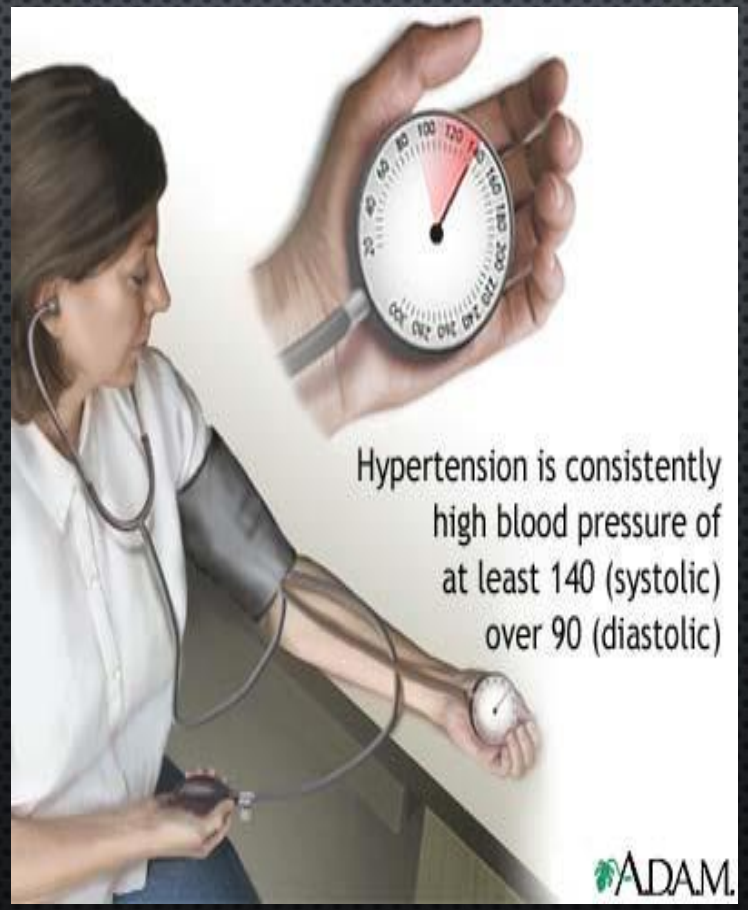
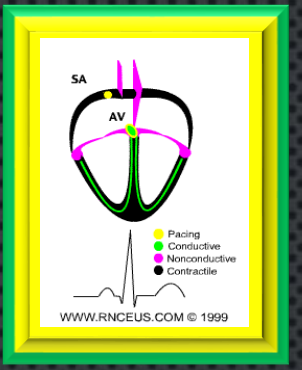
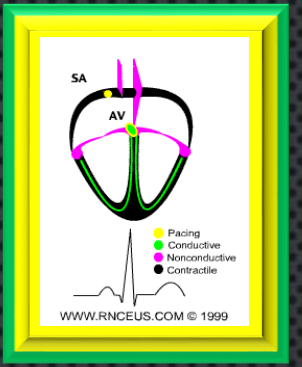
ANTIHYPERTENSIVE DRUGS



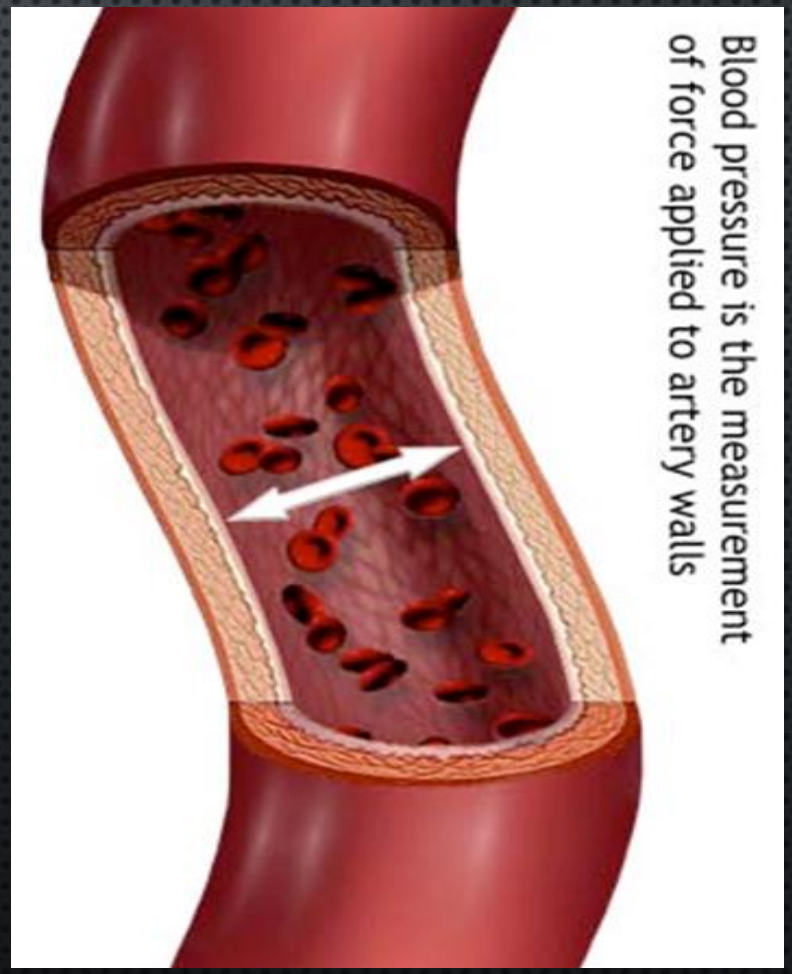


ANTIHYPERTENSIVE DRUGS

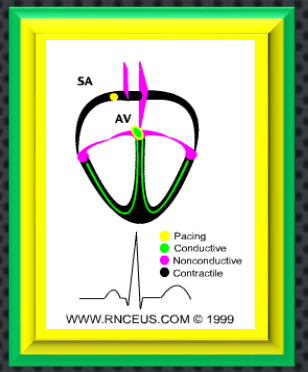


ILOS

- Identify factors that control blood pressure
- Outline the pharmacologic classes of drugs used in treatment of hypertension
- Describe mechanism of action, therapeutic uses & common adverse effects and contraindications of each class of drugs
- Select the suitable antihypertensive drug used to treat a specific patient according to efficacy, safety and cost



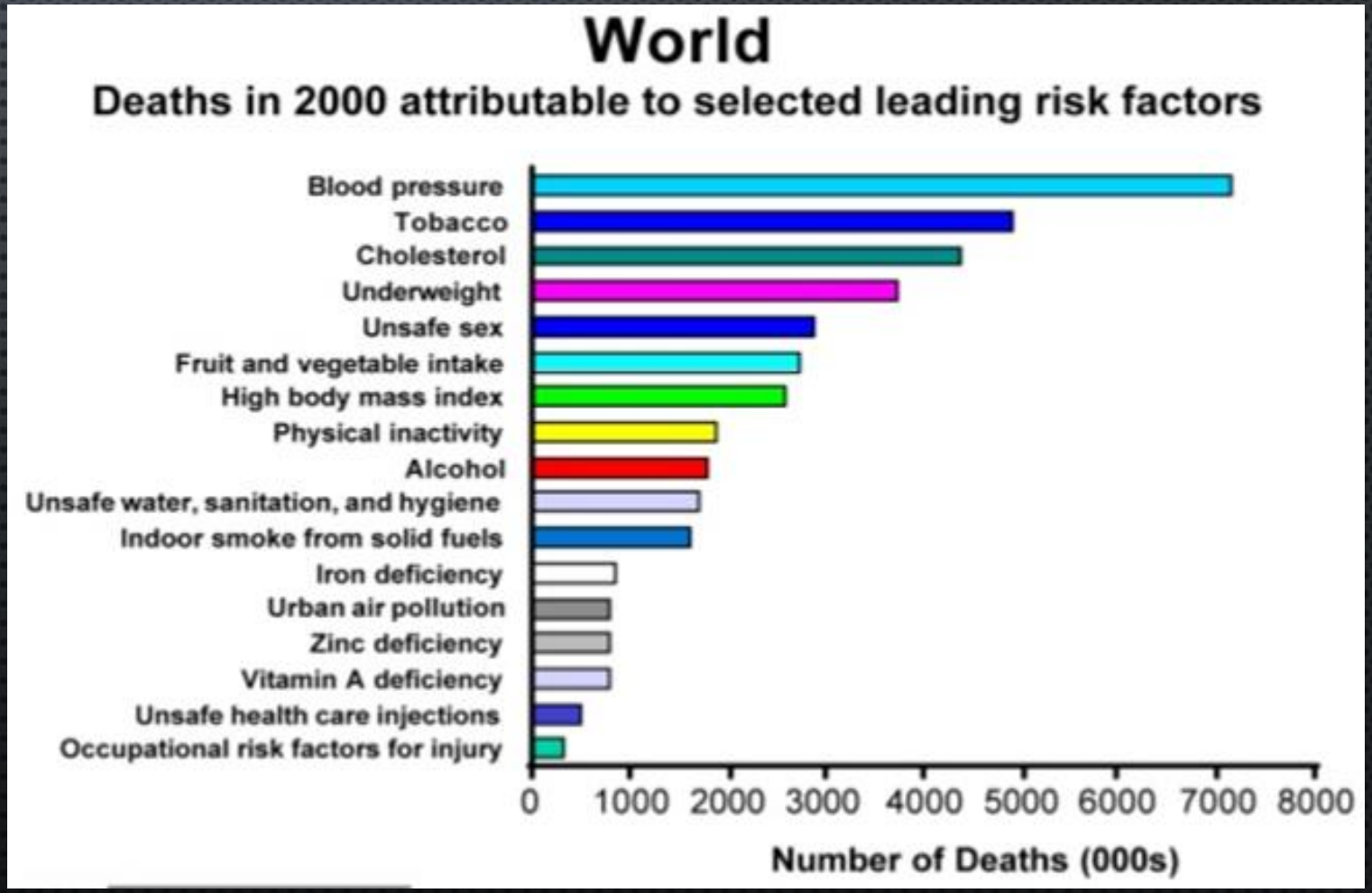
HYPERTENSION



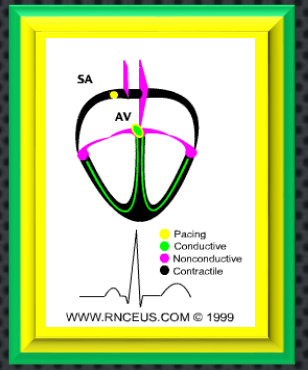
Prevalence 25-30%

In majority of cases, it is symptomless **"Silent Killer"**

Number One cause of death

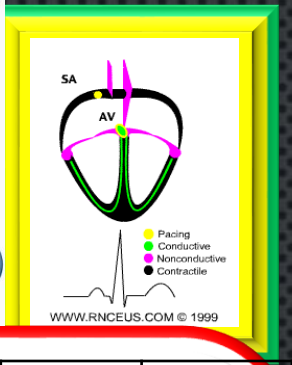


THE RULE OF HALVES OF HYPERTENSION



- For every **800** adults in the community
- **400** are hypertensive (either ↑ SBP or ↑ DBP or both)
- Of them only **200** are diagnosed HT
- Of them only **100** are started on treatment
- Of them only **50** are on correct drug
- Of them in only **25** the goal B.P. is attained
- Means 25 ÷ 400 = **6%** only have goal BP

CLINICAL CASE

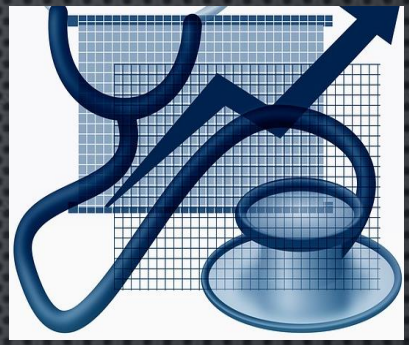


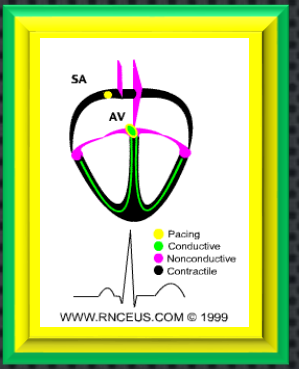
Osman a 51-year-old man (95 Kg weight, 176 cm tall) is referred for evaluation of his BP. He is **diabetic** for 5 years and **hypertensive** since 12 years, with no history of hypertension target-organ damage. Examination revealed normal heart sounds, no peripheral edema, and mild arteriolar narrowing in the fundus. His BP was 156/90 mmHg, similar in both arms and did not change on standing. Urine analysis showed an unremarkable dipstick evaluation. The patient was suspected as having drug-resistant hypertension.

His medications are listed in the accompanying table.

Name	Dose	Frequency
Hydrochlorothiazide	25mg	Daily
Valsartan	160mg	Daily
Diltiazem, long-acting	300mg	Daily
Clonidine	0.2mg	Twice daily
Metoprolol, long acting	100mg	daily
Simvastatin	40mg	Daily
Fenofibrate	145mg	Daily
Metformin	1g	Twice daily

CLINICAL CASE



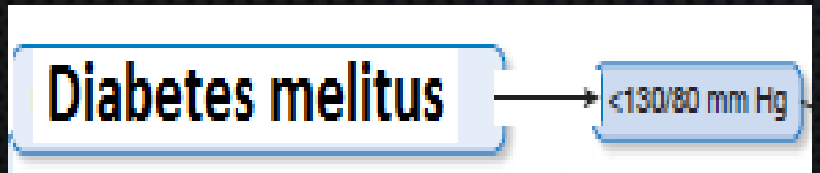


The seated BP of Osman was 156/90, what are the target BP values for treatment of hypertensive patients?

What are the classes of hypertension?

JNC VII CLASSIFICATION	SYSTOLIC BLOOD PRESSURE (SBP)		DIASTOLIC BLOOD PRESSURE (DBP)
LOW**	<90	or	<60
NORMAL	<120	and	<80
PREHYPERTENSION	120 – 139	or	80 – 89
HIGH: STAGE 1 HYPERTENSION	140 – 159	or	90 – 99
HIGH: STAGE 2 HYPERTENSION	≥160	or	≥100

Osman is diabetic, what are the target BP values for a diabetic?



CLINICAL CASE

Osman has no history of hypertension-target organ damage. What are organs affected adversely by persistent high BP?

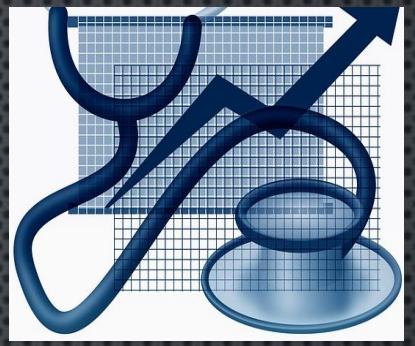
Osman is 95 kg. Is this weight proper for his length (176cm)?

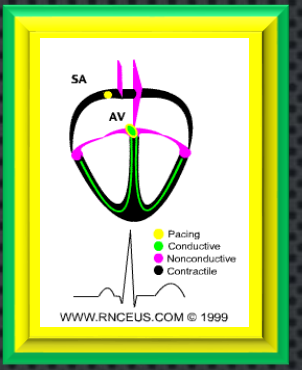
What are the lifestyle modifications, a hypertensive patient should follow?

Medscape® www.medscape.com

Modifioation	Reoommendation	Approx SBP (mmHg) Reduotion
Weight loss	BMI 18.5–24.9	5–20 mmHg/10-kg weight loss
DASH plan	• Increase fruit, vegetables • Consume low-fat dairy with reduced saturated and total fat	8–14 mmHg
Sodium reduction	Limit to 2.4 g/day	2–8 mmHg
Physical activity	Aerobic exercise or brisk walking at least 30 min/day 5 times weekly	4–9 mmHg
Moderation of alcohol intake	Limit to no more than 2 drinks/day for men. Two drinks = • 1-oz or 30-mL ethanol • 24-oz beer • 10-oz wine • 3-oz 80 proof whiskey Limit to no more than 1 drink/day for women and lighter persons	2–4 mmHg
Smoking cessation		

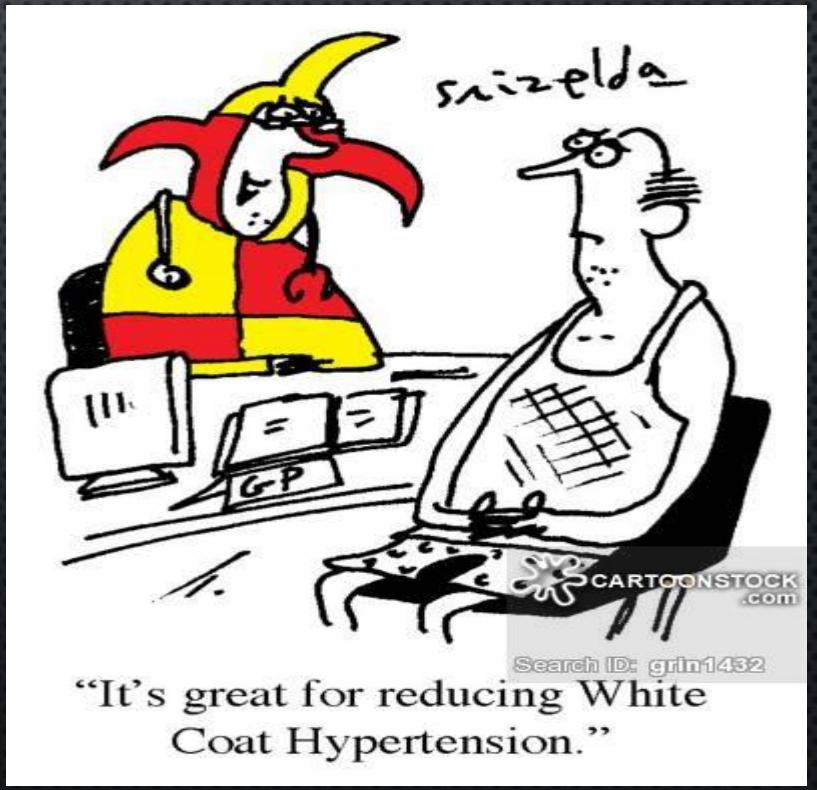
CLINICAL CASE



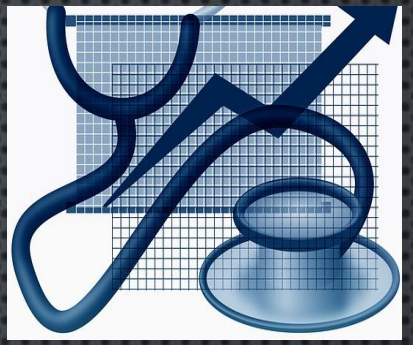


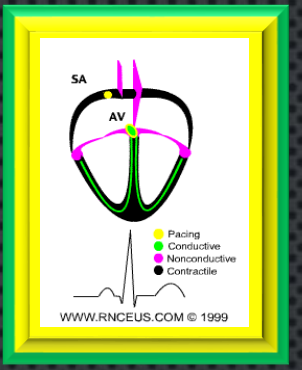
Could the "white coat phenomenon" be the cause for Osman's high blood pressure readings?

In a Turkish study involving 438 patients, 43% were found to be white coat hypertensives **(high pulse rate)**



CLINICAL CASE





Could the failure of control of Osman BP be due to secondary drug – induced effects?

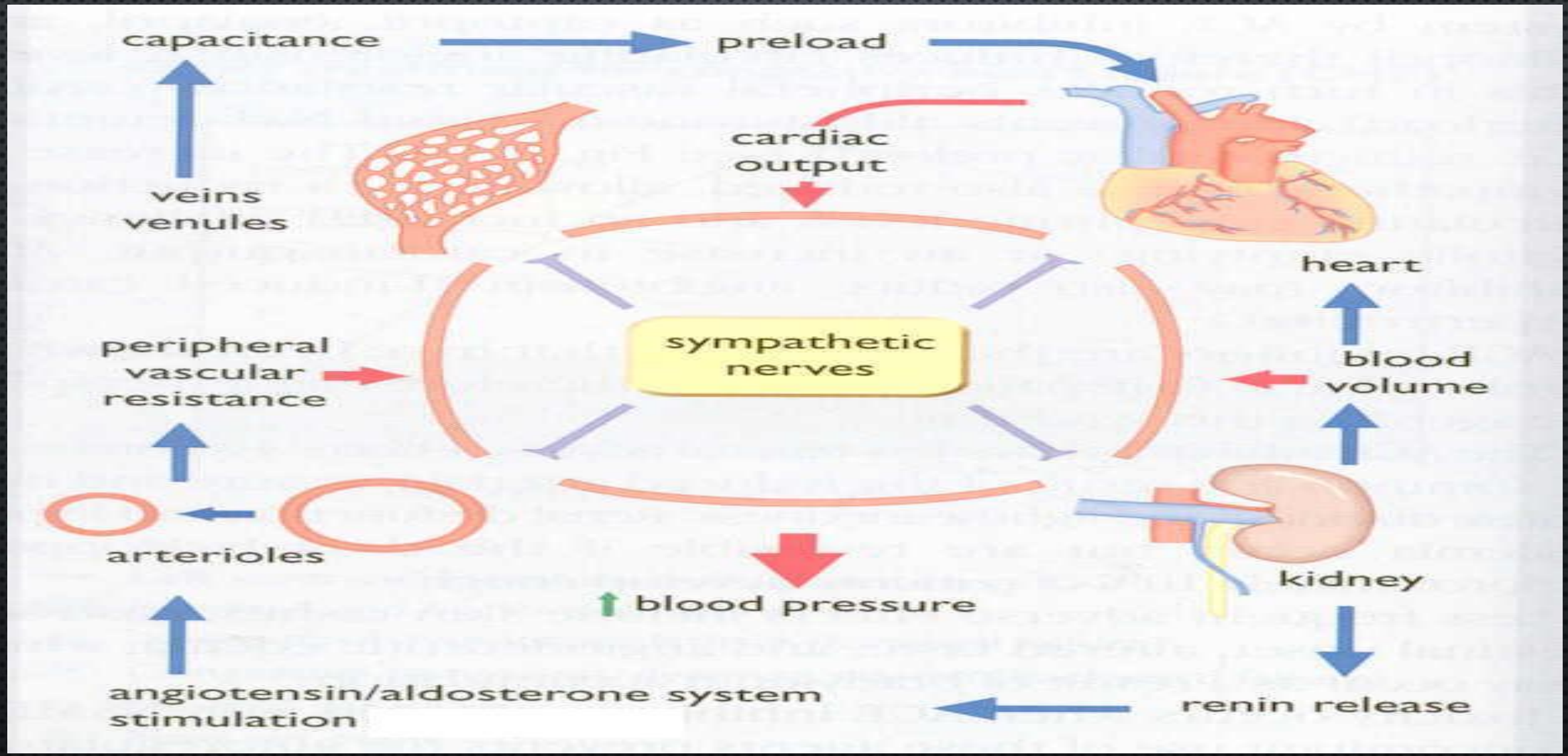
Which drugs elevate blood pressure?

Drug-Induced Hypertension: Prescription Medications

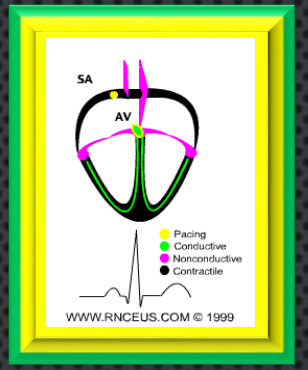
- Steroids
- Estrogens
- NSAIDS
- Phenylpropanolamines
- Cyclosporine/tacrolimus
- Erythropoietin
- Sibutramine
- Methylphenidate
- Ergotamine
- Ketamine
- Desflurane
- Carbamazepine
- Bromocryptine
- Metoclopramide
- Antidepressants
  - Venlafaxine
- Buspirone
- Clonidine

drtoufiq19711@yahoo.com

FACTORS IN BLOOD PRESSURE CONTROL



CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS



1-Diuretics

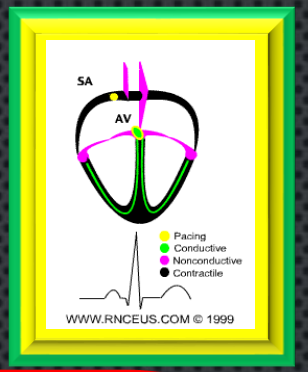
2- Drugs acting on the renin-angiotensin-aldosterone system (RAAS)

3- Calcium channel blockers

4-Vasodilators

5-Drugs acting on sympathetic nervous system

DIURETICS

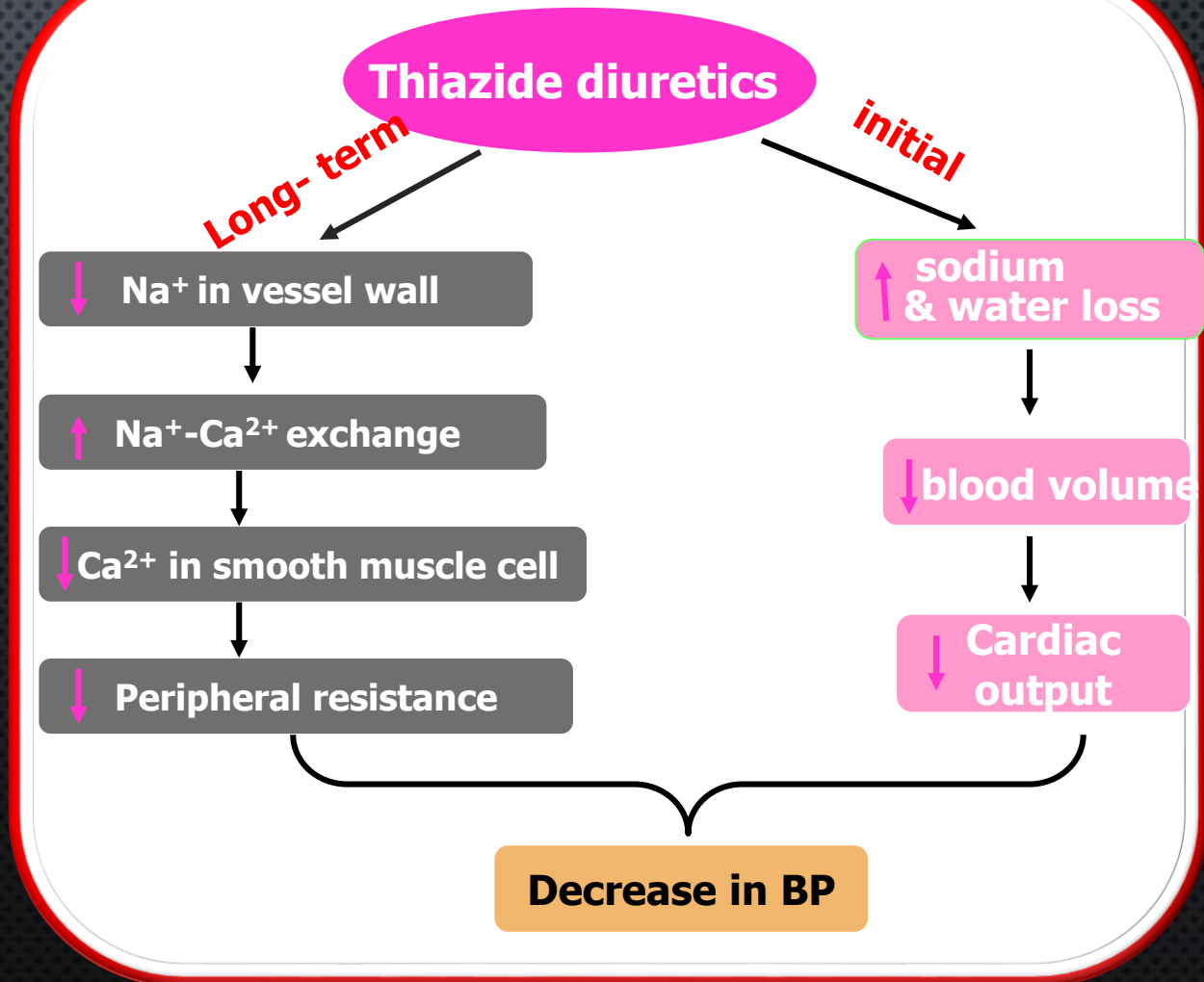


Hydrochlorothiazide , chlorthalidone

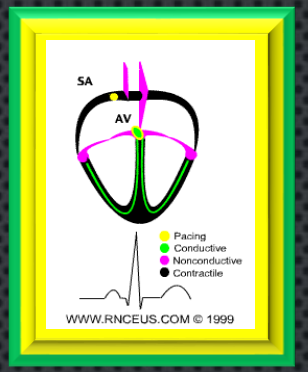
Duretics may be adequate in mild to moderate hypertension

MECHANISM OF ACTION

The initial diuresis lasts 4-6 weeks and then replaced by a decrease in PVR



DIURETICS

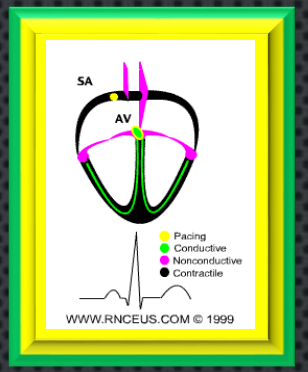


Loop diuretics produce **more potent diuresis** but a smaller decrease in PVR : **Furosemide**

Loop diuretics are useful in hypertensive patients with either renal impairment, or heart failure (edema)

Potassium- sparing diuretics have minimal effect on lowering BP

DRUGS ACTING ON THE RENIN- ANGIOTENSIN - ALDOSTERONE (RAAS) SYSTEM

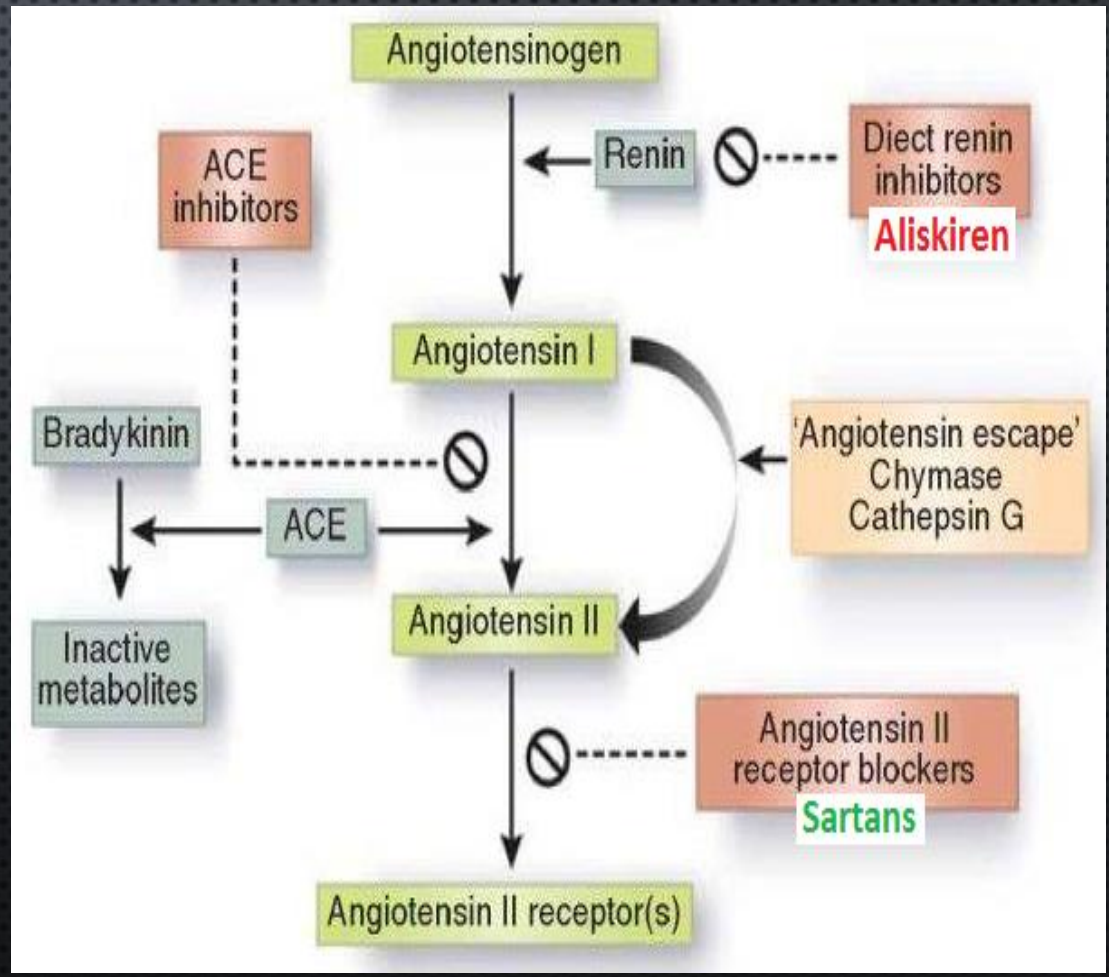


1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)

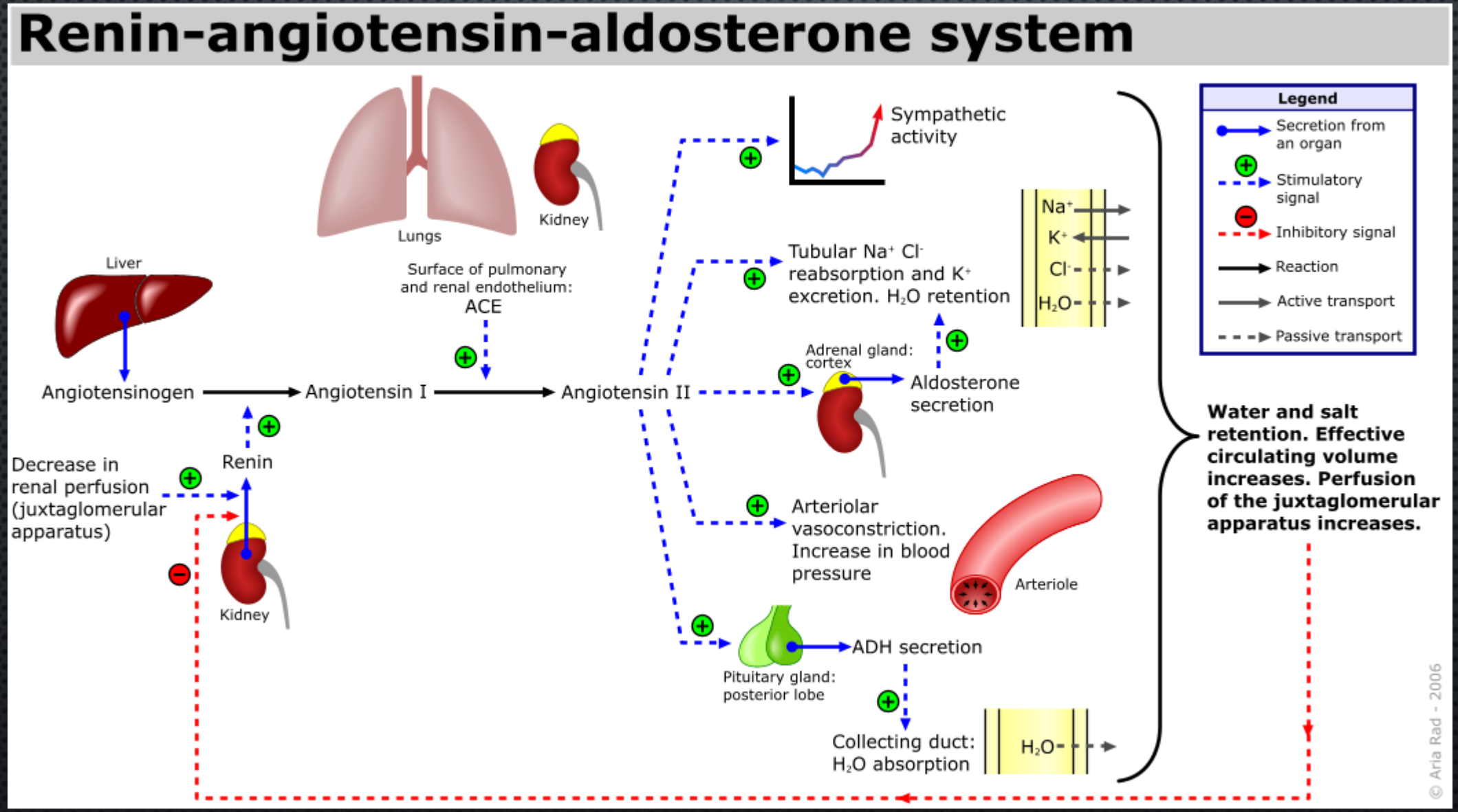
- Captopril
- Lisinopril
- Enalapril
- Ramipril

2-ANGIOTENSIN RECEPTORS BLOCKERS (ARBs)

- Losartan
- Valsartan



Renin-angiotensin-aldosterone system

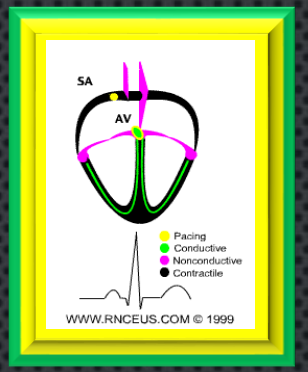


1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)

Particularly effective when hypertension results from excess renin production (renovascular hypertension, white & young)

- The antihypertensive effect of ACE inhibitors results primarily from vasodilatation (reduction of peripheral resistance) with little change in cardiac output;
- a fall in aldosterone production may also contribute

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



PHARMACOKINETICS

Polar, excreted in urine

Do not cross BBB

Have a long half-life & given once daily

Enalapril & ramipril are prodrugs

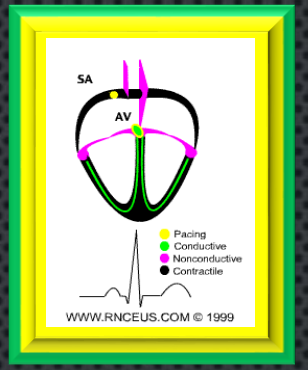
Rapidly absorbed from GIT after oral administration

Food reduces their bioavailability

It takes 2-4 weeks to notice the full antihypertensive effect of ACEIs

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

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



CLINICAL USES

1- Treatment of essential hypertension

2- Hypertension in patients with **chronic renal disease, ischemic heart disease, diabetes**

3-Treatment of heart failure

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ADRS

Dry cough

Acute renal failure, especially in patients with renal artery stenosis

Severe hypotension in hypovolemic patients

Cause renal agensia/failure in the fetus resulting in oligohydraminosis

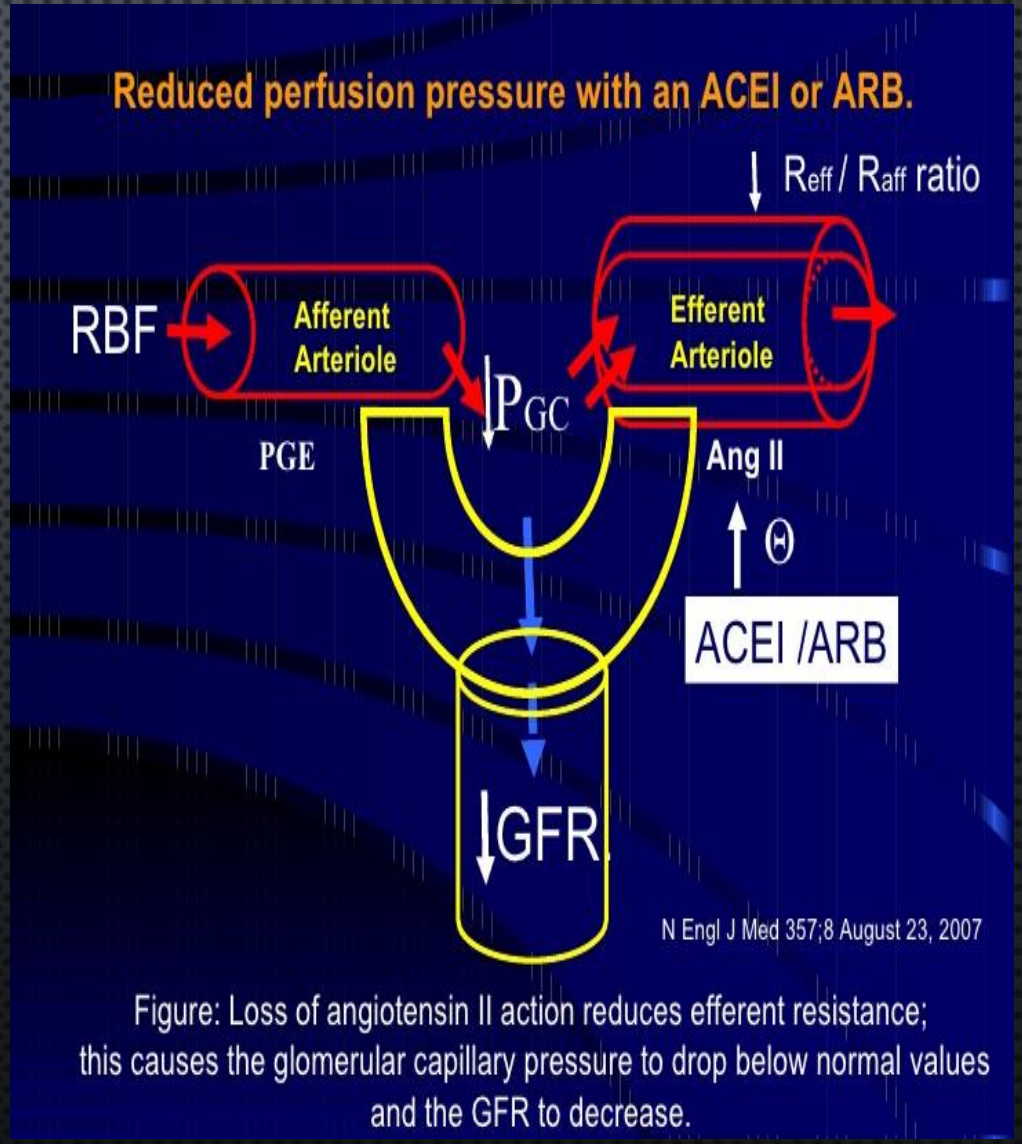
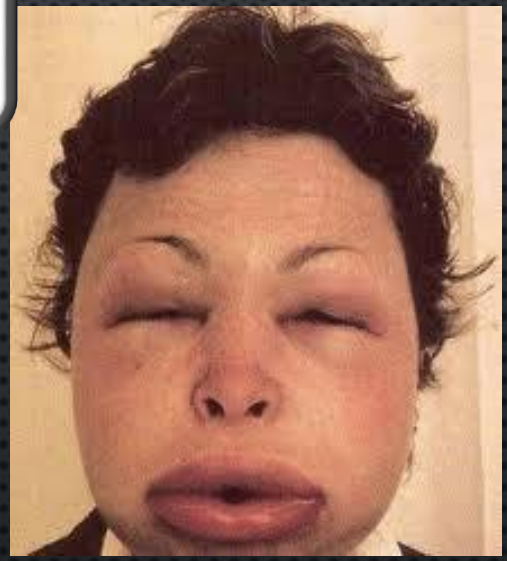


Figure: Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease.

ADRS OF ACEIS

Angioneurotic edema, swelling of the nose, throat, tongue, larynx (caused by inhibition of bradykinin metabolism which accumulate in bronchial mucosa)

First dose effect (severe hypotension) - give at bed time - starts with small dose and increase the dose gradually



ADRS SPECIFIC TO CAPTOPRIL

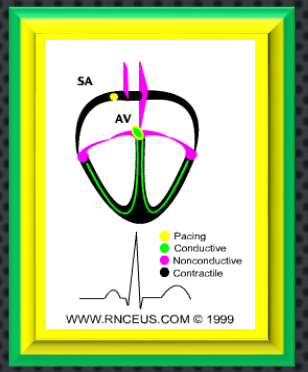
Skin rash, fever

Dysgeusia = reversible loss or altered taste

Proteinuria and neutropenia

These effects are due to a **sulfhydryl group** in the molecule of captopril

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



CONTRAINDICATIONS

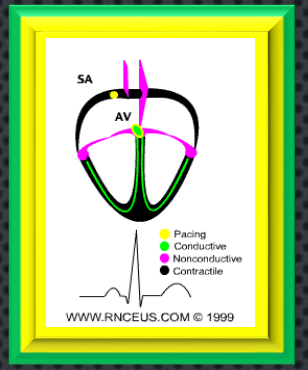
During the second and third trimesters of pregnancy due to the risk of: fetal hypotension, anuria ,renal failure & malformations

Renal artery stenosis

Potassium-sparing diuretics

NSAIDs impair their hypotensive effects by blocking bradykinin-mediated vasodilatation

2- ANGIOTENSIN RECEPTORS BLOCKERS (ARBS)



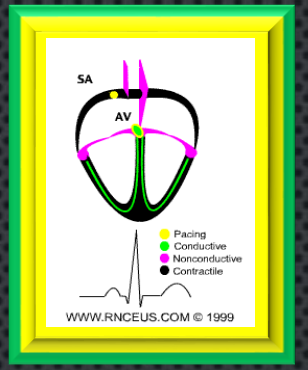
Losartan, Valsartan, Candesatran, Telmisartan

Cause selective block of AT1 receptors

No effect on bradykinin, no cough, no angioedema

Produce more complete inhibition of angiotensin as there are other enzymes (not only ACE) that can generate angiotensin

ANGIOTENSIN RECEPTORS BLOCKERS



LOSARTAN

Has a potent active metabolite

Orally effective

Long half-life, taken once daily

Do not cross BBB

VALSARTAN

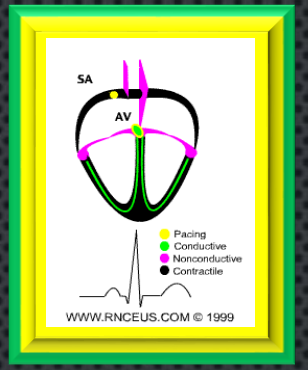
No active metabolites

Same contraindications as ACEI

Same ADRs, except for
dry cough & angioneurotic edema

Plasma Levels Before After
Aldosterone High Low
Potassium (mEq/L) 3.5 4.3
Renin Normal High
Angiotensin II High Low

THINK- PAIR-SHARE

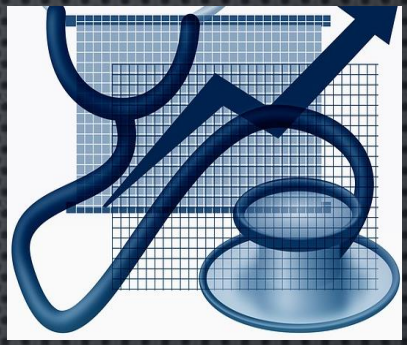


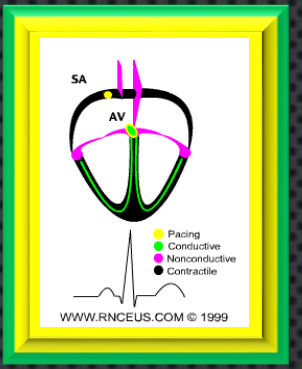
63-year-old hypertensive woman had been receiving an antihypertensive drug for 15 days. **The following serum values were obtained from the patient before and after drug therapy.**

Plasma level	Before	After
Aldosterone	High	Low
Potassium (mEq/l)	3.5	4.3
Renin	Normal	High
Angiotensin II	High	Low

Which drug the woman has been receiving

CLINICAL CASE

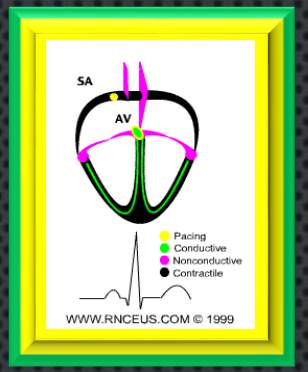




Osman was prescribed hydrochlorthiazide & valsartan.

What is the rationale for combining hydrochlorothiazide and valsartan?

3-CALCIUM CHANNEL BLOCKERS

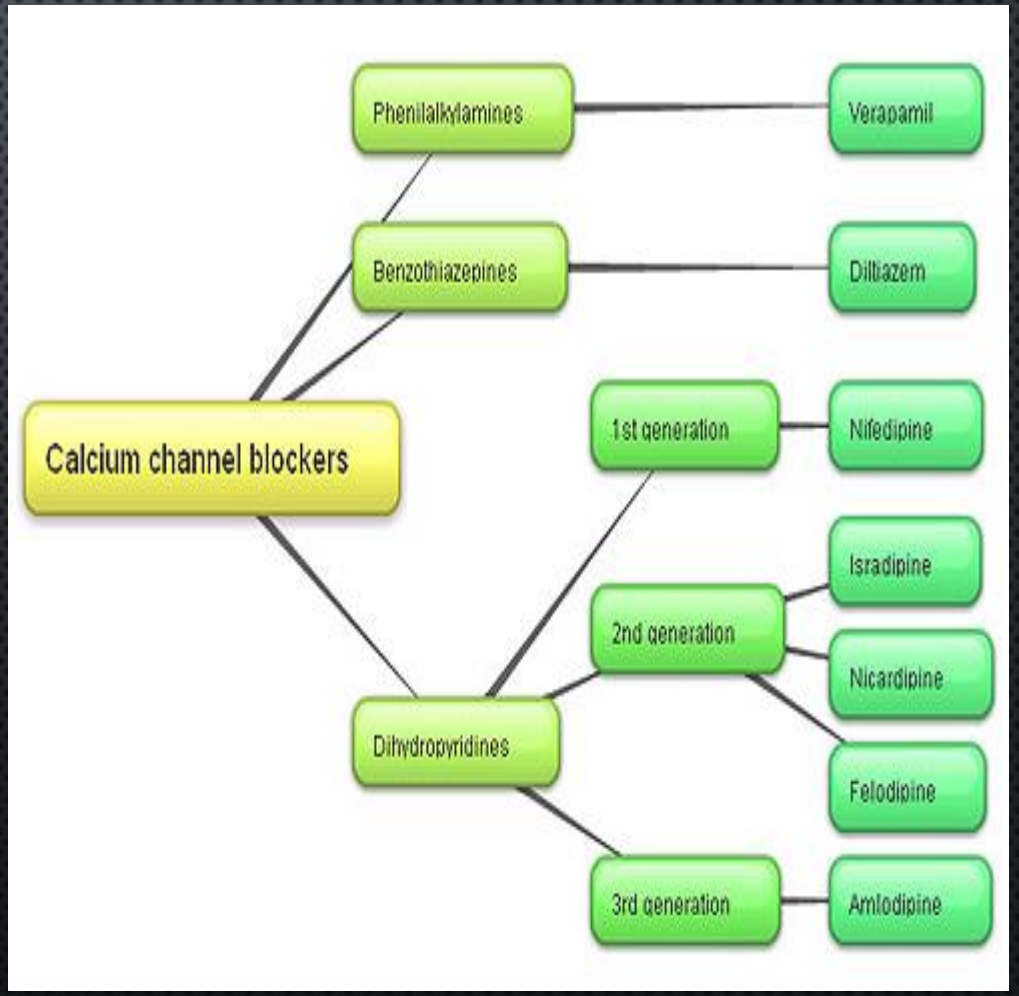


Very
Nice
Drugs

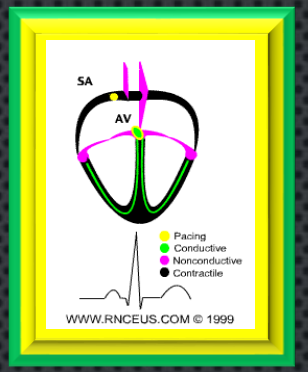
Verapamil act more on myocardium

Dihydropyridine group act mainly on smooth muscle, **Nifedipine**

Diltiazem has intermediate effect



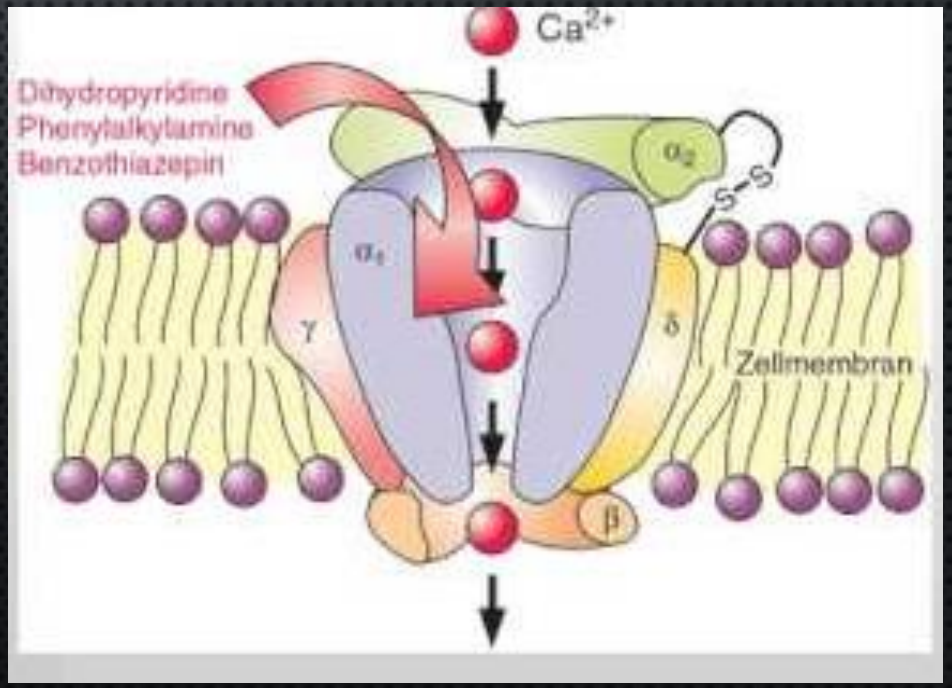
CALCIUM CHANNEL BLOCKERS



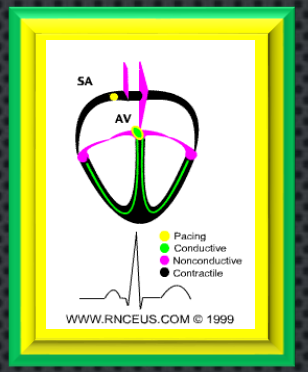
MECHANISM

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

1- Peripheral vasodilatation
2- Decrease cardiac contractility



CALCIUM CHANNEL BLOCKERS



PHARMACOKINETICS

Given orally or IV

Onset 1-3 min after IV, 0.5-2hr after oral

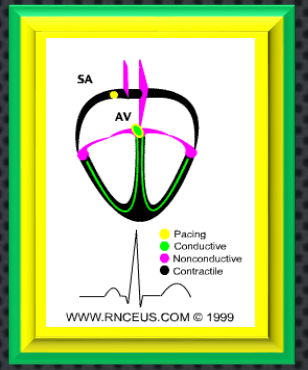
Well absorbed

Verapamil & diltiazem have active metabolites,
nifedipine has not

Verapamil and nifedipine are highly bound to plasma protiens (more than 90%) while diltiazem is less (70-80%)

Sustained-release preparations can permit once-daily dosing

CALCIUM CHANNEL BLOCKERS



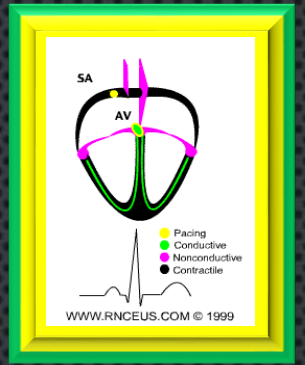
CLINICAL USES

Treatment of chronic hypertension

Nicardipine can be given by I.V. route in hypertensive emergency

Sustained- release formulations are preferred for the treatment of hypertension due to the short half- life of CCBs

CALCIUM CHANNEL BLOCKERS



ADRS

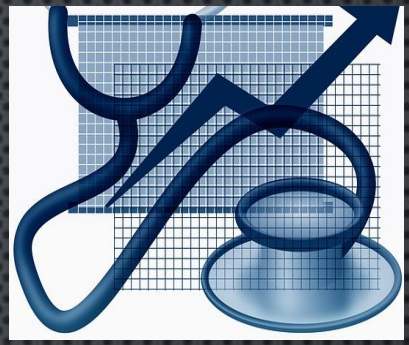
Headache, flushing, hypotension

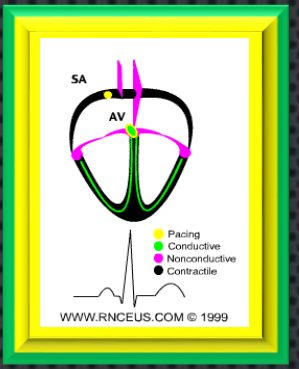
Nifedipine: Tachycardia

Verapamil & Diltiazem: peripheral edema (ankle edema*)

Verapamil: constipation

CLINICAL CASE



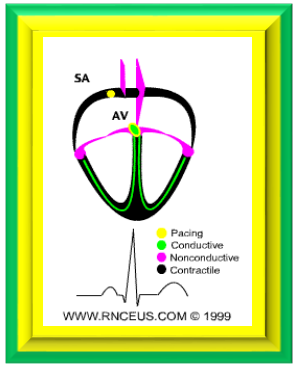


Osman was prescribed thiazides & diltiazem. What is the benefit of combining thiazides and diltiazem? (ankle edema)

The BP of Osman did not change on standing. What is your conclusion?

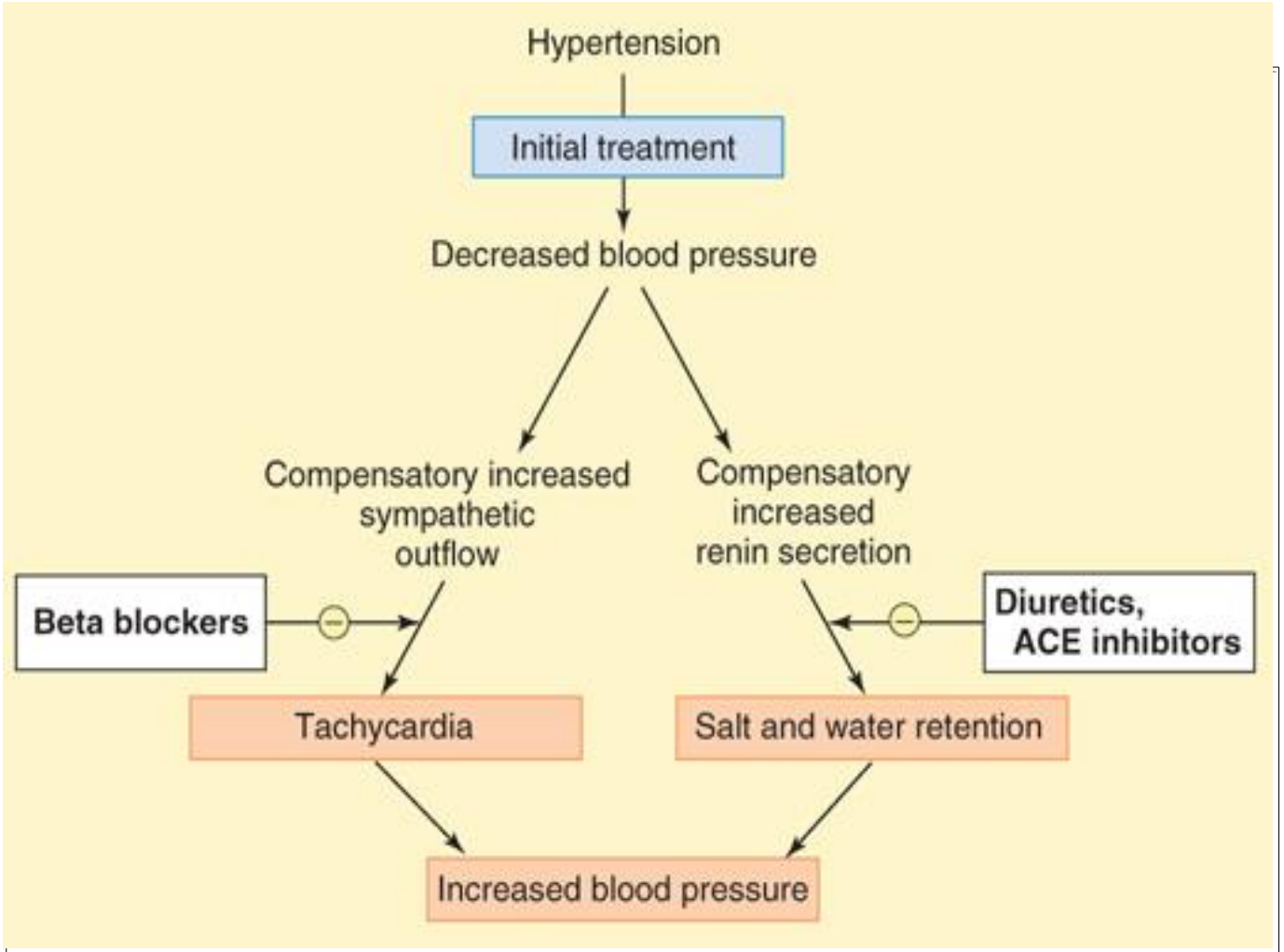
The BP of Osman was almost the same in both arms. What does that imply?

4- Vasodilators

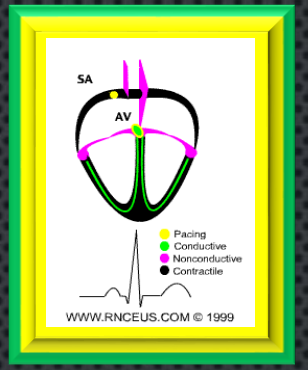


Classified into arterial, venous or mixed vasodilators

Once vasodilators are administered, fall in BP produced will activate the sympathetic system & the RAAS

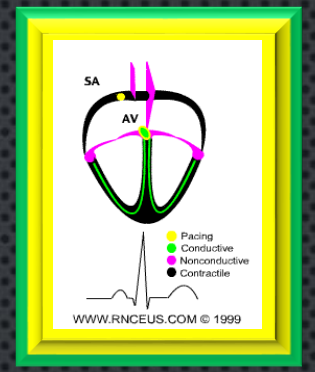


VASODILATORS



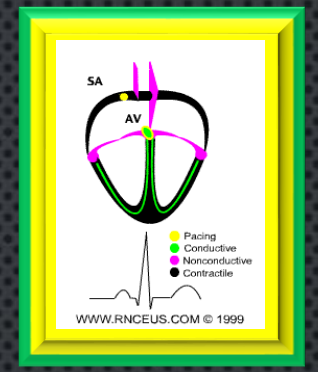
	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Site of action	Arteriodilator	Arteriodilator	Arteriodilator	Arterio & venodilator
Mechanism of action	Direct	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate (active metabolite)	Opening of potassium channels	Release of nitric oxide (NO)
Route of admin.	Oral	Oral	Rapid intravenous	Intravenous infusion

VASODILATORS



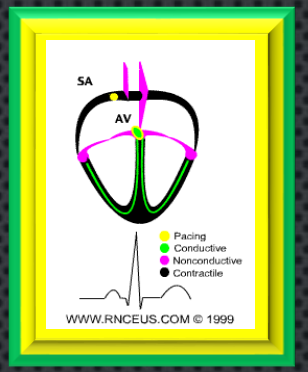
	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Adverse effects	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema)			Severe hypotension
Specific adverse effects	lupus erythematosus like syndrome	Hypertrichosis. Contraindicated in females	Inhibit insulin release from β cells of the pancreas causing hyperglycemia Contraindicated in diabetics	1.Methemoglobin during infusion 2. Cyanide toxicity 3. Thiocyanate toxicity

VASODILATORS



	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Therapeutic uses	1.Moderate - severe hypertension.	1.Moderate – severe hypertension	1.Hypertensive emergency	1.Hypertensive emergency
	In combination with diuretics & β-blockers			
	2.Hypertensive pregnant woman	2. baldness	2. Treatment of hypoglycemia due to insulinoma	2.Severe heart failure

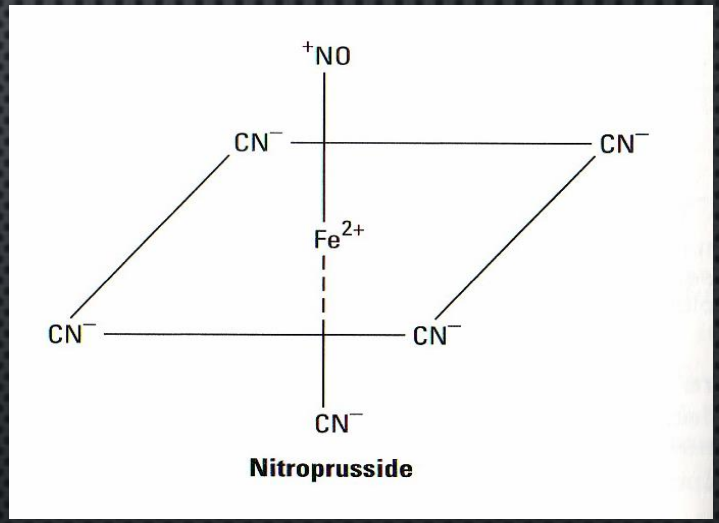
VASODILATORS



SODIUM NITROPRUSSIDE

ADRS

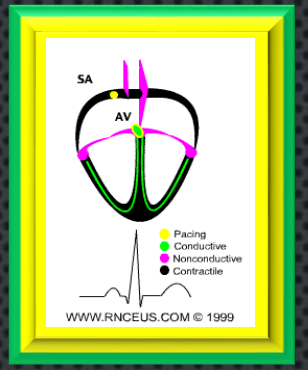
Headache, palpitations which disappear when infusion is stopped



Nitroprusside

Cyanide accumulation cause cyanide poisoning (metabolic acidosis, arrhythmias, severe hypotension and death)

5-SYMPATHOLYTIC DRUGS



i-ß Adrenoceptor blockers

Propranolol, atenolol, metoprolol

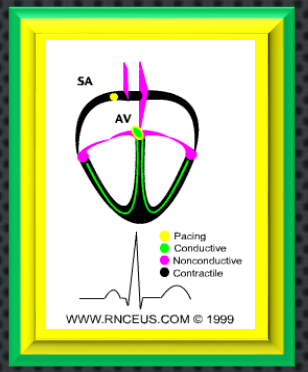
ß- adrenoceptors are used in mild to moderate hypertension
In severe cases used in combination with other drugs

May take two weeks for optimal therapeutic response

Evidence support the use of ß-blockers in patients with concomitant coronary artery disease

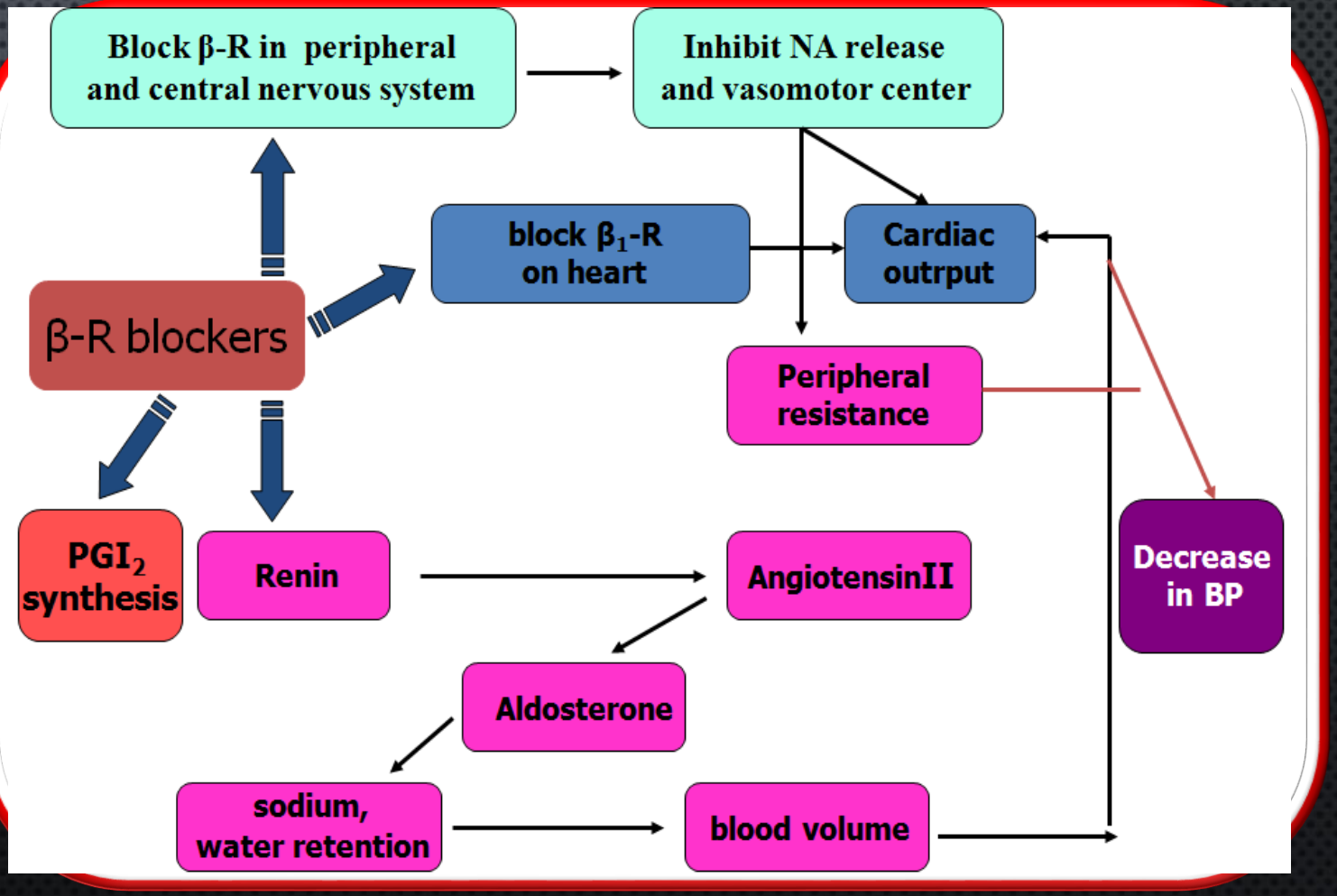
When discontinued, ß- blockers should be withdrawn gradually

ß- Adrenoceptor blockers

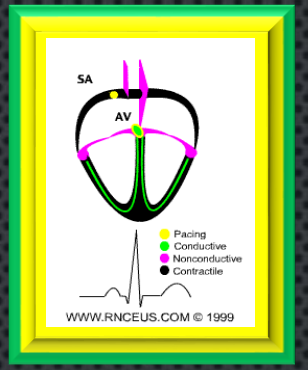


MECHANISM

They lower blood pressure by :
i-Decreasing cardiac output.
ii-Inhibiting the release of renin
iii- Central mechanism



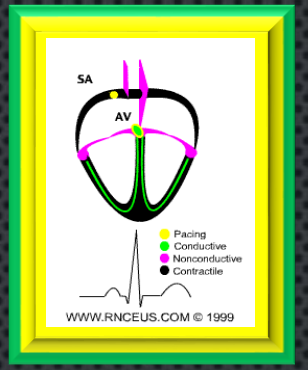
ß Adrenoceptor blockers



ADRS

- Hypoglycemia
- Fatigue
- Mask the symptoms of hypoglycemia in diabetes
- Increased triglycerides
- Aggravate peripheral arterial disease
- Erectile dysfunction

SYMPATHOLYTIC DRUGS



ii- α Adrenoceptor blockers

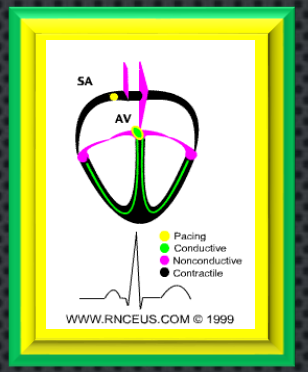
Block α- receptors in arterioles and venules

Reduce blood pressure by decreasing both afterload & preload

Prazosin, short- acting causes first dose hypotension & postural hypotension

Doxazosin, is preferred long half- life

III- CENTRALLY- ACTING SYMPATHOLYTIC DRUGS



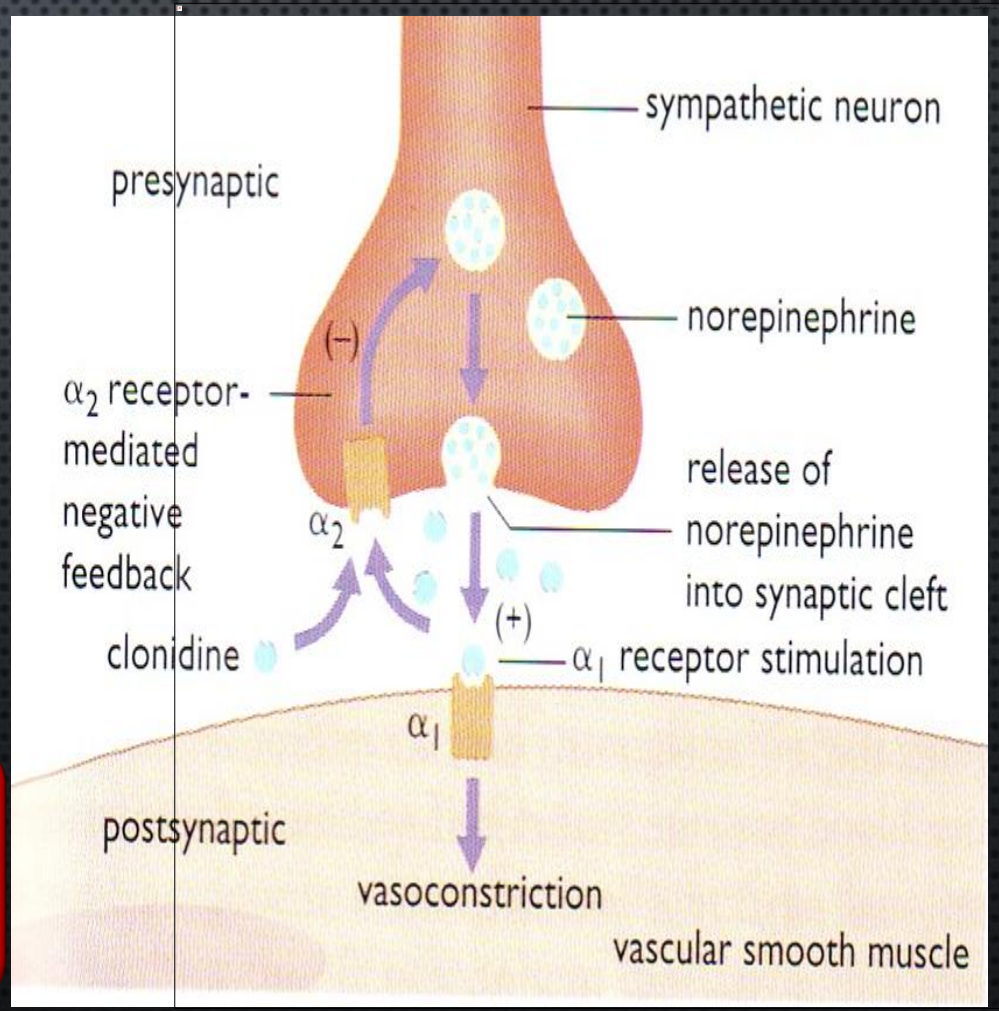
Clonidine

α2-agonist, diminishes central adrenergic outflow & ↑ parasympathetic outflow

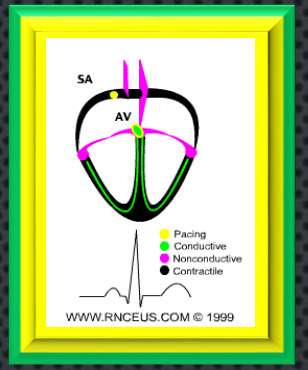
Abrupt withdrawal may lead to rebound hypertension

Does not decrease renal blood flow or glomerular filtration

Useful in the treatment of hypertension complicated by renal disease and resistant hypertension



III- CENTRALLY- ACTING SYMPATHOLYTIC DRUGS



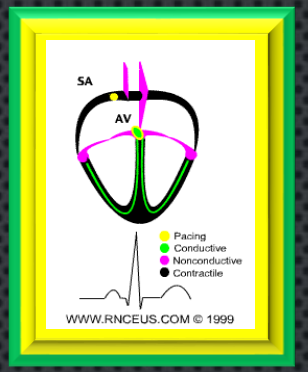
α- methyldopa

An α- 2 agonist, is converted to methyl noradrenaline centrally to diminish the adrenergic outflow from the CNS

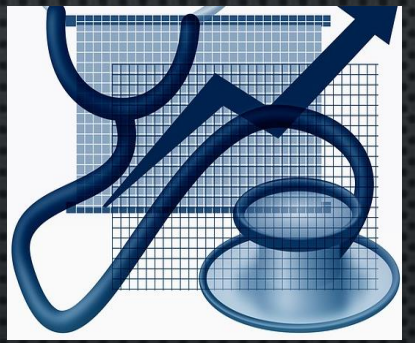
Lead to reduced total peripheral resistance, and a decrease in blood pressure

α -Methyldopa is the **first line treatment of hypertension in pregnancy**

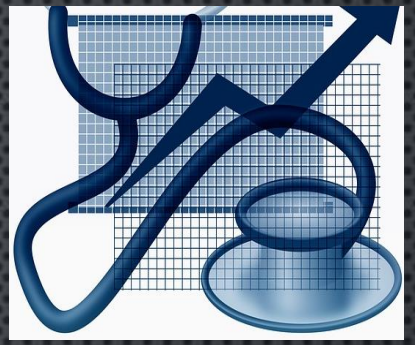
CLINICAL CASE

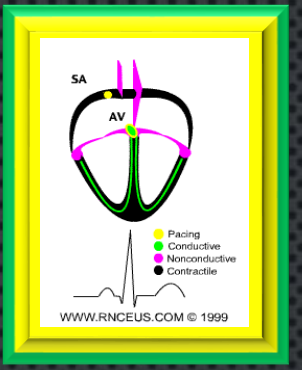


LIST THE REASONS, WHY OSMAN FAILED TO RESPOND TO ANTIHYPERTENSIVE THERAPY?



CLINICAL CASE



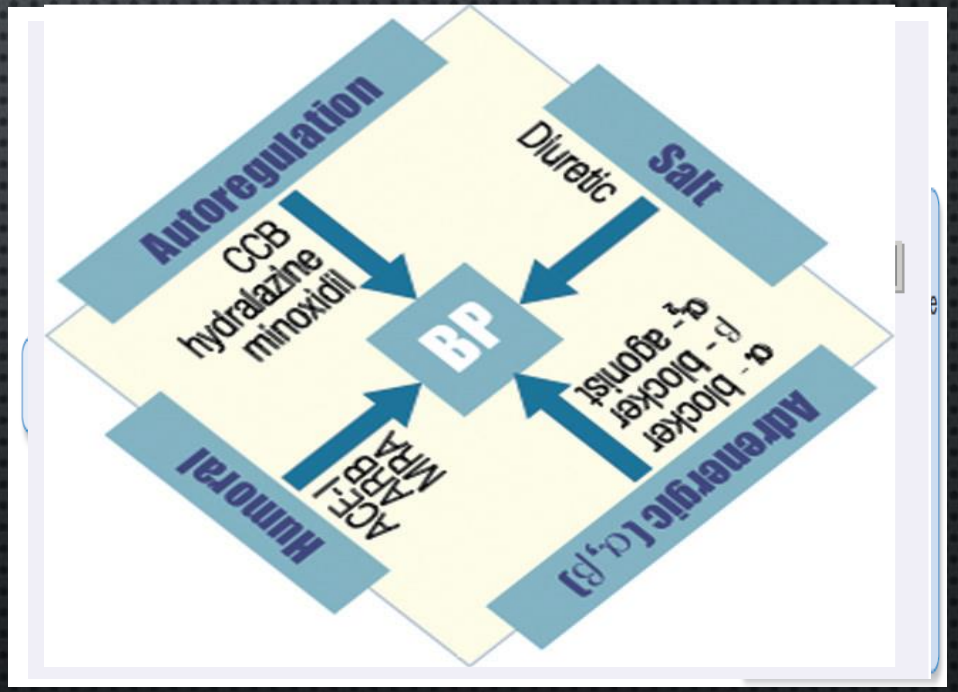


Could the failure of Osman control of BP be due to the use of inappropriate combinations of drugs?

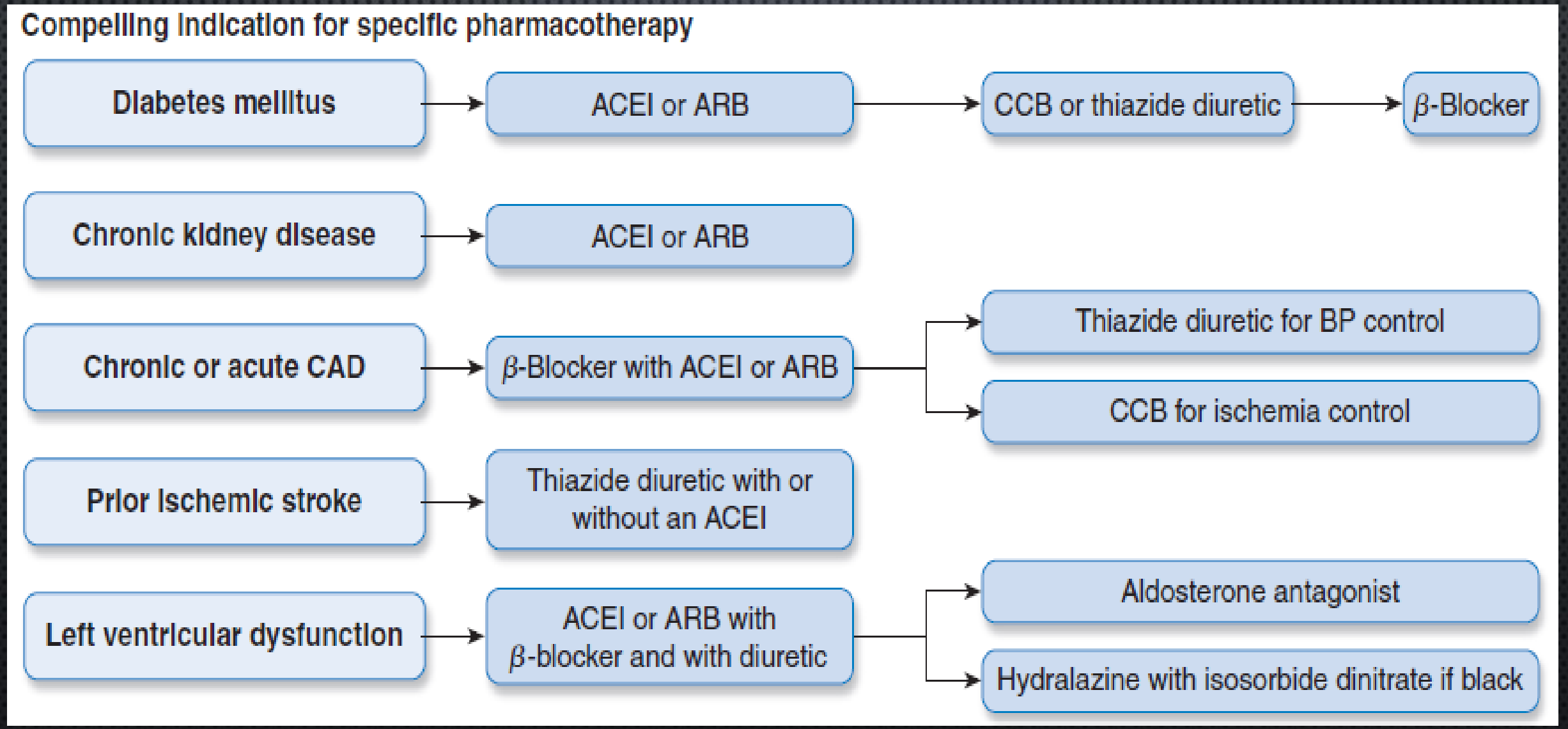
Use of combinations→↓ individual dose→↓ ADRs

Select a drug that ↓ the ADR of another, e.g. thiazides versus ACEI

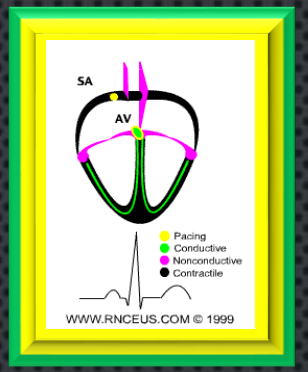
Select a drugs that act by different mechanisms



ANTIHYPERTENSIVE DRUGS



MEMORY MATRIX



ENTER + OR – IN THE CELLS TO INDICATE THE PRESENCE OR ABSENCE OF A FEATURE

COMPELLING CONTRAINDICATIONS OF ANTIHYPERTENSIVE DRUGS

	HF	Pregnancy	Hypokalemia	Bradycardia	Asthma	Hyperkalemia	Gout
Diuretics							
ACEI							
CCB							
ß-blockers							
ARB							

Antihypertensive Agent	Situations With Potentially Favorable Effects	Situations With Potentially Unfavorable Effects[b]	Avoid Use
ACEI	Low-normal potassium, elevated fasting glucose, microalbuminuria (with or without diabetes)	High-normal potassium or hyperkalemia	Pregnancy, bilateral renal artery stenosis, history of angioedema
ARB	Low-normal potassium, elevated fasting glucose, microalbuminuria (with or without diabetes)	High-normal potassium or hyperkalemia	Pregnancy, bilateral renal artery stenosis
CCB: dihydropyridine	Raynaud's phenomenon, elderly patients with isolated systolic hypertension, cyclosporine-induced hypertension	Peripheral edema, left ventricular dysfunction (all except amlodipine and felodipine), high-normal heart rate or tachycardia	
CCB: nondihydropyridine	Raynaud's phenomenon, migraine headache, supraventricular arrhythmias, high-normal heart rate or tachycardia	Peripheral edema, low-normal heart rate	Second- or third-degree heart block, left ventricular dysfunction
Thiazide diuretic	Osteoporosis or at increased risk for osteoporosis, high-normal potassium	Gout, hyponatremia, elevated fasting glucose (as monotherapy), low-normal potassium or sodium	