Doctor.021
no. 1

CVS
PHARMACOLOGY

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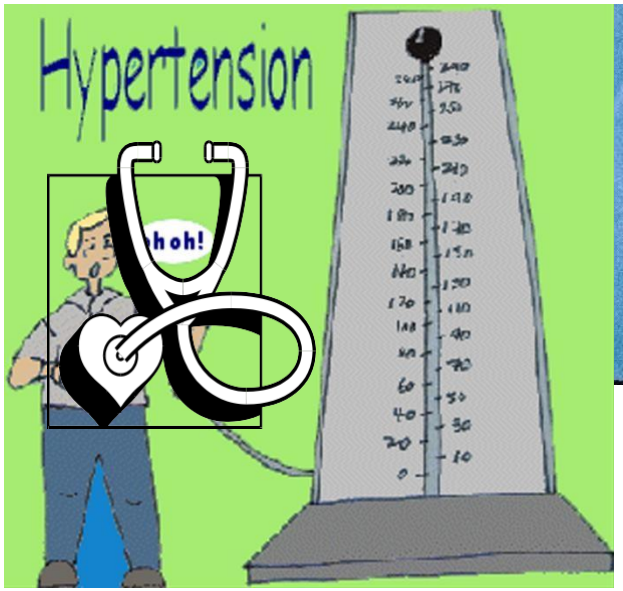
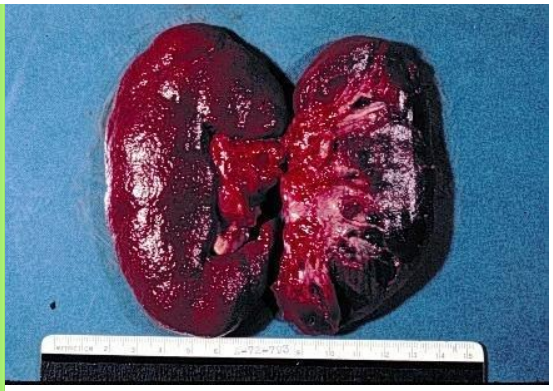
Thiazide

What a sweet lecture !

Hypertension: The Silent Killer





Hypertension is one of the most common problems of morbidity and mortality in the world , almost 1 out of 3 people suffer from hypertension in the US, and even more in Jordan according to the study in the previous slide.

Critical point!

Hypertension- asymptomatic
Morbidity and mortality **due to end organ damage (almost 18-20% of deaths worldwide)**

congestive heart failure, myocardiac infarction, renal damage, cerebrovascular accidents.

Hypertension as a disease

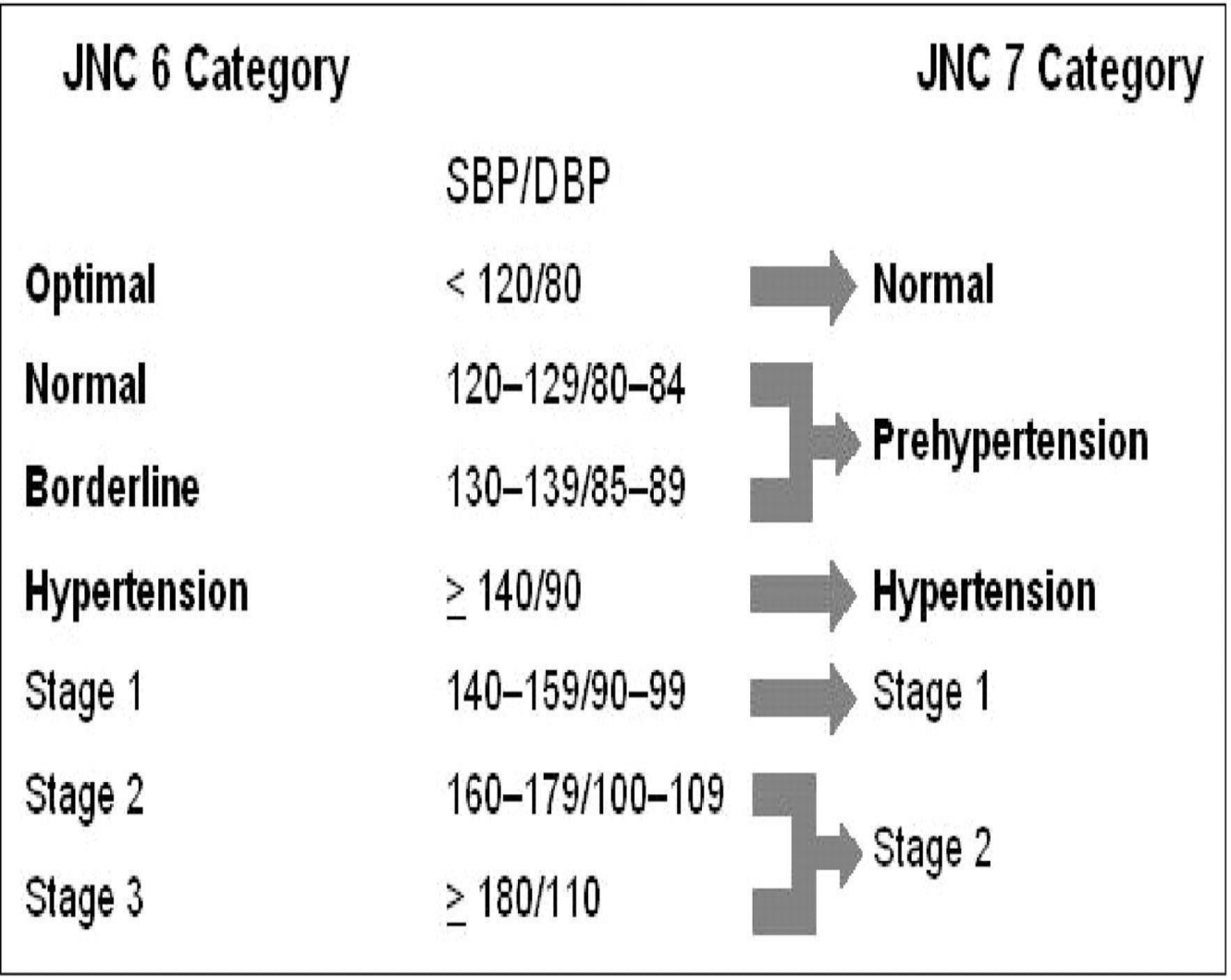
Most of the international committees classified hypertension in **four categories**

this classification is **old**, and its not used as much anymore , some books classify them into mild , moderate , and severe .What matters is that here **if the blood pressure is 140/90 > its hypertension** , but if the patient is old (60>) , its **150/90**

we don't care about the diagnosis here we just care about **targeting** , if we have an old patient (60>) we need to give him therapy to lower the blood pressure to 150/9,but for younger patients (18-60) our target is 140/90.

So if we have a **62 y.o** patient with her B.P being 145/89 **its normal.**

Guidelines



The doctor said **we are not required** to know all of this information its only guidelines.

Lifestyle Modification

Modification	Approximate SBP Reduction
Weight reduction	5-20 mmHg/ 10 kg weight loss
Adopt DASH eating plan (Fiber diet)	8-14 mmHg
Dietary sodium reduction	2-8 mmHg
Physical activity	4-9 mmHg
Moderation of alcohol consumption.	2-4 mmHg

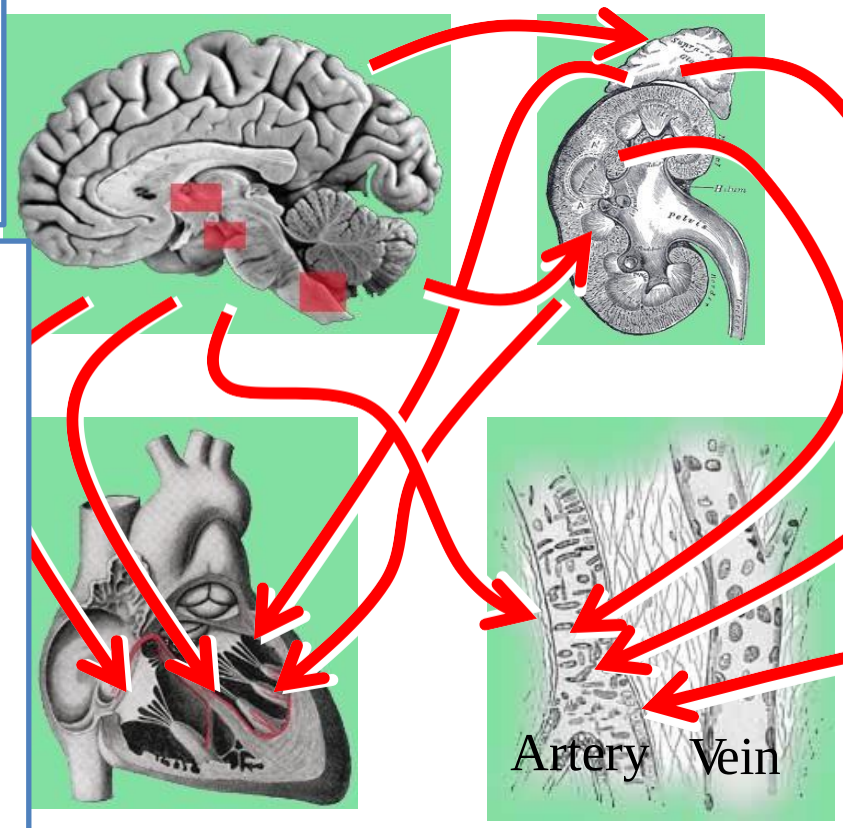
There is no such thing as moderate alcohol consumption its **either** alcohol or no alcohol.

If those are taken seriously by the patient , we could have results in the removal of hypertension irreversibly , works mainly on the systolic blood pressure.

Mechanisms Controlling CO and TPR

1-Neural Sympathetic nervus system and PSNS

This is for moment to moment control , for immediate response , via Acetylcholine and norepinephrine effects on the on the heart and blood vessels, **a1 causes** vasoconstriction,**a2 agonism** causes dilation,**b1** increases cardiac output and the chronotropic and inotropic activity,**b2** causes dilation.



2. Hormonal

(for more long-term effects)

Renal

- Ang II

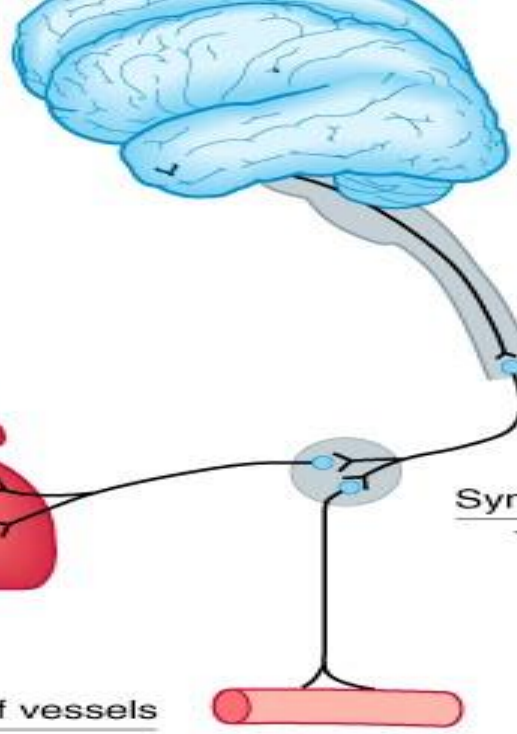
Adrenal

Catecholamines

Aldosterone

3. Local Factors

Such as NO, also Angiotensin could be considered a local factor sometimes , but it mainly belongs to the renal system



Vasomotor center
Methyldopa
Clonidine
Guanabenz
Guanfacine

Sympathetic nerve terminals
Guanethidine
Guanadrel
Reserpine

Sympathetic ganglia
Trimethaphan

β-Receptors of heart
Propranolol and other β-blockers

Angiotensin receptors of vessels
Losartan and other angiotensin receptor blockers

α-Receptors of vessels
Prazosin and other α_1-blockers

Vascular smooth muscle
Hydralazine
Minoxidil
Nitroprusside
Diazoxide
Verapamil and other calcium channel blockers
Fenoldopam

Kidney tubules
Thiazides, etc

β-Receptors of juxtaglomerular cells that release renin
Propranolol and other β-blockers

Angiotensin-converting enzyme

Angiotensin II ← Angiotensin I ← *Renin* ← Angiotensinogen

Captopril and other ACE inhibitors

Aliskiren

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: http://www.accessmedicine.com

Notes From the previous slide

Sympathetic nerve terminal , sympathetic ganglia , and vasomotor center , all part of the neural **control of the blood pressure, if we need to increase blood pressure** we **activate them** , and if we need to decrease it we deactivate them (most of the time).

Vasomotor center controls the release of Norepinephrine , which **increase** the inotropic and chronotropic activity when it acts on the heart, and causes **vasoconstriction** when acting on the vessels, if we deactivate it we decrease blood pressure , and that's by agonizing A2 receptors,(A2 are adrenergic receptors that cause feedback inhibition of norepinephrine release, which will decrease the blood pressure, it works indirectly , and its usage is useful for long term control effects, such as pregnancy)

Methyldopa and clonidine are the most important A2 agonists.

Sympathetic nerve terminal drugs **aren't used anymore**, they cause depletion of Norepinephrine in vessels, which causes reduction in its release.

Sympathetic ganglia drugs are also not used anymore.

B blockers' most important function is blocking b1 receptors which decreases the chronotropic and inotropic activity of the heart.
(chronotropic means rate of pumping, inotropic means strength of pumping)
they also block b2 and b3 receptors but that differs based on selectivity

Notes From the previous slide continued

Beta receptor blockers aren't used as much for **blood pressure** control , and they are pulled out of the guidelines for hypertension control , although most patients take them **because** most of those hypertensive patients also suffer from other heart problems, angina , MI ,arrhythmia, heart failure etc. , they are great for those problems.

They are now moved to 2nd line therapy

First line therapy is mainly focused on thiazides.

Angiotensin II is the most potent vasopressor , there are 2 ways to inhibit angiotensin :

1) we inhibit its synthesis via inhibiting ACE, the **ACE inhibitors** all end with the suffix -PRIL

2) Block the angiotensin itself after its synthesis , the **angiotensin receptor blockers** end with the suffix -SARTAN.(ARBS)

Aliskiren blocks renin , but this drug has failed and its no longer used.

Thiazides(one type of diuretics) exhibit their action on the proximal tubule, they decrease the blood volume , reducing the blood pressure.

the book says that Thiazides act mainly on the distal tubule , and the proximal tubule is just the entrance site for the drug, so I think the doctor made a mistake here.

Notes From the previous slide continued.

Another type of diuretics are **loop diuretics** which exhibit their action on the loop of Henle , the also decrease the blood volume and reduce the blood pressure.

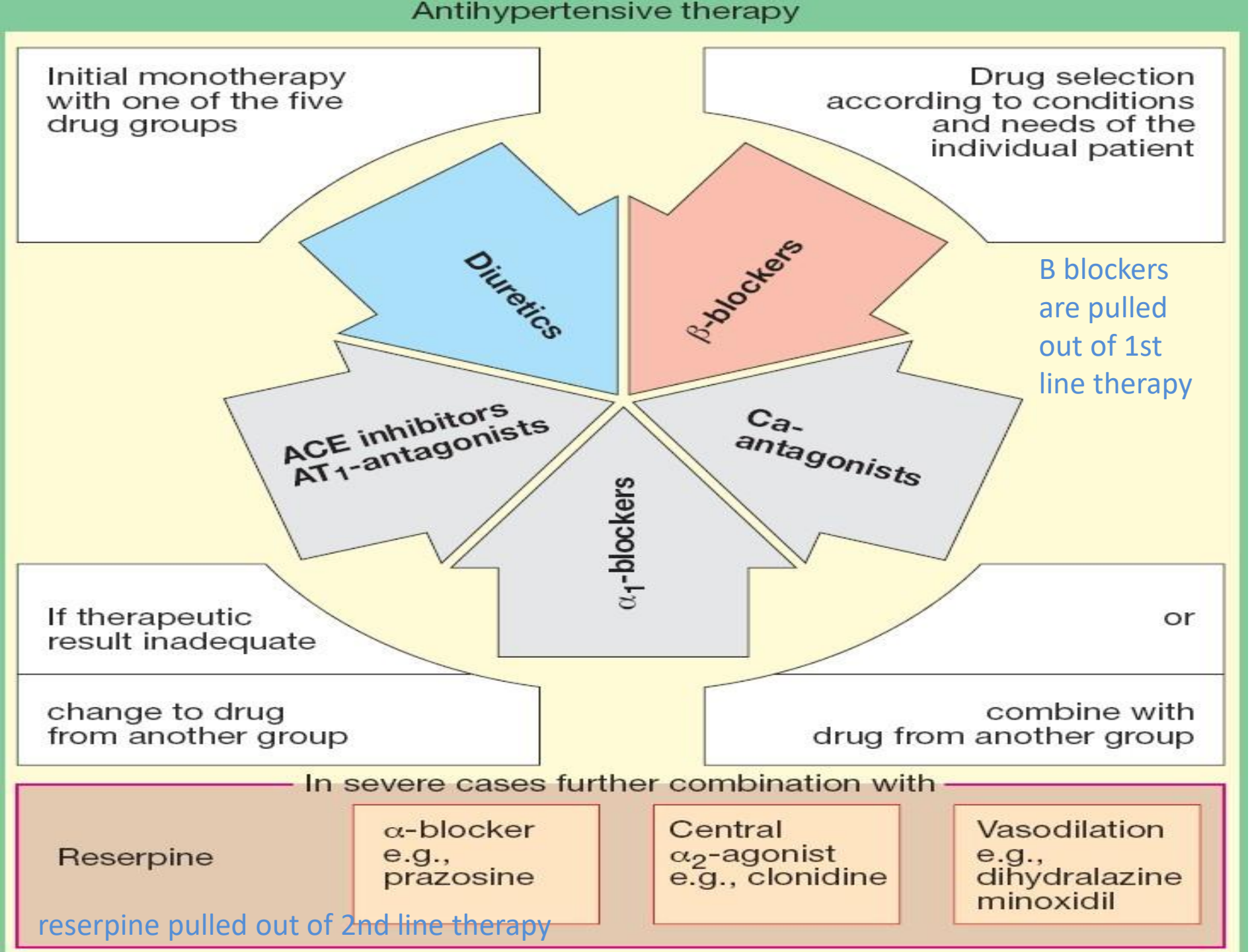
Drugs that exhibit their action on the vascular smooth muscles:-

1) Calcium channel blockers , we block calcium channels , which will block the generation of an action potential , which will cause relaxation of the smooth muscles and vasodilation.

2) Nitroprussides(nitrates): they increase NO levels, and they are important and valuable because they act on veins and arteries, when in emergent situations they are preferable.

3) Hydralazine and minoxidil are vasodilators that exhibit their action on potassium control.

Other drugs that could be used are diazoxide , and A1 antagonists.



B blockers are pulled out of 1st line therapy

reserpine pulled out of 2nd line therapy

Notes From the previous slide

A1 blockers are used for patients with hypertension with prostatic hyperplasia in 1st line therapy

The reason for all the different types of drugs is **because** don't have any single drug that would drop the blood pressure by 50-60 mmhg or big numbers like that.(their maximum efficacy cant give me my target blood pressure).

(Basically I **combine** different drugs to reach my target most of the time)

Those drugs (in the middle) are the first line therapy for hypertension, we use **diuretics** because they have little side effects, we use **ARBS** and **ACE inhibitors** when the blood pressure is higher in relation to other drugs.

2nd line therapy is used for severe therapy or resistant hypertension, a1 blockers as you see are found in both first line and 2nd line therapy but we use it in 1st line therapy when the patient has **prostatic hyperplasia.**

Monotherapy or combination

- Monotherapy of hypertension(treatment with a single drug) is **desirable** because compliance is likely to be better and cost is lower, and because in some cases adverse effects are fewer.

- However, **most patients** with hypertension require two or more drugs, preferably acting by different mechanisms (polypharmacy).

What to choose first?

- Initial antihypertensive therapy without compelling indications
  - JNC 6: Diuretic or a beta-blocker
  - JNC 7: Thiazide-type diuretics (recent guideline notice that we don't use beta blocker anymore and we depend mostly on thiazide)
- Most outcome trials base antihypertensive therapy on **thiazides**

Diuretics

- Diuretics are effective in lowering blood pressure by **10–15 mm Hg in most patients**, and diuretics alone often provide adequate treatment for mild or moderate essential hypertension.

- In more **severe** hypertension, **diuretics are used in combination** with sympathoplegic and vasodilator drugs to control the tendency toward sodium retention caused by these agents.

Lets say a patient with145/89. giving him diuretics alone **could** work.

Thiazide Diuretics

- Diuretics lower blood pressure primarily by depleting body sodium stores.(the drug goes to the proximal tubule (but as I said before I think the doctor made a mistake it's the distal tubule), and the drug blocks a channel, which inhibits sodium reabsorption ,thus depleting sodium stores, and pulls water with it).

- Initially, diuretics reduce blood pressure by reducing blood volume and cardiac output; peripheral vascular resistance may increase (As a reflux).
- After 6–8 weeks, cardiac output returns toward normal while peripheral vascular resistance declines.(in chronic use,a compensatory mechanism done by the collective duct that increases sodium reabsorption)
- Sodium is believed to contribute to vascular resistance by increasing vessel stiffness and neural reactivity, possibly related to altered reabsorption.

Notice that at the beginning of thiazide treatment, we might not decrease the blood pressure, give it some time to have the therapeutic effect.

Thiazide diuretics have a more gradual onset of action and a more long-lasting effect than **loop diuretics**(in the next lecture)

Notes From the previous slide

Don't give salt for patient taking thiazide, but why ?

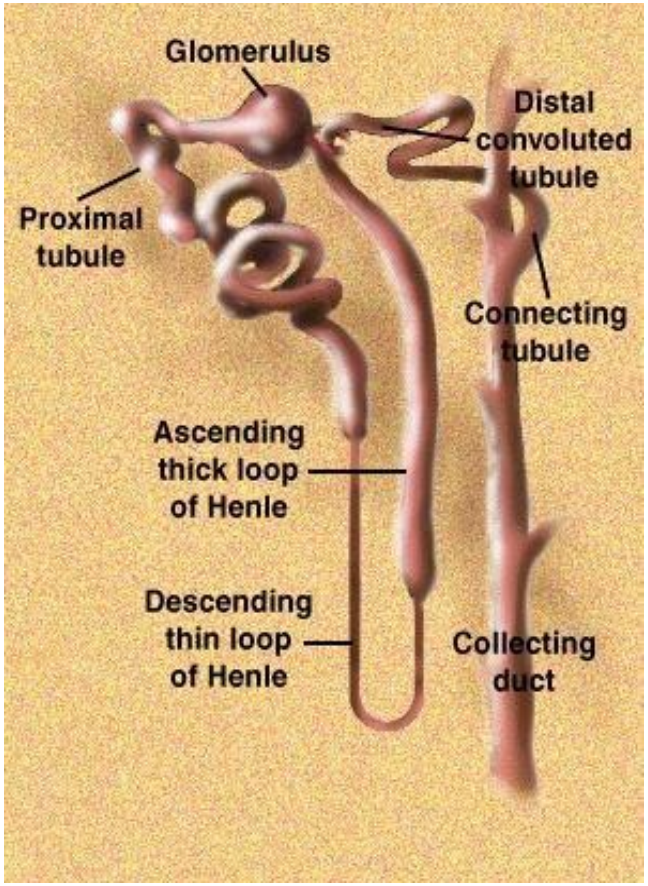
The main mechanism of action of thiazide is to decrease blood pressure by **depleting body sodium stores.**

As a result, Taking salt (NaCl) will result in the decrease of the effectiveness of thiazide. (Food-drug interaction !).

Moreover, salts can **worsen** the potassium loss and increase the risk of hypokalemia (remember that hypokalemia is an adverse effect of using thiazide and with salt there will be more potassium loss)

So, restriction of dietary sodium intake to minimizes potassium loss very important and you should eat foods that are rich in potassium.

Diuretics



2. Mechanism of Action

↑ Urinary Na+ excretion
↑ Urinary water excretion

↓ Extracellular Fluid
↓ and/or Plasma Volume

3. Effect on Cardiovascular System

↓ Acute decrease in CO

↓ Chronic decrease in TPR, normal CO
Mechanism(s) unknown

Thiazide diuretics. (Important).

- **lower doses** (25–50 mg) **exert** as much antihypertensive effect as do **higher doses.**

- In contrast to thiazides, the blood pressure response to **loop diuretics (another drug)** continues to increase at doses many times greater than the usual therapeutic dose.

- Decrease blood pressure **in supine and standing position**, and postal hypotension is rarely observed except in elderly.

There are many analogs, but the most important prototypes are:

1) Chlorothiazide, given orally 1-2 times a day.

2) Hydrochlorothiazide, 1-2 times a day.

could be combined with other drugs such as –Sartans

The **thiazide dose** does not need to be increased to have a better effect, because thiazide exerts the **same effect** regardless of the dose.

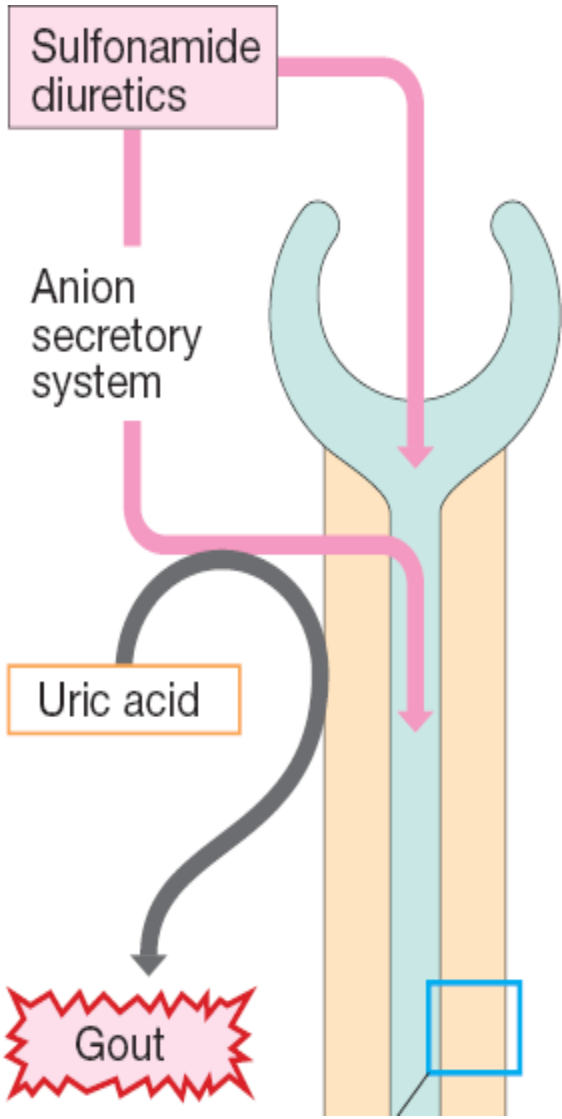
Thiazide diuretics: Adverse effect

1) **Hypokalemia** (70% of patients) : potassium supplementation is recommended.

2) hyperuricemia (70% of patients), result from the inhibition of renal tubular secretion of uric acid.

3) **hyperglycemia** (10% of patients), may interfere with the conversion of pro-insulin to insulin

Because of the possibility of Hyperglycemia (at end it could lead to **diabetes**), Guidelines of UK and Australia don't use thiazide as first line of treatment. Unlike USA which use thiazide as first line of therapy, they say that this adverse effect is **Insignificant** (in Jordan we follow USA):



Notes From the previous slide

The most prominent side effect of thiazide is hyperuricemia, what happen is a drug- drug interaction at the excretion site to uric acid and thiazide, thiazide excreted but uric acid stays in the body because of the inhibition of renal tubular secretion, and the net result is hyperuricemia. Uremic acid can deposit of joints especially big toe results in gout.

Hypokalemia as a side effect from thiazide not serious because we don't excrete large amount of potassium, but be carful It could be very serious if the patient taking Digoxin* which result in arrythmia and other severe problems.

If a patient comes to you complaining of pain in his big toe ask if he tacking thiazide, check his lab tests and look for the levels of uric acid.

Digoxin:

it has a very narrow therapeutic index, which means we need to lower the dose to avoid toxicity.

Hypokalemia as a side effect from thiazide not serious but again it could be serious if the patient ate salt. Tell your patient to avoid salty food please. It is really important.

Side effect

- mild degrees of hypokalemia are tolerated well by many patients, hypokalemia may be hazardous in persons taking digitalis(Digoxin), those who have chronic arrhythmias.

Potassium loss is coupled to reabsorption of sodium, and restriction of dietary sodium intake therefore minimizes potassium loss.

Again, when you eat salty food, the amount of sodium will rise, the secretion of potassium is coupled to sodium, that's means there will be more secretion of potassium, which leads to worse hypokalemia

اللهم كن مع اهلنا في غرة ومكنهم في الأرض.
اللهم انصر عبادك المجاهدين, اللهم استعملنا في نصرة دينك ولا تستبدلنا يا ارحم الراحمين.

Thank You

v2:a2 antagonists---> a2 agonists