CVS
PHARMACOLOGY

Modified NO: 1

كتابة: صهيب زعيتر وحسن النويهي

تدقيق: أحمد المطارنة

الدكتور: د مالك زحلف

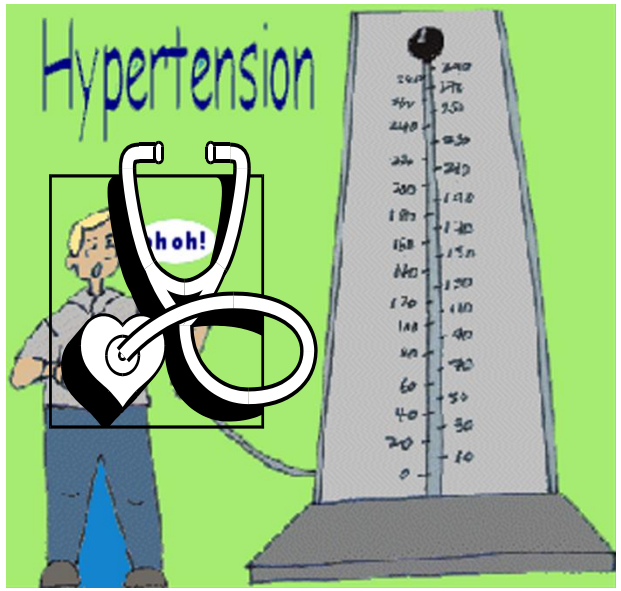
Anti-hypertensive drugs 1

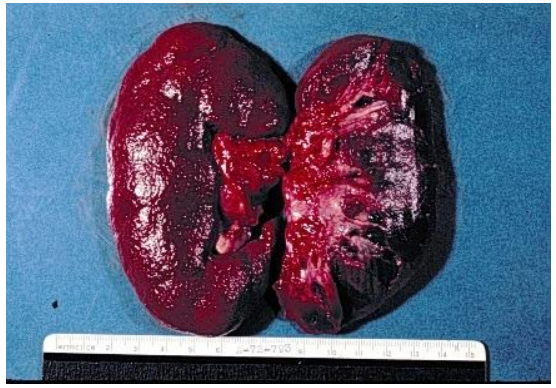
Color code
Slides
Doctor
Additional info
Important

دراسة صحية تظهر ان 39% من عينتها يعانون من ضغط الدم

- الراي - اظهرت دراسة نفذتها وزارة الصحة بالتعاون مع شركة أسترا زينكا الدوائية ضمن حملة (سلامة قلبك للوقاية من الامراض القلبية والوعائية) ان معدل انتشار ضغط الدم 39 بالمئة لجميع المشاركين في الحملة.
- وبينت الدراسة التي اعلنت نتائجها اليوم الاثنين في مؤتمر صحافي خصص لهذه الغاية، ان5ر34 بالمئة من المشاركين فيها لديهم أحد أفراد الأسرة مصاب بمرض في القلب و3ر52 بالمئة عندهم اقارب يعانون من السكري.
- وكشفت الدراسة التي اجريت في محافظات عمان واربد والزرقاء على مواطنين ضمن الفئة العمرية25 عاما فما فوق، أن أكثر من90 بالمئة من المواطنين يعرفون بخطورة ارتفاع ضغط الدم والسكري والكوليسترول بالتسبب بالإصابة بأمراض القلب، ولكن هذا لا ينطبق على ممارساتهم للوقاية من هذه الأمراض اذ أن نسبة كبيرة منهم8ر41 بالمئة لم يقوموا بقياس ضغط الدم خلال السنة الماضية. وبينت الدراسة كذلك ان7ر52 بالمئة من المشاركين لم يقوموا بفحص سكر الدم وان4ر70 بالمئة لم يجروا فحص الكوليسترول ايضا خلال العام الماضي

Hypertension: The Silent Killer





CRITICAL POINT!

Hypertension- asymptomatic

Morbidity and mortality due to end organ damage

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

Doctor notes on the pervious slide:

1. Maintenance of adequate perfusion pressure- critical
    a. Too low- inadequate nutrients, oxygen, removal of metabolic products
    b. Too high- organ damage, esp. heart, brain, kidney, eyes
    A. BP one of most closely controlled physiological variables
        a. multiple, redundant mechanisms- reflexes -To maintain blood pressure over the long term
2. Hypertension= pathology in one or more control mechanisms
    A. altered set point for BP control (resetting to higher pressure)
        1. defended by control mechanisms
        2. Often necessitates multiple pharmacological therapies
3. Cause of morbidity/mortality
    A. end organ damage
        1. myocardial infarction
        2. stroke
        3. kidney failure
4. Therapy=
    a. Life style
    b. Pharmacological Therapy
5. Therapeutic GOAL- Reduce CO and/or TPR

Hypertension as a disease

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

JNC 6 Category	SBP/DBP	JNC 7 Category
Optimal	< 120/80	**Normal**
Normal	120–129/80–84	**Prehypertension**
Borderline	130–139/85–89	
Hypertension	≥ 140/90	**Hypertension**
Stage 1	140–159/90–99	Stage 1
Stage 2	160–179/100–109	Stage 2
Stage 3	≥ 180/110	

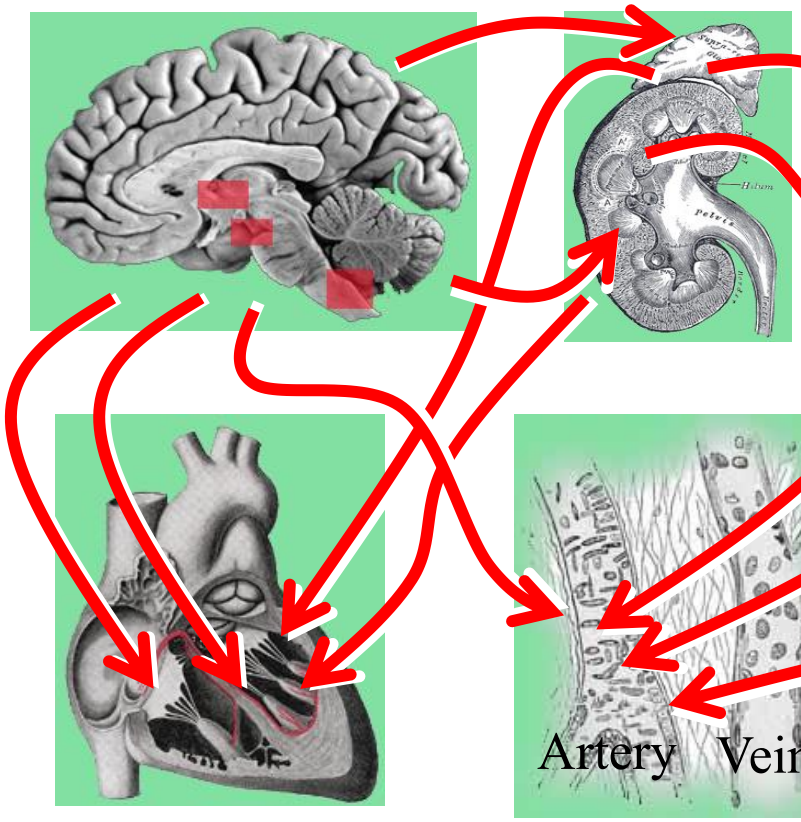
Lifestyle Modification

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

Doctor note in this slide : Weight reduction + DASH (dietary approach to stop hypertension) is equivalent to 1-2 antihypertensives

Mechanisms Controlling CO(cardiac output) and TPR(total peripheral resistance)

1. Neural
   SymNS
   PSNS



2. Hormonal
   Renal
      Ang II
   Adrenal
      Catecholamines
      Aldosterone

3. Local Factors

Review-

Major Mechanisms of BP control-

a. Neural- control of autonomic nervous system (PSNS, SymNS)

b. Vasoactive hormones

1. Controlled by CNS

a. vasopressin;

b. adrenal catecholamines; (SymNS activation)

c. renal renin (SymNS activation)

2. Systemic control

a. renal renin release (renal perfusion pressure; Na+

c. Local Factors

1. endothelial agents- derived from endothelial cells in arterioles

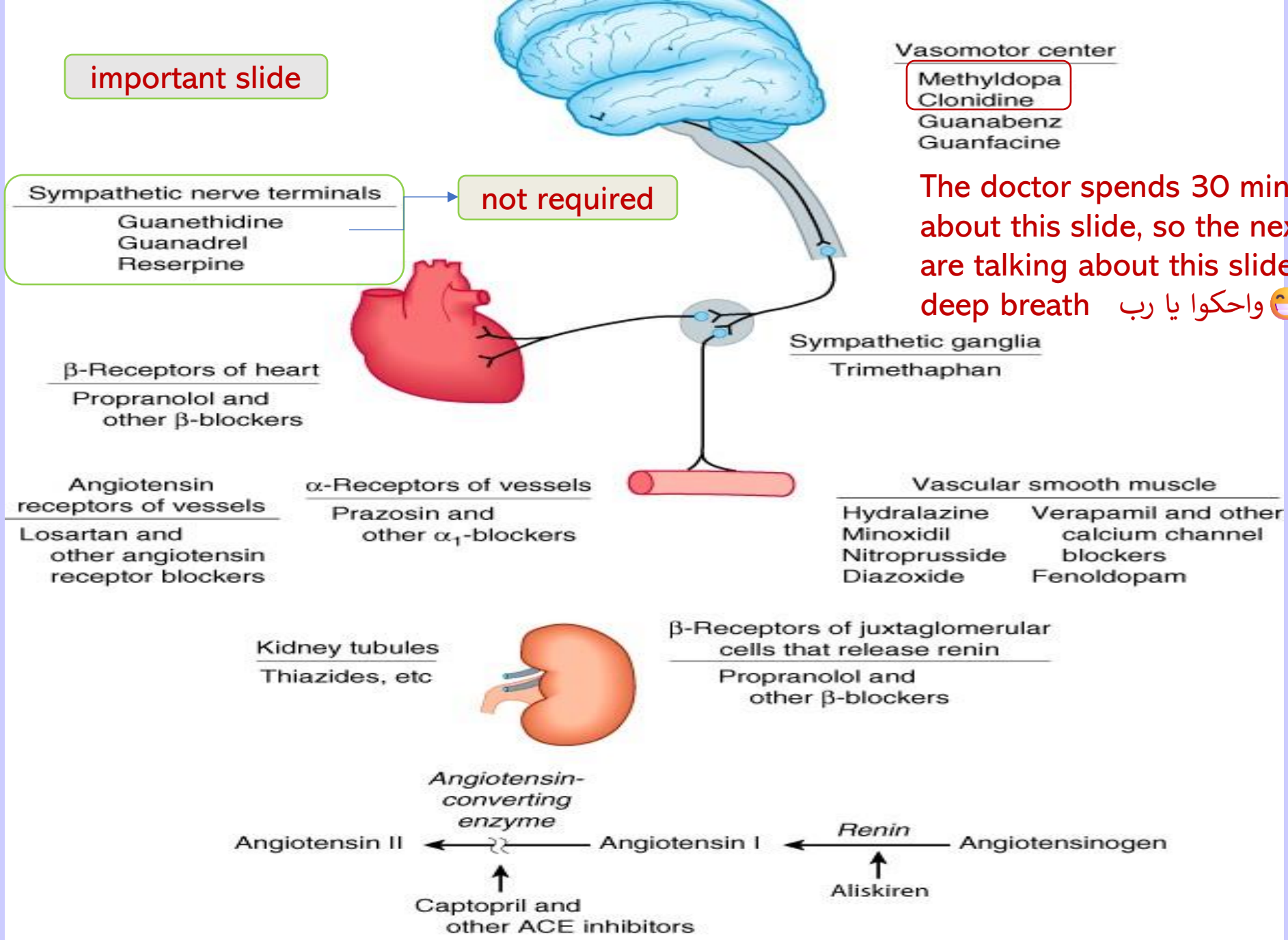
2. arteriolar gas concentration- circulating 0o, CO2, H+

2. All interact to control blood pressure

3. Targets of antihypertensive therapy

- There are three main factors that regulate blood pressure: neural, hormonal, renal, and local factors. Local factors are influenced by neural and renal activity.
- In the neuronal regulation, it is moment-to-moment. There are baroreceptors that trigger a reflex, and this reflex helps regulate blood pressure instantaneously.
- The renal angiotensin-aldosterone system is well-known to all of you :) , and it plays a key role in long-term blood pressure regulation.
- In the local factors, there are substances like nitric oxide, and calcium, all of which are involved in the contractility of vessels. These factors control vessel tone at specific moments, but ultimately, much of this local control is influenced by neural and hormonal regulation.

important slide



The doctor spends 30 min talking about this slide, so the next 10 slides are talking about this slide. Take a deep breath واحكوا يا رب 😁😭

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

- The goal is to increase hypotension and reduce hypertension to be around 120/80 mmHg
- We are satisfied with the elderly patient's blood pressure being 150/90 mmHg. (According to AHA)

- The efficacy of antihypertensive drugs is not intended to be very high, and we do not want them to be overly effective. If antihypertensive drugs are too potent, they can cause hypotension, which may lead to tachycardia and other complications. In reality, we produce an antihypertensive effect that is limited in terms of efficacy.

- If a patient's blood pressure is 200/120 mmHg, there is no single agent that can achieve your target. None of the available drugs will bring you to your target, (whether in the general population with a typical blood pressure of 130/90 mmHg or less, or in elderly patients with a blood pressure of 145/90 mmHg) whatever the number is. Therefore, we combine different antihypertensive drugs together to effectively manage blood pressure and reach the target.

- In pharmacology, in reality, we combine different antihypertensive agents to achieve the desired blood pressure reduction. For example, one drug may lower blood pressure by 10 mmHg, another by 10 mmHg, and a third by 5 mmHg.(additive activity)

- Why is a single agent not enough? Because there is a 1.Cmax (maximum concentration), and 2.side effects greatly influence our choice of treatment. Therefore, it's crucial to understand how antihypertensive drugs work, as we will be using them. In fact, it is rare to find a patient over the age of 60 in Jordan who is not on at least three antihypertensive drugs.

- The good news is that many antihypertensive drugs are also used to treat other cardiovascular conditions, such as angina, heart failure, and arrhythmias.

- Why are the same drugs used for different conditions? Because they all work on key cardiovascular factors such as cardiac output, peripheral resistance, the renal angiotensin system, preload, and afterload. These factors are interconnected, and by targeting them, the drugs can address multiple cardiovascular conditions.

- We divide antihypertensive drugs into three main categories: centrally acting drugs that target the sympathetic nervous system or the nervous system in general, renal-active drugs that affect kidney function, and local agents .

- These drugs [اللي حكينا عنهم مش مطلوبين بالصورة الي فوق] reduce the synthesis or release of norepinephrine in neurons, leading to lower levels of norepinephrine being released into the synaptic cleft. We don't use them.

- The Vasomotor Center is important . Remember, Alpha-2 receptors play a key role in feedback inhibition of sympathetic activity. In hypertension, we want to reduce sympathetic flow. So, we stimulate alpha-2 receptors. My name is alpha-2 agonist, even though I'm considered an antihypertensive drug.
  عشان ما تخربطو :)

- Alpha-2 receptors help manage high blood pressure by reducing norepinephrine release, which lowers heart rate and relaxes blood vessels, decreasing sympathetic activity and blood pressure.

sympathetic nervous system

1)Vasomotor center: 🧠 (alpha-2 agonists)

- Methyldopa and Clonidine are alpha-2 agonists that inhibit sympathetic outflow, which affects the entire cardiovascular system.
- By reducing the release of norepinephrine, beta-1 receptors are less stimulated, and alpha-1 receptors are not activated, leading to vasodilation, a reduction in cardiac output, and decreased contractility of the heart.

- Beta-1 receptors are located in the SA and AV nodes, as well as in myocardial cells, so inhibiting them reduces the heart's chronotropic (rate) and inotropic (contractility) activities. A negative chronotropic effect means a decrease in heart rate, and a negative inotropic effect means a reduction in stroke volume.

- Although alpha-1 inhibition occurs more slowly, these two drugs are effective and generally do not cause orthostatic hypotension (low blood pressure happens when a person stands up, symptoms → dizziness, weakness and other).

- The only side effect of Clonidine is sedation. Also, it does not cause depression. It is available, but its use is limited because better drugs have been developed. However, it is still used for patients with resistant hypertension.

- Methyldopa actually inhibits the production of dopamine and catecholamines, which leads to a decrease in the amount of norepinephrine in neurons. This drug is particularly useful because it is the drug of choice for managing gestational hypertension during pregnancy.

- Since patients will be taking these medications for a long time, physiological changes can occur, leading to resistance or tolerance. The difference between the two is that tolerance refers to a reduction in the response to a drug over time, while resistance means the loss of response entirely.

- When a receptor is stimulated for a prolonged period, the body may respond by downregulating or desensitizing the receptors because it starts to recognize the drug as a potentially toxic substance. As a result, the body decreases the number of available receptors to protect itself.

- In such cases, increasing the dose of the drug might help overcome tolerance. For example, with Clonidine, increasing the dose might be sufficient to manage tolerance. However, when the drug is stopped, the feedback inhibition decreases because the number of receptors has already been reduced.

- This can lead to rebound hypertension. As a result, the patient may experience tachycardia and hypertension. If the patient is susceptible, this could even lead to severe complications such as stroke, cerebral hemorrhage, arrhythmias, or worsening of the overall condition.

- An abrupt or sudden stop of Clonidine is not recommended, whereas it is generally safe to discontinue Methyldopa because of the differences in their mechanisms of action.

- Therefore, the definition of an alpha-2 agonist applies to Clonidine, not Methyldopa, because Clonidine works as an alpha-2 adrenergic agonist, which directly stimulates alpha-2 receptors in the brain to reduce sympathetic outflow.

- On the other hand, Methyldopa works by reducing the synthesis of catecholamines, specifically norepinephrine. When Methyldopa is stopped, the body can usually return to its normal state more easily, as the mechanism is more related to the reduction of neurotransmitter production rather than direct receptor stimulation.

2)Heart beta blocker 💔 (beta antagonist)

- By blocking beta receptors, you decrease both contractility and heart rate. However, the patient may experience fatigue and masking of hypoglycemia symptoms (main side effects), particularly the awareness of hypoglycemia.

- If a patient develops hypoglycemia, normally they would experience tachycardia as a compensatory response. But since beta-blockers are blocking the beta receptors, tachycardia may not occur, and the patient may not feel the symptoms of hypoglycemia as they would without the medication.

- Beta blockers are good drugs for treating hypertension, but they are used more commonly for managing angina and heart failure. This is where the dose varies, because the dose for treating angina is different from the dose for treating heart failure, which is also different from the dose used for hypertension.

- Why? Because if we use as hypertensive drug, we need a large dose, increasing the side effects, such as fatigue (the sympathetic system is not responding since it depend on beta-1 and beta-2)

- A) Beta-1 selective : atenolol
- B) Beta-1 non-selective: propranolol (inhibit beta-1 and beta-2),Carvedilol inhibit (beta-1, beta-2 and alpha-1)
- Have different uses(hypertension, angina, heart failure, arrhythmia, migraine or murmur) but you can find them in every house 🏠

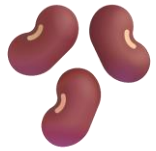
3)Alpha receptors of vessels (alpha antagonist) 🩸

- Prazosin and Doxazosin are Alpha-1 receptors antagonist

- blood vessels dilate (widen), which leads to lower blood pressure. This makes alpha-1 blockers useful in the treatment of hypertension

- Main side effect → Orthostatic hypotension that happen in the arteries (mainly, because they have more alpha-1 receptors and are more involved in contraction than veins) and the veins: A sudden drop in blood pressure when standing up, especially after the first dose .and they are often started in a hospital setting due to the risk of orthostatic hypotension.

- First-dose syncope (or first-dose hypotension) is a significant drop in blood pressure that can occur after the initial dose of alpha blockers. This effect can lead to dizziness, lightheadedness, or fainting (syncope) due to the sudden decrease in blood pressure, that's why alpha-1 antagonists only given in hospital under surveillance 👀, for two hours until the renin-angiotensin system and other system start work and compensate.

the Kidney (Renal): 

Now we finish talking about groups that are related to sympathetic nervous system (Alpha-1 blocker, Beta-1 blocker, Alpha-2 agonist).

Let's talk about the bigger group now, the Kidney (Renal):

- The simplest idea in kidney is the presence of diuretics.
- Every blood pressure depends on blood volume, decrease in blood volume will decrease blood pressure.
- 1)Thiazides primarily work by decreasing blood volume (though not always). When blood volume decreases, sodium is excreted, and the drug's activity is related to sodium content. This is why patients are advised to avoid excessive salt intake.
- Giving diuretic --> secreting water --> lowering blood pressure

2) We also act on a system called RAAS (renin-angiotensin-aldosterone system), take a look at slide 9.

A) We act on renin by a drug called "Aliskiren" (it is not effective so forget about it).

B) ACE inhibitors (ACEI) "captopril"

We inhibit the transformation of Angiotensin I into Angiotensin II, there is no vasoconstrictor like Angiotensin II, it is the strongest vasoconstrictor in the body, it works on arteries and veins.

- Angiotensin I in converted into Angiotensin II by an enzyme called Angiotensin converting enzyme (ACE), we inhibits this enzyme by a drug called captopril (or any other drug ending in "-pril"; they are all the same).

- ACE is responsible for the metabolism of bradykinin, an inflammatory mediator; therefore, inhibiting ACE will prevent the breakdown of bradykinin. In terms of hypertension, it is good because bradykinin will cause inflammation --> vasodilation --> good effect.

- The problem in inhibition bradykinin metabolism is that it accumulates in the upper and lower respiratory regions, leading to irritation toward cough (dry cough with irritation) so the first side effect of ACE inhibitors is Cough (10% of the population).

- If the patient very sensitive (especially naive patients) they might have high inflammation --> leakage of fluid --> causing Angioedema, the other prils could cause Angioedema as well (but at less percentage).
- Naive patients refer to individuals who are new to treatment with ACE inhibitors.

- Angiotensin II is a potent vasoconstrictor, and inhibiting its synthesis Might lead to an exaggerated effect, potentially causing First-dose syncope.

- So, the three side effects are: 1- Cough 2- Angioedema 3- First-dose syncope

- C) ARBs "losartan"
  - Now, instead of going into ACE inhibition story, we developed drugs called angiotensin II receptor blockers (ARBs), which act directly on the receptor itself. These drugs end with the suffix "sartan."

  - Why are "prils" used when we can act directly on the receptors? Prils are much better in terms of hypertension because of their effect on bradykinin, as well as their activity on ADH (antidiuretic hormone).

  - There is a connection between the kidney and the hypothalamus, which leads to a greater decrease in the release of ADH compared to ARBs. (ADH cause retention of water and sodium.)

😀 🤓 Side effects of ACEI عشان يتجنبوا ال ARB الدكاترة بريحوا راسهم وبعطوا

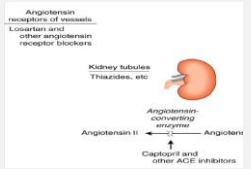
Vascular Smooth Muscles 💪 (important drugs)

- Calcium Channels Blockers “verapamil”
- are the most important, they act on calcium channels --> decreasing the entrance of calcium --> relaxation of vessels. mostly our effect on arteries more than veins.

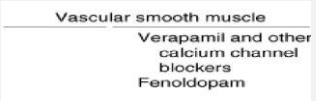
- ACEI and Calcium Channel Inhibitors are the most used drugs.

- In African Americans, the RAAS functions differently in terms of activity, resulting in stronger vessel contractility. Calcium Channel Blockers are preferred for these patients because they respond better to them than to diuretics, ACE inhibitors, or ARBs.

- First line therapy of hypertension in Jordanian --> diuretics, ACE inhibitors, or ARBs

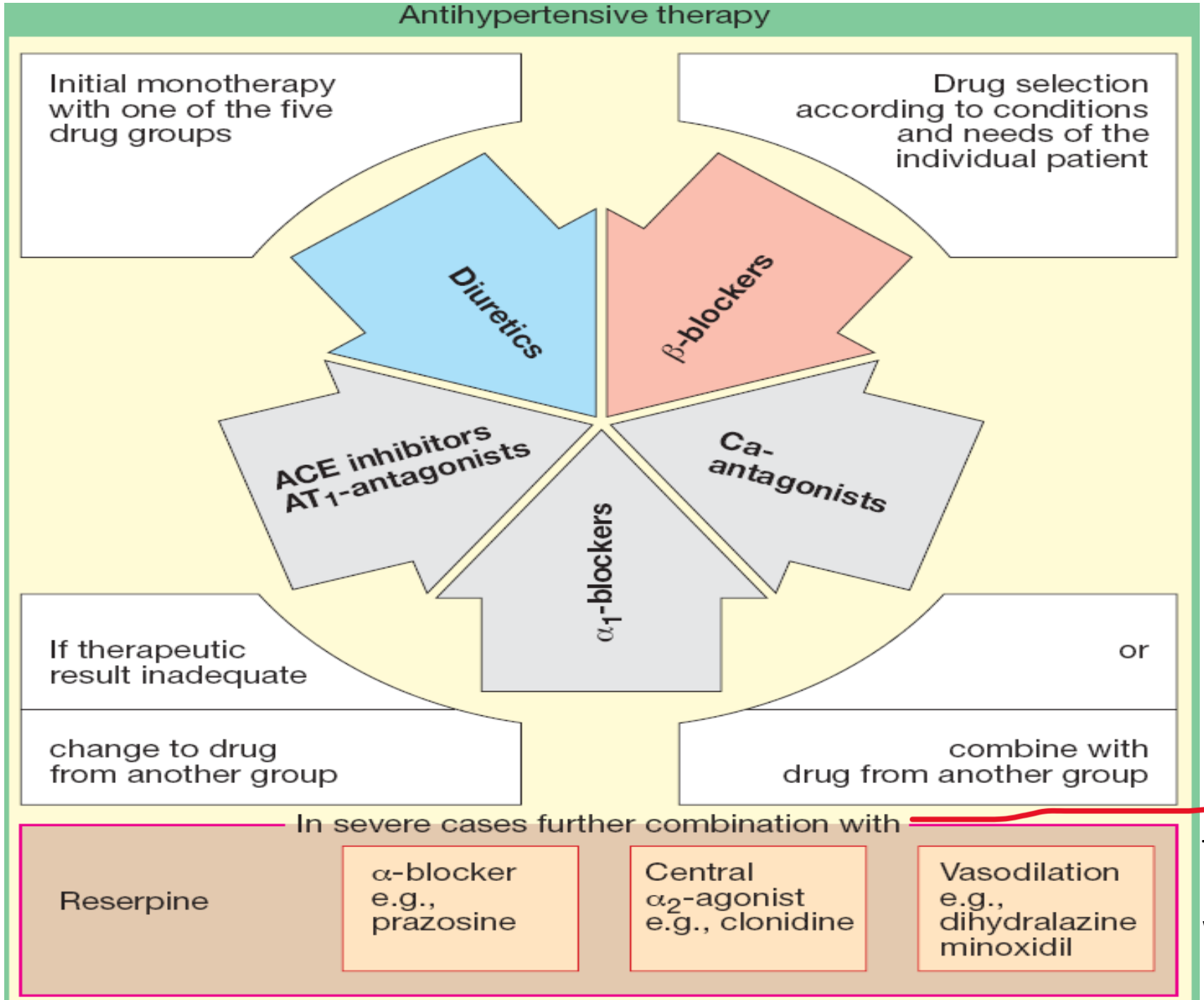


- First line therapy of hypertension in African Americans --> Calcium Channels Blockers “verapamil”



- Different physiology and increased contractility lead to stronger vasoconstriction, which is why calcium channel blockers are more effective in African Americans.

- Hydralazine is the drug of choice for heart failure in African Americans, whereas ACE inhibitors are preferred for Jordanians.
- African Americans starts with Hydralazine because it is vasodilator. Race Based Description
- The drug of choice for congestive heart failure is a combination of hydralazine and one of the nitrates, both of which are vasodilators.
- Nitroprusside relies on nitric oxide and has equal activity on both arteries and veins, although it may be slightly more effective on veins. This introduces the concept of preload reduction, which is essential in the management of angina.
- Reduction of preload refers to decreasing the amount of blood returning to the heart (specifically, the ventricles) before it contracts. Preload represents the initial stretching of the cardiac muscle fibers at the end of diastole (when the heart is filled with blood).



This might differ in black Americans. Why? لانه الي كتبوا الكتاب امريكان 😅

- We combine drugs together, How many of them? In some patients all of them, Why? Because they have or develop resistance.

- For example:

- For a patient with prostate hypertrophy, an alpha-1 antagonist can help by relieving prostate enlargement and reducing the constriction on the urethra.

- So, if the patient has prostate hypertrophy and resistant hypertension, he takes all of these drugs. Why? Because :

- Diuretics --> decrease blood pressure by 10 mmHg
- Beta blockers --> decrease blood pressure by 7 or 8 mmHg
- ACEI --> decrease blood pressure by 20 mmHg
- Calcium channel inhibitors --> decrease blood pressure by 20 mmHg
- Alpha 1 blockers --> for hypertrophy

- Almost decrease blood pressure by 60 mmHg

- This patient has Orthostatic Hypotension, which occurs when standing up from a sitting position, causing a rapid drop in blood pressure that leads to the patient falling immediately.

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

→ Not required

- Most outcome trials base antihypertensive therapy on thiazides

JNC 7 Express. JAMA. 2003 Sep 10; 290(10):1314

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.

Thiazide Diuretics

- Diuretics lower blood pressure primarily by depleting body sodium stores.
- Initially, diuretics reduce blood pressure by reducing blood volume and cardiac output; peripheral vascular resistance may increase.
- After 6–8 weeks, cardiac output returns toward normal while peripheral vascular resistance declines.
- Sodium is believed to contribute to vascular resistance by increasing vessel stiffness and neural reactivity, possibly related to altered level of sodium.

Very IMPORTANT slide (THIS AND THE NEXT ONE) to understand MOA for Thiazide, READ IT PLZ !! 🥺

Initial Effect of Thiazides:

- When a patient first starts taking a thiazide, the drug works in the distal tubules of the kidneys, where it blocks sodium reabsorption. This action causes more sodium to be excreted in the urine. Since water follows sodium, this also leads to water loss, reducing blood volume and initially lowering blood pressure.

Adaptation Over Time

- After about 6–8 weeks, the body begins to adapt to the effects of thiazides. The kidneys, recognizing the ongoing loss of sodium, try to compensate by activating alternative pathways to retain sodium. One of these pathways involves the sodium-calcium exchange channel (or sodium-calcium exchanger). Through this mechanism, the kidneys can retain some sodium that would otherwise be lost due to the thiazide's effect.

Why This Matters

- This sodium-calcium exchange allows the kidneys to gradually increase sodium reabsorption, even in the presence of a thiazide. This means:

- The initial diuretic effect (the sodium and water loss) becomes less pronounced over time.
- Blood volume partially returns to normal because the body is holding onto more sodium and water again.

Lasting Blood Pressure Control Despite Adaptation Despite this adaptation:

- Despite this adaptation, thiazides continue to help control blood pressure due to a secondary vasodilatory effect on blood vessels. This effect lowers peripheral vascular resistance (the resistance in small arteries), which helps keep blood pressure low, even though the kidneys are reabsorbing more sodium than they did initially.

You might now ask why sodium retention in the adaptive stage does not increase blood pressure, while consuming salt does.

- Very simple, The difference between sodium in the adaptive state (after the body has adjusted to thiazides) and sodium from dietary salt intake lies in how much sodium is retained.

In Summary:

- Thiazide diuretics work by inhibiting sodium reabsorption in the distal tubules of the kidneys, leading to increased sodium and water excretion, which lowers blood volume and blood pressure. Over time (6-8 weeks), the body adapts by activating the sodium-calcium exchanger, retaining some sodium to prevent excessive loss, but this adaptation does not fully reverse the blood pressure-lowering effect, as thiazides also induce vasodilation, relaxing blood vessels.

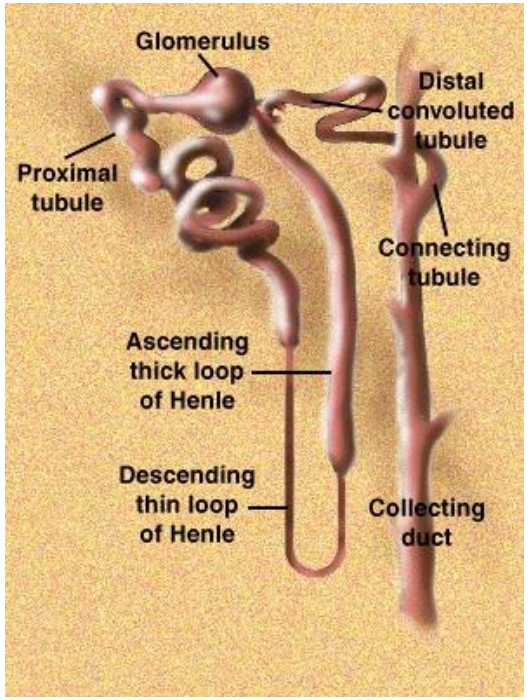
- However, excess salt intake overwhelms the kidneys' ability to regulate sodium and water, leading to increased blood volume and counteracting thiazide's effects on blood pressure.

Diuretics (cont)

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

Notes from the doctor in the slides

1. Site of Action
    a. renal nephron
    b. diuretic agents work at different segments of nephron
2. Mechanism of Action
    a. all diuretics decrease sodium reabsorption
    b. act on renal systems, transporters, hormones, ion channels
    c. Where Na+ goes, Water will surely follow
3. Effect on cardiovascular system
    a. acute decrease in plasma volume
    b. chronically, decrease in TPR, CO returns to normal
        mechanism unknown
    c. often used to compensate for Na+ retaining reflex induced by other antihypertensive agents.

A dental student came to the hospital with a blood pressure of 142/91 mmHg, so I started treatment by giving him diuretics.

Mechanism of action:

- Giving thiazide will cause diuresis initially, but tolerance to this diuretic effect will occur. Why is that?

- Thiazide work on distal tubules, on sodium channels and potassium channels, inhibiting the reabsorption of sodium, decreasing water retention, which will cause diuresis.

- At first, thiazide diuretics increase urinary sodium (Na+) excretion and urinary water excretion, leading to a decrease in extracellular fluid and/or plasma volume.

- When sodium reabsorption is inhibited by thiazide diuretics, other channels, such as sodium-calcium exchangers, may compensate by reabsorbing sodium. So, with time, water and sodium will return to normal, but blood pressure will remain decreased. Why?

توضيح في السلايد القادم لنهاية هذه الفقرة

- During the first 6-8 weeks, sodium is removed from the vessels, leading to a depletion of sodium in the patient's body. Stopping the drug will cause the body to return to its normal state. Therefore, the patient must continue taking the drug and avoid consuming salt. This is one of the most important reasons why we advise hypertensive patients not to take salt: because salt (sodium) will rebuild sodium levels in the vessels. Because it will look like that you are giving the patient B12, folic acid, sodium, which will lead to the back of contractility.

- The sentence is drawing an analogy: consuming excess salt while on thiazides is like replenishing the body with substances like B12, folic acid, or sodium. Just as these substances restore normal bodily functions, salt (sodium) restores sodium levels in the blood vessels, which counteracts the blood pressure-lowering effect of thiazides. This leads to increased blood volume and higher heart contractility, causing the heart to work harder, which could raise blood pressure and reverse the benefits of the medication.

- Blood pressure will decrease to 131/85 mmHg without side effects (such as orthostatic hypotension, reflex tachycardia, angioedema, or headache). Therefore, this drug remains the First-line Therapy to this day, as it has a nice effect with no side effects.

- Orthostatic Hypotension: A drop in blood pressure when standing up, causing dizziness or fainting.
- Reflex Tachycardia: An increase in heart rate in response to a drop in blood pressure, often to compensate for low blood volume.
- Angioedema: Swelling of deeper skin layers, typically around the eyes, lips, and throat, which can be a side effect of certain medications and may cause difficulty breathing.

Thiazide diuretics

- 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 continues to increase at doses many times greater than the usual therapeutic dose.

- it is not dose dependent --> increasing the dose of the drug may not result in the expected increase in its intended effect, as other factors in the body might limit or alter the response to the drug.

- Thiazides are not dose-dependent because their effect plateaus after a certain dose. Once the kidneys' sodium reabsorption mechanisms are fully inhibited, increasing the dose further does not significantly enhance the diuretic effect. This limits the benefit of higher doses and increases the risk of side effects without improving results.

Thiazide diuretics

- **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:**

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

  - **Hydrochlorothiazide, 1-2 times a day.**

IMPORTANT DRUG:

- Hydrochlorothiazide is not dose-dependent because its diuretic effect plateaus after a few weeks, as the body adapts to sodium depletion, and increasing the dose does not further enhance the therapeutic effect. Giving the drug with salt --> useless effect of the drug

Thiazide diuretics

Adverse effect includes:

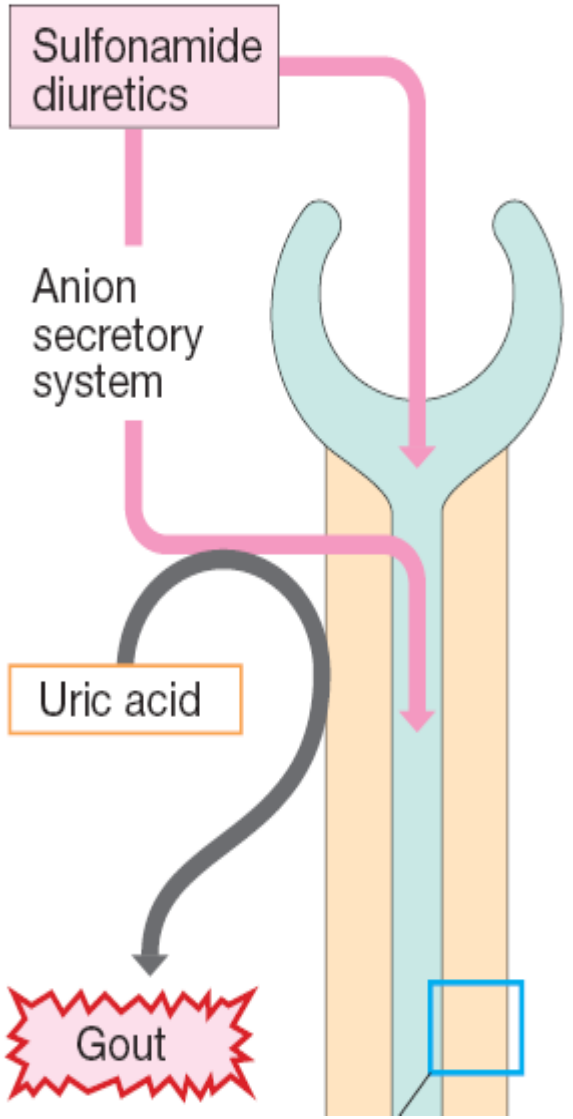
- **hypokalemia (70% of patients), thus a potassium supplementation is recommended.**

  In reality, the effect is minimal because, as we mentioned, the distal tubules are responsible for only 5%-7% of sodium reabsorption. Therefore, hypokalemia is not typically clinically manifested.

- **hyperuricemia because of drug drug interaction on the excretion site (70% of patients), result from the inhibition of renal tubular secretion of uric acid.**

  Uric acid and thiazides compete for the same excretion site, which can lead to the reabsorption of uric acid, resulting in hyperuricemia. This typically takes a long time (10 to 15 years), unless the patient already has gout, in which case thiazides are not prescribed.

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



Side effect

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

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

The second reason why I should avoid taking excess salt is that continued salt intake inhibits sodium reabsorption, which in turn inhibits potassium reabsorption, leading to potassium depletion.

So, if anyone ask me why hypertension patients should not take salts?
1- it increases tension
2- make drug drug interaction causing rebuild of sodium in vessels
3- increases secretion of potassium --> increasing hypokalemia

Loop diuretics

Same idea but they work on loop of Henle.

Loop of Henle has pumps that are responsible for reabsorption of sodium (25%), so this is a substantial effect.

- Furosemide (Lasix) , ethacrynic acid, and bumetanide, produce greater diureses than thiazides, but they have weaker anti-hypertensive effect and cause severe electrolyte imbalance.

Loop diuretics drugs are not good drugs for hypertension unless in 2 situations: (it's useless to use Thiazide so we use loop diuretics)

- Typically only beneficial in patients with

1. resistant HTN(hypertension) and evidence of fluid;
2. effective if CrCl (creatinine clearance) <30 ml/min (Kidney failure)

1- Too much fluid in their bodies

2- A Glomerular Filtration Rate (GFR) under 30 is problematic because, for Thiazides to work, they must first be secreted and then bind to their receptors from that side.
If the GFR is under 30, thiazide is not even secreted, so it can't bind to the pump inhibiting it.

- MUST be dosed at least twice daily (Lasix = Lasts six hours)
- Administer AM and lunch time to avoid nocturia

Activity of Loop diuretics:

- They inhibit reabsorption of water, sodium, magnesium, calcium, and potassium.
- Causing: Hyponatremia, Hypomagnesemia, Hypocalcemia, Hypokalemia, and hypovolemia. Respectively
- Loop diuretics drugs:
- Furosemide (Lasix) , Ethacrynic Acid, and Bumetanide. The difference between them is that Furosemide has sulfur, and some people have allergy to sulfur, so patient with Furosemide sensitivity is given Ethacrynic Acid.

- **Adverse effects of the loop diuretics summarized in**

  -Ototoxicity, specially when used with aminoglycosides.

  -hyperurecemia.

Hypocalcemia **loop**
hypercalcemia **thiazide**

Nocturia: loop diuretics are not preferred to be administered at night, due to their relatively high diuretic effects (when high amounts of Na+ are excreted)

Loop diuretics are very common to have drug-drug interactions especially with aminoglycosides (like Gentamicin and other drugs that end with the suffix: -micin)

Hypocalcemia in loop diuretics: because loop diuretics are not usually followed by compensatory actions (unlike thiazide which causes hypercalcemia as a late compensatory mechanism from the body to try to correct the initial Na+ loss—> drawing Ca2+ back to the body along with Na+ reabsorption)

Hypercalcemia of thiazide—> so we use thiazide in cases of calciuria (increased Ca2+ concentration in the urine)

ولذاكَ يَهوَى الموتَ طِفلٌ ثائرٌ إنّ الرّدى – في شَرْعِهِ – أقدارُ
شتّانَ بينَ عقيدةٍ لا تَنْحَنِي وعقيدةٍ عَرّابُها الدّولارُ

Additional sources
1- MOA of thiazide paper
2- MOA of thiazide paper

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	22	bradykinin	Bradykinin metaboldim
V2→V3			added slides : 45+46

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!