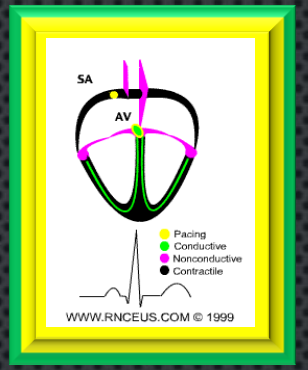
ANTIHYPERTENSIVE DRUGS

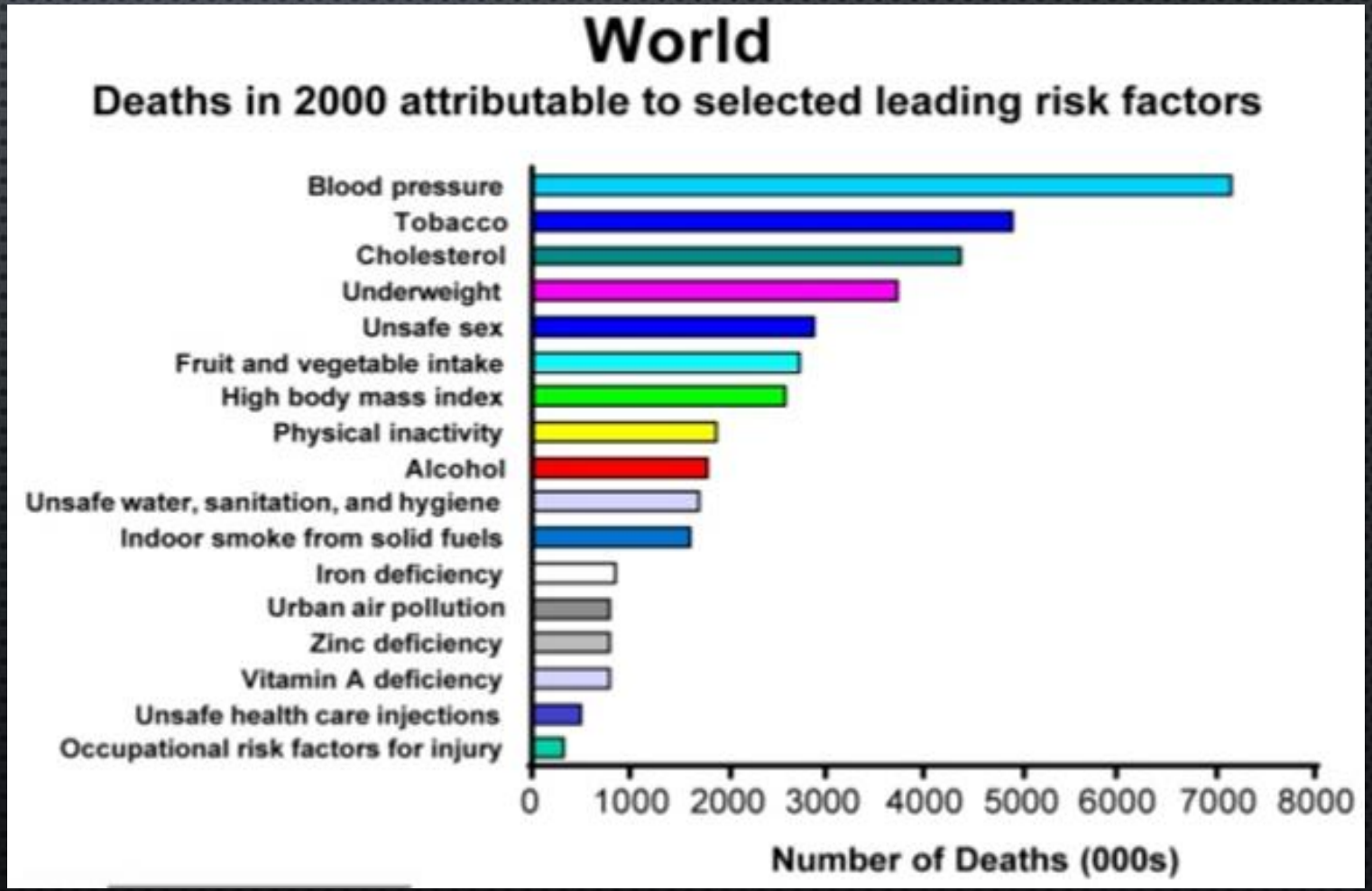


HYPERTENSION

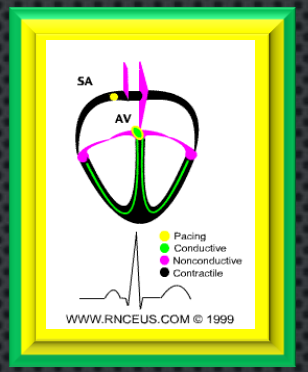
Prevalence 25-30%

In majority of cases, it is symptomless “Silent Killer”

Number One cause of death

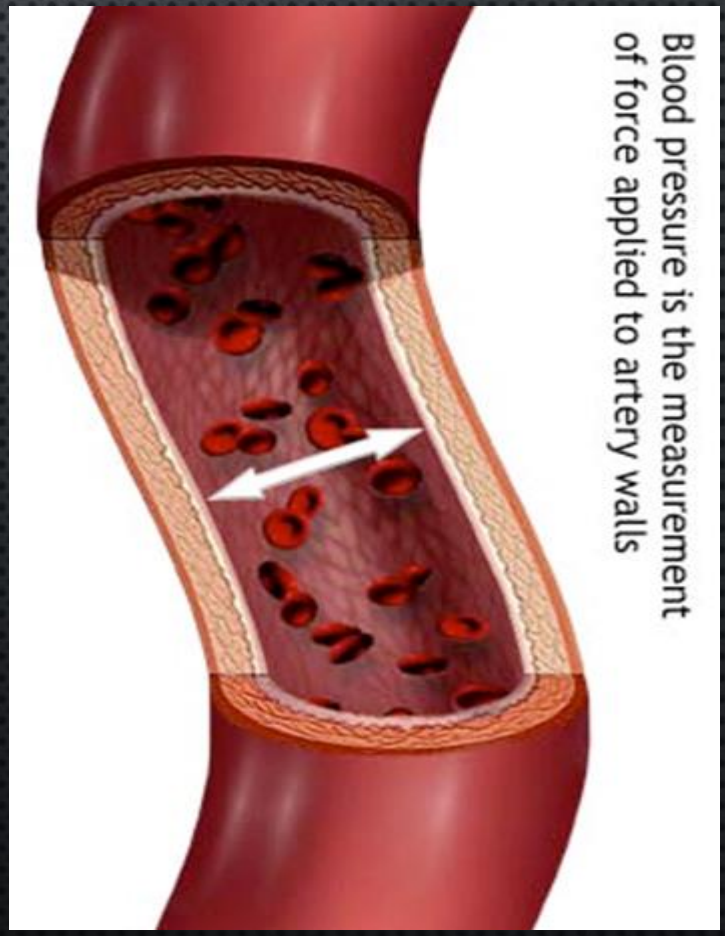


ANTIHYPERTENSIVE DRUGS

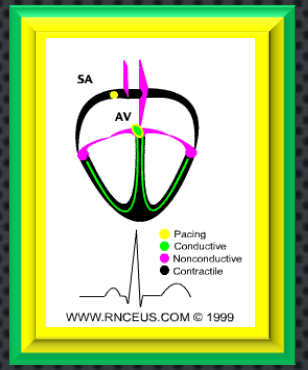


ILOS

- Identify factors that control blood pressure & how drugs modify them in hypertension
- Outline the pharmacologic classes of drugs used in treatment of hypertension
- Describe the mechanism of action , therapeutic uses & common ADRs of each class of drugs
- Select an antihypertensive drug to treat a specific patient according to efficacy, safety, suitability & cost



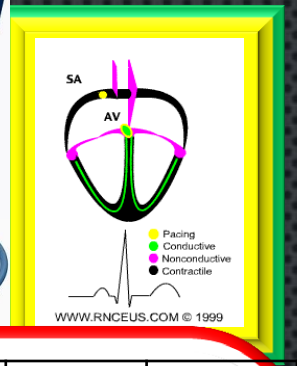
THE RULE OF HALVES OF HYPERTENSION



- 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

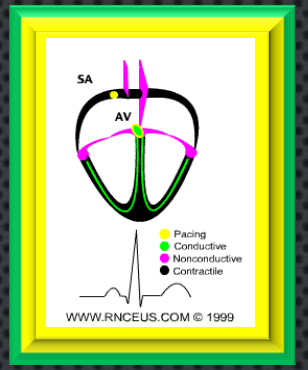
CLINICAL CASE

Osman a 51-year-old man (95Kg weight, 176cm tall) is referred for further evaluation of his BP. He is a computer engineer and has a past history of type 2 diabetes for 5 years and high BP for 12 years. His somatic complaints include fatigue and dry mouth. He has no known history of hypertension target-organ damage, and his medications are listed in the accompanying table .
He has no remarkable family history other than hypertension in both parents. His examination was otherwise unremarkable (including normal heart sounds and no peripheral edema), aside from mild arteriolar narrowing in the fundus. His seated BP was 156/90 mmHg and 158/90 mmHg in the right arm (similar to the left arm), with a regular heart rate of 70 beats/min. His BP did not change on standing. His urinalysis showed an unremarkable dipstick evaluation. The patient was suspected as having drug- resistant hypertension.

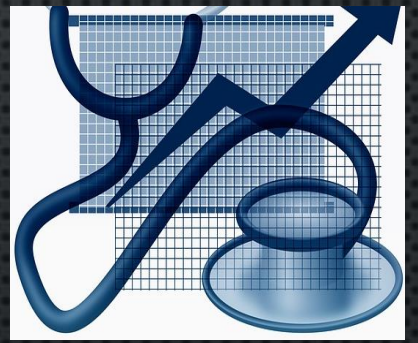


Name	Dose	Frequency
Hydrochlorothiazide	25mg	Daily
Valsartan	160mg	Daily
Diltiazem, long-acting	300mg	Daily
Clonidine	0.2mg	Twice daily
Metoprolol, long acting	100mg	daily
Simvastatin	40mg	Daily
Fenofibrate	145mg	Daily
Metformin	1g	Twice daily

CLINICAL CASE

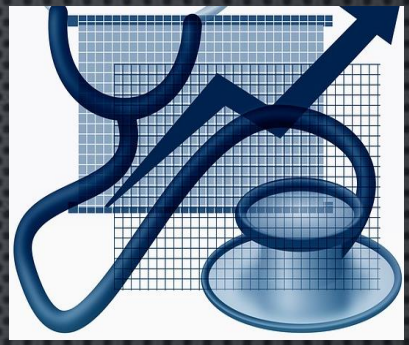


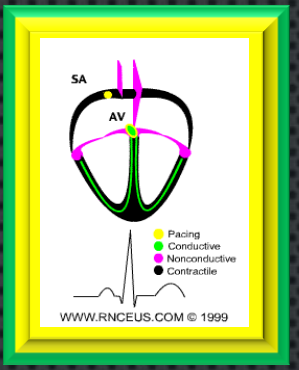
LIST AS MANY REASONS AS YOU CAN, WHY OSMAN FAILED TO RESPOND TO ANTIHYPERTENSIVE THERAPY?



CLINICAL CASE

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





Target BP → <140/90 mm Hg

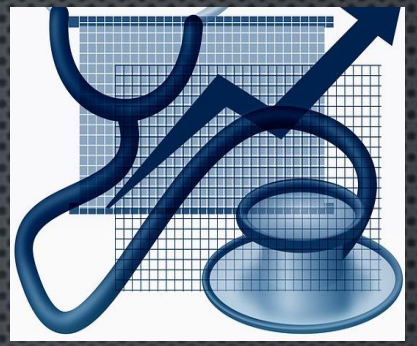
What stage of hypertension is Osman?

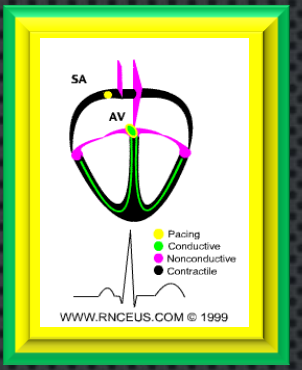
JNC VII CLASSIFICATION	SYSTOLIC BLOOD PRESSURE (SBP)		DIASTOLIC BLOOD PRESSURE (DBP)
LOW**	<90	or	<60
NORMAL	<120	and	<80
PREHYPERTENSION	120 – 139	or	80 – 89
HIGH: STAGE 1 HYPERTENSION	140 – 159	or	90 – 99
HIGH: STAGE 2 HYPERTENSION	≥160	or	≥100

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

Diabetes melitus → <130/80 mm Hg

CLINICAL CASE





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

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

If Osman has to reduce his weight, what other lifestyle modifications should he do?

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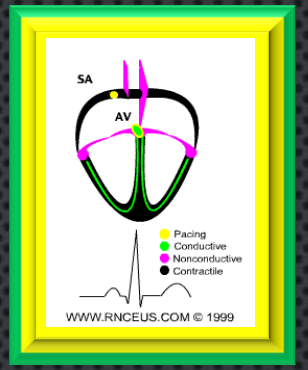
Modifioation	Reoommendation	Approx SBP (mmHg) Reduotion
Weight loss	BMI 18.5–24.9	5–20 mmHg/10-kg weight loss
DASH plan	• Increase fruit, vegetables • Consume low-fat dairy with reduced saturated and total fat	8–14 mmHg
Sodium reduction	Limit to 2.4 g/day	2–8 mmHg
Physical activity	Aerobic exercise or 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		

ANTIHYPERTENSIVE DRUGS



CLASSIFICATION

1-Diuretics

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

3-Calcium channel blockers

4-Vasodilators

5-Sympatholytic Drugs

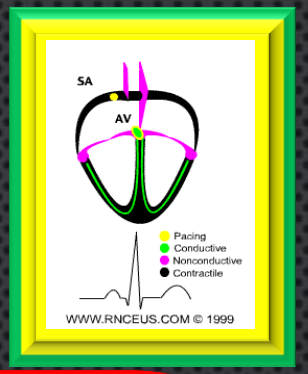
ANTIHYPERTENSIVE DRUGS

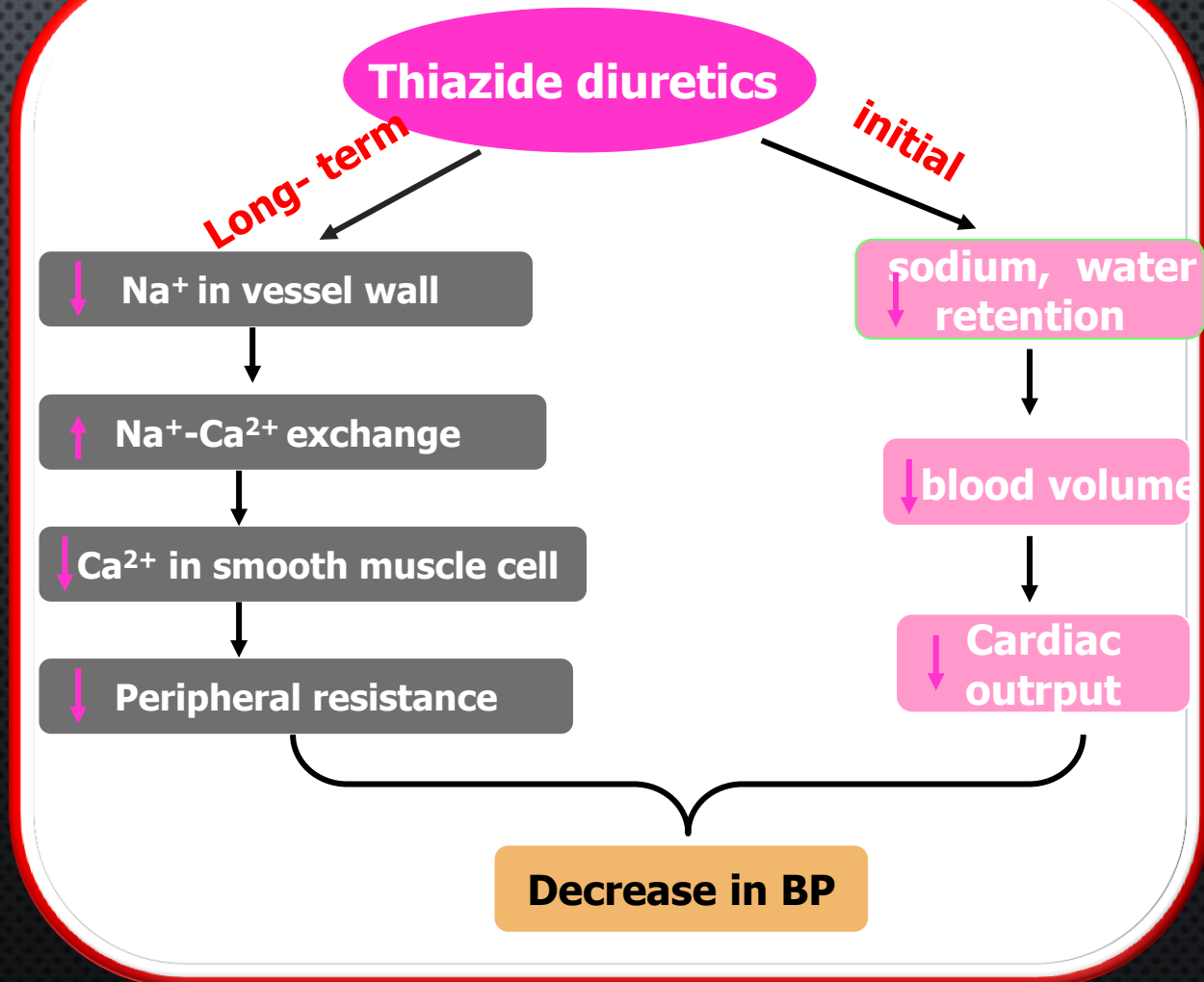
DIURETICS

Hydrochlorothiazide , chlorthalidone & furosemide

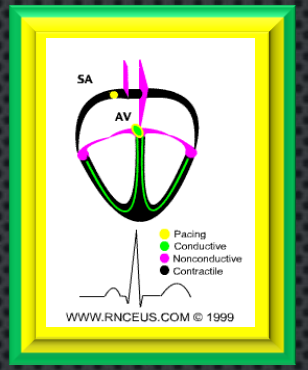
MECHANISM OF ACTIONTION

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





ANTIHYPERTENSIVE DRUGS



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

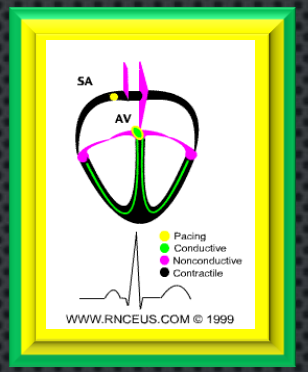
Loop diuretics are useful in hypertensive patients with either renal impairment, or heart failure

Potassium- sparing diuretics have minimal effect on lowering BP

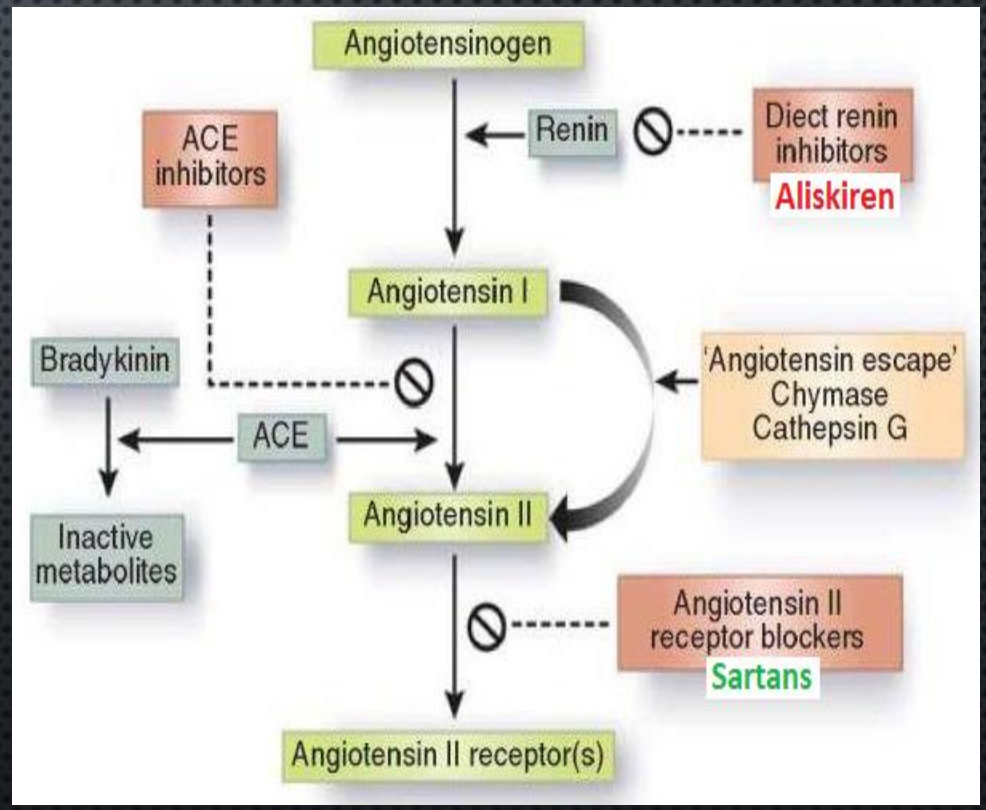
Diuretics may be adequate in mild to moderate hypertension

According to ALLHAT trial, chlorthalidone is superior to an ACE inhibitor, a calcium channel blocker and an alpha1-adrenergic antagonist in preventing one or more CVD events.

ANTIHYPERTENSIVE DRUGS



ii- Drugs acting on the renin- angiotensin - aldosterone system

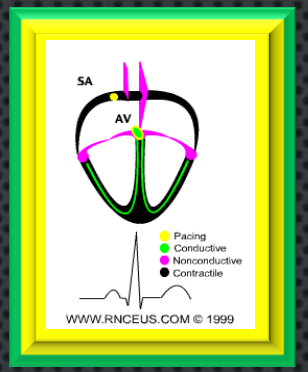


1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI)

- Captopril
- Lisinopril
- Enalapril
- Ramipril

2-ANGIOTENSIN RECEPTORS BLOCKERS

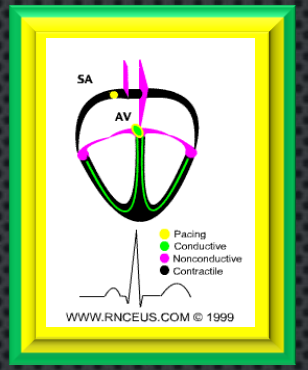
ANTIHYPERTENSIVE DRUGS



1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI)

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

1- 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

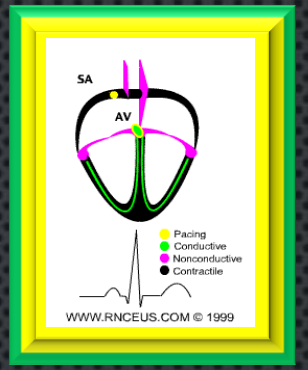
Rapidly absorbed from GIT after oral administration

Food reduces their bioavailability

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

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

1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



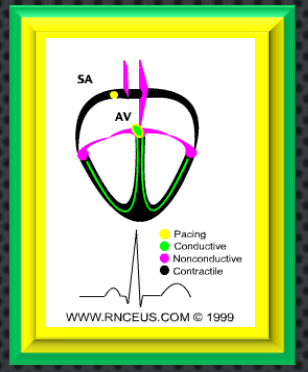
CLINICAL USES

1-Treatment of essential hypertension

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

3-Treatment of heart failure

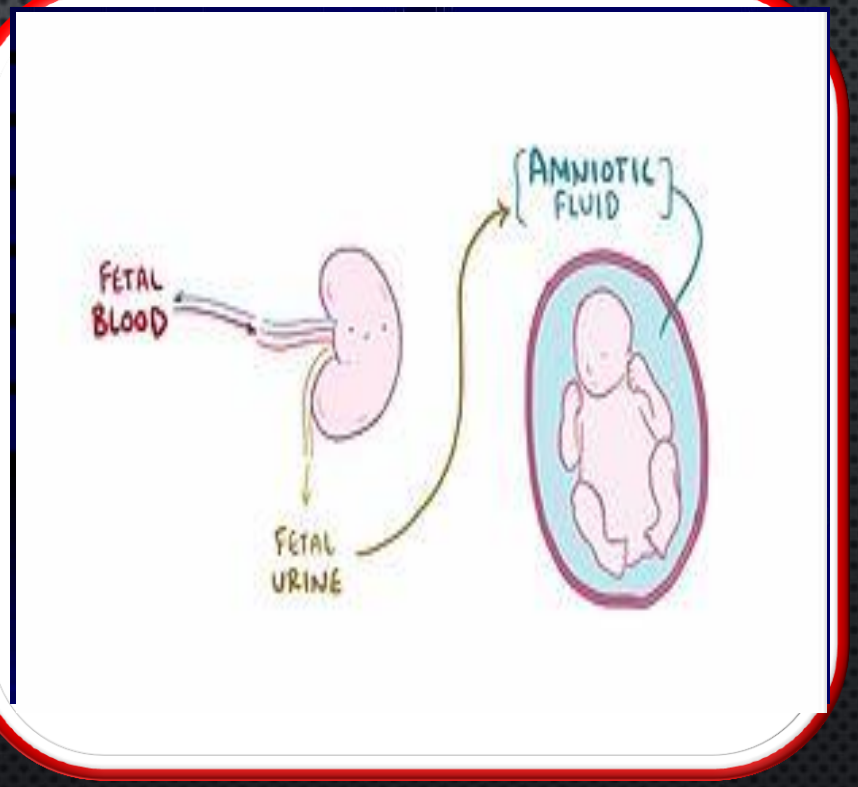
1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



ADRS

Dry cough

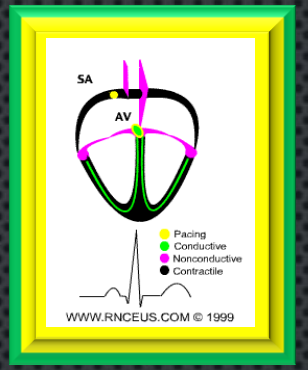
Acute renal failure, especially in patients with renal artery stenosis



Severe hypotension in hypovolemic patients

Cause renal agenesis/failure in the fetus, resulting in oligohydraminosis

1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



ADRS

Angioneurotic edema, swelling in the nose , throat, tongue, larynx

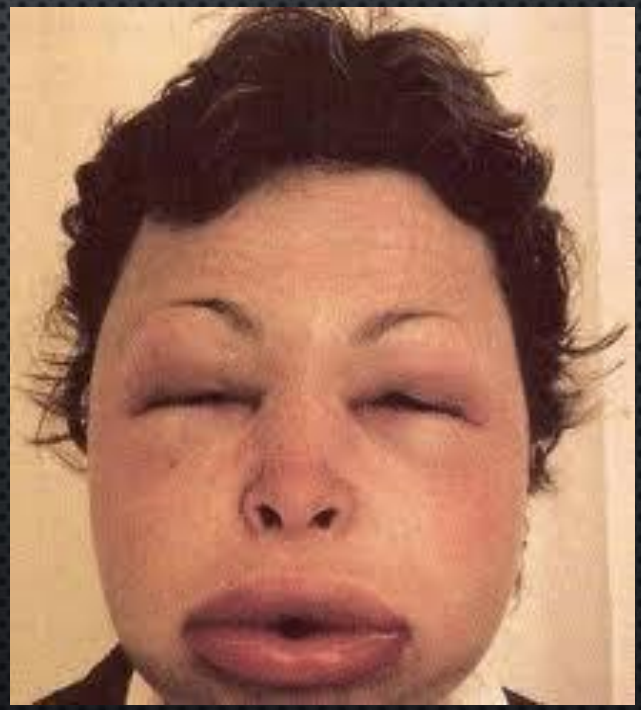
First dose effect

ADRS SPECIFIC TO CAPTOPRIL

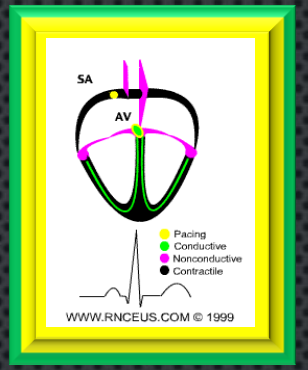
Skin rash, fever

Dysgeusia

Proteinuria and neutropenia



1- 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

2-ANGIOTENSIN RECEPTORS BLOCKERS

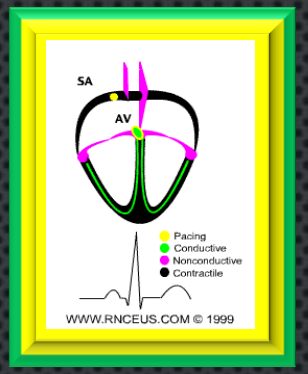
Losartan

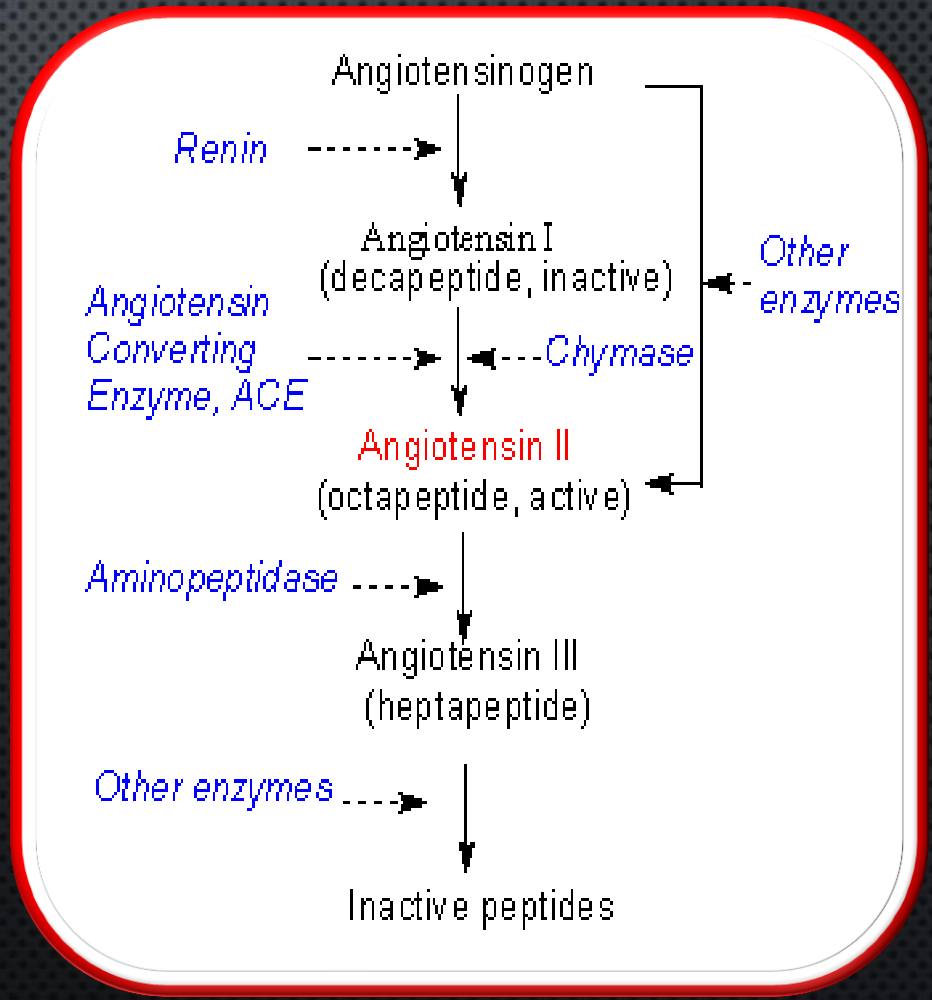
Valsartan

Cause selective block of AT1 receptors

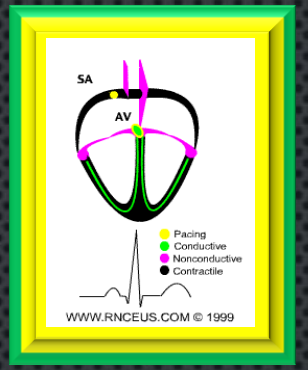
No effect on bradykinin, no cough, no angioedema

Produce more complete inhibition of angiotensin





2-ANGIOTENSIN RECEPTORS BLOCKERS



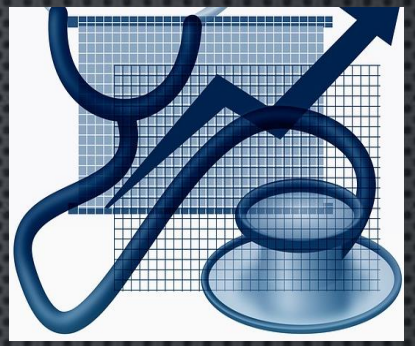
LOSARTAN

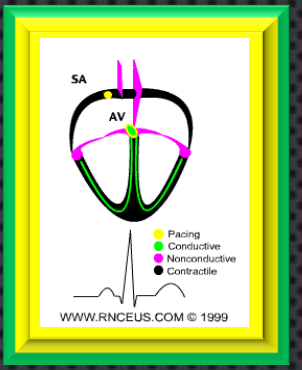
- Has a potent active metabolite
- Orally effective
- Long half-life, taken once daily
- Does not cross BBB

VALSARTAN

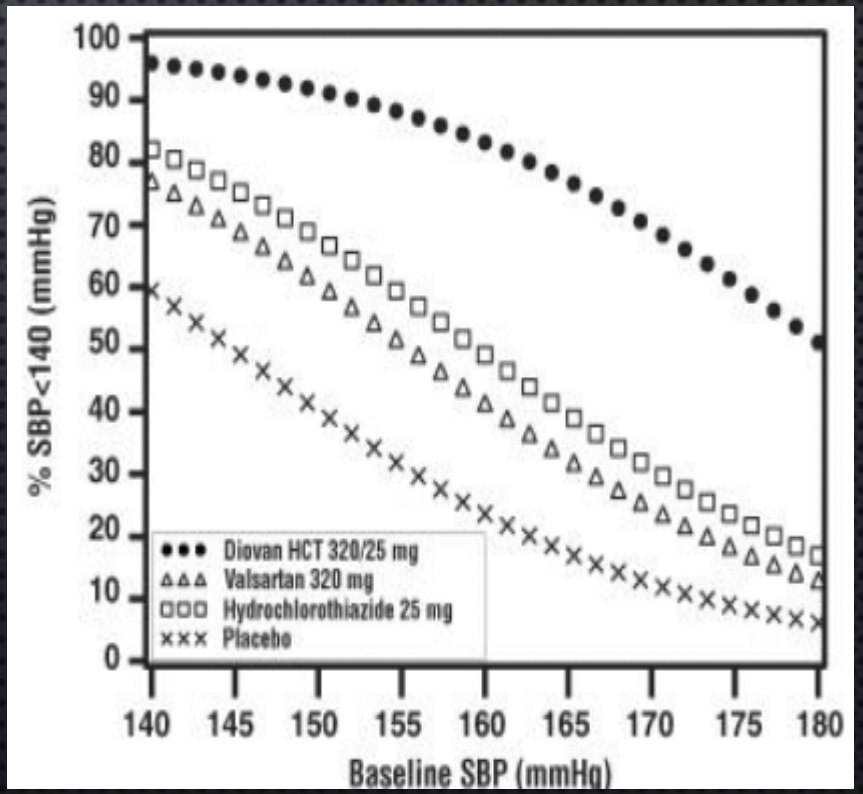
- No active metabolites
- Same ADRs, except for dry cough & angioneurotic edema
- Same contraindications as ACEI

CLINICAL CASE

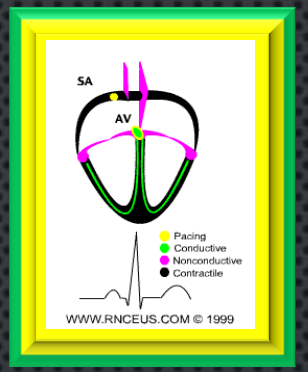




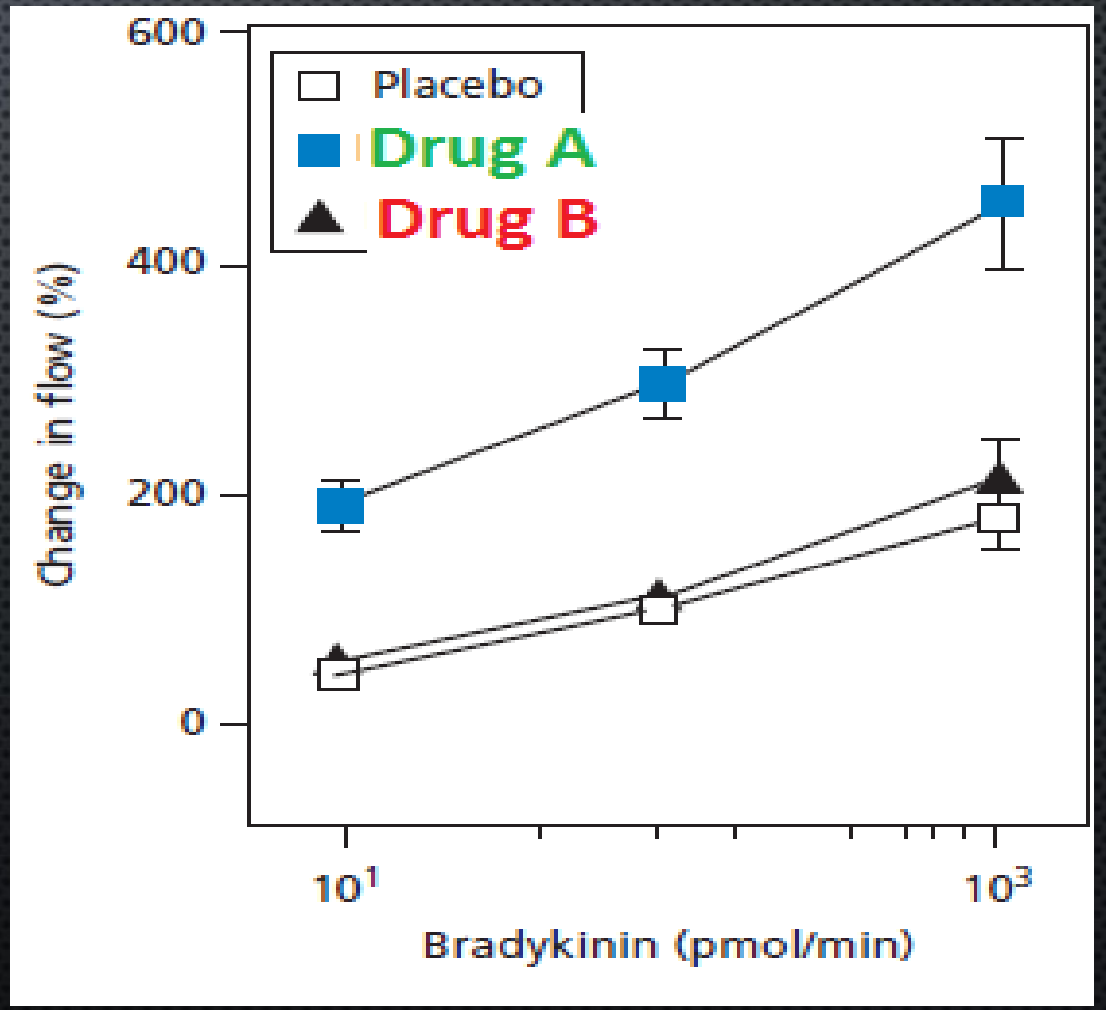
Osman was prescribed hydrochlorthiazide & valsartan. What is the rationale for combining hydrochlorothiazide and valsartan?



THINK- PAIR-SHARE



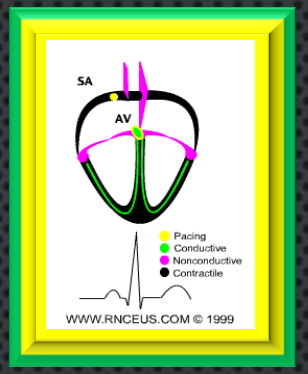
The brachial artery was continuously infused with bradykinin and the blood flow is monitored. Placebo, drug A and drug B (both affect the RAAS) induced the effects on blood flow shown in the graph.



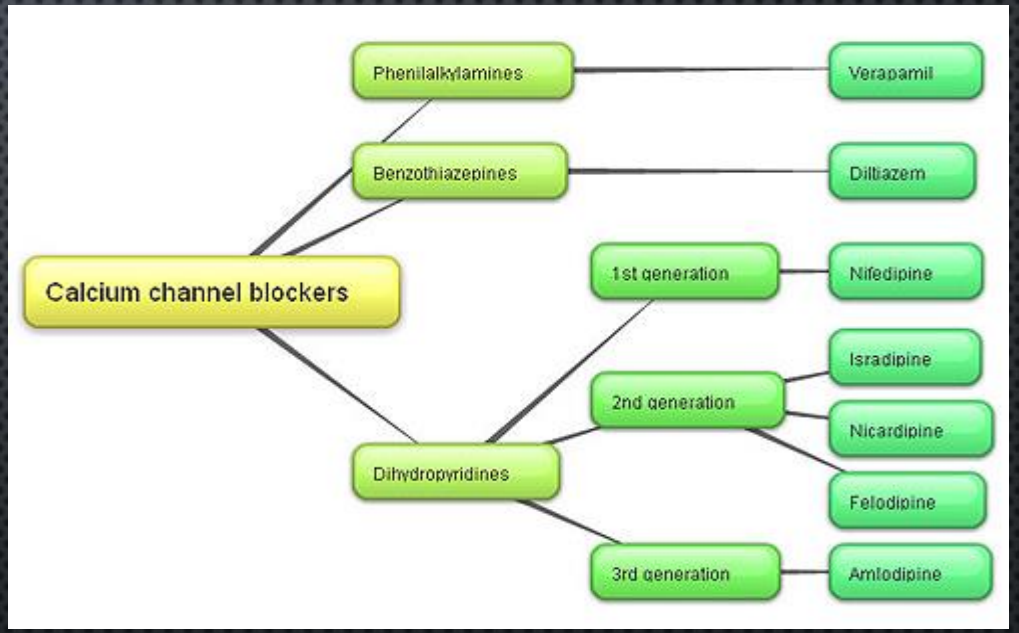
What is drug A? Justify!

What is drug B? Justify!

ANTIHYPERTENSIVE DRUGS



3-CALCIUM CHANNEL BLOCKERS



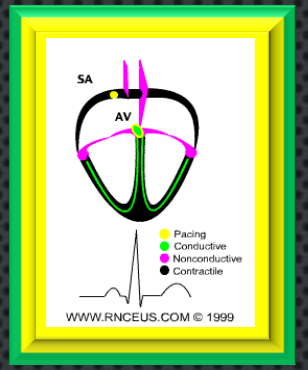
Verapamil act more on the myocardium

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

Diltiazem has intermediate effect

Very
Nice
Drugs

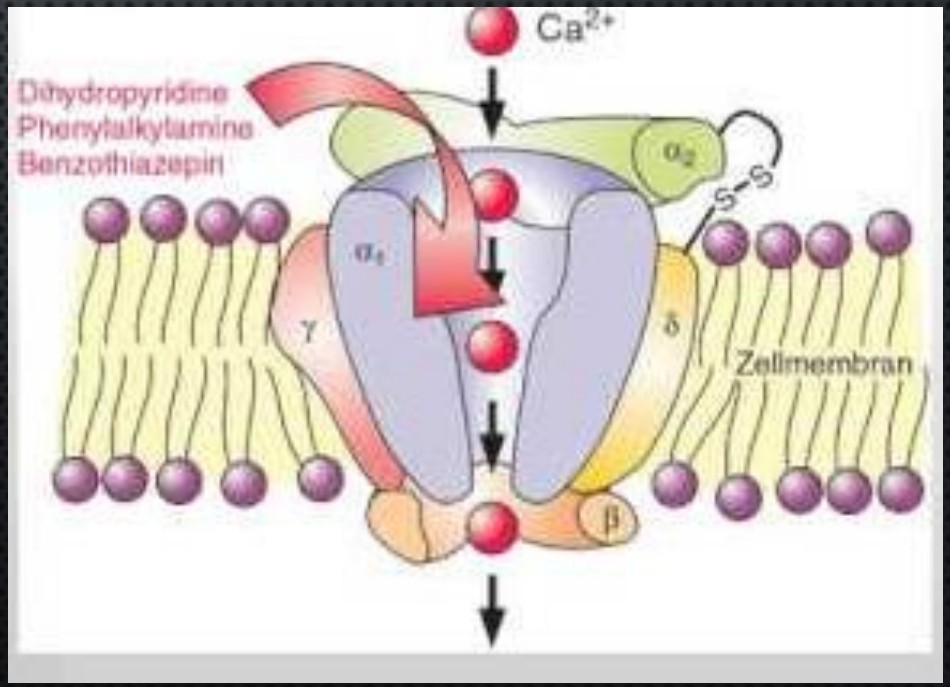
CALCIUM CHANNEL BLOCKERS



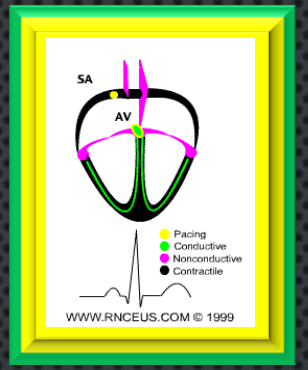
MECHANISM

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

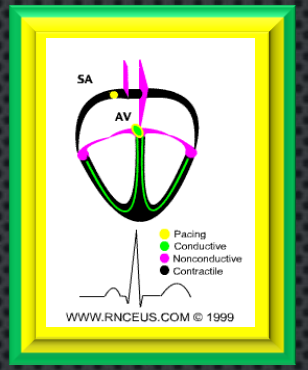
Well absorbed

Verapamil & diltiazem have active metabolites, nifedipine has not

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

Sustained-release preparations can permit once-daily dosing

CALCIUM CHANNEL BLOCKERS



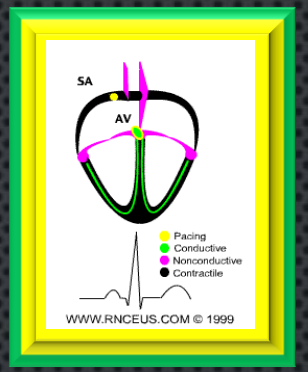
CLINICAL USES

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

ANTIHYPERTENSIVE DRUGS



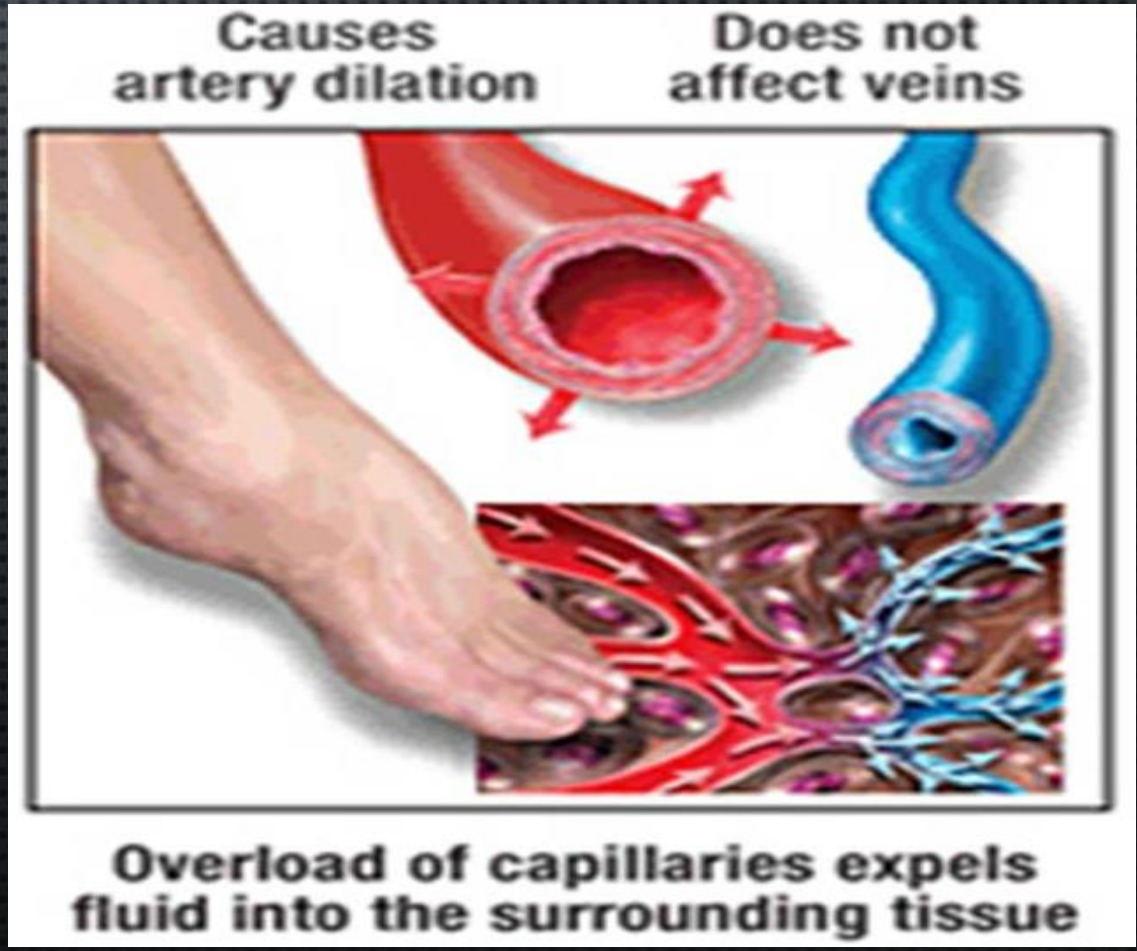
ADRS

Headache , Flushing , Hypotension

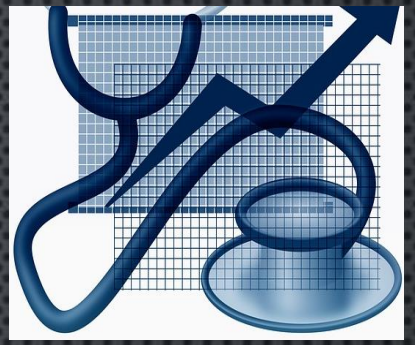
Nifedipine:-Tachycardia

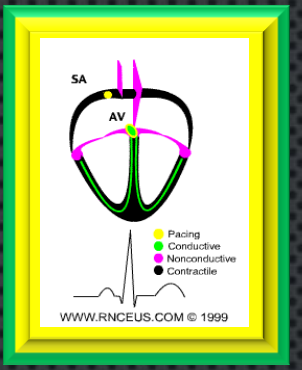
Verapamil & Diltiazem:-
peripheral edema (ankle edema)

Verapamil:- constipation



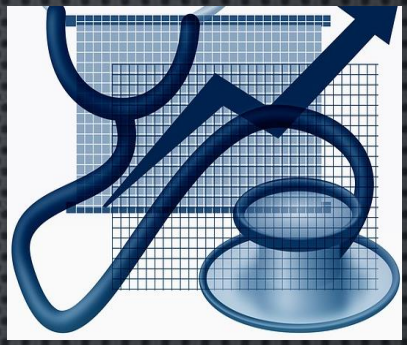
CLINICAL CASE

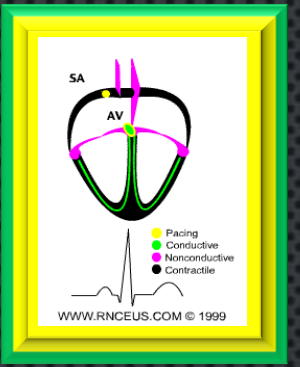




Osman was prescribed valsartan & diltiazem. What is the benefit of combining valsartan and diltiazem?

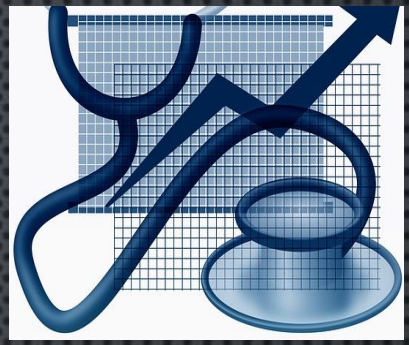
CLINICAL CASE

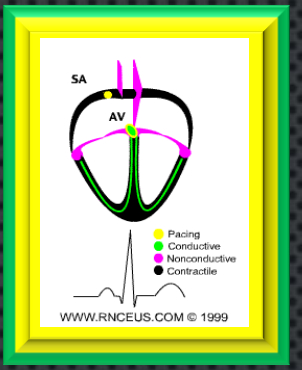




The BP of Osman did not change on standing. What is your conclusion?

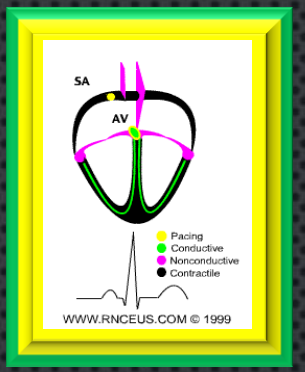
CLINICAL CASE





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

TASK- SELECTION OF A P-DRUG



Instructions:

1- Select a leader for your group

2- Discuss the case according to the steps shown in the sheet

3- Use your mobile & internet access to obtain evidence for efficacy, toxicity, convenience & cost.

4- Due to time constrains divide yourself into 4 groups, each doing one search e.g. evidence for efficacy.

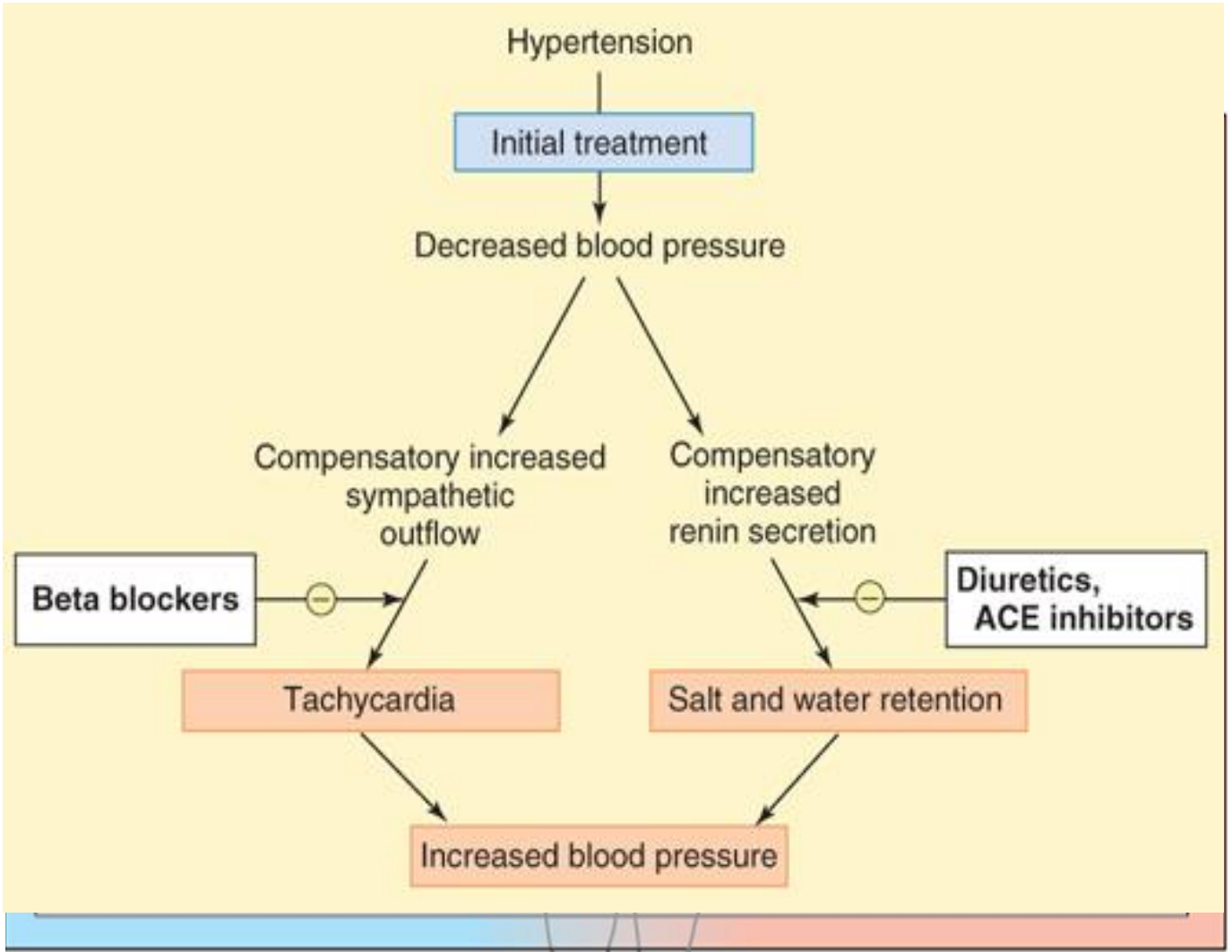
5- You have 10 minutes to do this and 1 minute to report to the class.

ANTIHYPERTENSIVE DRUGS

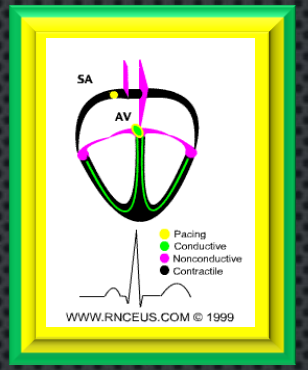
4- VASODILATORS

Classified into arterial, venous or mixed vasodilators

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



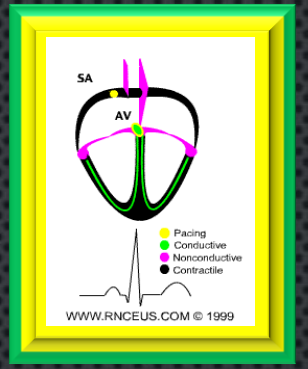
ANTIHYPERTENSIVE DRUGS



VASODILATORS

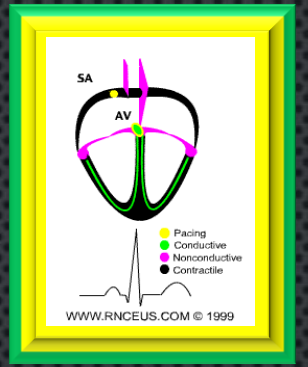
	Hdralazine	Minoxidil	Diazoxide	Sodium nitropruside
Site of action	Arteriodilator	Arteriodilator	Arteriodilator	Arterio & venodilator
Mechanism of action	Release of nitric oxide (NO)	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate (active metabolite)	Opening of potassium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

VASODILATORS



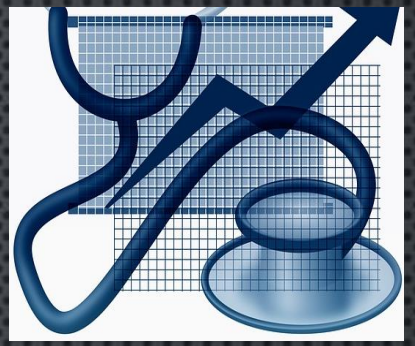
Continue Vasodilators	Hdralazine	Minoxidil	Diazoxide	Sodium nitropruside
Therapeutic uses	1.Moderate - severe hypertension.	1.Moderate – severe hypertension	1.Hypertensive emergency	1.Hpertensive emergency
	In combination with diuretic & β-blockers			
	2.Hypertensive pregnant woman	2. baldness	2.Treatment of hypoglycemia due to insulinoma	2.Severe heart failure

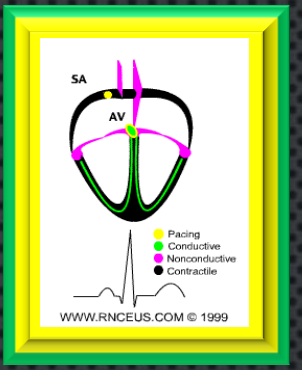
VASODILATORS



Continue Vasodilators	Hdralazine	Minoxidil	Diazoxide	Sodium nitropruside
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

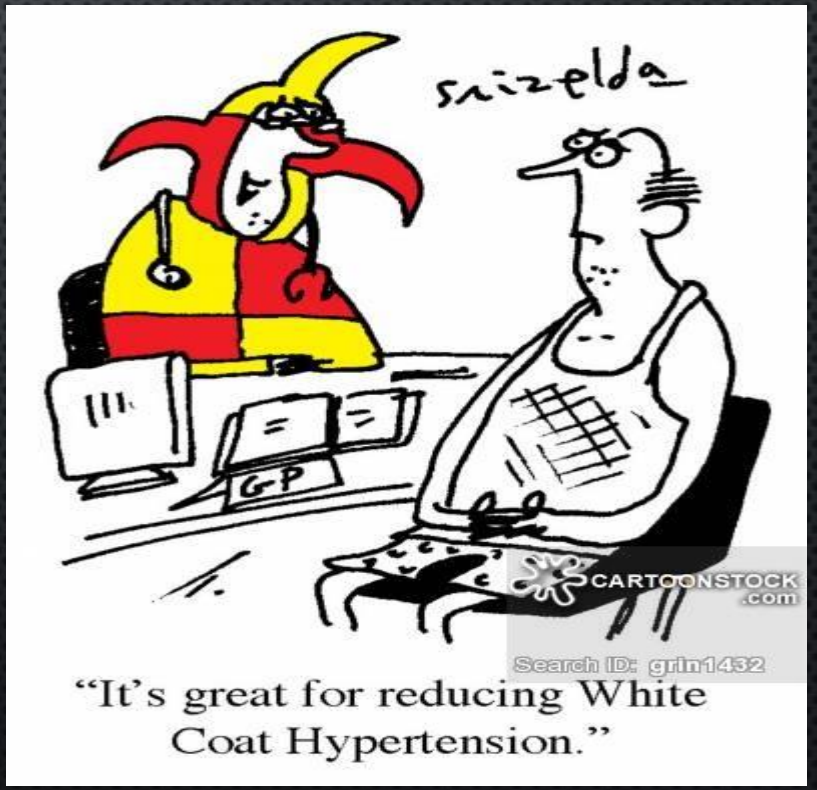
CLINICAL CASE





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



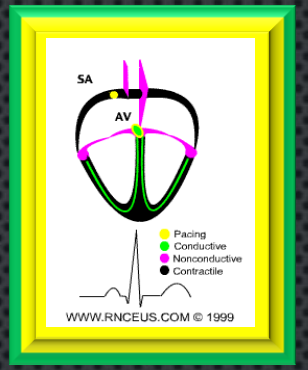
VASODILATORS

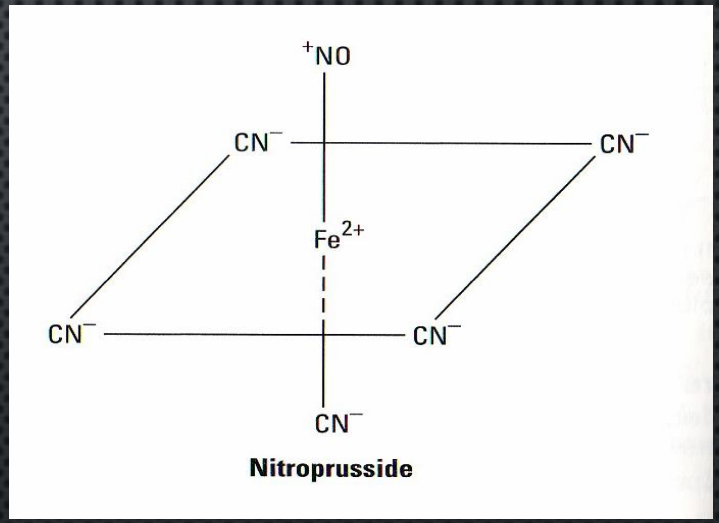
SODIUM NITROPRUSSIDE

ADRS

Headache, palpitations which disappear when infusion is stopped

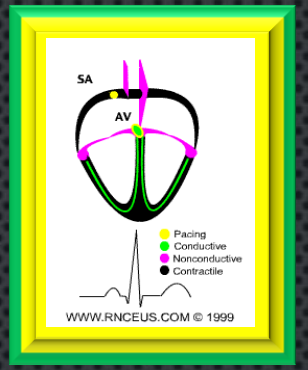
Cyanide accumulation cause cyanide poisoning (metabolic acidosis, arrhythmias, severe hypotension and death)





Nitroprusside

5-SYMPATHOLYTIC DRUGS



i-ß Adrenoceptor blockers

Propranolol, atenolol, metoprolol

They should not be the primary agent for primary prevention but are effective as add-on therapy

May take two weeks for optimal therapeutic response

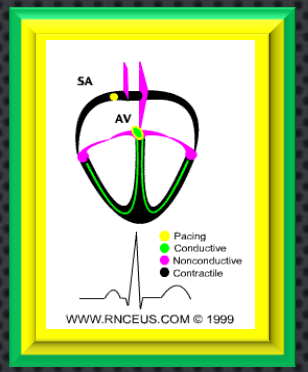
Evidence support the use of ß-blockers in patients with concomitant coronary artery disease

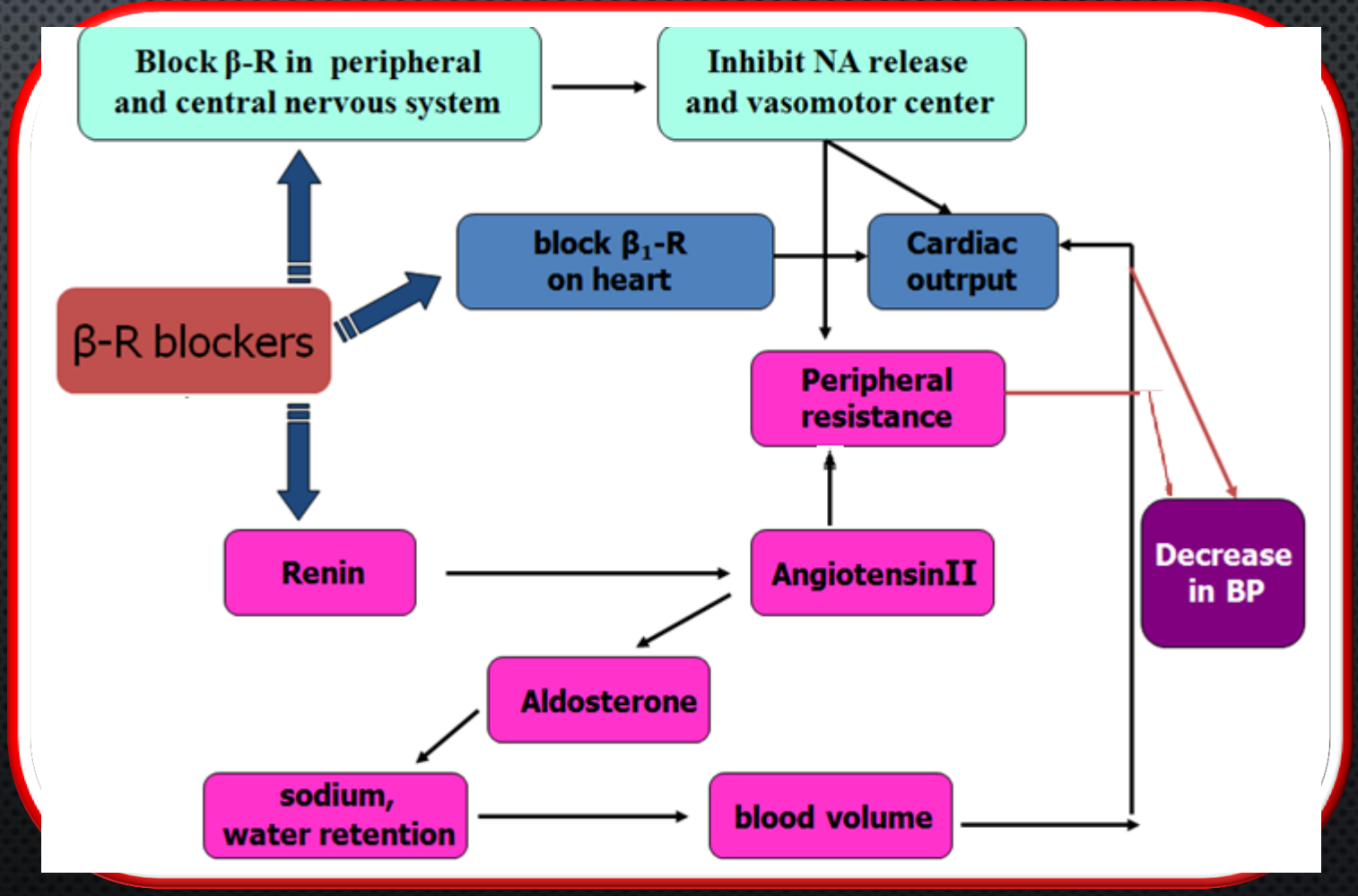
When discontinued, ß- blockers should be withdrawn gradually

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

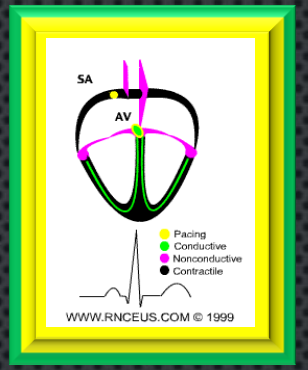
Fatigue

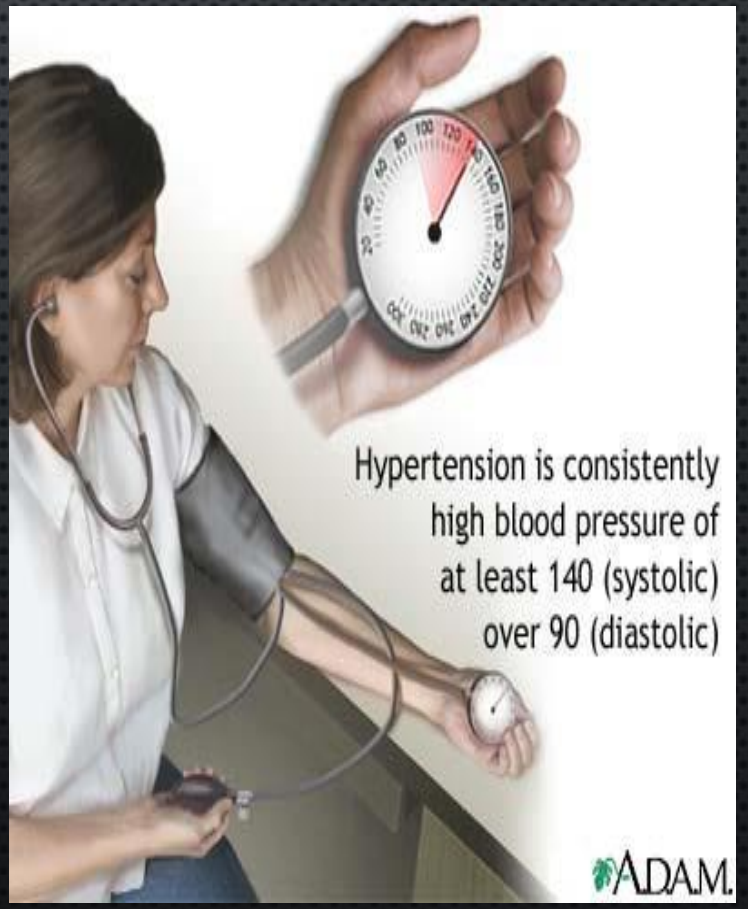
Mask the symptoms of hypoglycemia in diabetics

Increased triglycerides

Aggravate peripheral arterial disease

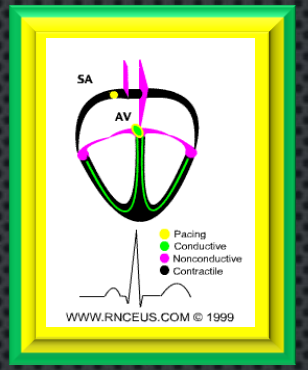
Erectile dysfunction





MEMORY MATRIX

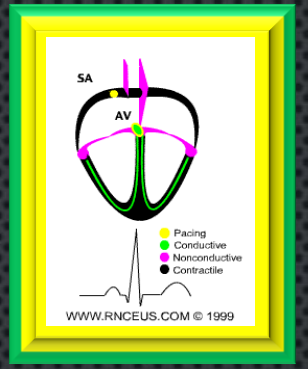
ENTER + OR – IN THE CELLS TO INDICATE THE PRESENCE OR ABSENCE OF A FEATURE



COMPELLING CONTRAINDICATIONS OF ANTIHYPERTENSIVE DRUGS

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

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

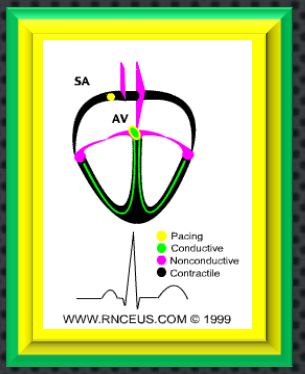
A- Clonidine

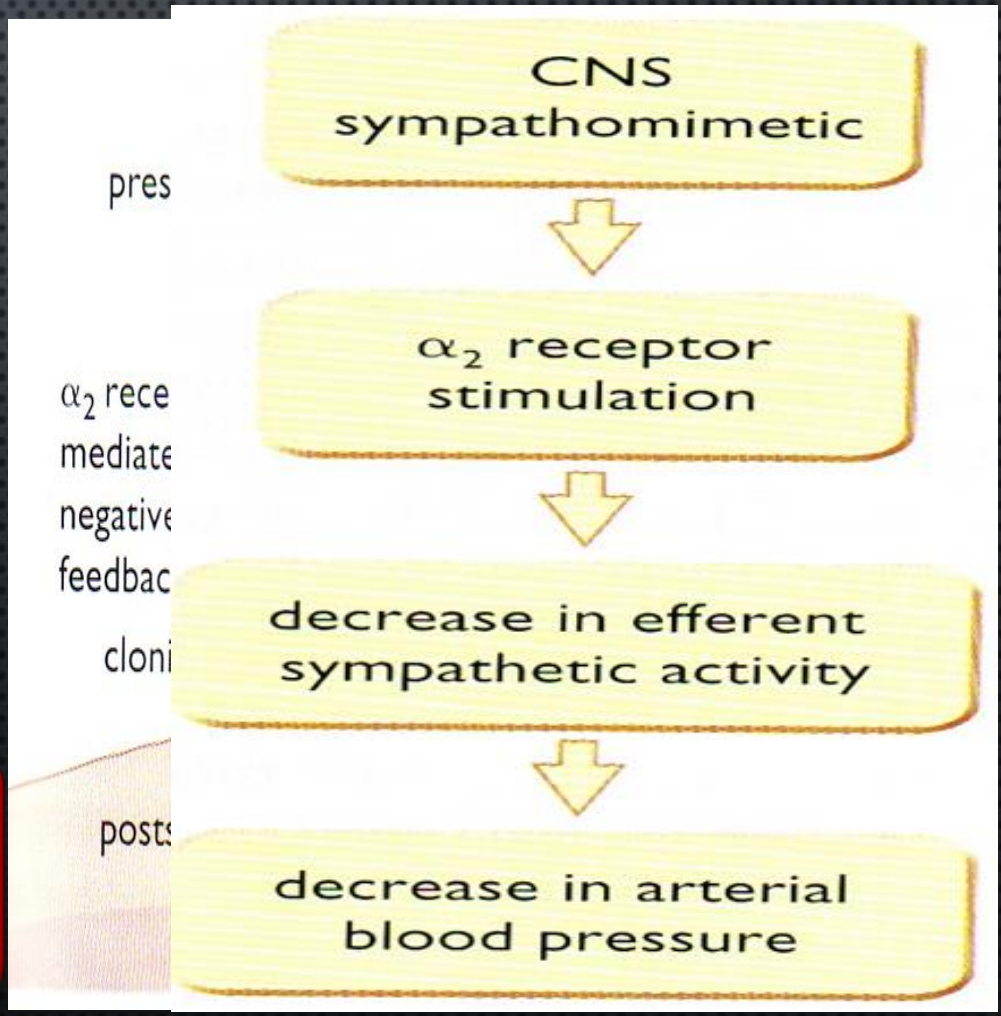
α2-agonist, diminishes central adrenergic outflow & ↑ parasympathetic outflow

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





SYMPATHOLYTIC DRUGS

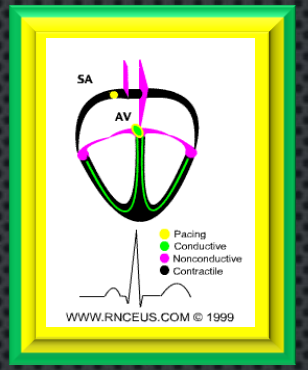
CENTRALLY- ACTING

B- α- methyldopa

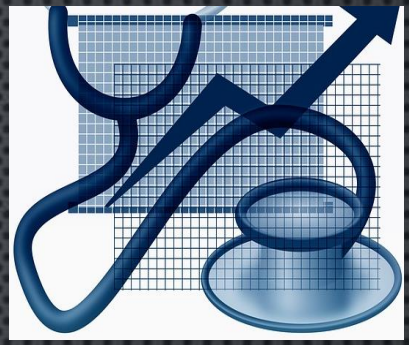
An α- 2 agonist, is converted to methyl noradrenaline centrally to diminish the adrenergic outflow from the C.N.S

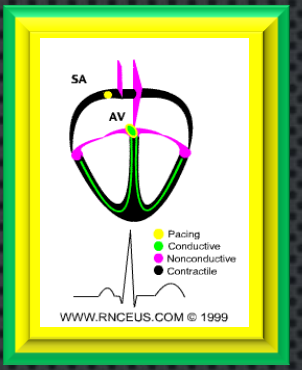
Lead to reduced total peripheral resistance, and a decreased in blood pressure

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



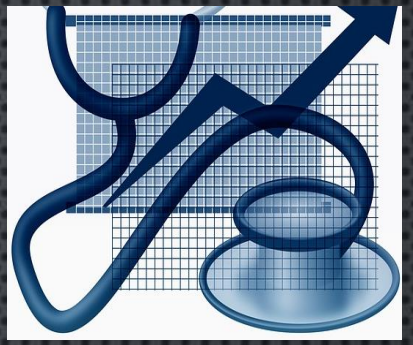
CLINICAL CASE

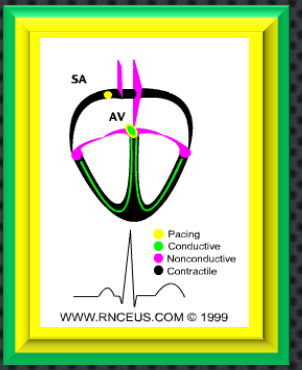




Is the concomitant prescribing of clonidine, diltiazem and metoprolol to Osman wise?

CLINICAL CASE





Could the failure of control of Osman's 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

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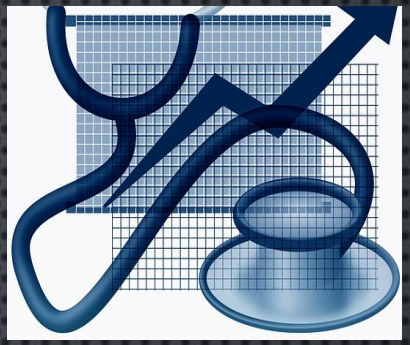
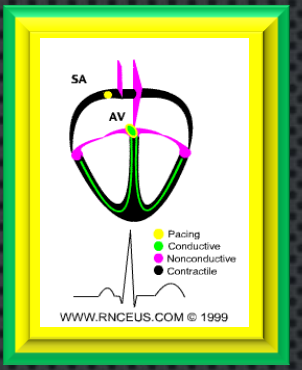
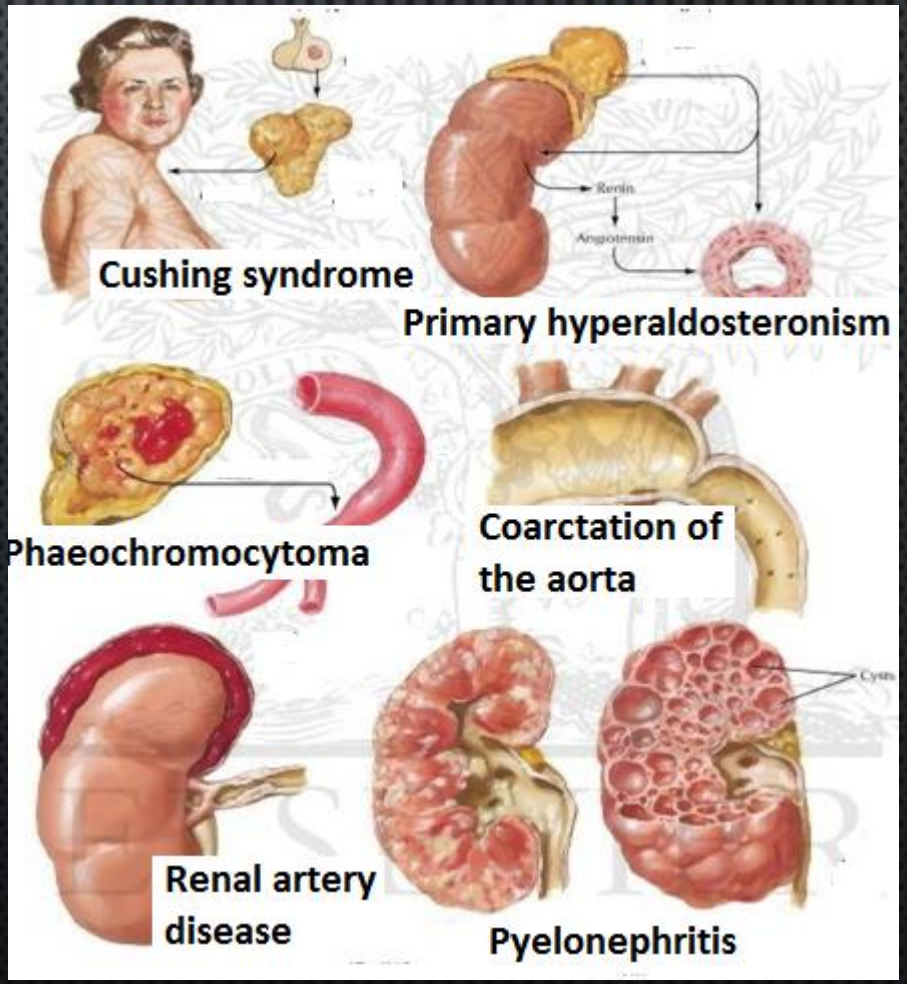
CLINICAL CASE





Could Osman be misdiagnosed? And the high BP is due to secondary disease causes?

Which secondary diseases cause elevation of BP?



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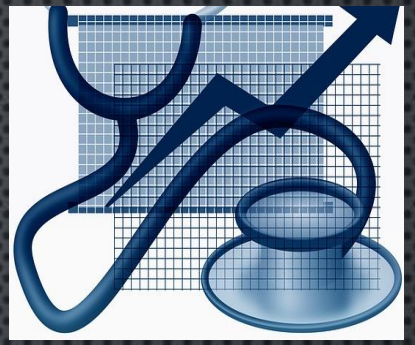
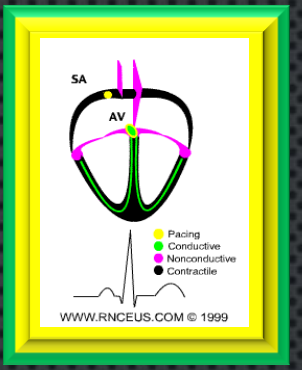


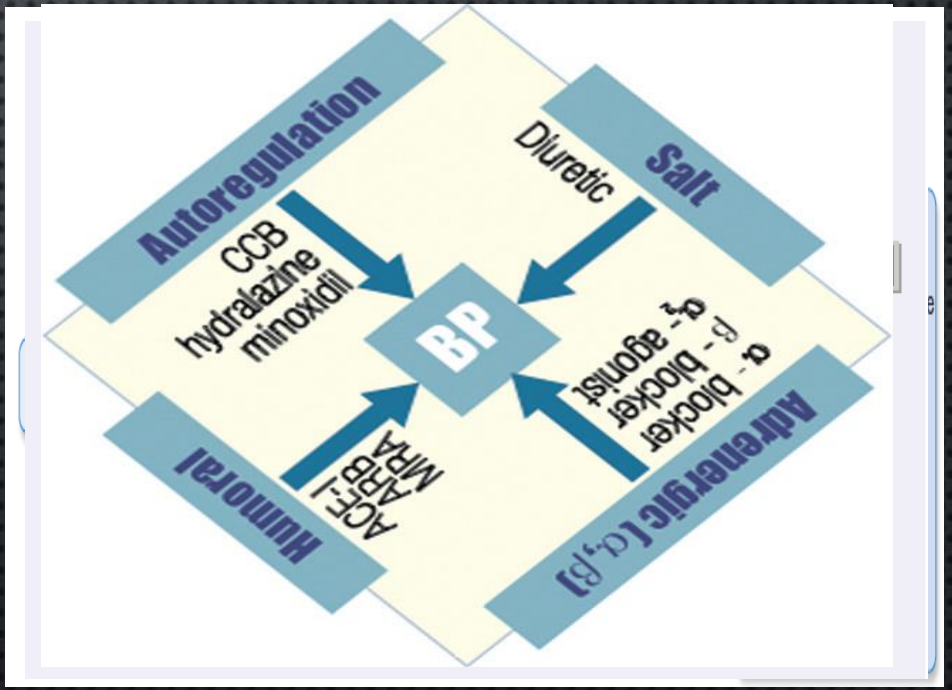


Could the failure of Osman control of BP be due to the use of inappropriate combinations of drugs?

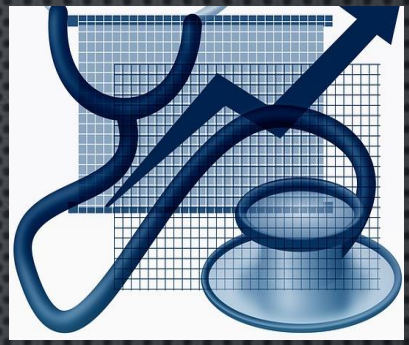
Use of combinations→↓ individual dose→↓ ADRs

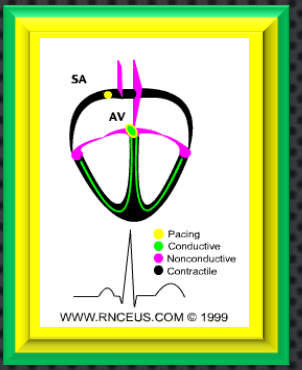
Select a drug that ↓ the ADR of another, e.g. thiazides versus ACEI

Select a drugs that act by different mechanisms



CLINICAL CASE





Could the failure of control of Osman's BP be attributed to non adherence?

Could the somatic complaints (fatigue and dry mouth) indicate the adherence of the patient to medication regimen and which drugs cause these symptoms?