

# CARDIOVASCULAR SYSTEM

SUBJECT : \_\_\_\_\_

LEC NO. : 6 \_\_\_\_\_

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وَقُلْ رَبِّ زِدْنِي عِلْمًا



SCAN ME!

# CVS- Pharmacology 6

# Antihypertensive1

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# Hypertension

- Blood pressure is elevated when systolic blood pressure exceed 120 mm Hg and diastolic blood pressure remains below 80 mm Hg.
- Hypertension occurs when systolic **blood pressure exceeds 130 mm Hg** or diastolic **blood pressure exceeds 80 mm Hg** on at least two occasions.
- Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system.

\*هسا مريض الضغط ما بقدر اشخصه من اول مرة ،، لازم يضل يسجل قراءات (multiple reading) لاسبوع كامل تقريبا على مدار 3 مرات باليوم (مثلا)،، طب

ليه؟؟؟ لانه في ناس عندها white coat HT ،، يعني

هو مش مريض ضغط بس لما يشوف دكتور

لابس لاب كوت يرتفع ضغطه

\*هسا انا ليه بدي اعمل تريمنت ومعظمهم ما عندهم  
اعراض بس ممكن بصيبيهم صداع ، عشان احميه  
من ال complications لإله

يعني لما ناخذ اكثر من قراءة كلهم  
بكونو عاليين

# Hypertension

- The diagnosis of hypertension is based on repeated, reproducible <sup>↑</sup> measurements of elevated blood pressure
- Although many patients have no symptoms, chronic hypertension can lead to heart disease and stroke<sup>①</sup>, the top two causes of **death** in the world. Hypertension is also an important risk factor in the development of **chronic kidney disease**<sup>②</sup> **and heart failure**<sup>③</sup> “ **silent death** “ ال الضغط هو ال
- only one-half of Americans with hypertension had adequate blood pressure control.  
الهدف
- **Effective pharmacologic lowering of blood pressure has been shown to** prevent damage to blood vessels and to substantially reduce <sup>②</sup> morbidity and mortality rates. <sup>+</sup>

# Hypertension

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Elevated	120– 129	or	<80
Stage 1 hypertension	130– 139	or	80–89
Stage 2 hypertension	≥140	or	≥90

\*\*الارقام بالزبط مش مطلوبة منا،،،+احنا ما منعالج على حسب الرقم بل على حسب المريض شو عندو

The majority of current guidelines recommend treatment decisions **based on goals of antihypertensive therapy**, rather than the category of hypertension.



# Etiology of Hypertension

Although hypertension may occur secondary to other disease processes, more than **90% of patients have essential hypertension (hypertension with no identifiable cause)**.

**Risk factors:** بعضها بقدر الجيره وبعضها لا

- A family history of hypertension لا
- Age لا
- Non-Hispanic blacks لا العرف
- Diabetes لا
- Obesity, بقدر
- Environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking. بقدر



يعني يكون فيه معاه مرض معين ادى الى الضغط،،فَ بس يكون عندي **secondary causes** لازم اعرفه ونحاول نعالجه واحنا هون عم نحكي على نسبة 10%،،،بينما 90% يكون ال HT هو ال **essential**

# Physiologic Control of Blood Pressure

Cardiac output\* systemic vascular resistance

→

- $BP = \underline{CO} \times \underline{SVR}$

\* يعني انا اذا بدى اقل ال BP لازم اقل واحد من المعاملان او both

- $CO = HR \times \text{Stroke Volume (aka SV)}$

ال CO عشو بعمل كونترول heart rate و SV ف اذا بدى اقل ال CO رح اقل من الي بعمل عليهم كونترول

- Factors to be considered:

- Heart Rate
- Blood Volume
- Contractility ! الي بتأثر حال VR
- Arteriolar Constriction →

→ \* انا بدى اومرية تشدقل على  
هذول

# Mechanisms Regulating Blood Pressure:

①

## • Sympathetic Nervous System

- عن طریق → • Baroreceptors

②

## • Renin -Angiotensin – Aldosterone System

- Angiotensinogen → activation by renin بصیرله
- Activated by Renin → Juxtaglomerular cells
- Produced by JG cells of kidney
- بصیرلها افواز مس؟ • Increased by decreased renal blood flow
- Increased with  $\beta_1$  stimulation



# Baroreceptors

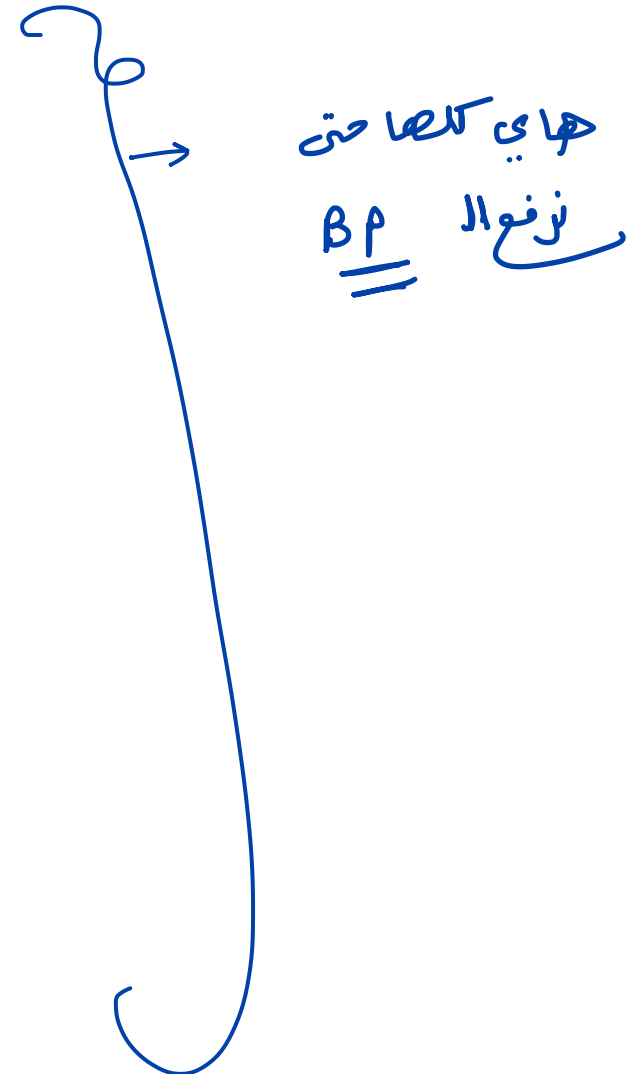
- Baroreflexes act by changing the activity of the sympathetic and parasympathetic nervous system.
- Baroreflexes are responsible for the **rapid, moment-to-moment regulation of blood pressure**.  
عبارة عن area فيها sensitive neurone في ال aortic arch + carotid sinus هذول بعمل sense لايتغير في ال BP
- A fall in blood pressure causes pressure-sensitive neurons (**baroreceptors in the aortic arch and carotid sinuses**) to send **fewer** impulses to **cardiovascular centers in the spinal cord**. This prompts a **reflex** response of **increased sympathetic and decreased parasympathetic** output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output. **These changes result in a compensatory rise in blood pressure.**  
كيف بشدقو؟  
النا شوبتقلا؟

بس تصيري  
ع بيصر حنا  
more  
 $\alpha + \beta$   
stimulation  
لو بعلو؟

تلخیصیں لیں فوٹے

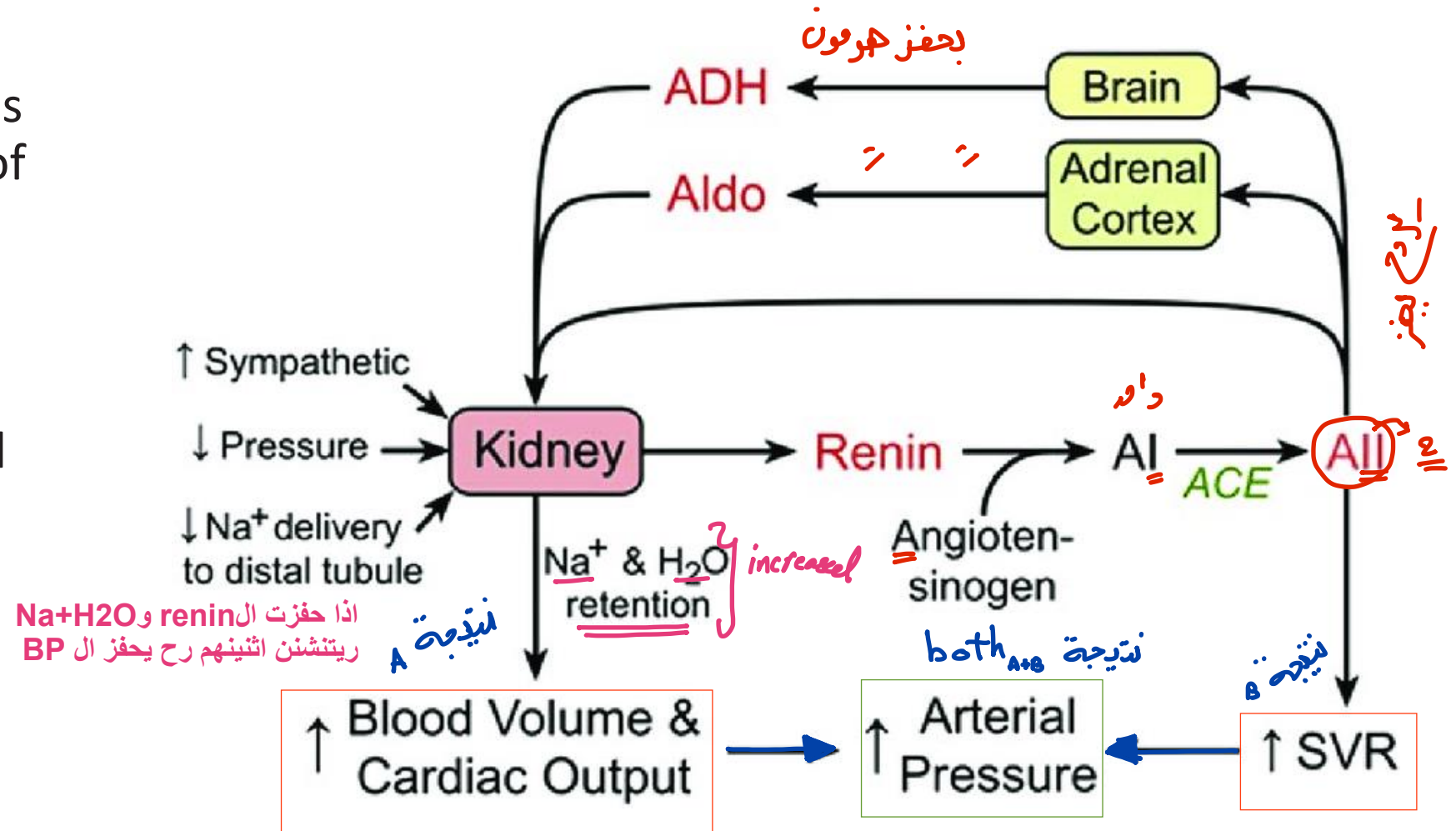
# Baroreceptors

- Falling blood pressure
- ↓
- Baroreceptors inhibited
- ↓
- Decreased impulses to brain
- ↓
- Decreased parasympathetic activity
- Increased sympathetic activity
- ↓
- Three mechanisms:
  1. Heart: increased heart rate and increased contractility
  2. Vessels: increased vasoconstriction
  3. Adrenal gland: release of epinephrine and norepinephrine (enhance heart rate, contractility, and vasoconstriction)



# Renin -Angiotensin – Aldosterone System

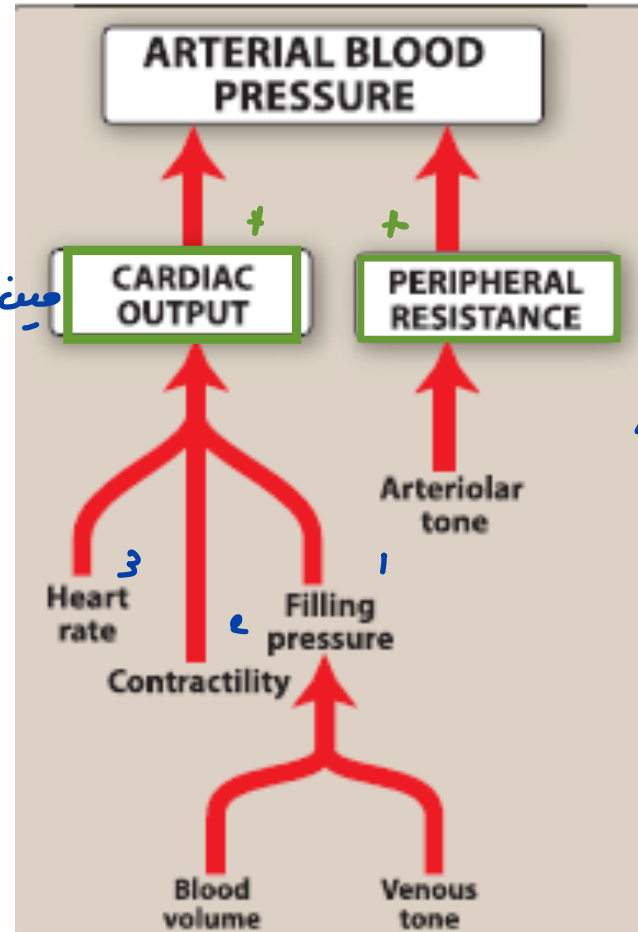
- The kidney provides long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure by releasing renin.



# Mechanisms Regulating Blood Pressure:

لفتنس اللى فوق

صين على تزيده؟



+ وحدة فيهم بتزيد  
مع ترفع ال BP

صين على تزيده

# Treatment Strategies

- The goal of antihypertensive therapy is **to reduce cardiovascular and renal morbidity and mortality.**
- The blood pressure goals a **systolic** blood pressure of **less than 130 mm Hg** and a **diastolic** blood pressure of **less than 80 mm Hg**.
- Current recommendations are to **initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker.**

على زحكي عندهم خلال المعاصرة و إلى جاي



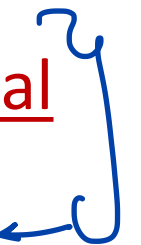
Initial drug therapy choice may vary depending on the guideline and concomitant diseases.

# Treatment Strategies

بس اعطيه دوا وما يجيب نتيجة كافية لازم اغيره حتى اقل من السايڊ ايفكت  
الي ممكن الدوا يكون عاملوا للمريضونعمل combined

- If blood pressure **is inadequately** controlled, a second drug should be added, with the selection based on minimizing the adverse effects of the combined regimen and achieving goal blood pressure. <sup>(1)</sup> <sub>(2)</sub>
- Patients with systolic blood pressure greater than 20 mm Hg above goal or diastolic blood pressure more than 10 mm Hg above goal <sup>150</sup> <sub>90</sub> should be started on two antihypertensives simultaneously. <sub>+</sub>
- Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with minimal adverse effects. <sup>(1)</sup> <sub>(2)</sub>

main goal



**Lifestyle Changes:**  
**Weight Reduction** ✓  
**Sodium Restriction** ✓  
**Alcohol Restriction** ✓  
**Exercise** ✓  
**Smoking Cessation** ✓

إذا غيرنا ال lifestyle للمريض ولسا ضغطه مرتفع لازم ابلش  
ب اول treatment

Continue Lifestyle Changes and initiate drug therapy

\* واذا بعد هذا الخطوة ما اقتصن؟

٣ حلول

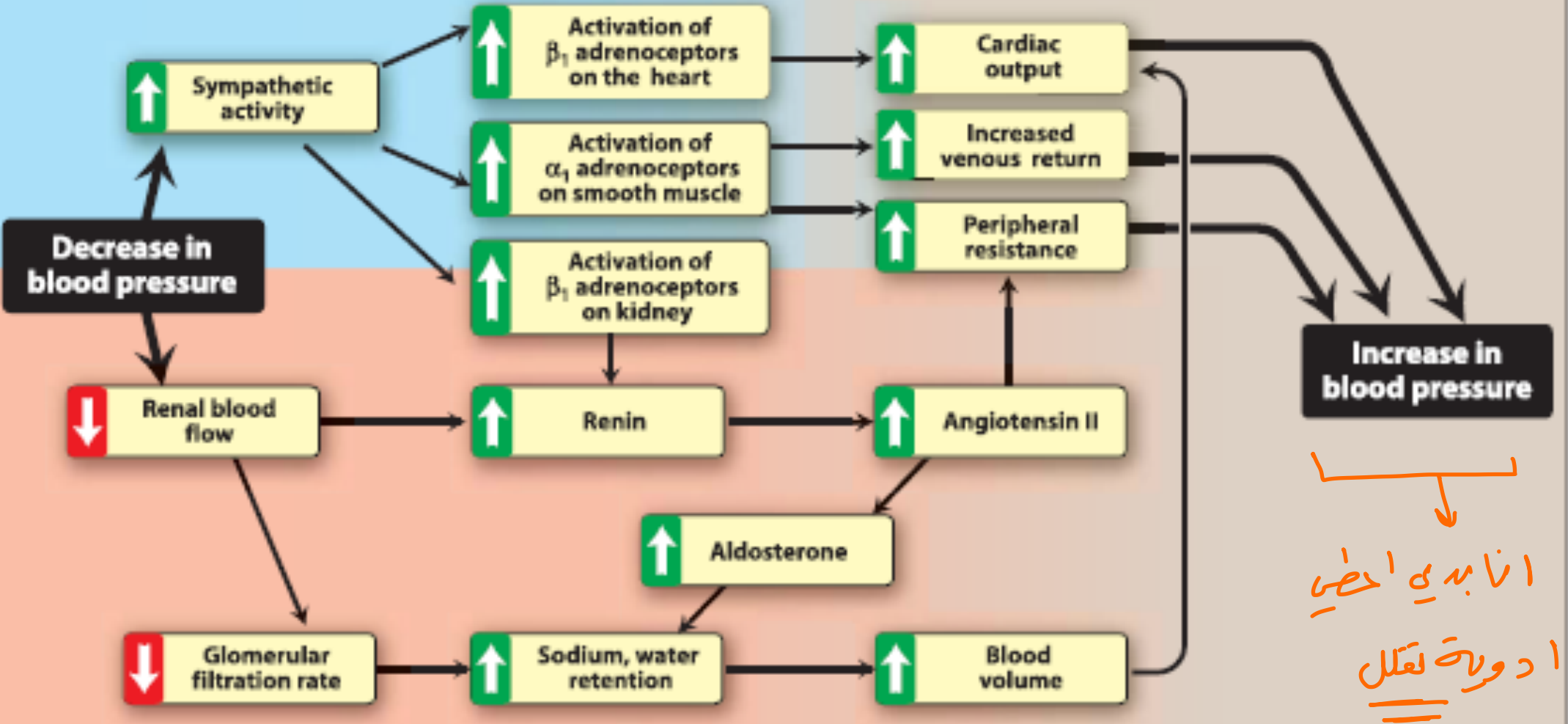
Increase drug dose ①

or Substitute another drug

② Or Add a second drug from a different class

تلخيص للقراءة

Response mediated by the sympathetic nervous system



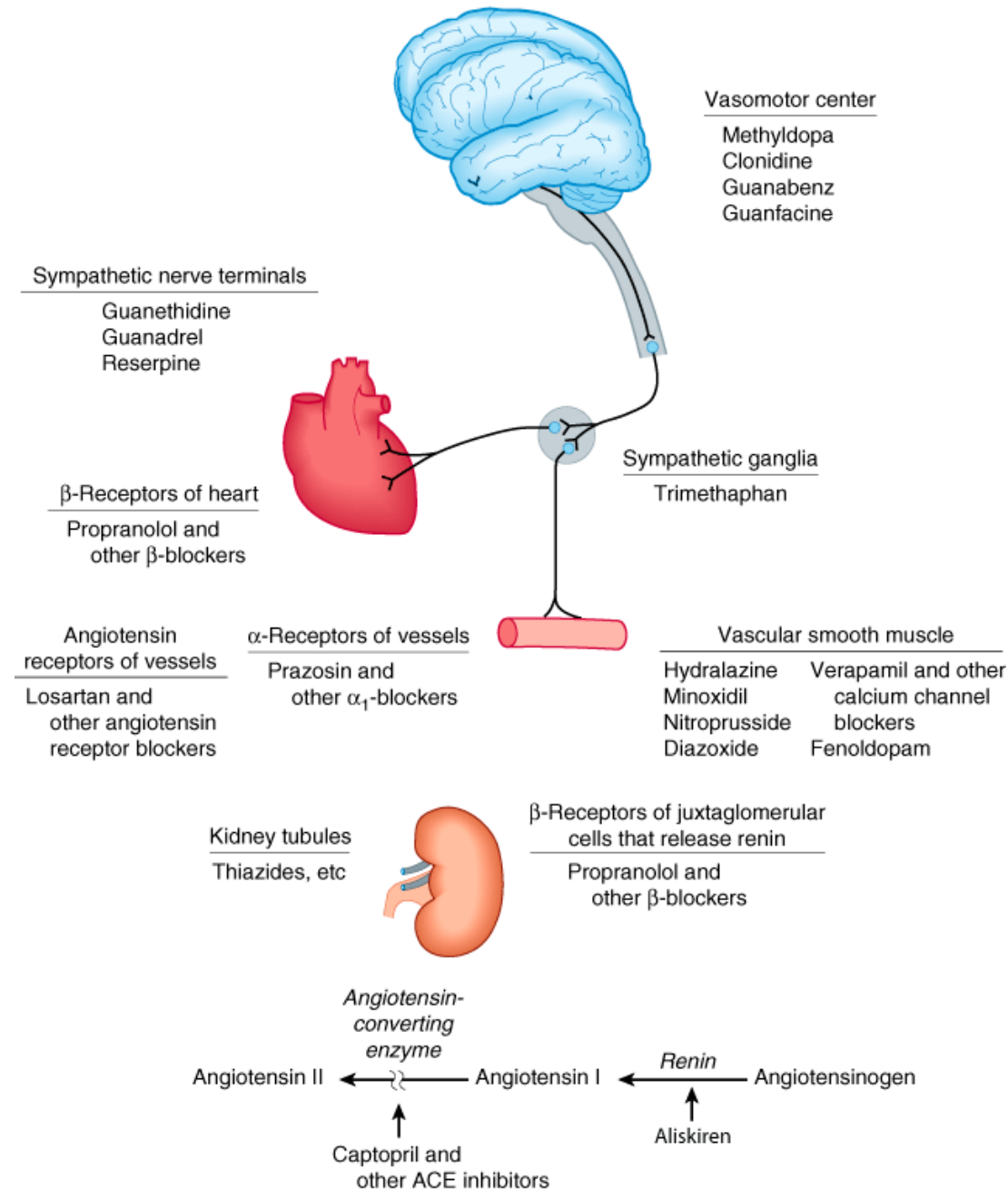
Response mediated by the renin-angiotensin-aldosterone system

اننا بهي الحضي  
ادوية لقلل



# برخو للقراءة

## Sites of Antihypertensive Drug Action



\* الملخص اني بدى اشد فل عكس ما

جسي بشت فل / بدى اخص بلو كرفلا لايسي

active حتى اقل الخوف مستوى ريش

مرتفع

# Antihypertensive Drugs

1. Diuretic agents
2.  $\beta$  Receptor Blockers
3. Calcium channel blockers
4. Angiotensin-Converting Enzyme Inhibitors
5. Angiotensin II Receptor Blockers
6. Renin inhibitors
7.  $\alpha_1$  Receptors Blockers
8. others

# Diuretics

- Diuretics are drugs that **increase** urine flow.
- Initial mechanism is based on decreasing blood volume: most of them lead to electrolyte excretion and consequently, to osmotic excretion of water, which increases the 24-hr urine volume.
- Often, diuretics change urine pH and the ionic composition of blood and urine
- Indications: **edema, heart failure, hypertension**

blood pressure بقاء

↓  
interstitial fluid

# Diuretics

Diuretics act on two mechanisms **to lower blood pressure:**

- 1) Diuretics act on the kidney to increase Na<sup>+</sup> and water secretion, which reduces blood volume and cardiac output, leading to a **fall in blood pressure.**

\* بس يزيدي ال Na<sup>+</sup> بال urine فبلحقتها المني و بتقل ال Blood Volume

- 2) By increasing the **synthesis of prostaglandins (PGs)**, which act on the smooth muscles of the blood vessels to induce their vasodilation. Thus, **there will be a reduction in peripheral vascular resistance (PVR)**. This reduction in PVR will then also contribute to a reduction in blood pressure.

↑ prostaglandin → Vasodilation

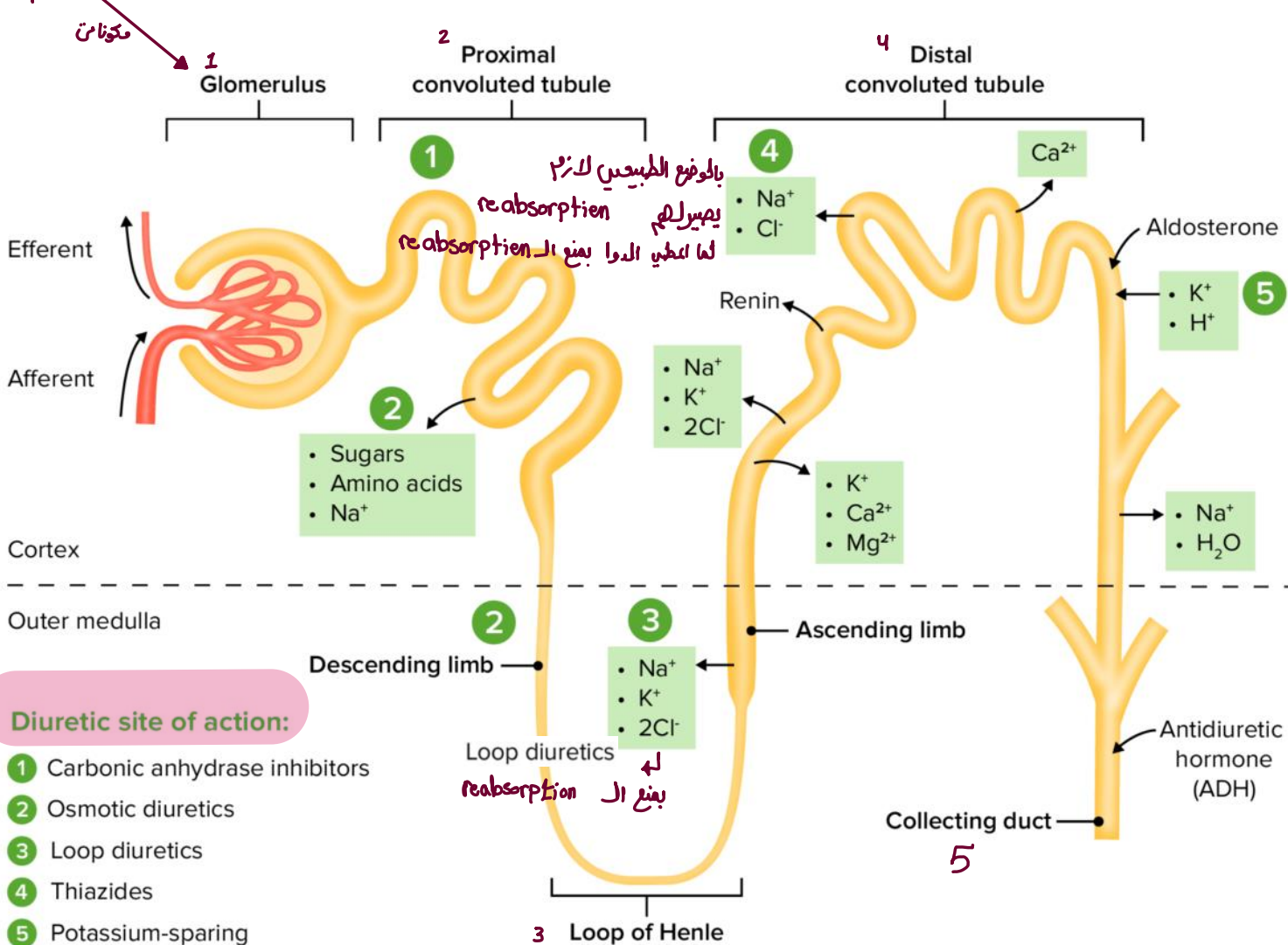
# Diuretic drugs

- Thiazides and thiazide-like diuretics.
- Loop diuretics
- Potassium -sparing diuretics
- Carbonic anhydrase inhibitors.
- Osmotic diuretics.

CVS ماله علاقة بال

# Diuretic drugs

\* (1-2) million of nephron



loop of henle  
Distal tubule  
collecting tubule

← يشغل على  
← يشغل على  
← يشغل على

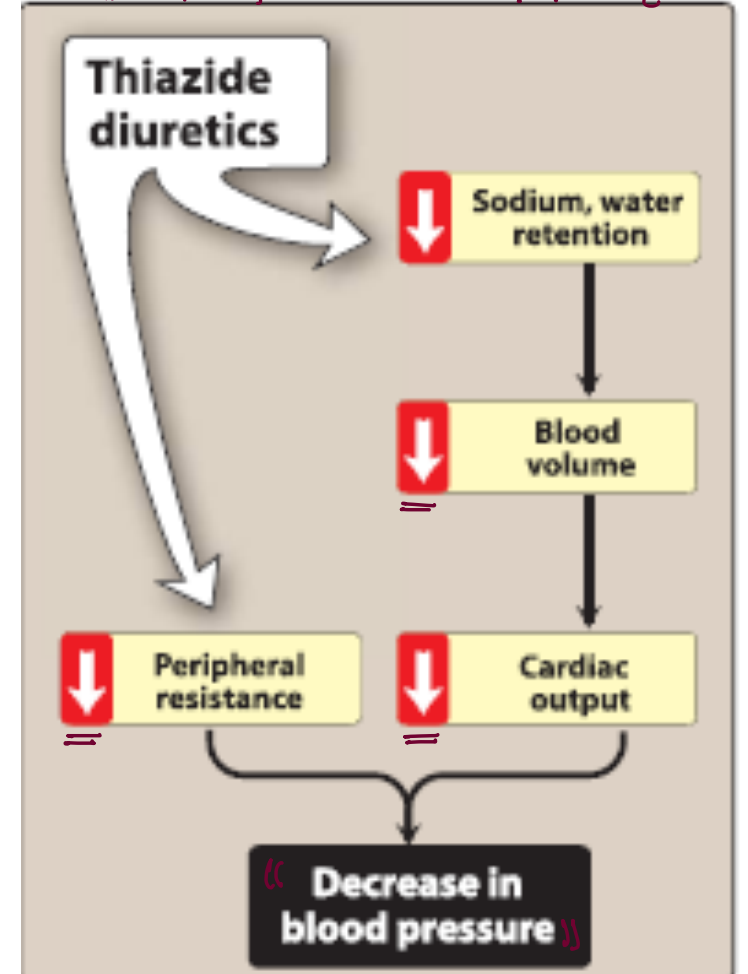
# Thiazides diuretics

- Thiazides are sulfonamide-related organic acids. Such as Hydrochlorothiazide and Chlorthalidone
- Thiazide diuretics primarily **inhibit  $\text{Na}^+/\text{Cl}^-$  transport in the distal convoluted tubule.**
- Natriuresis (excretion of sodium in the urine) may be accompanied by some loss of potassium and  $\text{H}^+$ .
- Thiazides enhance  $\text{Ca}^{2+}$  reabsorption in the distal convoluted tubule, by increasing  $\text{Na}^+/\text{Ca}^{2+}$  exchange. Thiazide diuretics also reduce the urinary excretion of  $\text{Ca}^{2+}$ .  
*→ lose of sodium, chloride, potassium, hydrogen*  
*↳ reabsorption of  $\text{Ca}^{+2}$*

# Thiazides diuretics

لما يطلع ال Na بال Urine بلحقوا الدم حسب التناحيات الاسعوية

- Thiazide diuretics can be used as **initial drug therapy for hypertension** unless there are compelling reasons to choose another agent.
- Thiazides are useful in combination therapy with a variety of other antihypertensive agents.
- Thiazide diuretics are **not effective in patients with inadequate kidney function**. Loop diuretics may be required in these patients.
- Thiazide diuretics can **induce hypokalemia, hyperuricemia, and, to a lesser extent, hyperglycemia** in some patients.



لهيك ما بنعطيهم لمرضى السكري



# Thiazides diuretics

تلتصيحو اللي اذكر فوق

بزيدي فيها كل اشئي  
علا ال  $Ca^{+2}$

← لعاد ال pH بول Urine بتقلح

Urine	Blood
↑ Na+	↓ <u>Hyponatremia</u>
↑ Cl-	<u>Hypochloremia</u>
↑ H <sub>2</sub> O	<u>Hypovolemia</u>
↑ K+	<u>Hypokalemia</u>
↑ H+	Alkalosis
↑ Mg <sup>++</sup>	<u>Hypomagnesemia</u>
↓ Ca <sup>++</sup>	<u>Hypercalcemia</u>

طلع  $H^+$  كثير  
معناها ال pH  
ارفع بالدم

بزيدي

# Loop diuretics

بس نعملهم inhibition بتلوا كلهم بالدم لانهم  
بتلوا مع ال urine

← Sodium Potassium chloride Co transport 2

- Loop diuretics **inhibit the NKCC2 (the luminal Na/K/2Cl co-transporter) in the thick ascending limb of the loop of Henle.**
  - **They works** even in patients with poor renal function or those who have not responded to thiazide diuretics.
  - Loop diuretics cause decreased renal vascular resistance and increased renal blood flow ↑ prostaglandin → Vasodilation ↑
1. **Furosemide( Lasix):** most commonly used
  2. **Bumetanide**
  3. **Ethacrynic acid.**
  4. **Torseamide**

# Loop diuretics actions

## 1. Diuretic:

Block the  $2 \text{ Cl}^- / \text{Na}^+ / \text{K}^+$  reabsorption pump in the thick ascending loop of Henle resulting in excretion of 20% of filtered  $\text{Na}^+$  .

## 2. Venodilatation:

Via enhancing prostaglandin synthesis  $\rightarrow \downarrow$  blood pressure

- Loop diuretics are rarely **used alone to treat hypertension**, but they are **commonly** used to manage symptoms of heart failure and edema.

# Loop diuretics

تلتبىس لى التذكر فوق  
↓

Urine	Blood
↑ Na+	Hyponatremia
↑ Cl-	Hypochloremia
↑ H <sub>2</sub> O	Hypovolemia
↑ K+	Hypokalemia
↑ H+	Alkalosis
↑ Mg <sup>++</sup>	Hypomagnesemia
↑ Ca <sup>++</sup>	Hypocalcemia

# Potassium-Sparing Diuretics

reabsorption to potassium

- They act on the **collecting tubule** to inhibit  $\text{Na}^+$  reabsorption and potassium excretion.

- **Potassium levels should be monitored** in patients treated with potassium-sparing diuretics.

↓ ↓ Potassium بخالي ← other cardiac Diuretics  
to maintain in the normal level ← البوناسيوم معهم

- **They should be avoided in patients with severe renal dysfunction.**

$\text{K}^+$  level كثير معهم تلاتهم احمافه عليه فيطبي hypertensis مع other drug ك-sparing

- Included:

1. **Aldosterone antagonists:** spironolactone and eplerenone.

2. **Epithelial sodium channel blockers:** Triamterene and amiloride.

# Potassium-Sparing Diuretics:

- **Spironolactone and eplerenone.**
- They are synthetic steroids that antagonize aldosterone receptors.
- They prevent Na<sup>+</sup> reabsorption and K<sup>+</sup> and H<sup>+</sup> secretion. +2 Na reabsorption علنا block الدم و يقلل ال
- **Eplerenone:** is more selective for aldosterone receptors and causes fewer endocrine effects. hyperkalemia برحجوا على الدم بصير
- **Spironolactone:** also binds to progesterone and aldosterone receptors, resulting in more endocrine effects such as gynecomastia. endocrine function و ال Side effect ↓ increased breast tissue in male
- Potassium-sparing diuretics **are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.**

# Spironolactone and eplerenone

- **Therapeutic uses:**

1. **Edema:**

2. **Hypokalemia:**  these agents are often given in conjunction with thiazide or loop diuretics to prevent K<sup>+</sup> excretion. *potassium level* ورفع ال

3. **Heart failure** : at lower doses **to prevent cardiac remodeling**. It has been shown that aldosterone antagonists decrease the mortality associated with heart failure.

4. **Resistant hypertension.**

# Spirolactone and eplerenone

**Adverse effects:**

**1. Hyperkalemia:**

الغالب  
endocrine function  
↓  
تنوع

**Gynecomastia in men and menstrual irregularities in women: only with Spirolactone.**



# Epithelial sodium channel blockers: Triamterene and amiloride.

Collecting tubule موجودة بال

- They **block epithelial sodium channels**, resulting in a decrease in Na<sup>+</sup>/K<sup>+</sup> exchange.

Normal → Na (reabsorption) // K → excretion  
blocker اعطيت → Na (lose) // K → reabsorption

- Don't depend on the presence of aldosterone.

إذا حدث عنده نقص K يستخدم هالدها حتى يرفعها

- Used **only** for their **potassium-sparing properties**, they are commonly used in combination with other diuretics.