Antihypertensive drugs

Revised by
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OBJECTIVES:

-Identify the factors that control blood pressure.
-Outline the pharmacological classes of drugs used in treatment of hypertension.
-describe mechanism of action, therapeutic uses and common adverse effect and contraindication of each class of drugs.
-select the suitable antihypertensive drug used to treat a specific patient according to efficacy, safety and cost.

- Titles
- Very important
- Extra information
- Doctor's notes

High blood pressure (hypertension) :

is a common condition in which the force of the blood is too high that can cause damage and health problem.

Epidemiology:

prevalence: 25-30% of adult population, only 6% of diagnosed hypertension patient have a goal BP even after correct treatment.
It is usually asymptomatic and that's why it is called silent killer. Untreated hypertension, hypotension will lead to target organ damage.
The damage occurring in major organs fed by the circulatory system (heart, kidneys, brain, eyes).
Number One cause of death

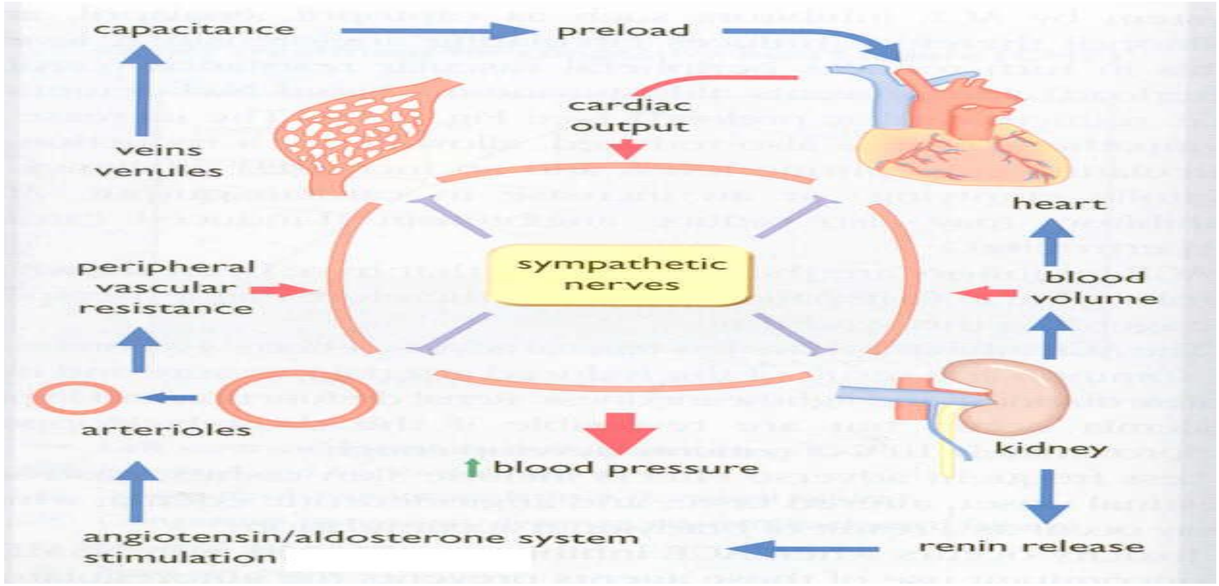
Classified into 2 types:

1-primary (essential): no identifiable cause, tends to develop gradually.
2-secondary: *secondary to another disease (kidney disease, adrenal gland tumors) it occurs suddenly.
*drug-induced hypertension, caused by a response to medication, as Estrogens, NSAIDs, corticosteroid, caffeine.
*rebound hypertension occurs after you stop taking or lower the dose of drug e.g.clonidine.

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

FACTORS IN BLOOD PRESSURE CONTROL



Stages of hypertension:

-Not important to know, mostly related to physiology.
-Target BP for diabetics is <130/80

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

1-lifestyle modification:

Risk factor : *old age, obesity, tobacco smoking, lack of physical activities
*chronic condition such as kidney disease and diabetes.
*increased salt (sodium) intake, decrease the potassium. decrease V6
So the patient should follow the lifestyle modification to decrease these risk factor.

2-drug thereby:

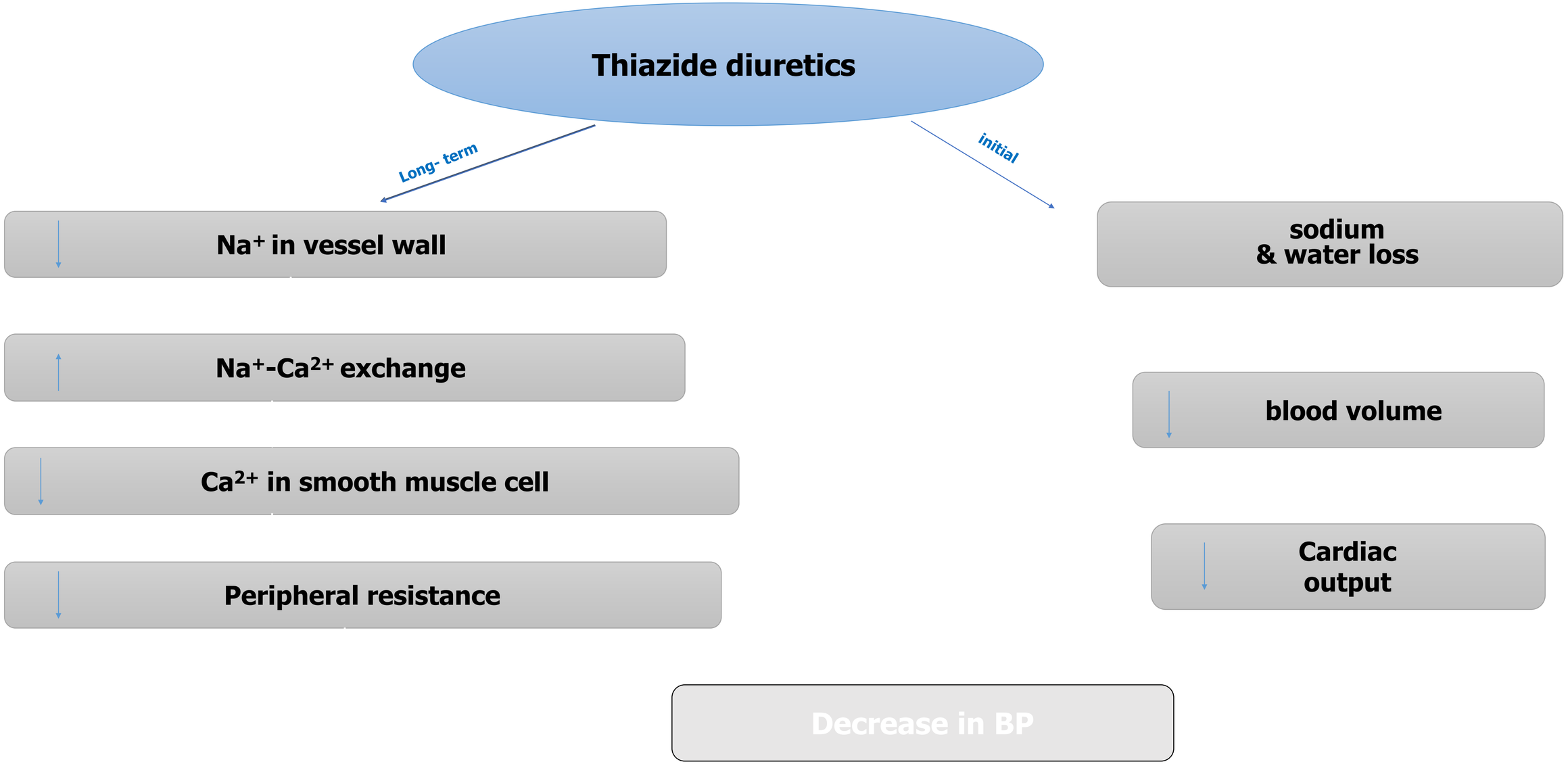
The target BP = < 140/90 mmHg
Diabetes melitus = < 130/80 mmHg

3-Classification of Antihypertensive drugs (drug management):

*diuretics.
*ACE Inhibitors.
*ARB.(angiotensin rceptors blockers)
*calcium channel blockers.
*vasodilators.
*drugs acting on the sympathetic nerves system.

Diuretics

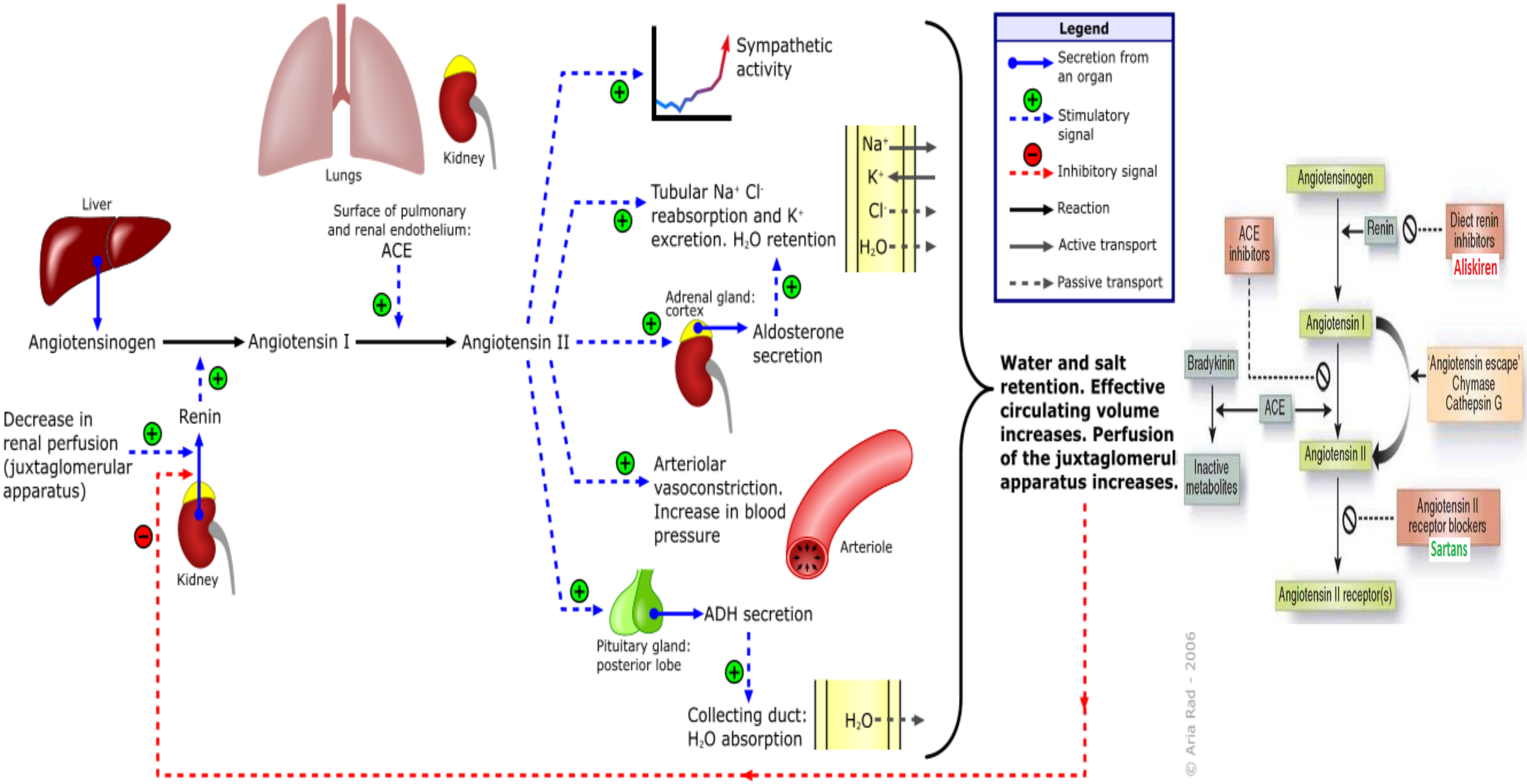
Group	Thiazides ممكن نقراه كذا " ذا يزيد" اليورينيشن Thi azide the urenation	Loop diuretics	Potassium-sparing diuretics
Examples	Hydro-chlorothiazide, Chlorthiazide, Chlorthalidone (longer duration of action) ممكن نقراه كذا " تمت التحلية" المويه والاملاح .. Thali done	Furosmide.	Aldosterone antagonists.
uses	Use as initial drugs therapy for 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.	*hypertension with renal impairment. *in heart failure to manage the symptoms (edema) more potent diuresis but with a smaller decrease in PVR	minimal effect in lowering BP
Mechanism	the action will last for 4-6 weeks and then replaced by a decrease in PVR(Peripheral vascular resistance). The diuretics will lower the BP by increasing sodium and water excretion which will decrease the blood volume, resulting in a decrease in Cardiac output and renal blood flow. With long term treatment it will cause a hypotension effect by decreasing the Peripheral resistance by ↓Na+ in vessel wall then ↑Na+ Ca++ exchange which ↓Ca++ in smooth muscles cell wall while the blood volume approaches a normal value. **Important**		


Thiazide diuretics
Long- term
initial
↓ Na+ in vessel wall
↑ Na+-Ca2+ exchange
↓ Ca2+ in smooth muscle cell
↓ Peripheral resistance
sodium & water loss
↓ blood volume
↓ Cardiac output
Decrease in BP

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

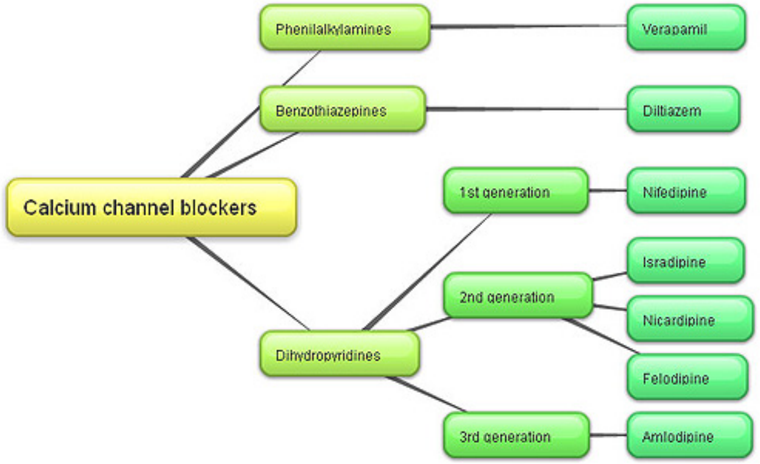
	Examples	pharmacokinetics	Mechanism of action	Clinical uses	ADRS	contraindications
Angiotensin-converting enzyme inhibitors ACE=ICE=Snow Ice in APRIL نزل ثلج بشهر ابريل	Listen Capto Rami Ena lalah, in APRIL اسمع كبتوا رامي انا لله وان اليه لراجعون، في شهر ابريل Lisinopril Captopril Ramipril ان علاء ورامي غير ناضجين	Polar, excreted in urine =Do not cross BBB Have a long half-life & given once daily / Rapidly absorbed from GIT / after oral administration Food reduces their bioavailability / It takes 2-4 weeks to notice the full antihypertensive effect of ACEIs . Enalapril & ramipril are prodrugs	➢ 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 ➢ Particularly effective when hypertension results from excess renin production (renovascular hypertension, white & young)	-Treatment of essential hypertension. -Hypertension in patients with chronic renal disease, ischemic heart disease, diabetes. -Treatment of heart failure	-Dry cough. -Acute renal failure, especially in patients with renal artery stenosis -Severe hypotension in hypovolemic patients -Cause renal *agensia* refers to a congenital absence of one or both kidneys/failure in the fetus resulting in oligohydraminosis -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. -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	-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 . Hypovolemic Pregnant women Renal problem Hyperkalemia is a possible complication of treatment with an ACE inhibitor due to its effect on aldosterone. Suppression of angiotensin II leads to a decrease in aldosterone levels. Since aldosterone is responsible for increasing the excretion of potassium, ACE inhibitors can cause retention of potassium. Hyperkalemia may decrease the velocity of impulse conduction in the nerves and muscles, including cardiac tissues. This leads to cardiac dysfunction and neuromuscular consequences, such as muscle weakness, paresthesia, nausea, diarrhea, and others.
	Enalapril Ena lalah, انا لله وان اليه لراجعون دخلوه الطوارىء	Enalaprilat is the active metabolite of enalapril given by i.v. route in hypertensive emergency				
Angiotensin receptors blockers (ARBs) Sartan ARBs سرطان العرب	Candesatran Telmisartan Losartan, Valsartan, Cande Tell me LoVal has Sartan	Losartan; Has a potent active metabolite, Long half-life, taken once daily, Orally effective, Do not cross BBB. Valsartan; No active metabolites.	-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.		Same ADRs, except for dry cough & angioneurotic edema	Same contraindications as ACEI.

Renin-angiotensin-aldosterone system



3- Calcium Channel Blockers (CCBs)

or calcium antagonists



*V*ery (Verapamil)
*N*ice (Nifedipine)
*D*rugs (Diltiazem)

أمل ونايف وعازم يحبوا يشربوا حليب
Verapamil
Nifedipine
Diltiazem
Calcium channel Blocker

- **Verapamil** acts more on myocardium. فيه رابر اسمها أمل قلبها رهيف
- Dihydropyridine group act mainly on smooth muscle, Nifedipine نايف دا باني عضل

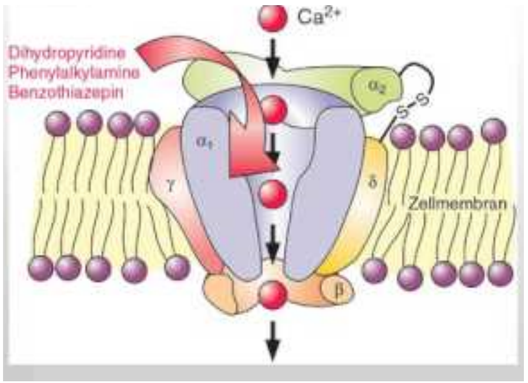
It is more selective as vasodilator than a cardiac depressant. This group is used for treatment of hypertension.

- **Diltiazem** has intermediate effect

Verpamil and Diltiazem are Non-Dihydropyridine, they used in treatment of atrial fibrillation.

Mechanism

- Block the influx of calcium through calcium channels (and block excitation-contraction coupling) resulting in:-
  1- Peripheral vasodilatation
  2- Decrease cardiac contractility



Pharmacokinetics

- Given orally (onset 0.5-2hr) or IV in emergency (onset 1-3 min)
- Well absorbed
- **Verapamil** and **nifedipine** are highly bound to plasma protiens (more than 90%) while **diltiazem** is less (70-80%)
- **Verapamil** & **diltiazem** have active metabolites, but **nifedipine** has not. nifedipine is Dihydropyridine , its particularly beneficial in treating hypertension.
- Sustained-release preparations can permit once-daily dosing.(are preferred for the treatment of hypertension due to the short half-life of CCBs)

Clinical Use

- Treatment of chronic hypertension. Usually the hypertension patient with diabetes or angina.

Nicardipine = Cardiac shock

- **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 (they maintain a constant concentration with less side effects)

ADRs

- Headache, flushing, hypotension (due to vasodilation)

Most of the drugs that treat hypertensive will cause hypotension

- **Nifedipine**: Tachycardia
- **Verapamil** & **Diltiazem**: peripheral edema (ankle edema*)
- **Verapamil**: constipation (VERY IMPORTANT)

Vasodilators

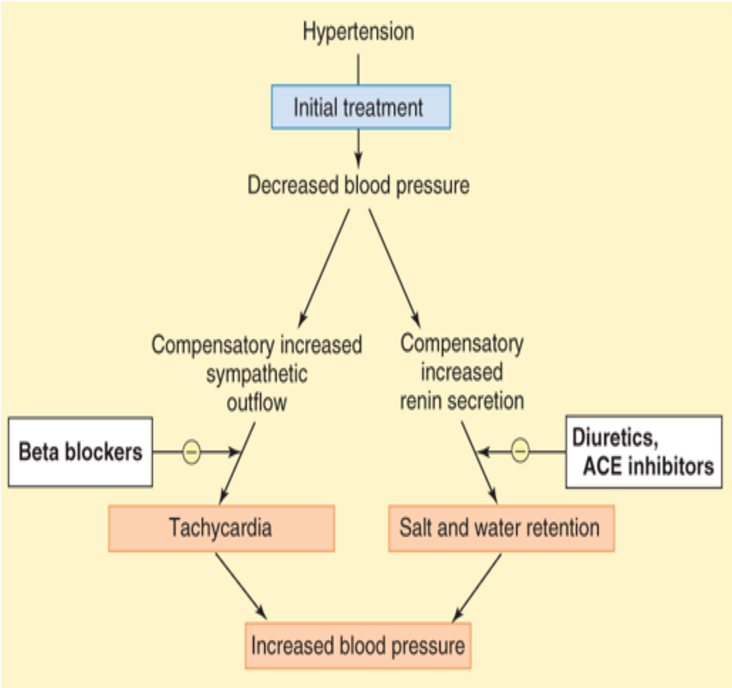
	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Site of action	ممكن نقرأه "حيدر علاء الزين" يحب الفن (Arteriodialiator)	Arteriodilator		Arteriodilator& venodilator
Mechanism of action	Direct (Release of nitric oxide (NO))	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate (active metabolite)	Opening of potassium channels (potassium comes inside the smooth muscle during relaxation, so the blood vessel will relax 'dilate' and that will decrease the blood pressure)	Release of nitric oxide (NO) which is vasodilator Na-nitroprusside release NO No or na الأجانب يقولون لا بطريقتين
Route of administration	Oral		Rapid intravenous	Intravenous infusion
Therapeutic uses	• Moderate to severe hypertension. • Hypertensive pregnant woman (not the first choice) مش حيضر علاء الزين وهو ببطن امه	• Moderate –severe hypertension • Baldness (because it cause growth of hair)	• Hypertensive emergency (because it's administer as IV) • Treatment of hypoglycemia due to insulinoma (tumor of the pancreas that secrete insulin)	• Hypertensive emergency (because it's administer as IV) • Severe heart failure (it increase the preload and afterload and decrease the resistant)
Adverse effects	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema) (sometimes we combine these drugs with diuretics to relive the edema)			Severe hypotension Headache, palpatation which dissapear when infusion is stopped
Specific adverse effects	lupus erythematosus like syndrome هيدرا تحب زين، ودايم اللي حولها يقولون هيدرا لَ زين (باللبناني) Hydralazine وهي تحمر من الخجل لمن تسمع هالكلام lupus erythematosus أو الذئبة الحمراء	Hypertrichosis (increase growth of hair) thus Contraindicated in females Minoxidil = used only for men	Inhibit insulin release from β cells of the pancreas causing hyperglycemia thus contraindicated in diabetics Diazoxide= contraindicated in diabetes.	• Methemoglobin during infusion • Cyanide toxicity (caused by cyanide accumulation and leads to metabolic asidosis, arrhythmias, sever hypotension and death) • Thiocyanate toxicity
Important note	In combination with diuretics & β-blockers (fall in blood pressure produced will activate the sympathetic system and RAAS, to inhibit these 2 mechanisms we use β-blockers 'inhibit sympathetic' and diuretics or ACE inhibitors 'inhibits RAAS')			

Sympatholytic drugs

β-adrenoceptor blockers			
drugs	Propranolol Non selective	Atenolol Selective	Metoprolol Selective
Uses	• Mile to Moderate hypertension in sever cases in combination with other drugs • They should not be the primary agent for primary prevention but are effective as add-on therapy • may take 2 weeks to optimal therapeutic response • evidence support using it with patient has concomitant coronary artery disease.		
Mechanism of action	Decrease blood pressure by: 1- Decreasing cardiac output (blocking β_1 which is in cardiac muscles) 2- Decreasing renin release (blocking β_1 which is in kidney) 3- Central Mechanism (blocking β-receptors in CNS 'presynaptic receptors)		
Adverse effects	• Hypoglycemia • Fatigue • Mask the symptoms of hypoglycemia in diabetes (contraindicate in diabetes patients) • Increase triglycerides • Aggravate peripheral arterial disease (as Reynaud's disease) • Erectile dysfunction		
Note	• When discontinued, β- blockers should be withdrawn gradually (to avoid rebound hypertension) • Beta blockers cause retention of sodium and water. Diuretics can cause mild volume reduction that leads to an increase in renin secretion by the kidney. The rationale for combining beta blockers with diuretics is twofold: beta blockers blunt the increase in the plasma renin level that is induced by diuretics, and diuretics decrease the sodium and water retention that is caused by beta blockers.		

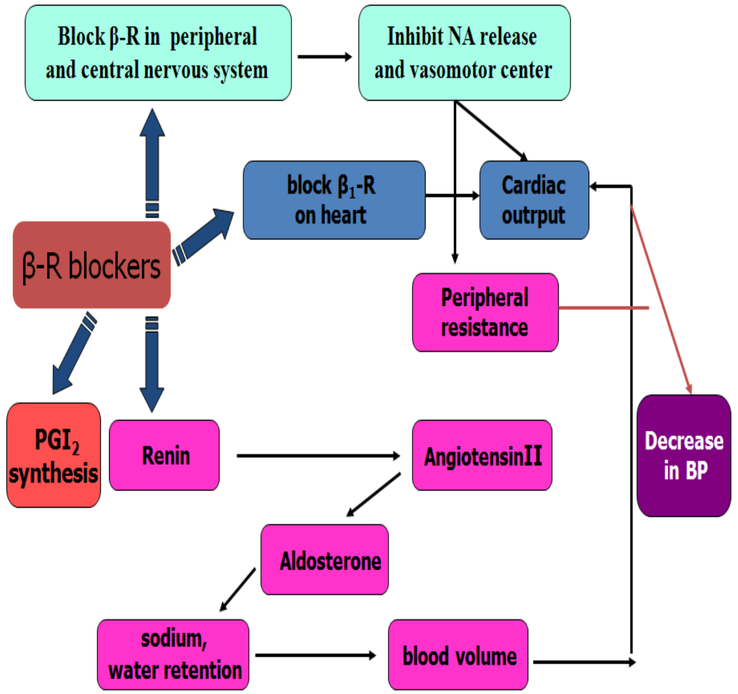
α-adrenoceptor blockers		
Drugs	Prazosin	Doxazosin (better or drug for choose , because of duration of action)
Site of effect	α- receptors in arterioles and venules	
Mechanism of action	Reduce blood pressure by decrease preload and afterload	
Duration of action	Short duration of action	Long duration of action (preferred)
Side effect	causes first dose hypotension & postural hypotension انخفاض الضغط لمن يوقف فجأة	-

Central acting		
Drugs	Clonidine	α- methyldopa
Mechanism of action	α2-agonist, diminishes central adrenergic outflow & ↑ parasympathetic outflow by decreasing heart rate & contractility	• 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
Uses	• hypertension complicated by renal disease (because it Does not decrease renal blood flow or glomerular filtration) • resistant hypertension	first line treatment of hypertension in pregnancy
Adverse effect	Abrupt withdrawal may lead to rebound hypertension (more sever than in beta-blockers)	-



This is a very helpful picture to show you the mechanism of action of the vasodilator and why we use the combination (beta blockers and the diuretics or ACE inhibitors)

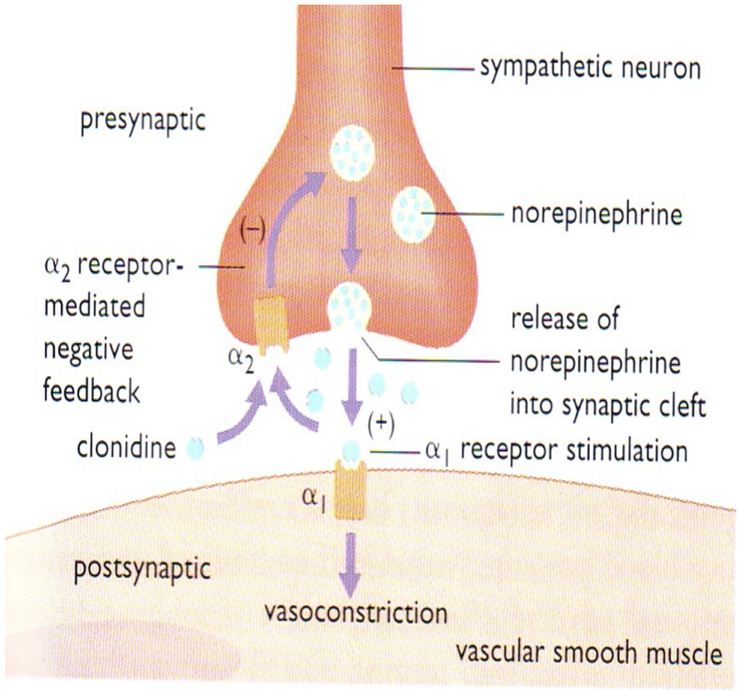
blocking of B2 receptor which is found pre-synaptically will inhibit the release of NE so it will inhibit the sympathetic outflow, plus blocking of B1 receptor will decrease renin secretion > decrease Ang II & aldosterone secretion thus decrease BP.



This picture show you the mechanism of action of beta blockers

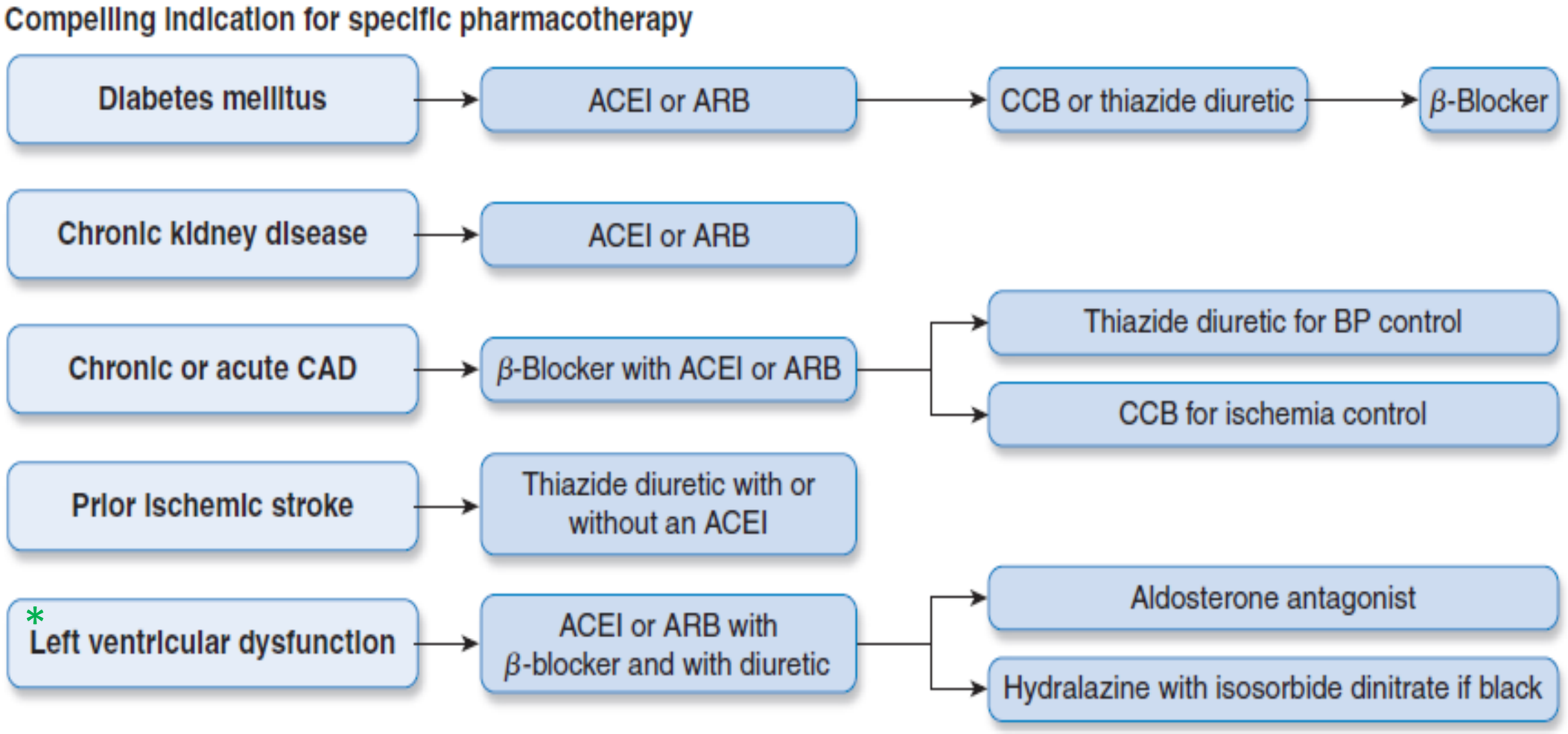
As we mentioned they decrease BP by blocking:

- (blocking β_1 which is in cardiac muscles so decrease the sympathetic stimulation → decrease heart rate
- (blocking β_1 which is in kidney → inhibit renin system → decrease BP
- Non-specific beta blockers will block all beta blockers 'post-synaptic or peripheral receptors and pre-synaptic receptors' which at the end decrease BP



This picture show you the mechanism of action of central acting blockers:

- Clonidine: the α2 receptors works by reuptakes the NE, so low sympathetic effect. The drug will increase the receptors' work, so more uptake of NE and more less of sympathetic effect
- The vesicles (the circles with white-blue droplet) has methyl noradrenaline which will converted into norepinephrine, the drug will come and convert the methyl noradrenaline into α-methyldopa which cannot produce sympathetic effect



Last one isn't important

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	

The next few slides are clinical cases, the doctor said it wont be in the exam, but you should go through them.

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

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

<140/90 mm Hg

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

130/80 mm Hg

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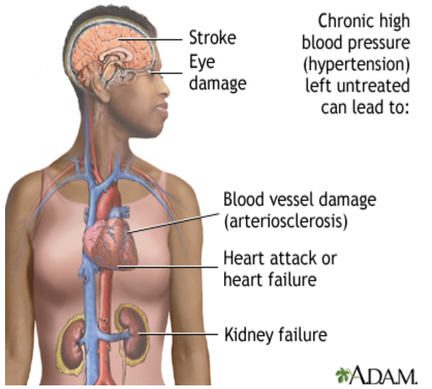
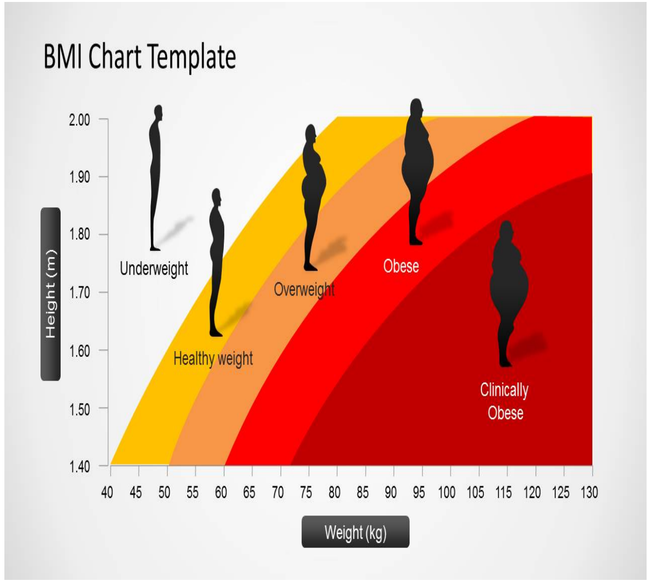
Osman has no history of hypertension- target organ damage. What are organs affected adversely by persistent high BP?



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



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

- Weight loss
- DASH plan
- Sodium reduction
- Physical Activity
- Moderation of alcohol intake
- Smoking Cessation

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)

Could the failure of control of Osman BP be due to secondary drug – induced effects?
Which drugs elevate blood pressure?

A 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. Which drug the woman has been receiving?

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

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

“It’s great for reducing White Coat Hypertension.”

By causing volume and sodium depletion, thiazide diuretics stimulate the production of renin and angiotensin. This leads to a relative increase in blood pressure and sodium retention, which counteracts some of the other antihypertensive effects of the thiazide diuretics. ACE inhibitors interfere with the conversion of angiotensin I to angiotensin II and thereby decrease angiotensin II levels. These effects lead to decreased sodium retention and an enhanced antihypertensive effect.

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

  Thiazides cause increase secretion of salts and water which treats the ankle edema caused by diltiazem.

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

  No postural hypertension. (On standing the vessels constrict to maintain blood supply to the head)

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

  A slight fluctuation below 5 mmHg is normal between two arms, and can be explained by asymmetrical differences in muscles and tissue in each arm. But a big difference in BP could be a result of atherosclerosis, stenosis, of a large artery.

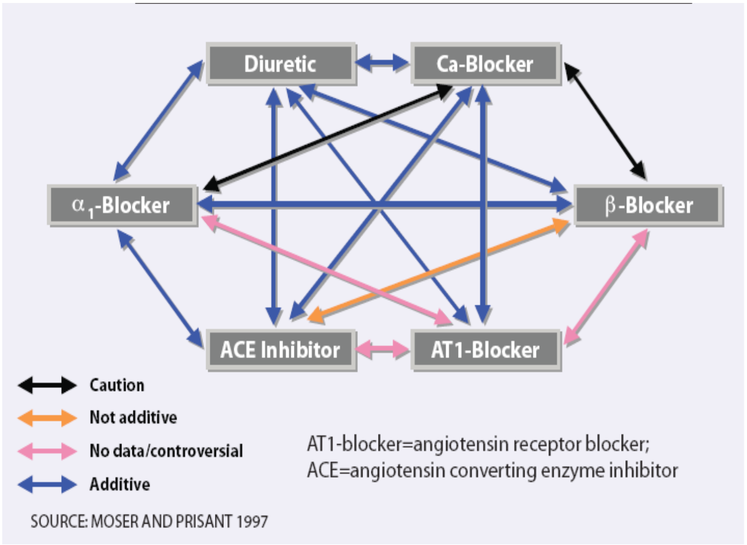
List the reasons, why Osman failed to respond to antihypertensive therapy?

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

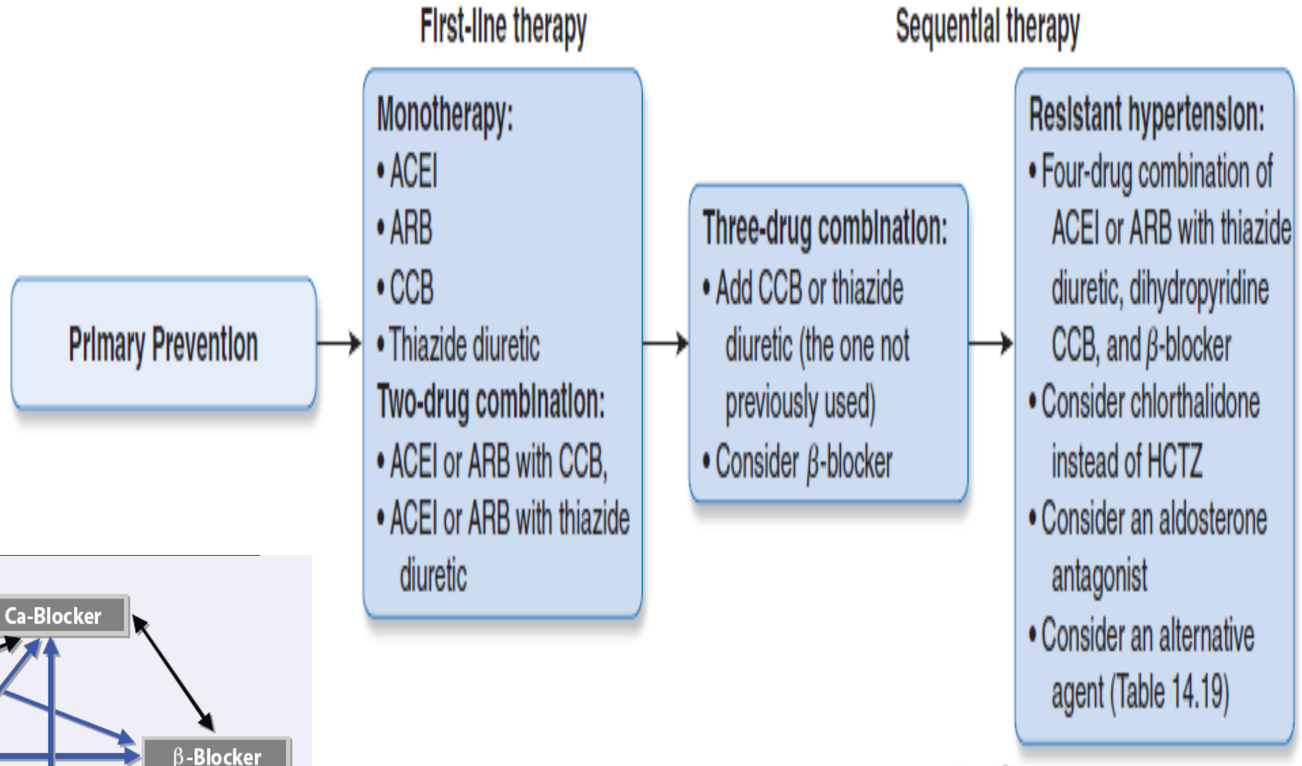
Use of combinations→↓ individual dose→↓ ADRs

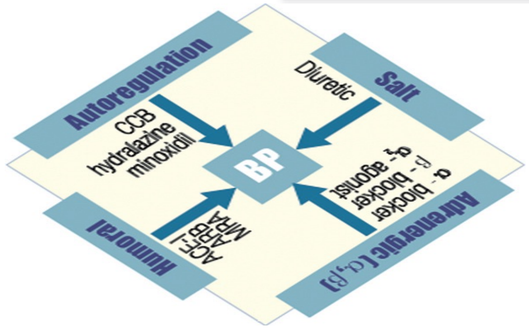
Select a drug that ↓ the ADR of another, e.g. thiazides versus ACEI

Select a drugs that act by different mechanisms



Specific evidence-based pharmacotherapy recommendations





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