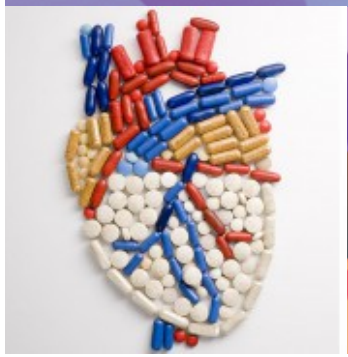
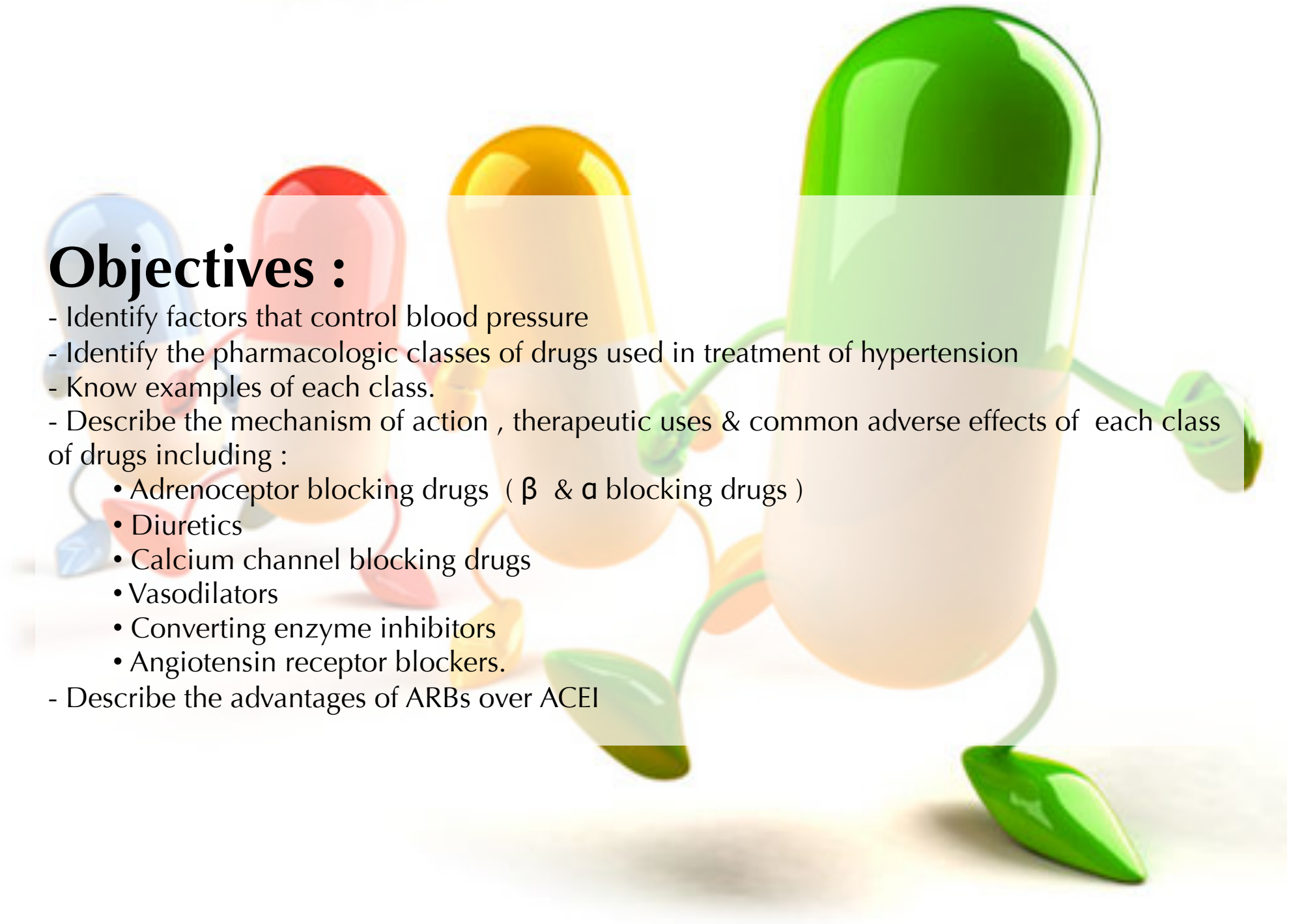
King Saud University
College of Medicine
1st Year, 4th Block

Treatment of Hypertension

7&8



Cardiovascular Block



Objectives :

- Identify factors that control blood pressure
- Identify the pharmacologic classes of drugs used in treatment of hypertension
- Know examples of each class.
- Describe the mechanism of action , therapeutic uses & common adverse effects of each class of drugs including :
    - Adrenoceptor blocking drugs (β & α blocking drugs)
    - Diuretics
    - Calcium channel blocking drugs
    - Vasodilators
    - Converting enzyme inhibitors
    - Angiotensin receptor blockers.
- Describe the advantages of ARBs over ACEI

Blood Pressure = CO x Systemic vascular resistance

*Cardiac output is a function of heart rate and stroke volume.

Hyper-tension (silent killer):

It is asymptomatic until organ damages, and risk factor for :

1-MI & HF

2-renal insufficiency

3-cerebeovascular disease

Antihypertensive therapy:

Begin by changing lifestyle as

1-weight reduction.

2-salt reduction.

3-increase exercise.

4-smoking &alcohol cessation.

Indications for Drug Therapy :

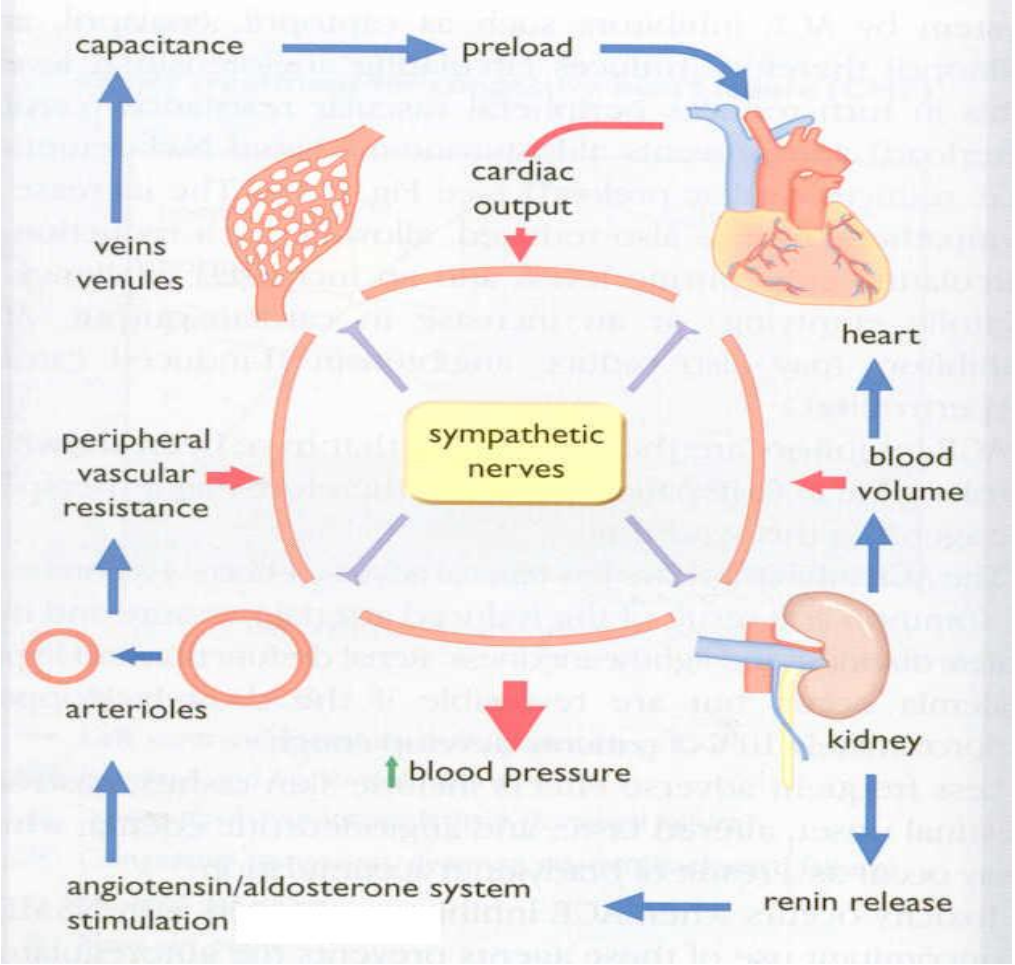
1- When blood pressure is > 140/90 mmHg

2- when minimally elevated blood pressure is associated with other **cardiovascular risk factors :**

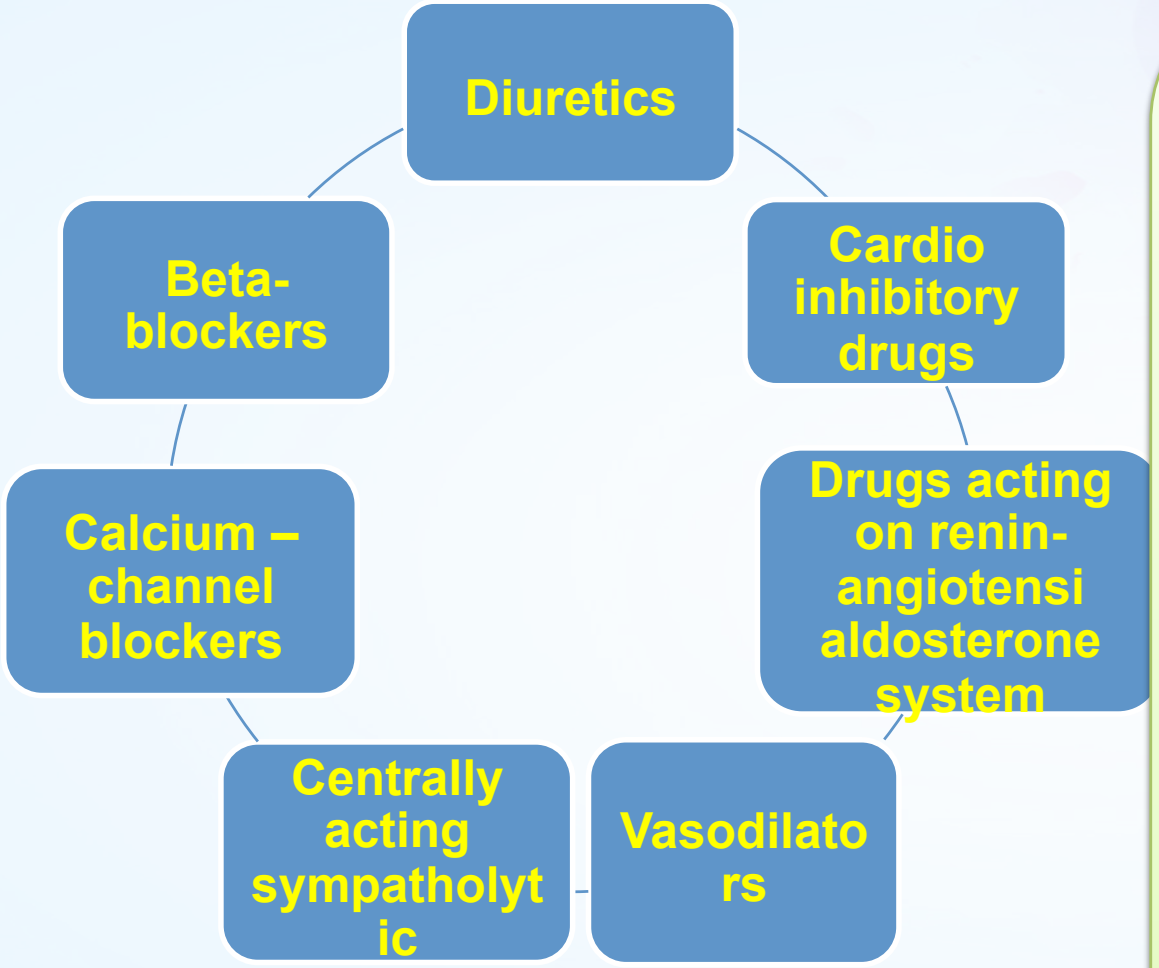
(smoking, diabetes, obesity, hyperlipidemia, genetic predisposition).

- The most affected organs are (kidney, heart, brain)

Factors in blood pressure control



Drug Management of Hypertension



Diuretics

1- Thiazides:

e.g. Hydrochlorothiazie, Indapamide

-**Mechanism of action**:
cause sodium and water loss → decrease volume of blood → decrease cardiac output → lower blood pressure.

-Diuretics may be adequate in mild to moderate hypertension.

2- Potassium-sparing diuretics :

e.g. Amiloride, Spironolactone

–**Mechanism of action:**
reduce potassium loss in the urine. Spironolactone has the additional benefit of diminishing the cardiac remodeling that occurs in heart failure.

Cardio inhibitory Drugs
(Adrenoceptor –Blocking Agents)

β - adrenoceptor blocking agents:

- Are used in mild to moderate hypertension.
- In severe cases used in combination with other drugs.

- They lower blood pressure by:
1-Decreasing cardiac output.
2- Decreasing renin release.

e.g.
Nadolol (non cardio selective)
Bisoprolol, Atenolol, metoprolol (cardio selective)

α-adrenoceptor blockers

e.g.
Prazocin, Terazocin

Added to β- blockers for treatment of hypertension of pheochromocytoma

Labetalol and Carvidalol
(α and β adrenergic blockers)
Labetalol can be used in pregnancy

Calcium Channel Blockers

Dihydropyridine (Nifedipine & Nicardipine & Amlodipine)

- More selective as **vasodilator** than a cardiac depressant, this group is used for treatment of hypertension

Verapamil

- More effective as **cardiac depressant** , is not used as antihypertensive agent

Diltiazem

- Used mainly for angina

Drug	Main action	Clinical uses	Pharmaco-kinetics	Adverse effects*
Dihydropyridine	Block the influx of Ca through L-type calcium channel resulting in : 1- Peripheral vasodilatation. 2- Decrease cardiac contractility and heart rate. (Both effects lower blood pressure)	➢ Treatment of chronic hypertension ➢ Nicardipine can be given I.V & used in hypertensive emergency	*Given orally and IV. *Well absorbed. *Rapid onset of action after I.V *Verapamil and Diltiazem have active metabolites while Nifedipine does not. *Verapamil and Nifedipine are highly bound to plasma protiens while Diltiazem is less bound.	➢ **Reflex tachycardia**
Verapamil		➢ Treatment of chronic hypertension		➢ **Cardiac depression** ➢ **AV block** ➢ **Bradycardia** ➢ **constipation**
Diltiazem		➢ Treatment of chronic hypertension		➢ **Cardiac depression** ➢ **AV block** ➢ **bradycardia**

All the ca channel blockers can cause headache , flushing , hypotension, Peripheral edema

Centrally acting sympatholytic drugs

Clonidine

direct
(α_2-agonist)

- Reduce sympathetic outflow to the heart → decreasing cardiac output (by decreasing heart rate & contractility)
- Reduce sympathetic output to the vasculature, decreases sympathetic vascular tone, → vasodilation
- Reduce systemic vascular resistance, → decreases arterial pressure.

α-methyl dopa

indirect
(α_2-agonist)

- Converted to methyl norepinephrine centrally to diminish the adrenergic outflow from the C.N.S , which causes :
  - reduced total peripheral resistance .
  - decreased blood pressure .
- **Safely used in hypertensive pregnant women**

Side effects:

- **Depression.**
- **Dry mouth & nasal mucosa.**
- **Bradycardia.**
- **Impotence.**
- **Fluid retention & edema with chronic use.**
- **Sudden withdrawal of clonidine can lead to rebound hypertension.**

Vasodilators

	Hdralazine	Minoxidil	Diazoxide	Na nitropruside
Site of action	Arteriodilator	Arteriodilator	Arteriodilator	Arterio & venodilator
Mechanism of action	Direct	Opening of potassium channels in smooth muscle membranes by **minoxidil sulfate** (active metabolite)	Opening of potassium channels	Release of nitric oxide (NO)
Route of admin.	Oral	Oral	Rapid intravenous	Intravenous infusion
Therapeutic uses	1. Moderate to severe hypertension. 2. CHF 3.**Hypertensive pregnant woman**	1.Moderate to severe hypertension 2.correction of baldness	1.Hypertensive emergency 2.Treatment of hypoglycemia due to insulinoma	Hypertensive emergency
Adverse effects	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema)			Severe hypotension
Specific adverse effects	Systemic lupus erythematosus like syndrome	Hypertrichosis “abnormal hair growth” *Contraindicated in females	Inhibit insulin release from β cells of the pancreas causing hyperglycemia. *Contraindicated in diabetic	1.Methemoglobinduring infusion 2. Cyanide toxicity 3. Thiocyanate toxicity

ACE Inhibitors

	Captopril	Enalapril	Ramipril
M.O.A	Reducing angiotensin II production, and ↑vasodilator peptides like (Bradykinin). ↑Na^+ and ↓K^+ excretion in kidney. ↓ Sympathetic activity. Inhibition of aldosterone secretion. Reduce the arteriolar and left ventricular remodelling		
Pharmacokinetic	**Rapid absorbed after oral admin. Food reduce bioavailability, distributed to all tissues except CNS**. has a short half-life & given twice daily, it isn't a prodrug*	**Rapid absorbed after oral admin. Food reduce bioavailability, distributed to all tissues except CNS,** has a long half-life & given once daily, it's a prodrug*. **Enalaprilat is the active metabolite of enalapril given by i.v. route in hypertensive emergency.**	**Rapid absorbed after oral admin. Food reduce bioavailability, distributed to all tissues except CNS,** has a long half-life & given once daily, it's a prodrug*, given I.V. in hypertensive emergency
Clinical uses	Treatment of hypertension, CHF, diabetic nephropathy		
Adverse Effect	Hyperkalemia, Skin rash, fever, dry cough, Taste loss (due to a sulfhydryl group in the molecule of captopril), Angioneurotic edema*, severe hypotension (in hypovolemic patients), Renal failure		
Contraindications	Pregnancy, bilateral renal artery stenosis, stenosis of a renal artery with solitary kidney.		
Drugs Interaction	With: -potassium-sparing diuretics. -NSAIDs.		

*Prodrug is a medication that is administered in an inactive or less than fully active form, and then it becomes converted to its active form through a normal metabolic process.

* swelling in the nose, throat, tongue, larynx

BLOCKERS OF AT_1 RECEPTOR Losartan, Valosartan, Irbesartan	
Characterized	**competitively inhibit angiotensin II at its AT1 receptor site**
Actions	**-most of the effects of angiotensin II including vasoconstriction and aldosterone release are mediated by the AT_1 receptor.** **-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).**
Adverse effects	**As ACEI except cough ,wheezing , andangioedema because they have no effect on bradykinin system**
contraindications	**Same contraindications as ACEI**

Drugs for treatment of hypertensive crisis

Labetalol (in pregnancy)
Hydralazine (in pregnancy)
Sodium nitroprusside (2nd line)

General characters:

Fast & short acting
Given by IV

SUMMARY

Drug	Type	Uses	Note
Indapamide, Amiloride	Diuretics	mild to moderate hypertension	
Bisoprolol , Atenolol, Metoprolol	B cardio selective	mild to moderate hypertension	
Nifedipine & Nicardipine & Amlodipine	Calcium channel blockers	chronic hypertension	Nicardipine can be given I.V & used in hypertensive emergency
Diltiazem	Calcium channel blockers	Used mainly for angina	
Verapamil	Calcium channel blockers	More effective as cardiac depressant	
α methyl dopa	α_2-agonist	Hypertensive pregnant patients	
Minoxidil, Hdralazine	Vasodilators	Moderate -severe hypertension	Hdralazine can be used in pregnancy
Diazoxide	Vasodilators	hypoglycemia due to insulinoma	Contraindicated in diabetic patients
Na nitropruside	Vasodilators	Hpertensive emergency	Arterio & venodilator
Enalapril, Captopril, Ramipril	ACE inhibitors	hypertension, CHF, diabetic nephropathy	
Labetalol	(α and β adrenergic blockers)	hypertensive crisis	In pregnancy

MCQs

1- Which one of the following drugs is a vasodilator :
A- Hdralazine
B- Verapamil
C- Clonidine
D- Terazocin

2- A 30years old pregnant woman developed hypertension during the 15th week of gestation.
Which one of the following drugs can she safely use?
A- Alpha-methyl dopa
B- Clonidine
C- Prazocin
D- Deltiazem

3- Which group of these drugs will impair the hypotensive effect of ACE inhibitors :
A- Potassium-sparing diuretics
B- NSAIDs
C- AT1 receptors blockers
D- Both A&B

4- AT1 receptor blockers differ from ACE inhibitors in :
A- More rapid absorbed
B- Have 1st pass metabolism
C- Less selective blocking
D- Have no effect on bradykinin system

5- All the following drugs are cardio selective except :
A- Bisoprolol
B- Atenolol
C- Metoprolol
D- Nadolol

1-A 2-A 3-D 4-D 5-D 6-A 7-C 8-A 9-B 10-B

6- Which group should be added to beta-blockers for the treatment of pheochromocytoma :
A- Alpha-blockers
B- ACE inhibitors
C- Alpha-agonists
D- None of them

7- Which one of the following vasodilators act by releasing NO :
A- Diazoxide
B- Minoxidil
C- Na nitropruside
D- hdralazine

8- Which one of the following drugs is contraindicated in diabetic patients due its insulin release inhibition effect :
A- Diazoxide
B- Minoxidil
C- Na nitropruside
D- hdralazine

9- Which of the following drugs is a potassium sparing diuretic :
A- Indapamine
B- Amiloride
C- Captropil
D- Diazoxide

10- A hypertensive patient was told by his doctor to take a Ca-blocker drug, which of them is best for him :
A- Diltiazem
B- Amlodipine
C- Verampil
D- All of them work good in hypertension.

PHARMACOLOGY 433

THIS WORK WAS DONE BY :

Nada Dammas	Ahmed Aldakhil
Raneem Alotaibi	Abdulrahman Althaqib
Noha Almndeel	Abdulaziz Almasoud
	Ziyad Alajlan
	Abdulrahman Alqahtani
	Mohamed Alnafisah

Contact us for any questions or comments :

Pharma_433@yahoo.com

@pharma_433

We hope that we made this lecture easier for you

Good Luck !