Drugs used in treatment of Cardiovascular System

Hypertension

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Hypertension

- Persistant elevation of systolic and /or diastolic B.P. to above 140/90 mmHg in person aged 18 years or older.

Hypertension	Systolic	Diastolic
Grade I (mild)	140-159	90-99
Grade II (moderate)	160-179	100-109
Grade III (sever)	>180	>110
Isolated systolic hypertension	>140	<90

Etiology

1. Primary; Essential; Multifactorial.
2. Secondary:

I. Renal failure.
II. Drug induce.
III. Hormonal.
IV. Pregnancy.
V. Coarctation of the Aorta.

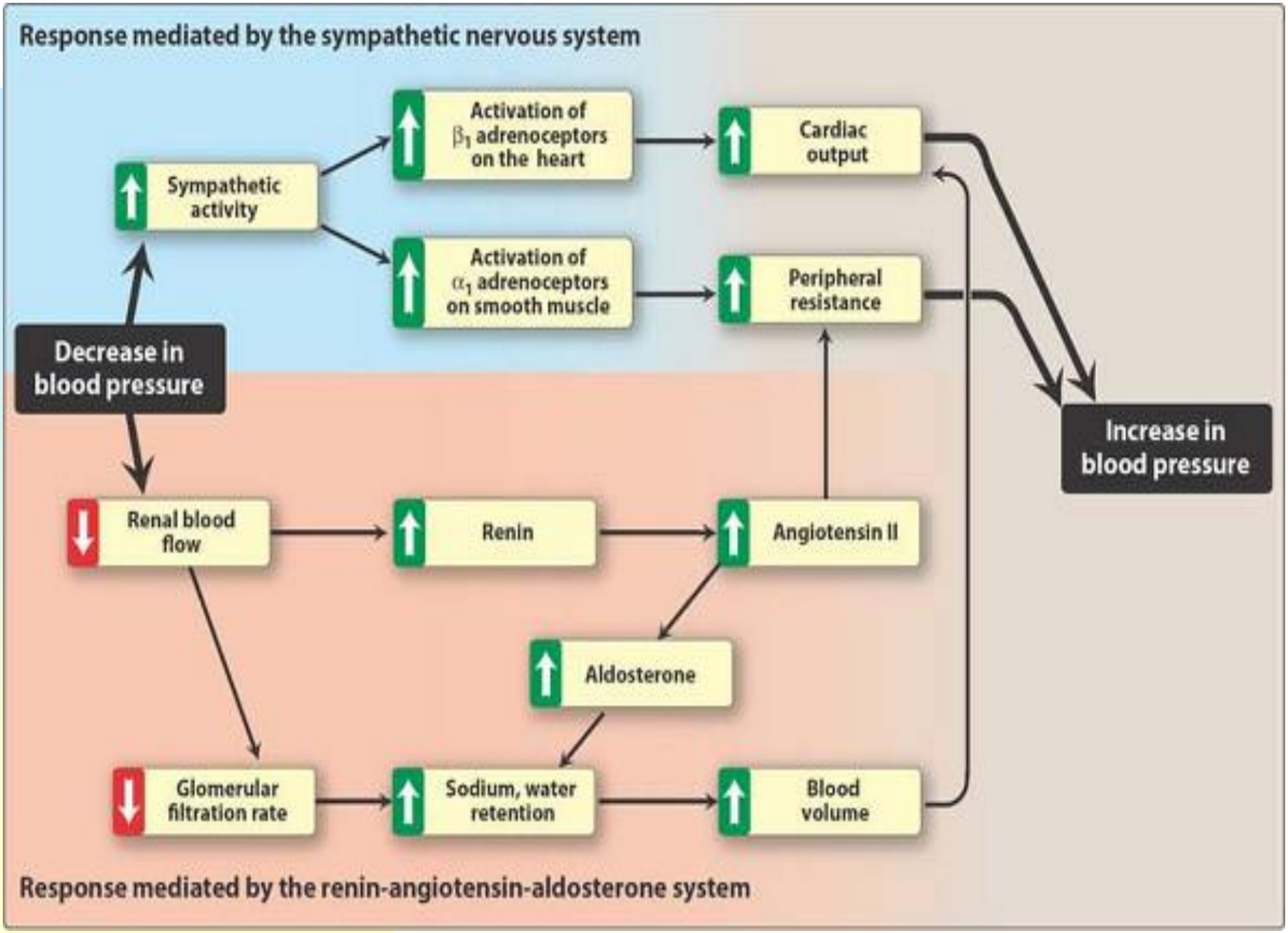
Mechanism for controlling B.P.

A. Baroreflexes & the sympathetic N.S.:

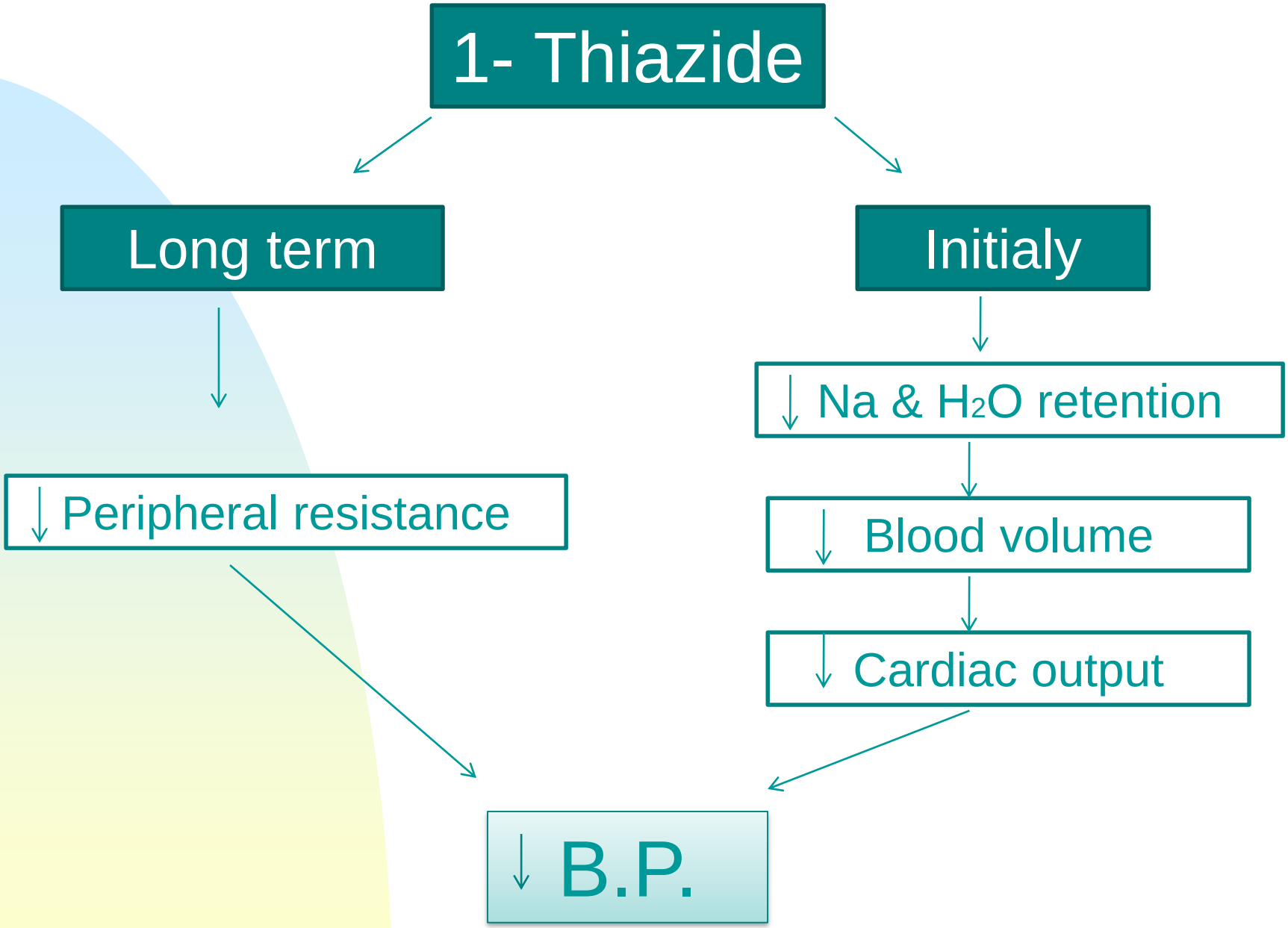
   Moment-to-moment regulation of B.P.

B. Renin-Angiotensin-Aldosterone system

Therefore, Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.


Response mediated by the sympathetic nervous system
Activation of β_1 adrenoceptors on the heart
Cardiac output
Sympathetic activity
Activation of α_1 adrenoceptors on smooth muscle
Peripheral resistance
Decrease in blood pressure
Increase in blood pressure
Renal blood flow
Renin
Angiotensin II
Aldosterone
Glomerular filtration rate
Sodium, water retention
Blood volume
Response mediated by the renin-angiotensin-aldosterone system

Diuretics


1- Thiazide
Long term
Initialy
↓ Peripheral resistance
↓ Na & H2O retention
↓ Blood volume
↓ Cardiac output
↓ B.P.

2- Loop Diuretics:

- Act even in patients with poor renal function.
- Cause decrease in renal vascular resistance & renal blood flow.
- Increase the Ca^{2+} content of urine.

3- Potassium-Sparing Diuretics:

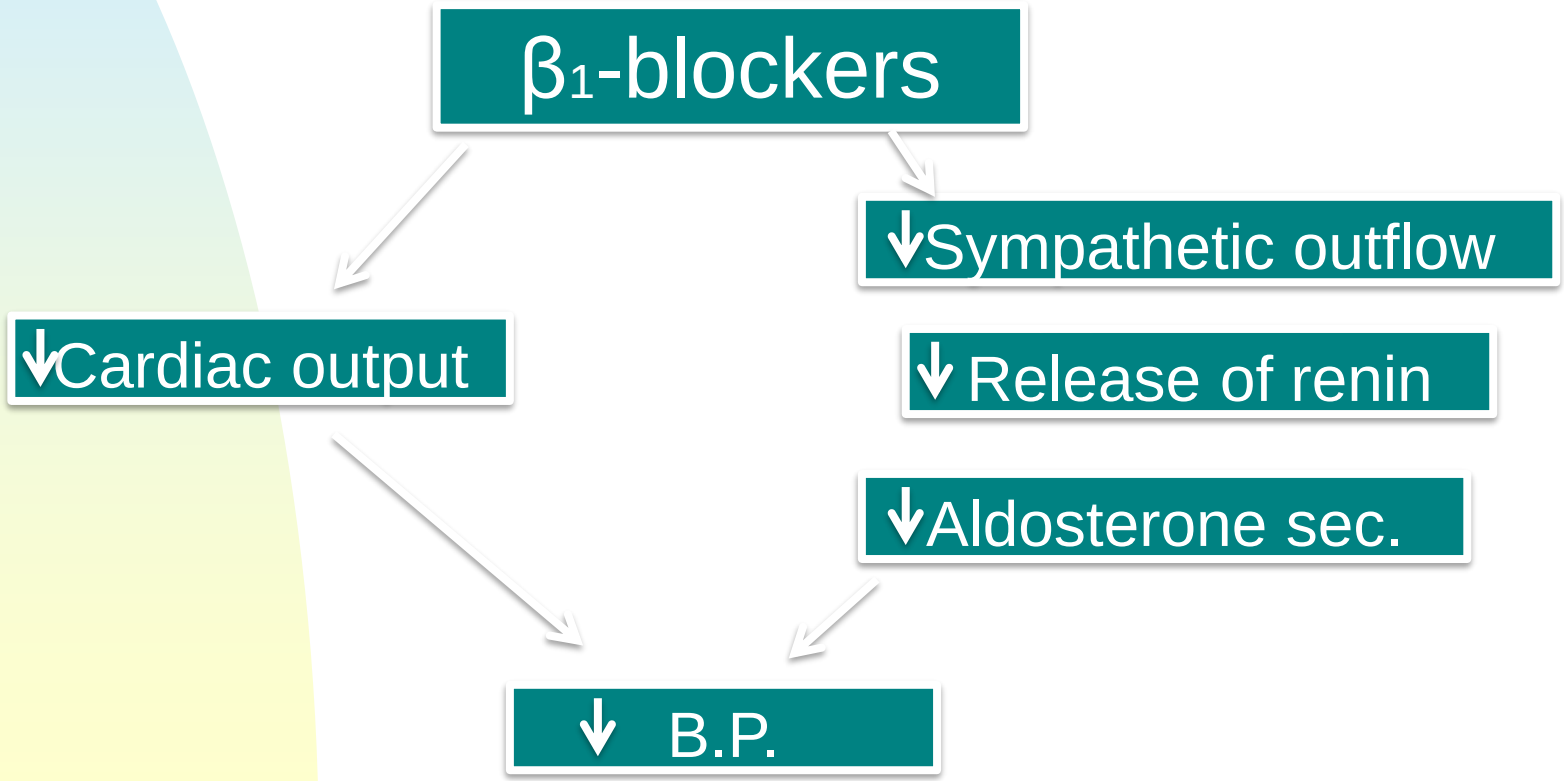
- Reduce K loss in urine.
- **Amiloride & Triamelorine:**

  inhibitors of Na^+ transport in distal & collecting ducts.
- **Spirinolactone & Eplerenone:**

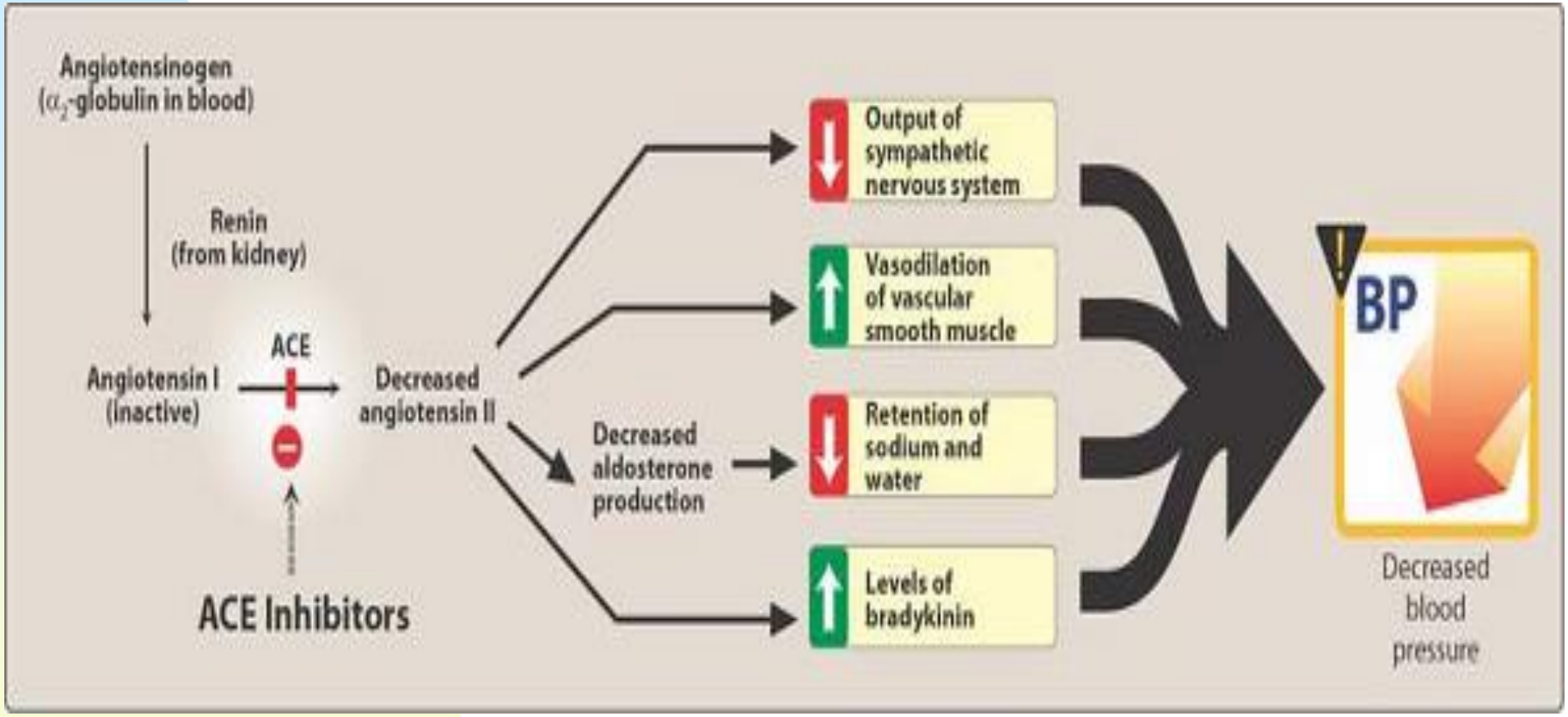
  aldosterone-receptor antagonist.
- **Spirinolactone** reduce cardiac remodeling in heart failure.

β_1- adrenoceptor blocking agents

- ***Metoprolol and Atenolol:*** Recommended as first-line drug therapy for hypertension when concomitant disease is present (with heart failure) in white than in black patients and in young compared to elderly patients.



ACE Inhibitors



Therapeutic uses of ACEIs:

1. Hypertensive patients (white and young), they are now the 1st line drugs in all grades of hypertension.

Angiotensin II-receptor antagonists:

- Alternative to ACEIs. e.g. *Losartan; valsartan; Candesartan; Ebrosartan; Irbesartan; Olmesartan; Telmisartan.*
- **Pharmacological effects:**

1. They block aldosterone secretion & Na and H_2O retention.
2. They produce arteriolar & venous dilation.

- **Uses of ARBs:**

ARBs decrease the nephrotoxicity of diabetes, making them an attractive therapy in hypertensive diabetics.

- **Adverse effects**

similar to those of ACE inhibitors but ARBs don't increase Bradykinin level.

Renin inhibitors: *Aliskiren*

- It acts directly by inhibiting renin & thus acts earlier in the R-A-A-S than ACEIs or ARBs.
- It lowers BP & effective as ARBs, ACEIs and Thiazides.
- It can be combined with diuretics, ACEIs, ARBs or CCBs.

Calcium-Channel Blockers

- Calcium-channel blockers are recommended when the preferred first-line agents are contraindicated or ineffective.
- They are effective in treating hypertension in patients with *angina* or *diabetes*.
- High doses of short-acting calcium-channel blockers should be avoided because of increased risk of myocardial infarction *due to excessive vasodilation and marked reflex cardiac stimulation*.

Classes of calcium-channel blockers

1. **Diphenylalkylamines:**

   Verapamil is the least selective of any calcium-channel blocker and has significant effects on both **cardiac and vascular smooth muscle cells**. It is used to treat *angina, supraventricular tachyarrhythmias, and migraine headache*.

2. **Benzothiazepines:**

   Like verapamil, Diltiazem affects both **cardiac and vascular smooth muscle cells**; however, it has a less pronounced negative inotropic effect on the heart compared to that of verapamil. Diltiazem has a favorable side-effect profile.

3. **Dihydropyridines:**

   Nifedipine, Amlodipine, Felodipine, Isradipine, Nicardipine, and Nisoldipine . All dihydropyridines have a much greater affinity for **vascular calcium channels than for calcium channels in the heart**. They are therefore particularly attractive in treating hypertension.

- Some of the newer agents, such as amlodipine and nicardipine, have the advantage that they show little interaction with other cardiovascular drugs, such as digoxin or warfarin, which are often used concomitantly with calcium-channel blockers.

Therapeutic uses

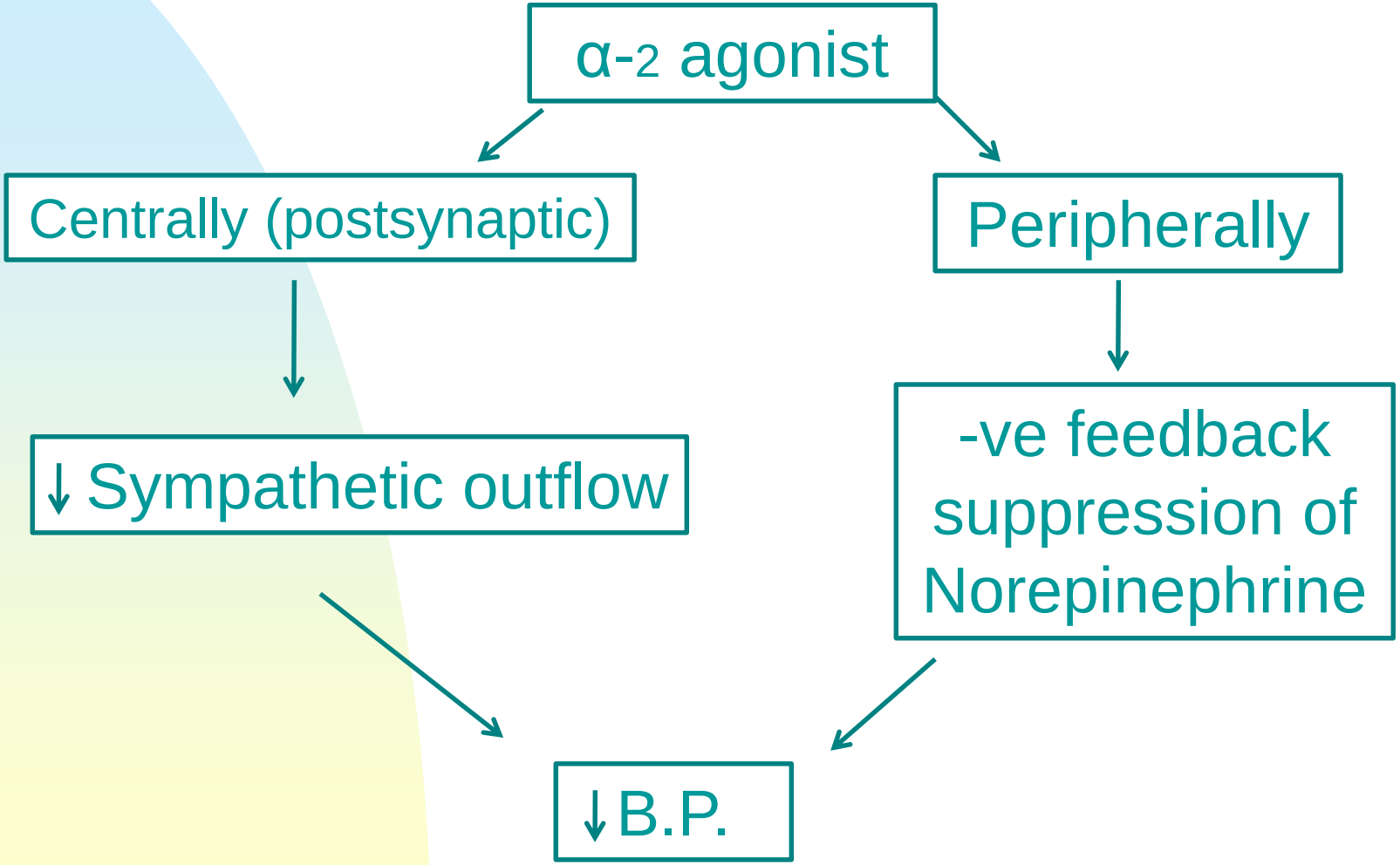
- Calcium-channel blockers have an intrinsic natriuretic effect and, therefore, *do not usually require the addition of a diuretic.*
- These agents are useful in the treatment of hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease.
- Black " people with dark skin" hypertensives respond well to calcium-channel blockers.

α-adrenoceptor blocking agents

- Prazosin, Doxazosin, and Terazosin decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.

Centrally acting adrenergic drugs

1. **Clonidine:** (α-2 adrenoceptor agonist)



- **Therapeutic uses:**

1. H.T. that not respond to 2 or more drugs.

2. H.T. complicated by renal disease (clonidine dosen't decease renal blood flow or GFR).

3. With diuretics.

2) α- Methyl Dopa:

This α_2-agonist is convert to CH_3NE centrally to diminish the adrenergic outflow:

- *False transmitter.*
- *Not metabolised by MAO.*
- *Selectively stimulates α2-adrenoceptors.*

- **Pharmacological effects:**

1. *α2-agonist* $\longrightarrow \downarrow$ *P.R.* $\longrightarrow \downarrow$ *B.P.*
2. *No effect on C.O. & Blood flow to vital organ.*

- Therapeutic uses:

1. Hypertensive patients with renal insufficiency.
2. Hypertensive pregnancy patients (safety profile).

α-β- adrenoceptor blocking agents

- ***Labetalol & Carvedilol:***

  α1, β1, β2 receptors blockers.

- ***Carvedilol:***

1. An effective antihypertensive.
2. Mainly used in treatment of heart failure (reduce mortality).

Vasodilators

direct acting smooth muscle relaxant

1. Hydralazine:

Direct vasodilator acting primarily on arteries and arterioles → ↓ P.R.&B.P.

reflex → heart rate & C.O.

- *Therapeutic uses:*

1. H.T. in pregnancy.
2. Moderately sever H.T. (always with BB & Diuretics).

Minoxidil:

this drug cause dilation of resistance vessels (aterioles but not capacitance vessels (venules).

- ***Therapeutic uses:***

1. Orally:

   For treatment of *severe to malignant hypertension that is refractory to other drugs*.

   Reflex tachycardia and fluid retention may be severe and require the concomitant use of a loop diuretic and BB.

2. Topically:

   To treat male pattern baldness.

But, what is the mechanism of action ?

Hypertensive emergency:

- Hypertensive emergency is a rare but life-threatening situation in which the DBP is
- *either* >150 mm Hg in an otherwise healthy person
- *Or* >130 mm Hg in an individual with pre-existing complications, such as encephalopathy, cerebral hemorrhage, left ventricular failure, or aortic stenosis.

- The therapeutic goal is to rapidly reduce blood pressure.

A. Sodium nitroprusside

- Nitroprusside is administered intravenously because it is poisonous if given orally because of its hydrolysis to cyanide.
- Nitroprusside is light sensitive, and when in solution, it should be protected from light.
- ***Pharmacological action:***

1. Has little effect outside the vascular system.
2. Acting equally on arterial and venous smooth muscle.

- Nitroprusside is metabolized rapidly (half-life of minutes) and requires continuous infusion to maintain its hypotensive action.

B. Labetalol

- Labetalol is both an α- and a β-blocker and is given as an intravenous bolus or infusion in hypertensive emergencies.

- Labetalol does not cause reflex tachycardia.

C. Fenoldopam

- Fenoldopam is a peripheral dopamine-1 receptor agonist that is given as an intravenous infusion.
- Unlike other parenteral antihypertensive agents, fenoldopam maintains or increases renal perfusion while it lowers blood pressure.
- Fenoldopam can be safely used in all hypertensive emergencies and may be particularly beneficial in patients with renal insufficiency.

D. Nicardipine

- A calcium-channel blocker, can be given as an intravenous infusion.
- Its long half-time (approximately 8 hours) is a major limitation.

Combination therapy

- Combination of a low dose of thiazide diuretic with a B-blocker, an ACEI, or ARBs has a synergetic effect ==== controlling up to 85% of patients.

- Combination list !!!

The End of Hypertension