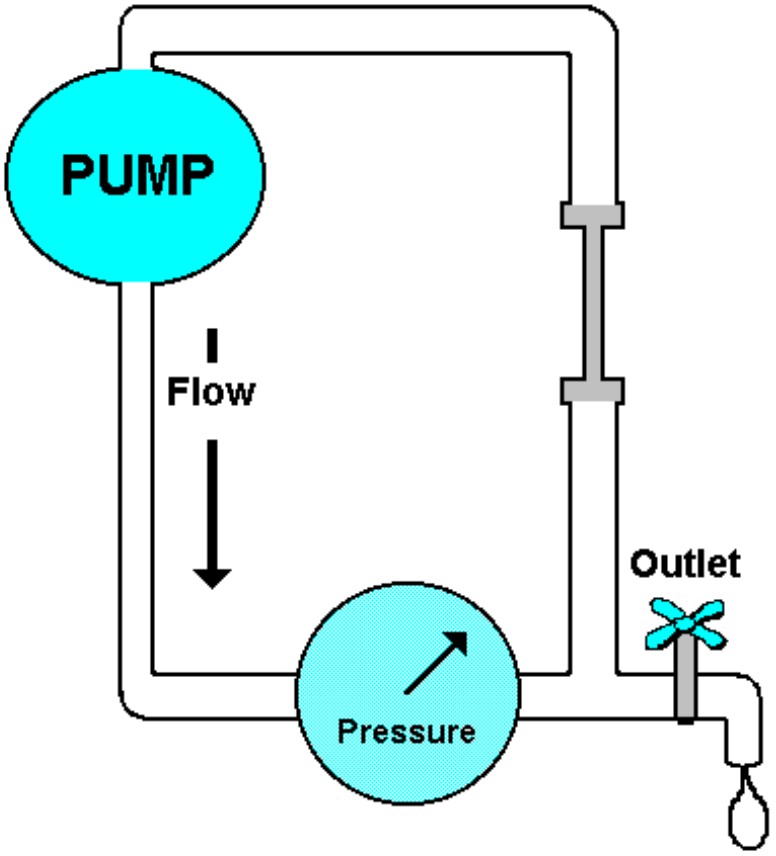
2. **Lifestyle Changes Recommended for all Patients**

1. Mental relaxation.
2. Smoking cessation
3. Regular exercise(mild) in mild and moderate cases.
4. Weight reduction
5. Salt (Nacl) restriction (reduce to 1.5g/day) and increase K in diet.
6. Dietary Modifications: Decreases saturated fatty acid and cholesterol & Increase fruits & vegetables, fibers

111-*Drug therapy:*

Start with monotherapy but if it is ineffective, combinations of two or more drugs can be used, based on age, sex , race, concomitant diseases and / or drugs.

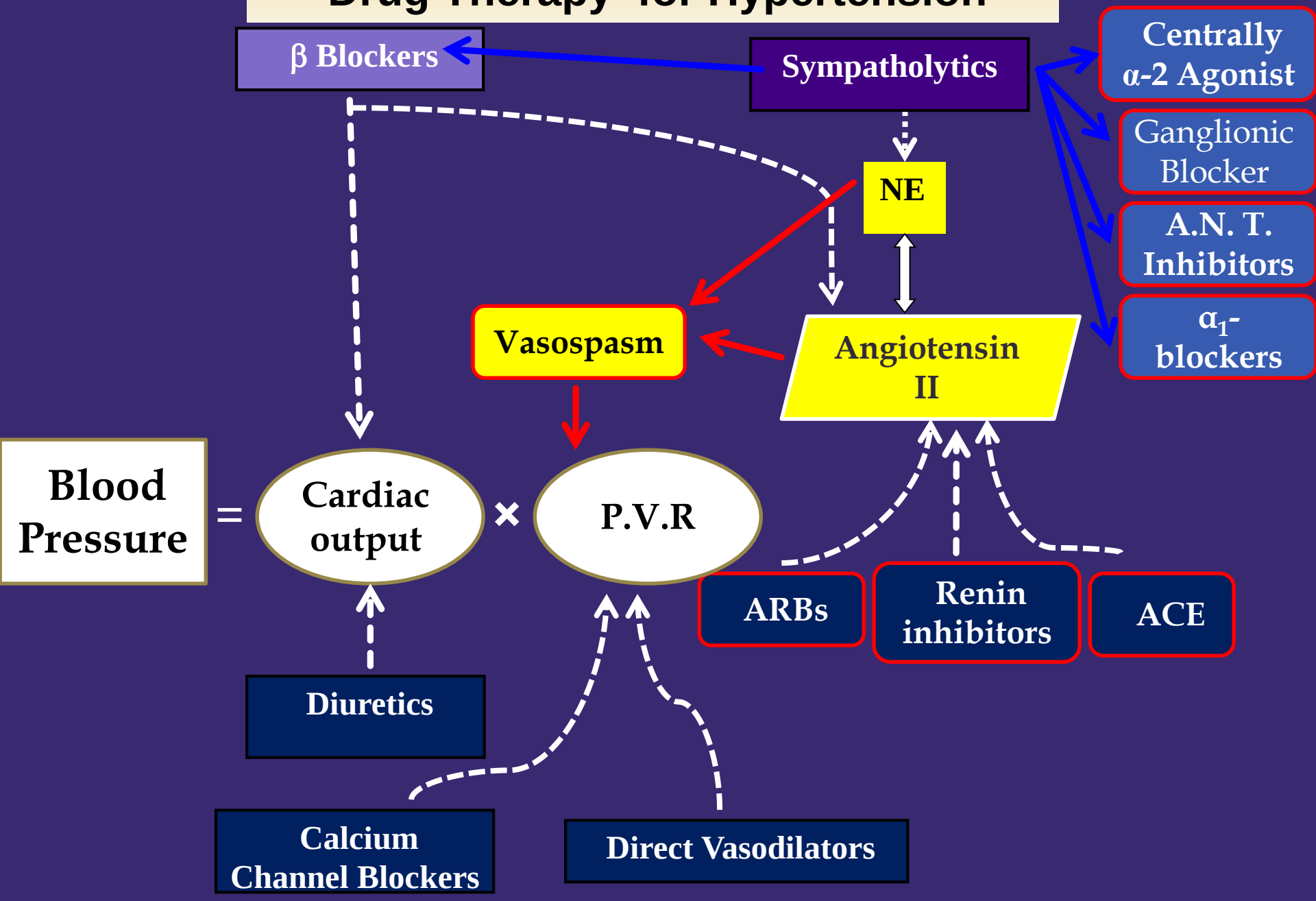
Ways of Lowering Blood Pressure



MAP = CO X TPR

- Reduce cardiac output (ß-blockers, Ca^{2+} channel blockers)
- Reduce plasma volume (diuretics)
- Reduce peripheral vascular resistance (vasodilators)

Drug Therapy for Hypertension



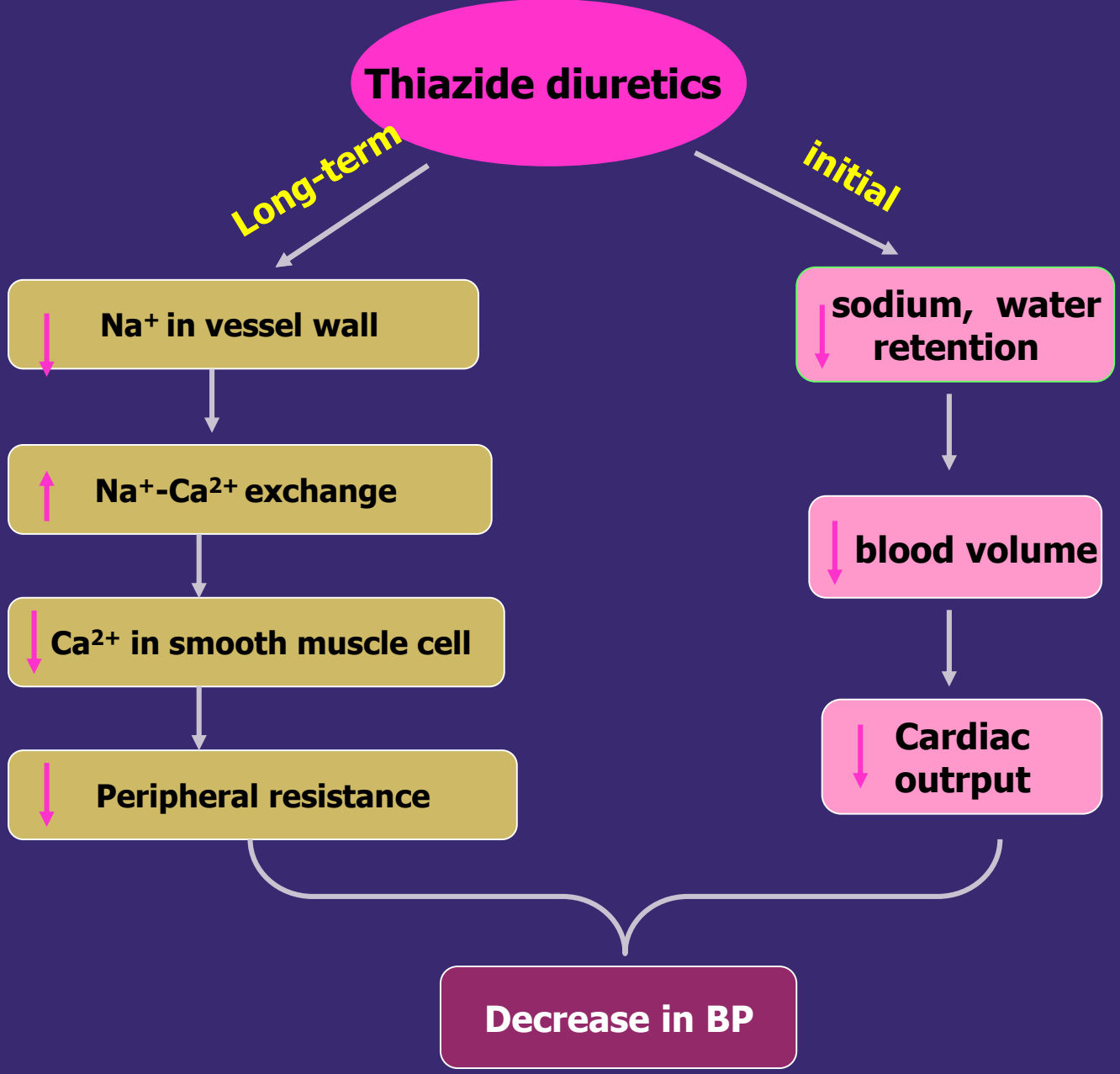
I. Diuretics

Mechanism of Action

- **Initially**, they act by reducing plasma volume and COP, **followed by** vasodilation and reduction in peripheral vascular resistance.

Advantages

- Reduce mortality, stroke and cardiovascular complications of hypertension.
- The least expensive antihypertensives.



The mechanism for reduction of BP of thiazide Diuretics

Clinical uses

- 1st choice in uncomplicated hypertension.
- Systolic hypertension.
- Hypertension in elderly, black and obese patients
- heart failure and renal failure???.
- Combined with other antihypertensives to potentiate their effect:

1. vasodilators.
2. ACEIs and β blockers.

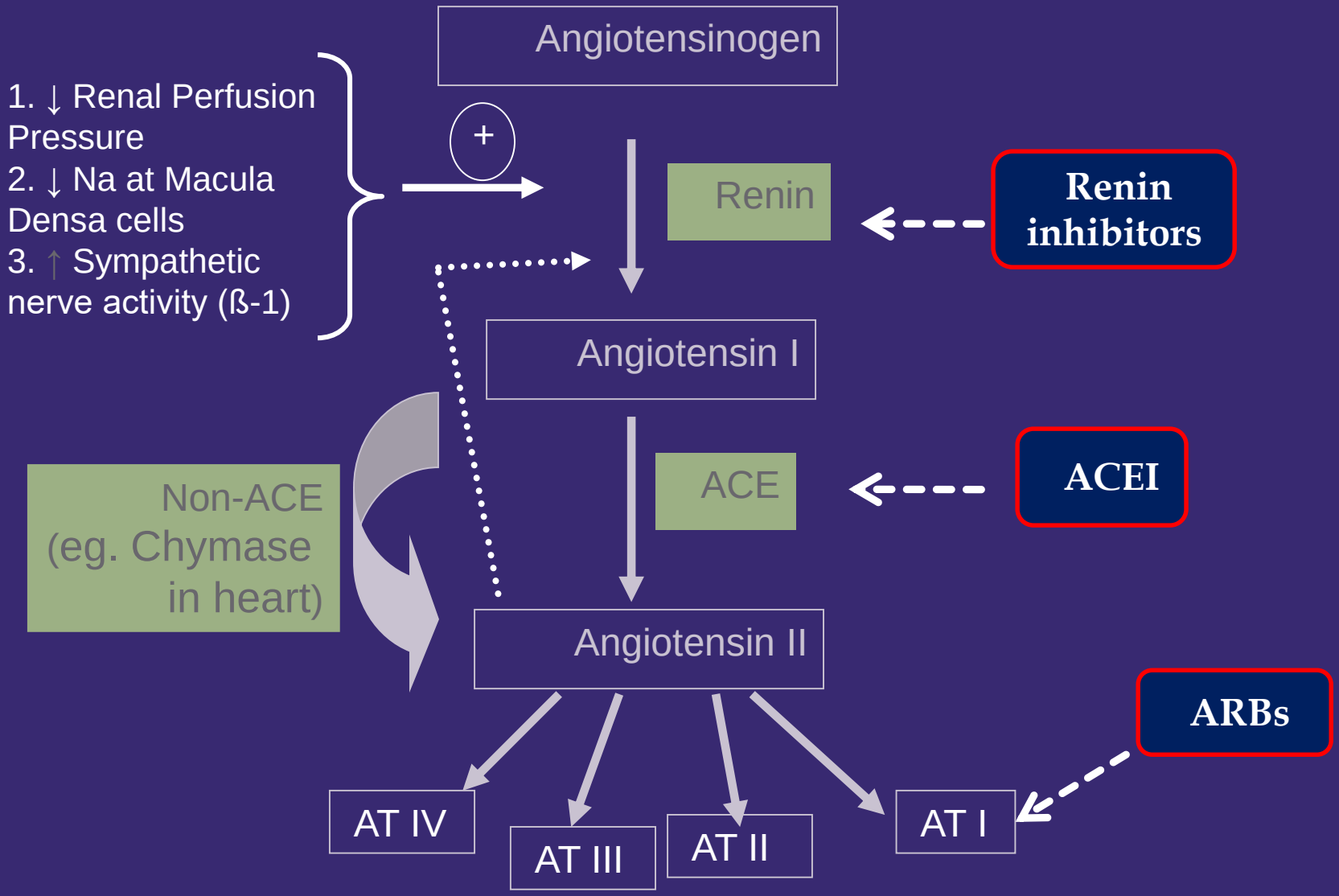
Side Effects:-

1. Metabolic Side Effects
   - Hyperuricemia - hyperglycemia -hyperlipidemia.

2. Electrolyte Disturbances
   - Hypokalemia - hyponatremia -hypomagnesemia.

3. Sulfonamide hypersensitivity reactions (rare) .

The Renin-Angiotensin System



ACE Inhibitors

- **Mechanism of Action in hypertension**

1. Vasodilation due to
   - ↓ angiotensin II
   - ↑ vasodilator BK.
2. Anti-adrenergic effect by blocking central & peripheral adrenergic activity of angiotensin II (thus ACEIs decrease BP without reflex tachycardia).
3. Inhibition of aldosterone → Na+ loss.

PHARMACOKINETICS:

A. **Captopril: Active**

given orally, well absorbed in fasting state, metabolized in liver by conjugation and less than half the dose is excreted unchanged in the urine. The half-life is 3 h.

B. **Enalapril: Prodrug**

is converted to enalaprilate with a half-life 11 h.

C. **Lisiniopril: Active**

1. slowly absorbed with a half-life 12 h.
2. Primarily the kidney eliminates all ACEI except **fosinopril and moexipril.**

D. ***Dosage:***

1. **Captopril:** start with 25 mg 2-3 times/day before meals; increase the dose at 1-2 week's intervals to control B.P.
2. **Enalapril:** oral dose 10-20 mg once or twice/day
3. **Lisinopril:** oral dose 10-80 mg/day.

- **Advantages**

1. ↓ Cardiovascular mortality and morbidity.
2. Protect renal function especially in diabetics.
3. No metabolic side effects (no effect on glucose, lipid or uric acid).
4. May improve glucose intolerance in insulin resistance.
5. No changes in heart rate.

- **Indications**

1. Diabetic hypertensives.
2. Hypertension with nephropathy in diabetics or nondiabetics.
3. Hypertension in HF or after myocardial infarction.

ADVERSE EFFECTS

1. **Dry cough (5-20%).** with or without wheezing, angioedema. thiazide **Hypotension → In hypovolaemic patient. (2%).**
2. **Acute renal failure** (in patients with bilatral renal artery stenosis).
3. **Hyperkalemia**
4. **They are contraindicated with 2nd or 3rd trimester** of pregnancy (to avoid fetal hypotension, anurea or renal failure associated with fetal malformation or death).

Angiotensin II Receptor Blockers (ARBs) (Losartan – Valsartan – Telmisartan)

Advantages over ACEI :

1. They have no effect on bradykinin system **so,no cough, wheezing, angioedema.**

2. Complete inhibition of angiotensin action compared with ACEI. **Explain?**
3. **Indirect activation of AT2. Explain?**

ADRs: Same as ACEI except **no cough ,wheezing,angioedema.**

Same contraindications as ACEI

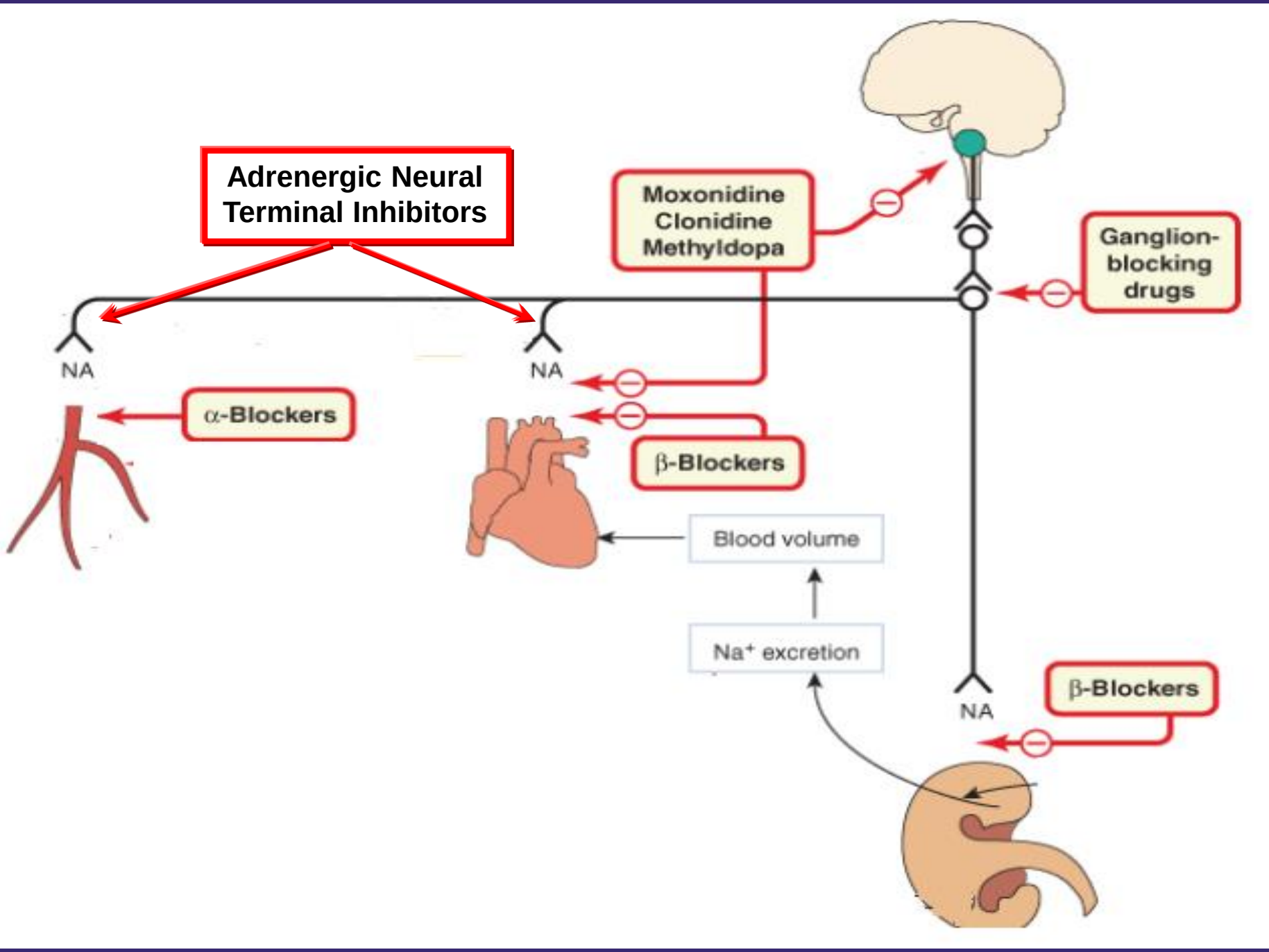
Sympatholytics

Mechanisms of Action

Reduce sympathetic activity to heart and/or blood vessels thereby decreasing cardiac output and/or total peripheral resistance

They include

- centrally-acting α-2 agonist
- Ganglionic Blocker
- Adrenergic Neural Terminal Inhibitors
- Adrenoceptor blockers.


Adrenergic Neural Terminal Inhibitors
Moxonidine
Clonidine
Methyldopa
Ganglion-blocking drugs
NA
NA
NA
α-Blockers
β-Blockers
Blood volume
Na+ excretion
β-Blockers

Centrally Acting Agents

Clonidine

- α_2 agonist at CNS; ↓ sympathetic outflow from CNS

Side Effects:

- Rebound hypertension
- sedation
- dry mouth
- bradycardia

Centrally Acting Agents

- **Methyldopa**
- Converted to methylnorepinephrine that acts on central alpha$_2$ receptors
- Used in management of hypertension in pregnant women (first line agent)
- **Side effects:**
  - ❖ Sedation
  - ❖ Nightmare
  - ❖ Movement disorders
  - ❖ Hyperprolactinemia

Ganglionic Blockers

- Ganglion blockers competitively block nicotinic cholinergic receptors on postganglionic neurons in both sympathetic and parasympathetic ganglia.
- Most of these agents are no longer available clinically because of unacceptable adverse effects related to their primary action

Adrenergic Neural Terminal Inhibitors

Reserpine

- **Reserpine binds to noradrenergic storage vesicles ⟶ lose the ability to store (N.E.)**

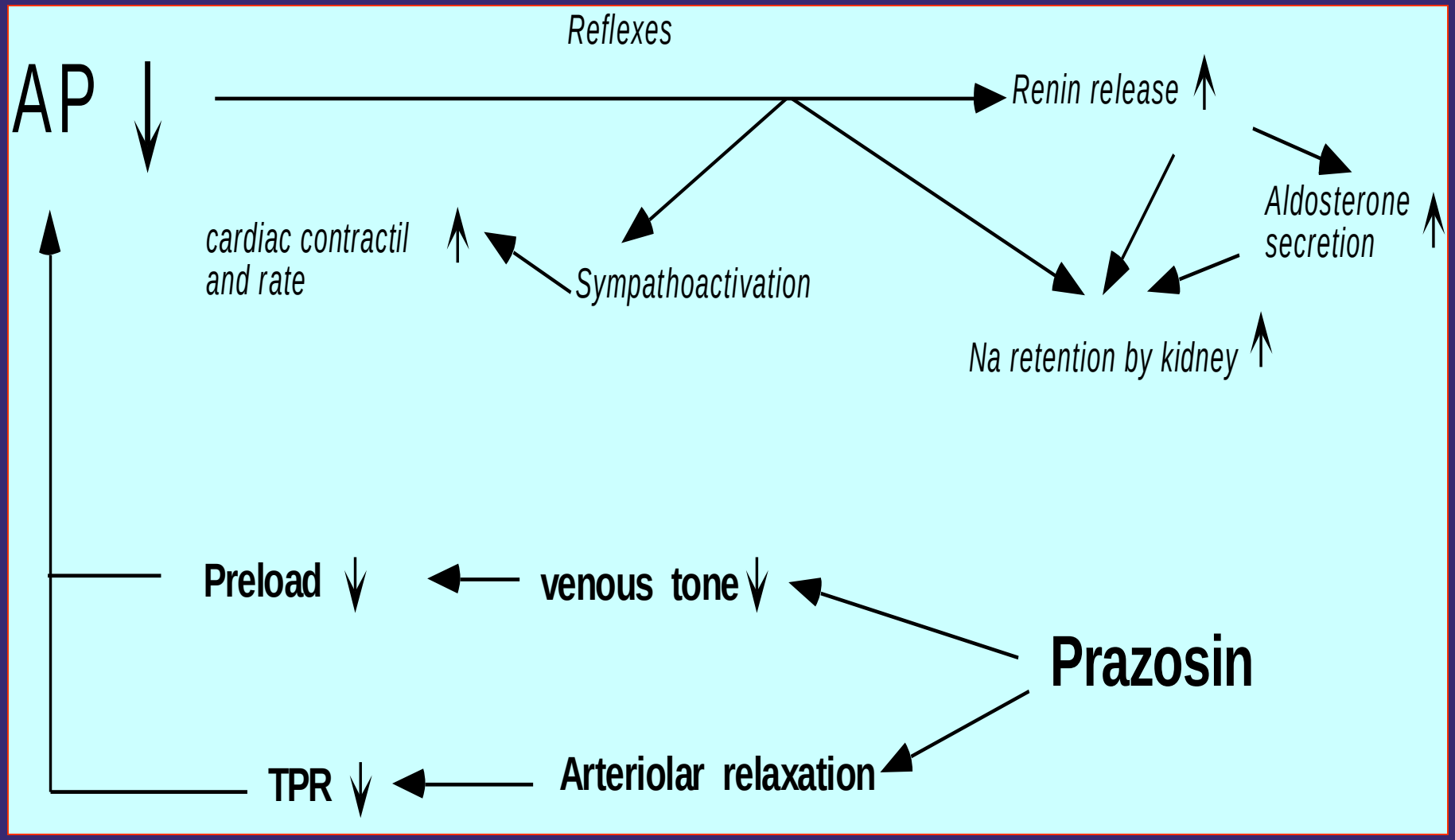
  ⟶ little transmitter is released upon nerve ending depolarization.

- **Adverse Effect**
  - CNS effects predominate, including sedation, inability to concentrate, and depression.

α-1 -Adrenergic Blockers

- Blocking the action of norepinephrine at α1 receptors in arteries and veins.
  - **Reduces systemic vascular resistance without Causing reflex-mediated tachycardia**
  - Improve lipid profile
- **Adverse effect**
  - Orthostatic hypotension
  - Fluid retention
  - Nasal congestion

Alpha 1-blockers: mechanism of action



β–Adrenergic Blockers

Mechanism of Action :-

- Initially, they decrease COP without effective drop in BP due to reflex vasospasm with early increase in TPR.
- Later, they decrease TPR and BP through↓ Renin release.

Advantages

- Decrease cardiovascular mortality & morbidity and protect against coronary heart disease.
- Relatively not expensive.

Indications

- Alternative to diuretics as 1st line treatment of uncomplicated hypertension.
- Used in young hypertensives where COP is high.
- Hypertension associated with coronary heart disease.

Side Effects (Less with B1-selective)**:**

1. Bronchospasm, cold extremities.
2. Metabolic: glucose intolerance, dyslipidemia.
3. Bradycardia, heart block.
4. Sense of fatigue.

Calcium Channel Blockers

Mechanism of Action

- Peripheral VD and ↓ TPR.
- Diuretic action secondary to ↑ renal blood flow.

Advantages

- No metabolic side effects (no changes in glucose, lipid or uric acid levels).
- May improve renal function.

Indications :

- 2nd Choice after diuretics in elderly hypertensives or in isolated systolic hypertension.
- 2nd Choice after b blockers in hypertensives with coronary heart disease.
- Hypertension with peripheral vascular disease (PVD).
- Hypertension with renal impairment.

Direct Vasodilators
Hydralazine

Mechanism of Action

- It is an arteriolar vasodilator that may act as a K+ channel opener with hyperpolarization of vascular membrane which prevents Ca2+ influx into the wall of blood vessels.

Pharmacokinetics

- It is rapidly absorbed from the gut.
- It is metabolized in the liver by acetylation. Fast acetylators need large dose, while slow acetylators may develop lupus syndrome.
- It is excreted by the kidney (↓the dose in renal disease).

Hydralazine & **Hypertension**

- IV hydralazine is the drug of choice in severe hypertension with pregnancy.

- The chronic use of hydralazine in hypertension is associated with rapid tolerance .

Adverse Effects

- Salt retention and edema.
- Reflex tachycardia.
- Lupus syndrome

Sodium Nitroprusside

Mechanism of Action

- It is a donor of nitric oxide (NO) that increases the level of cGMP which induces vasodilation by inhibiting Ca2+ influx into the wall of blood vessels.

Pharmacological Properties

- It has a potent direct vasodilator (arteriolar and venular) effect decreasing both preload and afterload.
- It has an immediate effect and very short duration of action (2 minutes).
- It is converted in the body into cyanomethemoglobin and free cyanide which is metabolized into thiocyanate in liver and excreted by the kidney.

indication :-

- It is useful in most hypertensive emergencies as hypertensive encephalopathy, severe hypertension with acute HF and dissecting aortic aneurysm.

Side effects:-

1. **Hypotension**
2. **Reflex tachycardia**
3. **Cyanide toxicity**

Population	Goal BP, mmHg	Initial drug treatment options
General ≥ 60y General < 60y Diabetes CKD	<150/90 <140/90 <140/90 <140/90	Non-black: thiazide-type diuretic, ACEI, ARB, or CCB Black: thiazide-type diuretic, or CCB Diabetes: thiazide-type diuretic, ACEI, ARB, or CCB CKD: ACEI or ARB


Thank You