



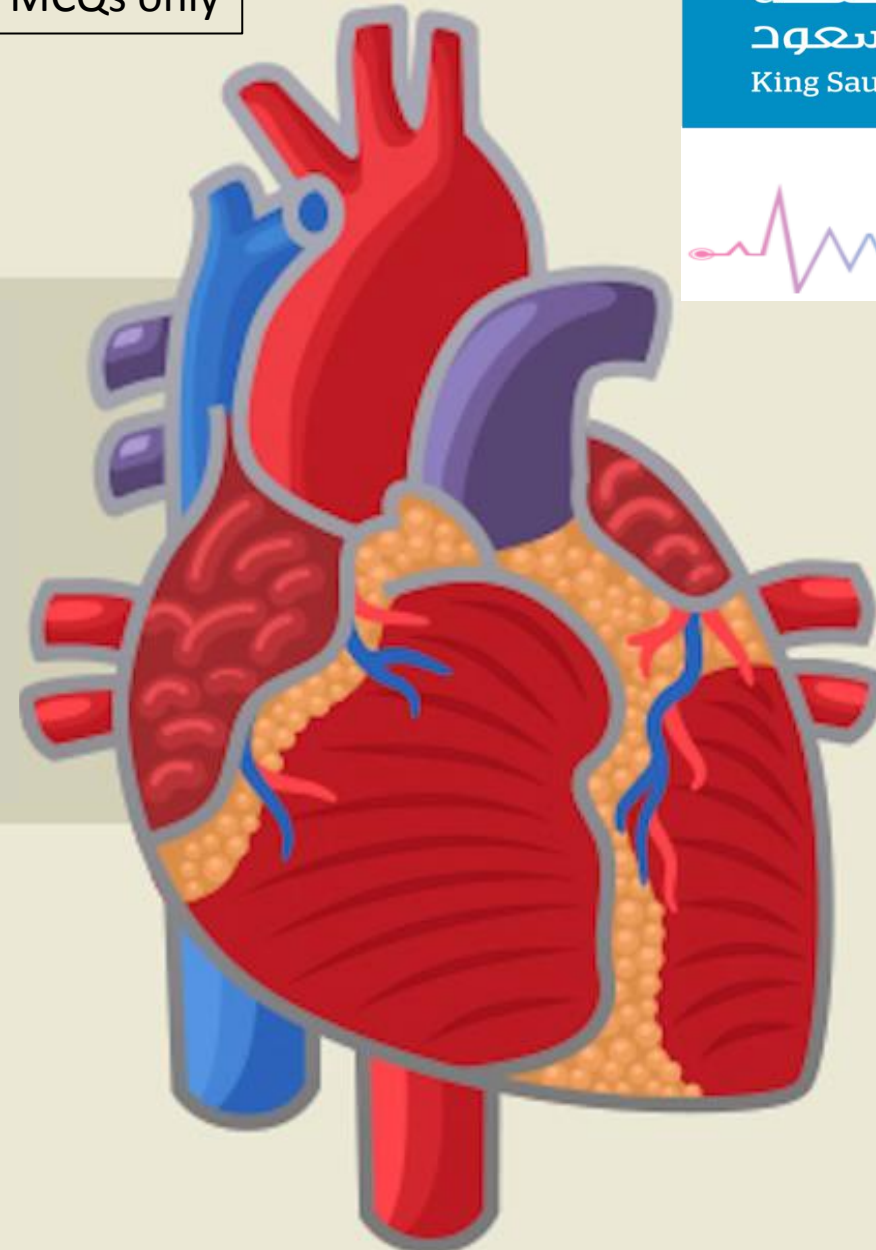
\* About Editing: There are a changes in MCQs only

جامعة  
الملك سعود  
King Saud University



# 7&8

## Antihypertensive Drugs.



## Cardiovascular Block.

Red = Important

Summary & MCQs Also Important

For any correction, suggestions or any useful information do not hesitate to contact as: [Pharmacology434@gmail.com](mailto:Pharmacology434@gmail.com)

# Introduction of Hypertension:

Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure is summarized by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). Is a major risk factor for cerebrovascular disease, heart failure, renal insufficiency and myocardial infarction. It is often asymptomatic until organ damages reaches a critical point.

**Blood pressure is determined by :**

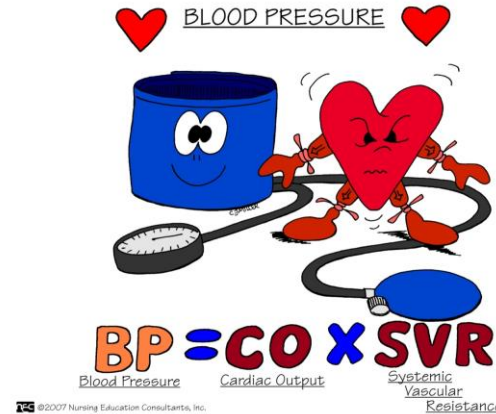
$$BP = CO \times PVR$$

1- Blood Pressure

2- Cardiac output ( rate & contractility )

3- Peripheral (Systemic) vascular resistance

\* Blood pressure determined by Blood volume

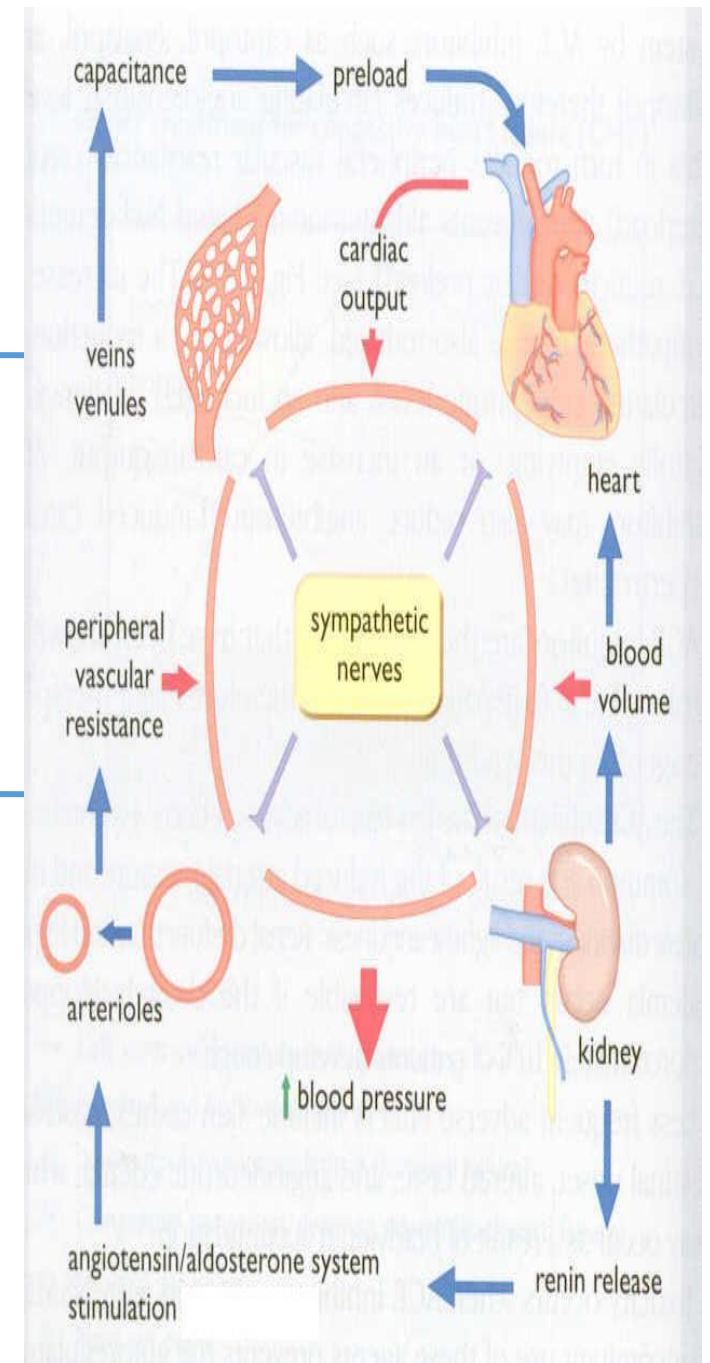


**Non-pharmacological therapy for hypertension :**

Initially consists of lifestyle changes , such as:

1. weight reduction
2. smoking cessation,
3. reduction of salt
4. saturated fat
5. Excessive alcohol intake
6. increased exercise

These methods used before drug therapy is initiated.



# Hypertension:

- **Definition:** Persistent diastolic blood pressure greater than 90 mmHg and systolic pressure greater than 140 mmHg
- **What is the types of Hypertension?**

1- **Primary (Essential):** It is 90-95% in patients of hypertension, it is with unknown etiology (**Most common**).

2- **Secondary:** A hypertension secondary to other disease.

- **What is the complication of hypertension:**

Coronary artery disease, heart failure, renal failure, and stroke

- **What is the ultimate goal of antihypertensive drugs?**

**Reduce either** Cardiac Output & Peripheral vascular resistance, this two lead to reduce blood pressure.

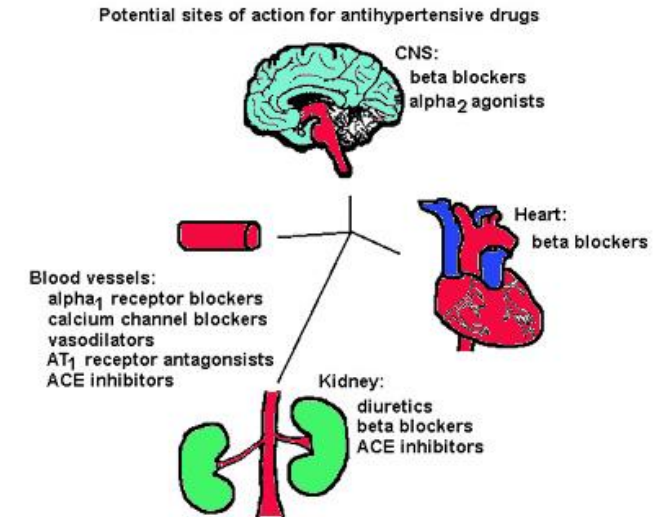
- **Indication of using drug therapy:**

- Sustained blood pressure elevations > 140/ 90 mmHg.

- When minimally elevated blood pressure is associated with other cardiovascular risk factors (smoking, diabetes, obesity, hyperlipidemia, genetic predisposition)

- When end organs are affected by hypertension (heart, kidney , brain).

- **Classification of antihypertensive drugs: (in the table below)**



Classification of Drug	Examples
<b>β- Adrenoceptor Blockers</b>	Nadolol, Bisoprolol, Atenolol, metoprolol, Labetalol, & carvedilol
<b>α- Adrenoceptor Blockers</b>	Prazocin & Terazosin
<b>Calcium channel blockers</b>	Verapamil, Diltiazem, & Nifedipine
<b>Centrally acting sympatholytic</b>	Clonidine & α methyl dopa
<b>Vasodilators</b>	Hydralazine, Minoxidil, Diazoxide, & Na nitropruside
<b>Diuretics</b>	Hydrochlorothiazide, Furosemide, Amiloride, & spironolactone
<b>ACE Inhibitor</b>	captopril, lisonopril, enalapril, ramipril, & fisonopril
<b>Angiotensin receptor Blockers</b>	Losartan, valsartan, & irbesartan

# DIURETICS DRUGS

Groups	Thiazides	Loop diuretics	Potassium-sparing diuretics
Example	Hydrochlorothiazide	Furosemide	Amiloride as well as spironolactone
Clinical uses	Mild hypertension	-Sever & Moderate hypertension -Sever heart failure	-Hypertension. (Not potent in hypertension mainly used in Heart failure)
Mechanism of Action	Cause sodium and water loss: -decrease volume of blood -decrease cardiac output -lower blood pressure.		- Reduce potassium loss in the urine (return K) - <b>Spironolactone</b> has the additional benefit : Reduce aldosterone effect (diminishing cardiac and blood vessels remodeling that occurs in heart failure ) *doesn't need to K supplementation

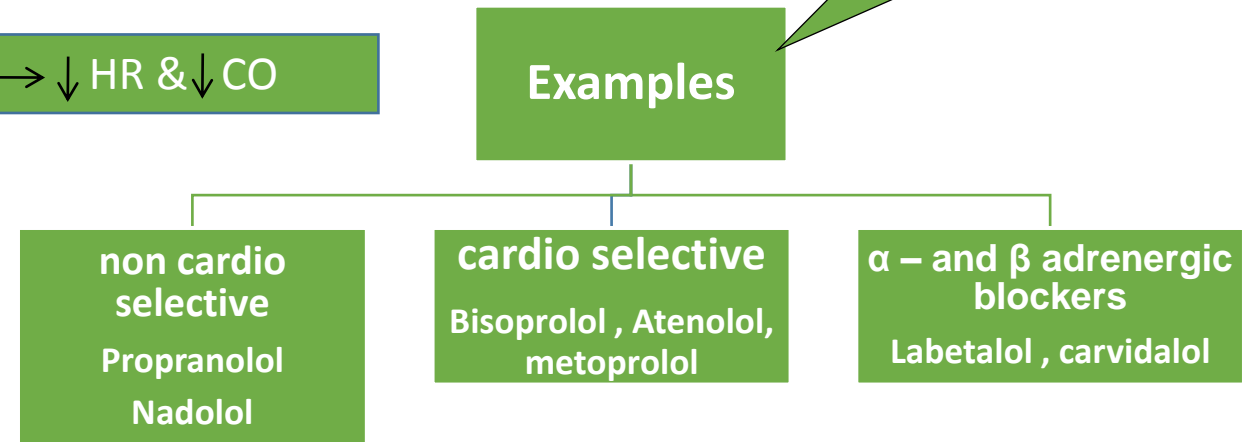
Diuretics most effective in Hypertension patient (Obese, Black people and elderly) because they salt sensitive

# $\beta$ - Adrenoceptor – blocking agents

- $\beta$ - adrenoceptor blocking agents can be used monotherapy in mild to moderate hypertension.
- In severe cases used in combination with other drugs.
- They lower blood pressure by : **Decreasing cardiac output**.
- **Decreasing renin release (very important effect and more related to the clinical response)**

Decreases sympathetic tone  $\longrightarrow$   $\downarrow$  Myocardial contractility  $\longrightarrow$   $\downarrow$  HR &  $\downarrow$  CO

- Non cardioselective ( $\beta_1$  &  $\beta_2$  ) drugs as propranolol are contraindicated in patients with asthmatic patients



## $\alpha_1$ -Adrenoceptor blockers

### Prazocin & Terazosin

- Selectively block postsynaptic  $\alpha_1$  adrenergic receptors. They dilate arterioles  $\rightarrow$  lowering BP
- Added to  $\beta$ - blockers for treatment of hypertension of pheochromocytoma

Due to the postural hypotension  $\alpha_1$ -adrenoceptor blockers are not commonly used for Rx of HTN

# CALCIUM CHANNEL BLOCKERS

## Classification

### Dihydropyridine

It is **more selective** as **vasodilator** than a cardiac depressant. This group is used for **treatment of hypertension**.

Nifedipine

Nicradipine

Amlodipin (Ankmlor)

### Verapamil

It is more effective as **cardiac depressant**, therefore it is **not** used as antihypertensive agent & used as antiarrhythmic.

### Diltiazem

Used mainly for **angina pectoris**

## PHARMACOKINETICS

Given orally and intravenous injection

Well absorbed from G.I.T

Verapamil and Nifedipine are highly bound to plasma proteins ( more than 90%), while Diltiazem is less ( 70-80%).

Onset of action within:

1-3 min after I.V.

30min - 2 h after oral dose

Verapamil & Diltiazem have active metabolites, Nifedipine does not.

**Sustained-release preparations of Nifedipine can permit once-daily dosing.**

## MECHANISM OF ACTION (ARTERIAL) :

Block the influx of calcium through L-type calcium channels resulting in:

1- Peripheral vasodilatation (at arteries) (because it depends on calcium channel to contract)

2- Decrease cardiac contractility & heart rate (because when you block calcium channel you will decrease the inflow of sodium)

Both effects lower blood pressure



## CLINICAL USES

- Treatment of **chronic hypertension** with oral preparation (Nifedipine; Amlodipine)
- Nifedipine used for **Reynolds phenomena**. (تبرد الأطراف)
- Nicardipine can be given by I.V. route & used in **hypertensive emergency**

## ADVERSE EFFECTS

Verapamil	Diltiazem	Nifedipine
Headache - Flushing - Hypotension		
Peripheral edema (ankle edema)		
Cardiac depression - A-V block - bradycardia		<b>Reflex Tachycardia</b> (result of artery vasodilation there is a release of norepinephrine > tachycardia, ankle edema & retention)
Constipation		

## Centrally acting sympatholytic drugs

drugs	Clonidine	α methyl dopa
<b>Mechanism of action</b>	<p><u>Direct α<sub>2</sub>-agonist</u> :</p> <p>Reduce sympathetic outflow to the heart thereby decreasing cardiac output (by decreasing heart rate &amp; contractility ).</p> <p>Reduce sympathetic output to the vasculature, decreases sympathetic vascular tone , which causes vasodilation &amp; reduced systemic vascular resistance, which decreases arterial pressure.</p>	<p><u>Indirect α<sub>2</sub> agonist</u> :</p> <p>α methyl dopa is converted to methyl norepinephrine centrally to diminish the adrenergic outflow from the C.N.S. This lead to reduced total peripheral resistance, and a decreased blood pressure.</p> <p>Safely used in hypertensive pregnant women</p>
<b>Adverse effects</b>	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Dry mouth, nasal mucosa</li> <li>• Bradycardia</li> <li>• Impotence</li> <li>• Postural hypotension</li> <li>• Fluid retention &amp; edema with chronic use</li> <li>• Sudden withdrawal of <b>clonidine</b> can lead to rebound hypertension</li> <li>• α methyl dopa can cause hemolytic anemia <u>contraindicated</u> ( patient with blood diseases )</li> </ul> <p>*<u>Important Note</u>: α methyl dopa Safely used in hypertensive pregnant women</p>	

# Vasodilators

Drugs	Hydralazine	Minoxidil	Diazoxide (Less important)	Na nitropruside
<b>Site of action</b>	Arteriodilator	Arteriodilator	Arteriodilator	Arterio & venodilator
<b>Mechanism of action</b>	Direct	Opening of <b>potassium channels</b> in smooth muscle membranes by minoxidil sulfate ( active metabolite )	Opening of potassium channels	Release of nitric oxide (NO)
<b>Route of admin.</b>	Oral	Oral	Rapid intravenous	Intravenous infusion
<b>Therapeutic uses</b>	1.Moderate -severe hypertension. CHF	1.severe hypertension	1.Hypertensive emergency ( in the past )	1.Hpertensive emergency
	2.Hypertensive pregnant woman	2.correction of baldness	2.Treatment of hypoglycemia due to insulinoma	
<b>Adverse effects</b>	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema)			Severe hypotension
<b>Specific adverse effects</b>	lupus erythematosus like syndrome	Hypertrichosis.  Contraindicated in females	Inhibit insulin release from $\beta$ cells of the pancreas causing hyperglycemia  Contraindicated in diabetic	1.Methemoglobin during infusion 2. Cyanide toxicity 3. Thiocyanate toxicity

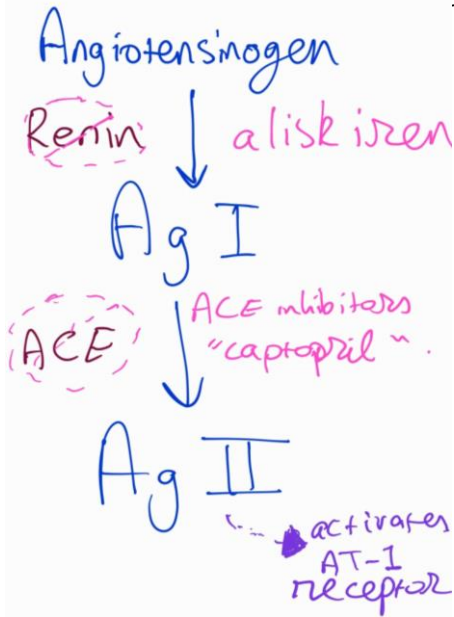


# ACE INHIBITORS

## Quick Review

As we start talking about this class of antihypertensive drugs, we should review the RAS:

1. **Angiotensinogen** is produced by the liver
2. **Renin** is produced from the kidneys due to various triggers such as decreased renal perfusion
3. Renin acts as follows: Angiotensin 1 → Angiotensin 2
4. **Ag II is the active substance and it activates AT-1 receptors**
5. AT-1 cause vasoconstriction & increases aldosterone production
  - Aldosterone increases Na excretion & decreases K excretion
  - **Bradykinin is inactivated by ACE**
  - Bradykinin has different functions, such as vasodilation & it also takes part in inflammation
  - ACE Inhibitors increase the levels of bradykin



## Important Notes

- Note that ACE I all end with the suffix "-pril"
- Drugs include captopril, lisinopril, enalapril, ramipril, fisonopril

## CLINICAL USES

- Hypertention
- Heart failure
- Diabetic nephropathy

## MECHANISM OF ACTION

ACE Inhibitors decrease the levels of Ag II; which leads to the following:

1. Dilation of the arterioles → decrease total peripheral resistance → decrease BP → decreased workload on the heart ↓**afterload**
2. Decrease aldosterone levels → increased sodium Na excretion → decrease blood volume → decrease BP ↓**preload**
3. Decreased aldosterone levels → less potassium K excretion
4. Reduction of sympathetic activity : Reduce the arteriolar and left ventricular remodelling that are believed to be important in the pathogenesis of human essential hypertension and post-infarction state

ACE I are not associated with baroreceptor reflex → no reflex tachycardia with use  
ACE I decrease left ventricle remodeling; which is good

## PHARMACOKINETICS

**Captopril**, Lisinopril; **Enalapril** and **Ramipril**; **Fisonopril** .

All are rapidly absorbed from GIT after oral administration.

Food reduce their bioavailability.

**Enalapril** , **ramipril** are prodrugs, converted to the active metabolite in the liver, Have a long half-life & given once daily except Captopril

**Enalaprilat** is the active metabolite of enalapril given by i.v. route **in hypertensive emergency**.

**Captopril** is not a prodrug, Has a short half-life & given twice /day

All ACEI are distributed to all tissues except CNS.

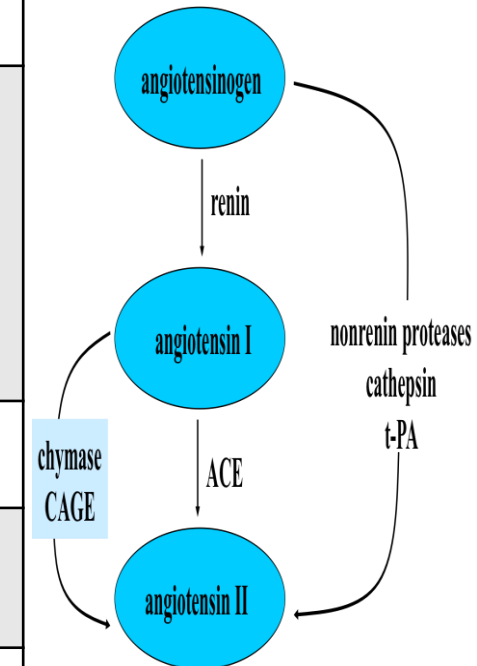
## Adverse Effects, Drug Interactions, & Contraindications

- **Acute renal failure** → therefore they are contraindicated in pts. with bilateral renal artery stenosis (or renal artery stenosis in a patient who only has one kidney) because it increases the risk of acute renal failure
- Hyperkalemia
- Persistent cough → because of increased bradykinin levels
- Angioneurotic edema
- Severe hypotension in hypovolemic patients
- **Contraindicated in pregnancy due to teratogenicity +**
- Interacts with potassium sparing diuretics (spironolactone)
- **NSAIDs** impair their hypotensive effect because they block bradykinin's vasodilatory effect
- taste loss ( due to SH group in captopril molecule +Skin rash, fever)

# BLOCKERS OF AT<sub>1</sub> RECEPTOR

Angiotensin II: Vasoconstriction, aldosterone release .

Drug	losartan	valosartan	irbesartan
<b>Characteristic</b>	<ul style="list-style-type: none"> <li>- Inhibit angiotensin II at its AT<sub>1</sub> receptor site <u>competitively</u>.</li> <li>- They have no effect on <u>bradykinin</u> system: No <u>cough</u>, <u>wheezing</u> or <u>angioedema</u>.</li> <li>- They influence RAS more effective because of selective blockade(angiotensin II synthesis in tissue is not completely dependent only on renin release, but could be promote by serin -protease -</li> </ul>		
<b>Clinical Uses</b>	In <u>asthmatic patients</u> who they have hypertension.		
<b>Adverse effects</b>	As ACEI <u>except</u> cough ,wheezing , and angioedema.		
<b>Contraindication</b>	Same contraindications as <u>ACEI</u> : Pregnancy, Bilateral renal artery stenosis		
<b>Drug Interaction</b>	Hydrochlorothiazide 12.5 mg + Losartan 50 or 100 mg.	Hydrochlorothiazide 12.5 mg+ Valsartan 60 or 80 mg	-



## Precaution in management of hypertensive emergencies

Avoid using short-acting nifedipine because of the risk of rapid, unpredictable hypotension & the possibility of precipitating ischemic events

## Drugs for treatment of hypertensive crisis

BP > 180/120 mmHg associated with end-organ damage

Sodium nitroprusside (2<sup>nd</sup> line)

Hydralazine (in pregnancy)

Labetalol

Nicardipine

Enalaprilat

**General characters of good drug for Crisis:**

Fast & short acting

Given by IV

## Drug Combination for Hypertension

- Hydrochlorothiazide (12.5 mg+ **Valsartan** (60 or 80 mg) (Co-Diovan<sup>R</sup>)

- Hydrochlorothiazide (12.5 mg + **Losartan** (50 or 100 mg)

- Hydrochlorothiazide (12.5 mg + **Lisinopril** (10 or 20 mg)

## Drugs used for management of hypertension in pregnancy

Methyldopa ( the preferred first line )

Labetalol

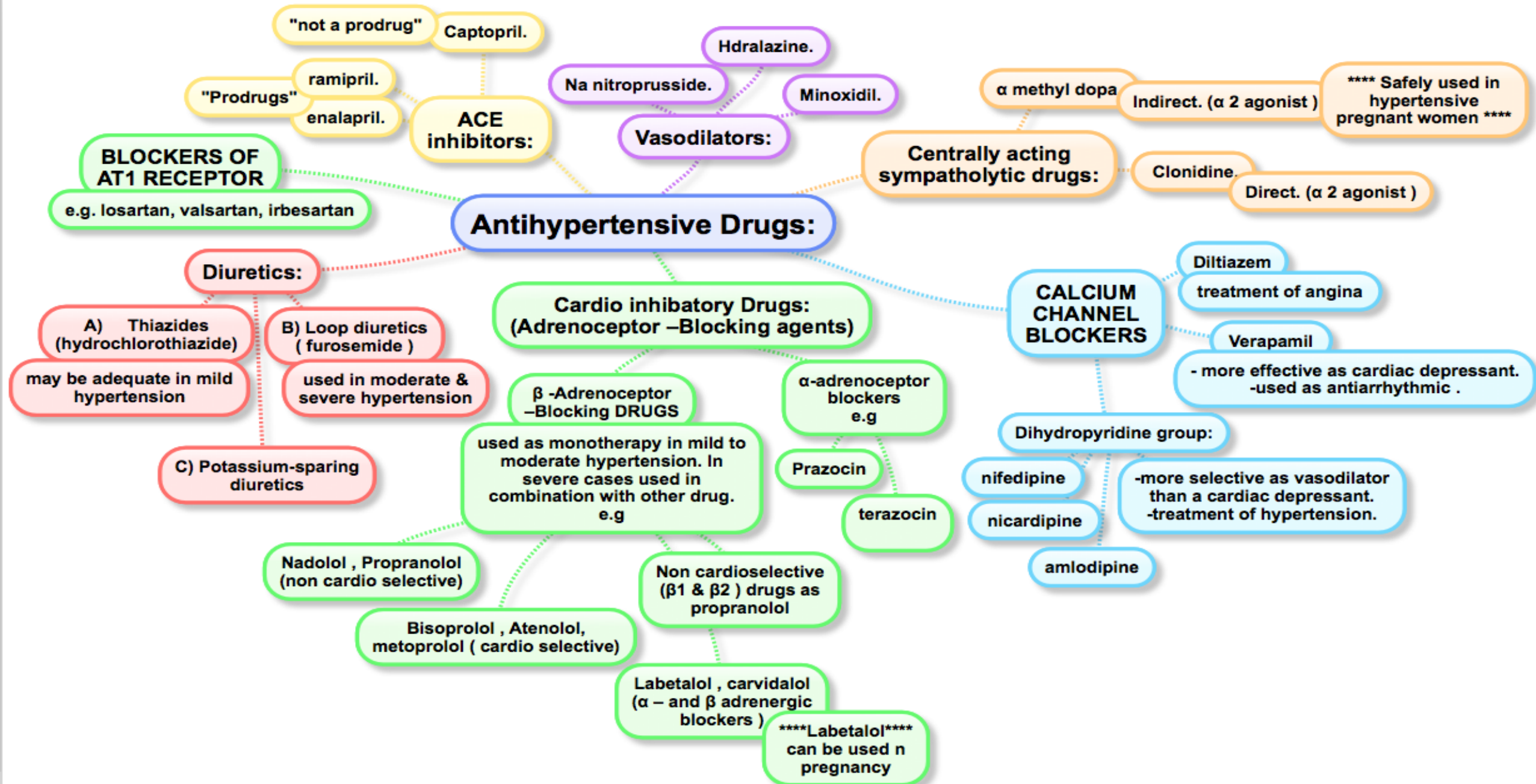
Hydralazine

Diuretics

# SUMMARY:

Classification of Drug	Examples	Important Notes
<b>β- Adrenoceptor Blockers</b>	Nadolol, Bisoprolol, Atenolol, metoprolol, Labetalol, & carvedilol	In severe cases used in combination with other drugs. These drugs decreasing <b>renin release</b>
<b>α- Adrenoceptor Blockers</b>	Prazocin & Terazosin	-
<b>Calcium channel blockers</b>	Verapamil, Diltiazem, & Nifedipine	Treat chronic hypertension    <b>Nifedipine</b> : side effect reflex tachycardia & Use for Reynolds phenomena.
<b>Centrally acting sympatholytic</b>	Clonidine & α methyl dopa	<b>clonidine</b> can lead to rebound hypertension <b>α methyl dopa</b> : Safe in Pregnant woman & not given to patient with blood disease
<b>Vasodilators</b>	Hydralazine, Minoxidil, Diazoxide, & Na nitropruside	<b>Hydralazine</b> Cause: and used in Hypertensive pregnant woman <b>Minoxidil</b> Cause: ( <b>Hypertrichosis</b> ) increase hair growth, That's why it is contradicted in female <b>Na nitropruside</b> Cause: Cyanide toxicity & used in hypertension emergency
<b>Diuretics</b>	Hydrochlorothiazide, Furosemide, Amiloride, & spironolactone	<b>Amiloride &amp; spironolactone</b> Reduce potassium loss in the urine <b>Also spironolactone</b> : Reduce aldosterone effect <b>Hydrochlorothiazide &amp; Furosemide</b> :decrease the B.P by decreasing volume of blood & cardiac output
<b>ACE Inhibitor</b>	captopril, lisonopril, enalapril, ramipril, & fisonopril	Cause and increase the risk of renal failure so it is contradiction in patient with renal diseases & Pregnant women
<b>Angiotensin receptor Blockers</b>	Losartan, valsartan, & irbesartan	Used In asthmatic patients & Same contraindications as <u>ACEI</u>

# Mind Map



# MCQs

1- A patient seeing his family doctor because of having several asthma attacks, the doctor tested the patient blood pressure and he had moderate hypertension, What of these drug can be used to treat this patient high blood pressure?

- A) Nadolol
- B) Propranolol
- C) Captopril
- D) Bisoprolol

2- Patient with chronic hypertension with unknown cause, The doctor start to treat this patient with calcium channels blocker (nifedipine) . Which ONE of the following drugs should be accompanied with the calcium channels blocker?

- A) Atenolol
- B) Thiazides
- C) Prazocin
- D) Methyl dopa

3- Pregnant women with hypertension visited a doctor asking for a treatment for the hypertension and she was scared of the effect of hypertension on her child, The doctor start the patient with a2 agonist which of the following did the doctor use assuming that he made the right call?

- A) Thiazides
- B) Methyl dopa
- C) Hdralazine
- D) Labetalol

4- You decided to treat a hypertensive patient with Clonidine, What should you do besides giving him that drug ?

- A) Give B blocker drug to inhibit the reflex tachycardia
- B) Ask the patient to lower the dose gradually
- C) Giving potassium syrup
- D) Run Coombs test before starting the treatment

5- You have seen a patient in the ER with hypertensive crisis, What is the mechanism of action of the drug that should be given immediately in this situation?

- A)Release of nitric oxid
- B) Opening of potassium channels
- C)Inhibit angiotensin II at its AT1 receptor site
- D) Cause sodium and water loss

6- Doctor treated a patient with hypertension with the combination of Hdralazine + thiazides + metoprolol . Which one of following may happen as side effect?

- A) Constipation
- B) Bradycardia
- C) lupus erythematosus like syndrome
- D) Cyanide toxicity

7- Which of the following can be used to prevent the ventricular remodeling ?

- A) Enalapril
- B) Hydralazine
- C) Sodium nitroprusside
- D) Verapamil

8- Patient with renal artery stenosis had hypertension and he had been treated with antihypertensive drugs, Which of the following drugs that most likely this patient used?

- A) Enalaprilat
- B) Captopril
- C) Losartan
- D) Clonidine

9- You have prescribed a captopril drug to a patient with hypertension, Which of the following drugs can lead to loss of the effect of the captopril?

- A) Spironolactone
- B) Aspirin
- C) Labetalol
- D) thiazides

10- A hypertensive woman take a antihypertensive drug, after a while suddenly she notice a hair growth in his hand, Which of the following drugs that most likely this patient used?

- A) Methyl dopa
- B) Captopril
- C) Minoxidil
- D) Spironolactone

 <https://www.youtube.com/watch?v=tdlWllw6ijA>

 <https://www.youtube.com/watch?v=lqDUSlfoUQ>

Long video but it  
is helpful

# GOOD LUCK!

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