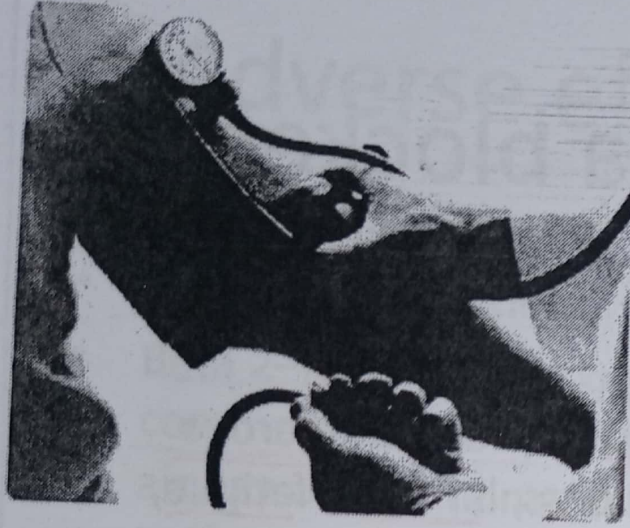




Artery Academy

Ayah Rabba'



Antihypertensive Drugs

Pharmacology I
Dr. Heba Khader

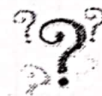
«اللهم : كرمنا بنور الفهم وافتح علينا بعمرة العلم ، وحسن اُخلاقنا بالعلم ،
وسهل لنا ابواب فضلك وانشر لنا من خزائن رحمتك يا ارحم الراحمين »

Hypertension

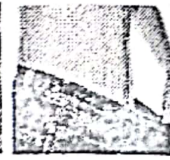
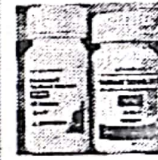
Causes and risk factors



Symptoms



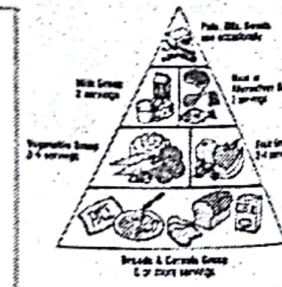
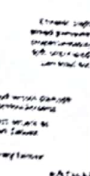
Treatment



Prevention



Complications



- ارتفاع الضغط المزمن
- **Hypertension (HTN)** or **high blood pressure**, sometimes called **arterial hypertension**, is a **chronic medical condition** in which the **blood pressure** in the **arteries** is **elevated**.
- Hypertension is the most **common cardiovascular disease**.

* يتم تشخيصه بطلب الطبيب من المريض
قياس ضغطه لفترة محددة من الزمن و
أكثر من مرة في اليوم الواحد .
لا ارتفاع الضغط بسبب التوتر أو تبادل
دواء معين ليس دليلاً على مرض (HTN) المزمن .

Complications of hypertension

- مضاعفات
- Complications of hypertension are clinical outcomes that result from persistent elevation of blood pressure.
 - Sustained arterial hypertension damages blood vessels in kidney, heart, and brain and leads to an increased incidence of renal failure, coronary disease, heart failure, stroke, and dementia. (مرض الخرف) نسبة

- HTN complications include:

Heart (hypertensive cardiomyopathy)

Eyes (hypertensive retinopathy)

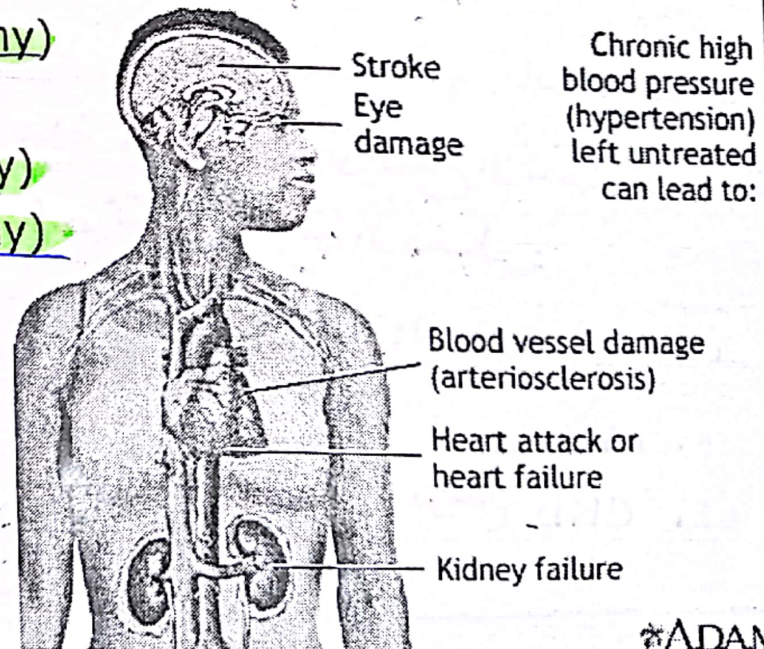
Kidneys (hypertensive nephropathy)

Brain (hypertensive encephalopathy)

* ارتفاع الضغط يسبب تلف في الأوعية الدموية عند ما يكون الارتفاع حاداً .

* تلف للأوعية الدموية يؤدي إلى مضاعفات

أخرى في أجهزة الجسم .



*ADAM

Hypertension Categories

- ▶ Hypertension is defined as an arterial pressure greater than 140/90 mm Hg in adults on at least three consecutive visits to the doctor's office.
- ▶ The diagnosis serves primarily as a prediction of consequences for the patient.
- ▶ Epidemiologic studies indicate that the risks of damage to kidney, heart, and brain are directly related to the extent of blood pressure elevation.

* كلما زاد حجم ارتفاع الضغط
تزيد خطورة تلف الأعضاء والأوعية
الدموية.

* هذا الجدول حفظ .

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Prehyper- tension	120- 139	or	80-89
Stage I	140- 159	or	90-99
Stage II	≥160	or	≥100

* لازم يكون قياس الضغط أكثر من 140/90
لمدة 3 زيارات متتالية للعييب .

Blood Pressure Treatment goals

- ▶ The JNC8 guidelines recommend BP goals for the management of hypertension: (Recommendations 1-5)
- ▶ **Persons 60 years or older without diabetes or CKD**
 - ▶ **BP < 150/90** (based on strong evidence) يد بالاعتماد على إحصاءات داخل المستشفيات.
- ▶ **Persons less than 60 years of age, with diabetes, and/or with CKD**
 - ▶ **BP < 140/90** (based on expert opinion) يد بالاعتماد على رأي الأطباء والجنرال.

لا تختلف قياسات الضغط حتى يتم تحديد إصابة الشخص بمرضى ارتفاع الضغط المزمن باختلاف حالة الشخص ، ومن العوامل المؤثرة في نتيجة قياس الضغط :

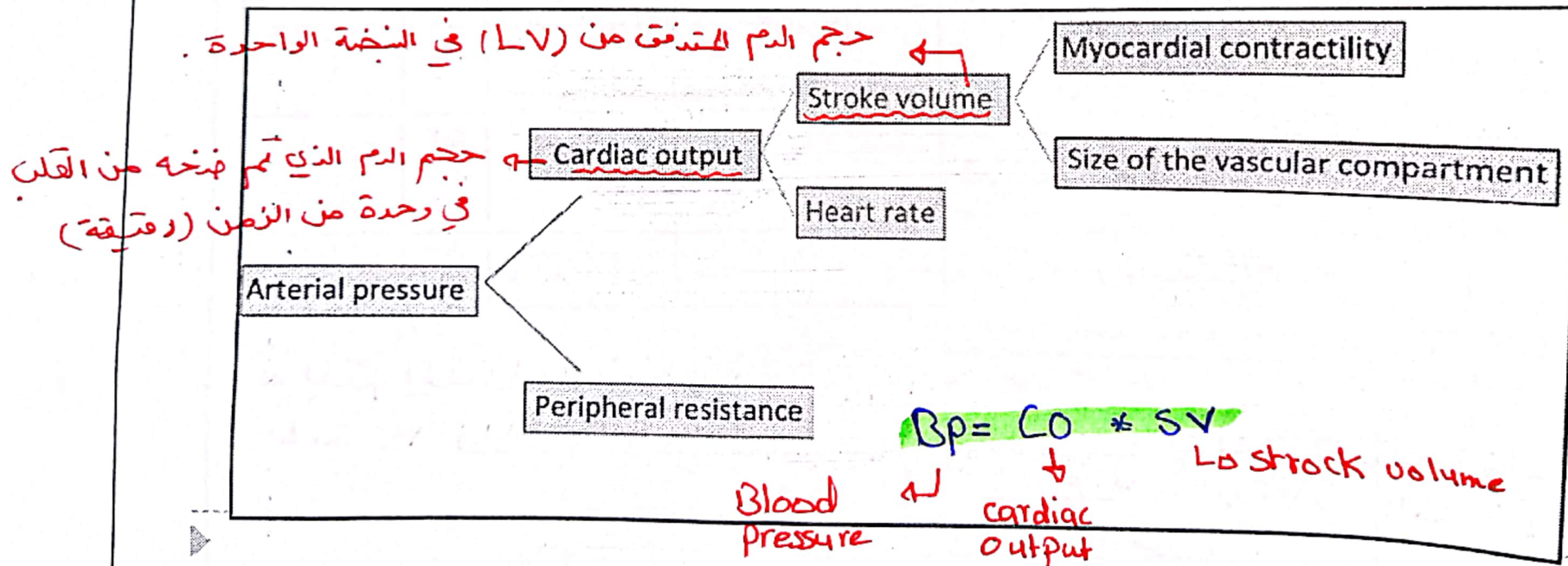
1. age (العمر)
2. Diabetes (السكري)
3. أمراض القلب المزمنة CKD

Mechanisms for controlling blood pressure

- Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system, particularly the endothelium.

تناسب طردياً مع ..

- Arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance. ②



Mechanisms for controlling blood pressure

Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping control mechanisms:

The baroreflexes → can increase or decrease BP depending on situation.

The renin-angiotensin-aldosterone system (RAAS)

↳ increases blood pressure by more mechanisms than one.

× يمكن التحكم بضغط الدم عن طريق آليتين :-

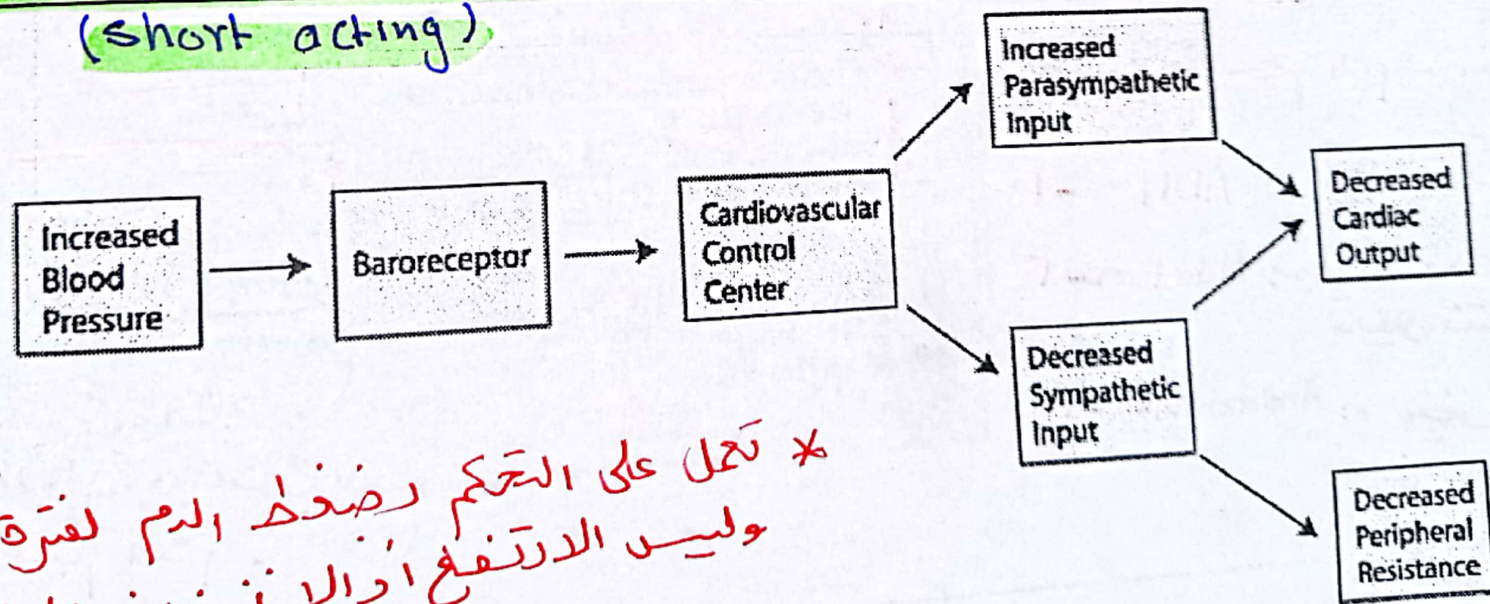
١. ردود فعل عكسية لـ baroreceptors الموجودة على باطن جدران الشرايين الدموية .
(تقلل ضغط الدم أو تزيده)

٢. عن طريق إفراز الإنزيم renin وزيادة ضغط الدم من خلال (RAAS).

Baroreflexes

* حساسات عصبية على جدران الأوعية الدموية تتحفظ
بتمدد الأوعية الدموية أو تضيقها بسببها .

- ▶ **Baroreceptors** are sensors located in the blood vessels of all vertebrate animals. They are a type of mechanoreceptor sensory neuron that is excited by stretch of the blood vessel.
- ▶ Baroreceptors act immediately as part of a negative feedback system called the baroreflex.
له الفعل العكسي الذي تسمى به
- ▶ Baroreflexes act by changing the activity of the autonomic nervous system. Therefore, they are responsible for the rapid, moment-to-moment regulation of blood pressure.
(short acting)



* تعمل على التحكم بضغط الدم لفترة قصيرة
وليس الارتفاع أو الانخفاض المزمع

Renin-angiotensin-aldosterone system

- ▶ The kidney provides for the long-term control of blood pressure by altering the blood volume.
- ▶ Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β_1 -adrenoceptors) by releasing the enzyme renin.
- ▶ Low sodium intake and greater sodium loss also increase renin release.
- ▶ Renin converts angiotensinogen to angiotensin I, which is converted, in turn to angiotensin II, in the presence of angiotensin-converting enzyme (ACE).

* عندما يقل ضغط الدم في الذوعية التي بداخل الكلية ، تتحفز Baroreceptors وتحفز الكلية لزيادة افراز انزيم (Renin).

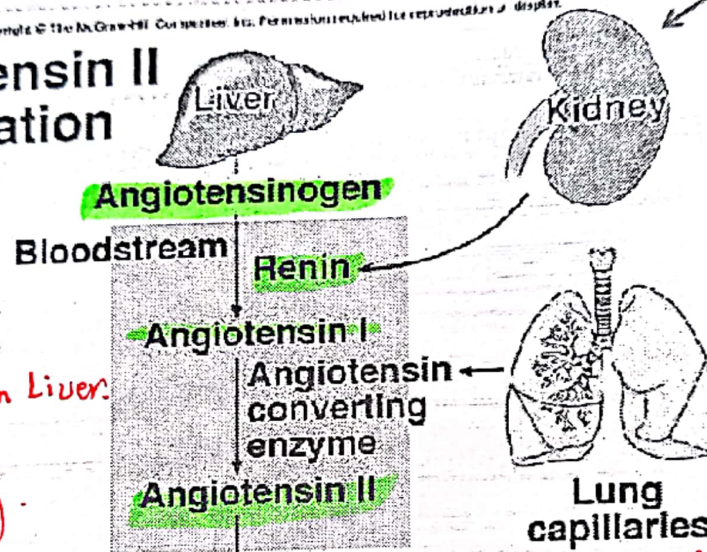
* أيضاً يتحفز افراز انزيم (Renin) من الكلية عندما تقل كمية Na^+ الداخلة للكلية وتزداد كمية فقبات Na^+ من الجسم .

Renin stimulate Angiotensin I convert by (ACE) → Angiotensin II stimulate aldosterone
 * يعمل قنور الكلية ::

1. Reduced blood pressure
2. Beta1 activation
3. Low sodium intake or excessive sodium loss

* β_1 activation causes renin secretion.

Angiotensin II Formation



- Renin → from kidney

- Angiotensinogen → from Liver.

- ACE → from Lung.

* يزيد حجم الدم من خلال ::

١- ADH :- يقلل فقدان الماء غير المتبول.

٢- Aldosterone :- يزيد احتباس الماء والصوديوم ويقلل فقدانها من الدم.

٣- Angiotensin II :- يحفز مراكز العطش في الدماغ فيزيد شرب الشخص للماء.

1. Vasoconstriction
2. Increased aldosterone secretion
3. Increased ADH Secretion
4. Increased thirst

• Increases blood pressure

Aldosterone

increases sodium and water retention

ADH: Anti diuretic hormone

* تقل كمية إنتاج

البول وبالتالي يزيد حجم الدم.

↑ Blood volume → ↑ Blood pressure.

Drugs used in hypertension (أدوية علاج ارتفاع الضغط)

1. Diuretics

2. Sympathoplegic agents

- ▶ 1. Beta blockers
- ▶ 2. Alpha blockers
- ▶ 3. Centrally acting adrenergic drugs

3. Agents that block production or action of angiotensin

- ▶ 1. Angiotensin Converting Enzyme Inhibitors (ACEIs)
- ▶ 2. Angiotensin Receptor blockers (ARBs)
- ▶ 3. Renin inhibitor

4. Vasodilators

Treatment of hypertension

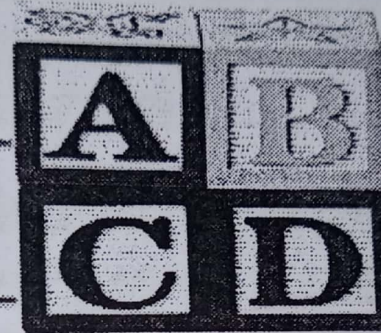
Medical MCQs Cases

Spot Diagnosis

Hints & Mnemonics

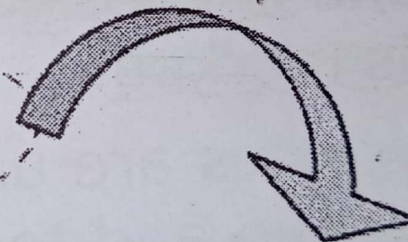
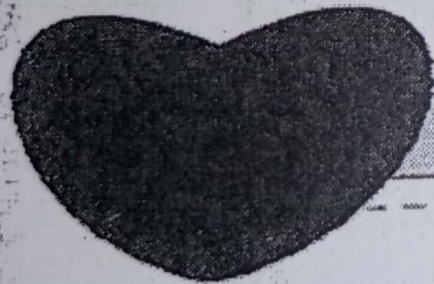
Angiotensin converting
enzyme inhibitor
(ACE I)

Calcium channel
blocker



Beta blocker

Diuretic



-- cardiac contractility

Vasodilatation

-- blood volume

B

A

C

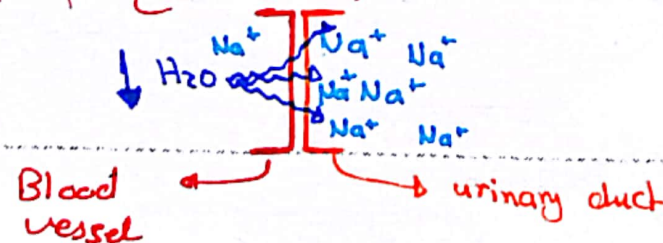
D

1. Diuretics (مدرات البول)

- Diuretics lower blood pressure by ^{تقليل} (depleting the body of sodium and reducing blood volume) and perhaps by other mechanisms.
- Diuretics can be used as first-line drug therapy for hypertension unless there are compelling reasons to choose another agent.
- Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and congestive heart failure, all of which can cause mortality.
- The diuretics most important for treating hypertension are the **thiazides** (eg, hydrochlorothiazide) and the **loop diuretics** (eg, furosemide).

• هي الاختيار الأول في علاج ارتفاع الضغط. إلا إذا في أسباب ثانية عند المريض بتدخلنا فنختار دواء ثاني.

* صبدأ عملها: • تعمل على زيادة إفراز الصوديوم Na^+ خارج الدم فيقل حجم الماء في الدم وهذا يقلل من حجم الدم.



• يارب تفهم الرسمة

2. Sympathoplegic agents . (تسبط تانس Sympathetic system)

Sympathoplegic agents lower blood pressure by reducing ^① peripheral vascular resistance, ^② inhibiting cardiac function, and ^③ increasing venous pooling in capacitance vessels. (The latter two effects reduce cardiac output.)

mechanism of drug.

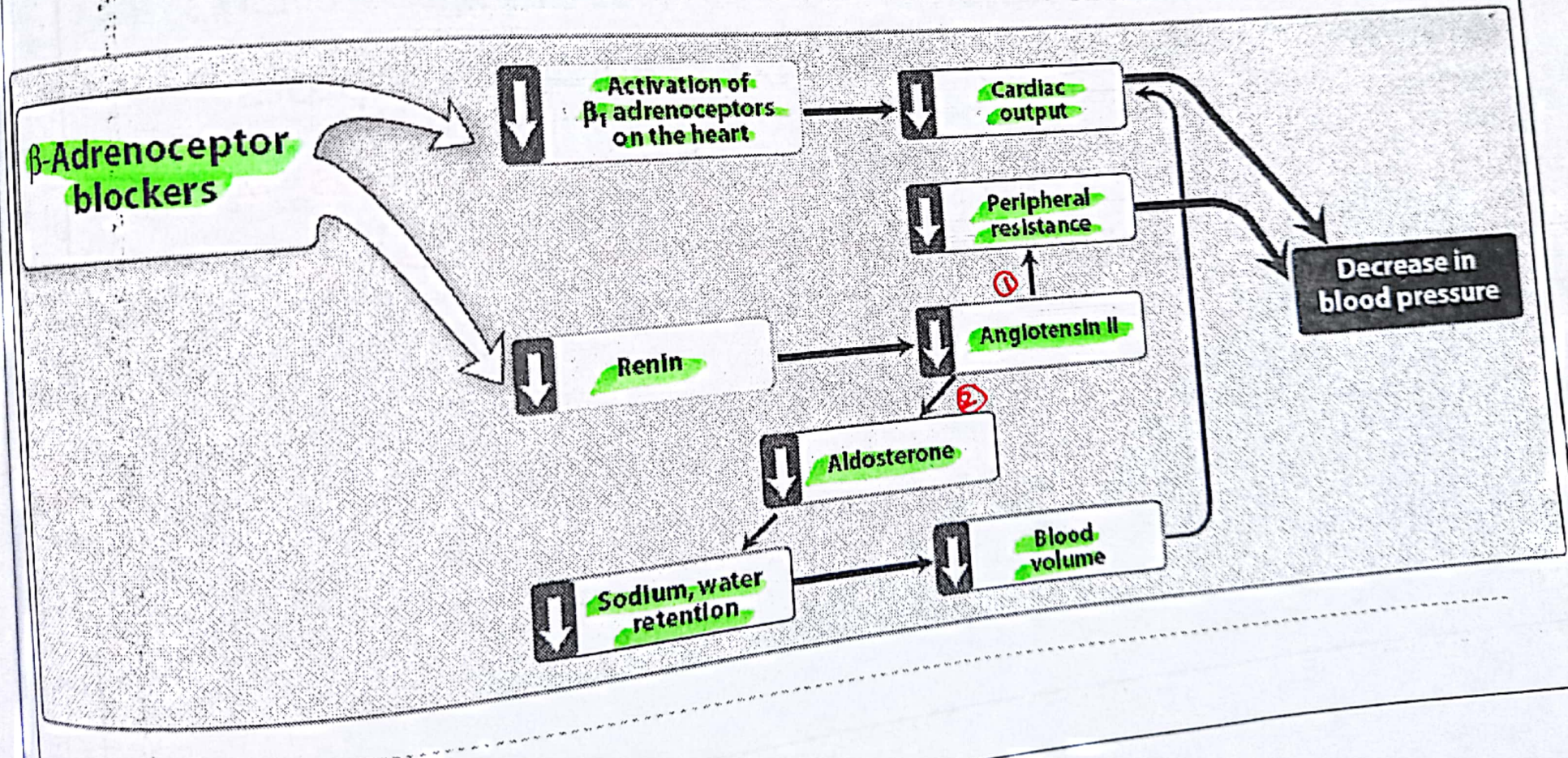
These agents are further subdivided according to their putative sites of action in the sympathetic reflex arc to:

- A. Beta blockers
- B. Alpha blockers
- C. Centrally acting adrenergic drugs

A. Beta blockers . (Beta receptor antagonist)

Mechanism of action involves ^① reduction in cardiac output and suppression of renin release.

② تثبيط



A. Beta blockers

- ▶ The **non-selective β blockers** such as **propranolol** can be used to treat hypertension.
- ▶ **Selective blockers of β_1 receptors**, such as **metoprolol** and **atenolol** are among the most commonly prescribed **β -blockers**.
- ▶ **Nebivolol** is a **selective blocker of β_1 receptors**, which also **increases the production of nitric oxide** leading to **vasodilation**.
(eNOS) relaxing factor.
- ▶ The **selective β -blockers** may be administered cautiously to **hypertensive patients who also have asthma**.
- ▶ The **nonselective β -blockers**, such as **propranolol** and **nadolol**, are contraindicated in patients with **airway diseases** due to their **blockade of β_2 -mediated bronchodilation**.
- ▶ **Adverse effects** include **fatigue, bradycardia, insomnia** and **disturbances in glucose metabolism**.

*non selective β blockers
(asthma, COPD) التنفسي*
تضيق الشعب الهوائية وبالتالي لا تغطي المرضى الجهاز

B. Alpha 1 blockers

- ▶ **Prazosin, doxazosin, and terazosin.**
- ▶ Mechanism of action is by dilating vessels which decrease peripheral vascular resistance.
- ▶ Side effects include reflex tachycardia and orthostatic hypotension.
- ▶ Labetalol and carvedilol block α_1 , β_1 , and β_2 receptors.

* كمان ما بنفع فيهم لمرض asthma لأنه بالهم تاثير على β_2 receptors (ممكن زيولهم
صح اخذ الكذر والبقاد بجاجة مرض الذرمة. بجانبهم ماعا .

C. Centrally acting adrenergic drugs

Clonidine and methyldopa

mechanism of action:

- ① α_2 -agonists that reduce the central adrenergic outflow,
- ② decreasing the firing rate of the sympathetic nerves and the
- ③ amount of norepinephrine release.

Not a first-line or second line treatment.

Clonidine adverse effects are generally mild, sedation and dry mouth, are common.

التوقف المفاجئ عن أخذها

Rebound hypertension occurs following abrupt withdrawal of clonidine. The drug should be withdrawn slowly if the clinician wishes to change agents.

Methyldopa was widely used in the past but is now used primarily for hypertension during pregnancy. (safe drug)

The most common side effects of methyldopa are sedation particularly at the onset of treatment.

بداية العلاج

* عند التوقف عن استخدام Clonidine يجب تقليل الجرعات تدريجياً ، حتى لا يحدث انخفاض الضغط
بارتفاع الضغط الناتج عن التوقف المفاجئ لاستخدام الدواء .

3. Agents that block production or action of angiotensin

Agents that block production or action of angiotensin and thereby reduce peripheral vascular resistance and blood volume. ① mechanism of action: ①, ②

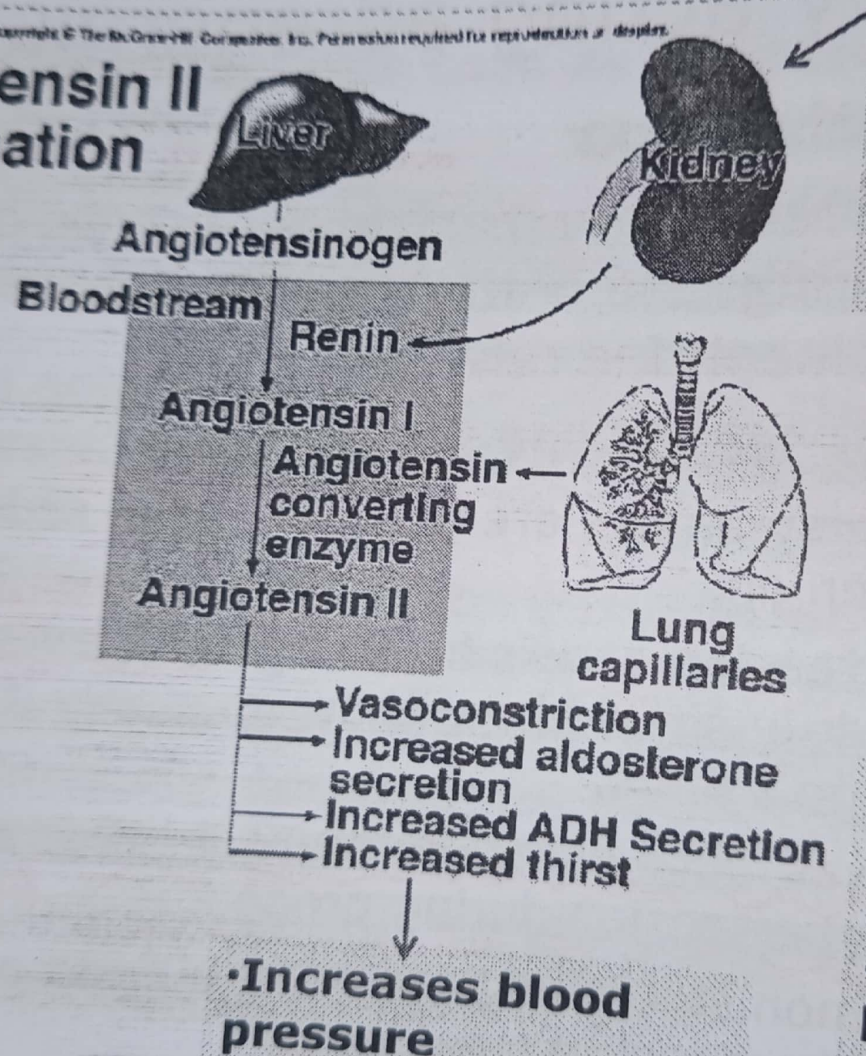
A. **Angiotensin Converting Enzyme Inhibitors (ACEIs)**

B. **Angiotensin Receptor blockers (ARBs)**

C. **Renin inhibitor**

Angiotensin II Formation

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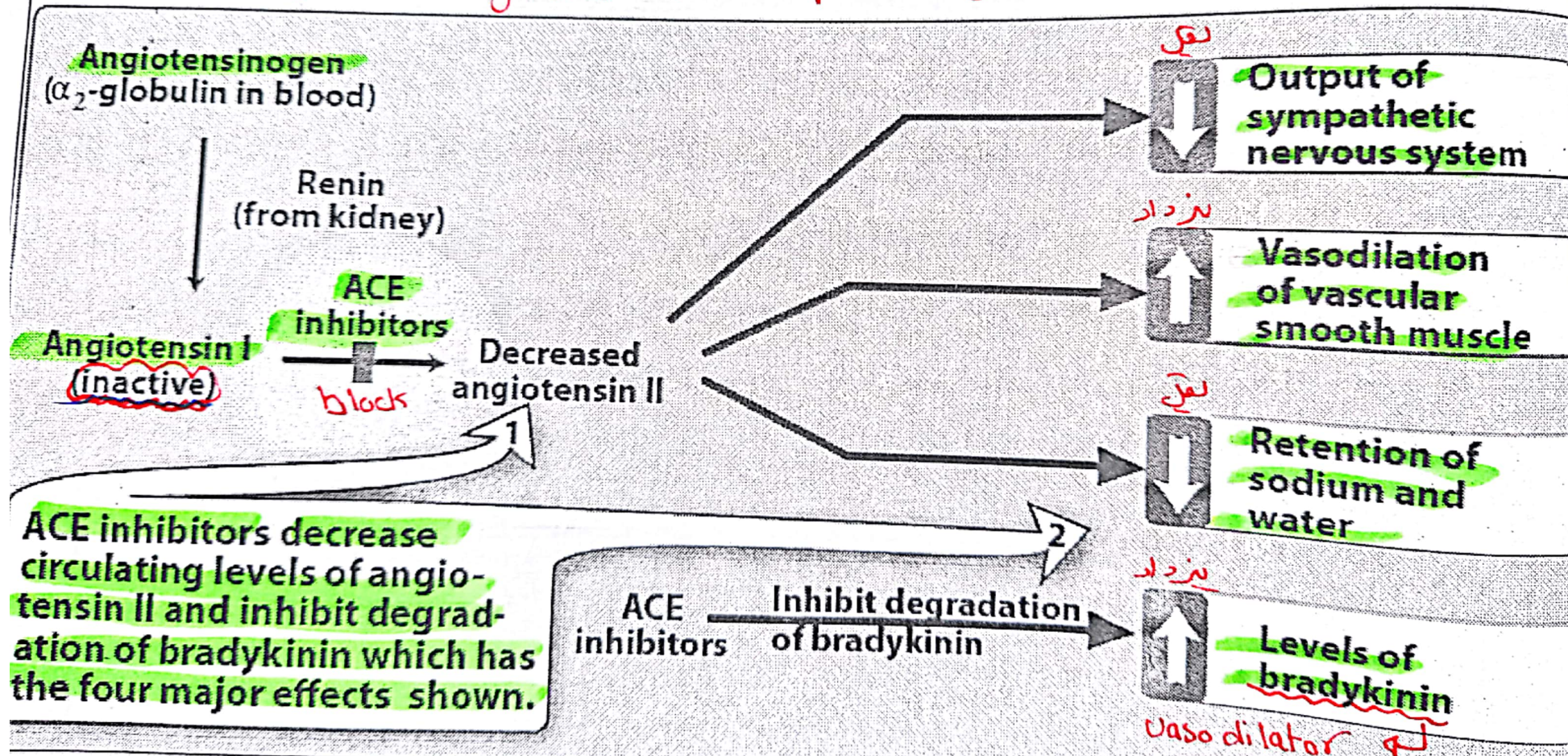
1. Reduced blood pressure
2. Beta1 activation
3. Low sodium intake or excessive sodium loss

•Aldosteron increases sodium and water retention
•ADH: Anti diuretic hormone

* أدوية تثبط عمل الإنزيم الذي يساهم في زيادة ضغط الدم .

A. ACEIs

+ inhibit ACE that convert angiotensin I to angiotensin II, Thus inhibit the effect of angiotensin II in BP increasing.



A. ACEIs

* mechanism of action:

- ▶ The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, rate, or contractility.^①
- ▶ These drugs block the ACE that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II.^②
- ▶ By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.^③ cause
- ▶ The converting enzyme is also responsible for the breakdown of bradykinin. ACEIs also reduce the rate of bradykinin inactivation.
- ▶ ACE inhibitors decrease angiotensin II and increase bradykinin levels.
- ▶ Vasodilation occurs as a result of the combined effects of lower vasoconstriction caused by diminished levels of angiotensin II and the potent vasodilating effect of increased bradykinin.^④ ⑤, ⑥

Brady Kinin → vasodilator

* ACE هو إنزيم مسؤول عن تحطيم جزيئات bradykinin وبالتالي عن تثبيط الإنزيم بزيادة تركيز bradykinin وتوسع الأوعية الدموية التي.

A. ACEIs

ACE inhibitors have a particularly useful role in treating patients with chronic kidney disease because they diminish proteinuria and stabilize renal function (even in the absence of lowering of blood pressure).

This effect is particularly valuable in diabetes, and these drugs are now recommended in diabetes even in the absence of hypertension.

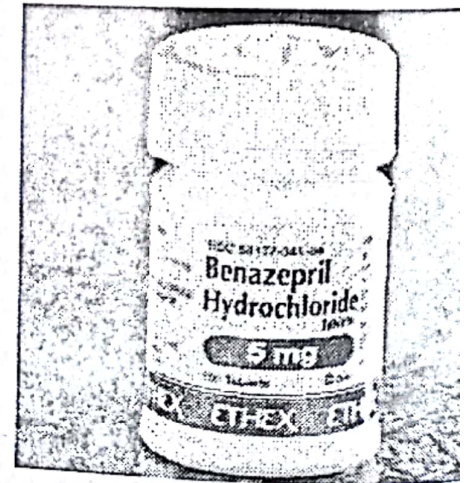
* تستخدم ACEIs في ممراف الكلى المزمنة لعدم أسباب ع. (حتى في عدم ارتفاع الضغط)
1- تقليل البروتين في البول - ثبت عمل الكلى.
* تستخدم أيضاً في ممراف السكري حتى بعدم وجود ارتفاع ضغط الدم.

ACEIs Pharmacokinetics

- Specific agents: **enalapril**, **captopril**, **benazepril**, **fosinopril**, **moexipril**, **perindopril**, **quinapril**, **ramipril**, and **trandolapril**.
- All ACE inhibitors are **adequately absorbed following oral administration**.
يتم امتصاصه بشكل جيد
- Because the **presence of food may decrease absorption**, they **should be taken on an empty stomach**.
- Except for **captopril**, ACE inhibitors are **pro-drugs that require activation by hydrolysis via hepatic enzymes**.

❌ ادوية ACEIs تُؤخذ على معدة فارغة عدا (Captopril).
↳ pro-drug (activate by Liver.).

6.



ACEIs adverse effects

Common side effects include:

▶ Dry cough especially at night (ACE cough)

▶ Skin rash

▶ Hypotension

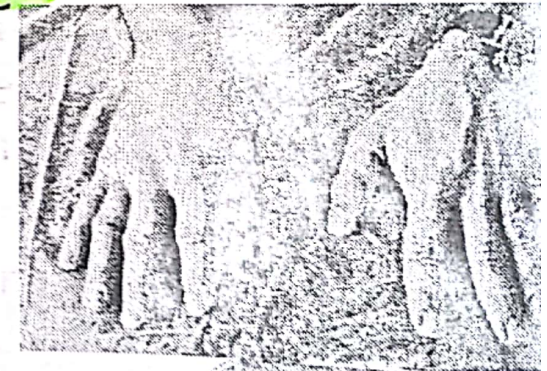
▶ Hyperkalemia (Potassium levels must be monitored, and potassium supplements or spironolactone are contraindicated).

هنا نأخذ
صوديوم بوتاسيوم لأنه
يعمل hyperkalemia

▶ Angioedema is a rare but potentially life-threatening side effect (Because of the risk of angioedema and first dose

4 و اعراض syncope, ACEIs are first administered in the physician's office with close supervision.

▶ ACEIs inhibitors are fetotoxic and should not be used in pregnant women.



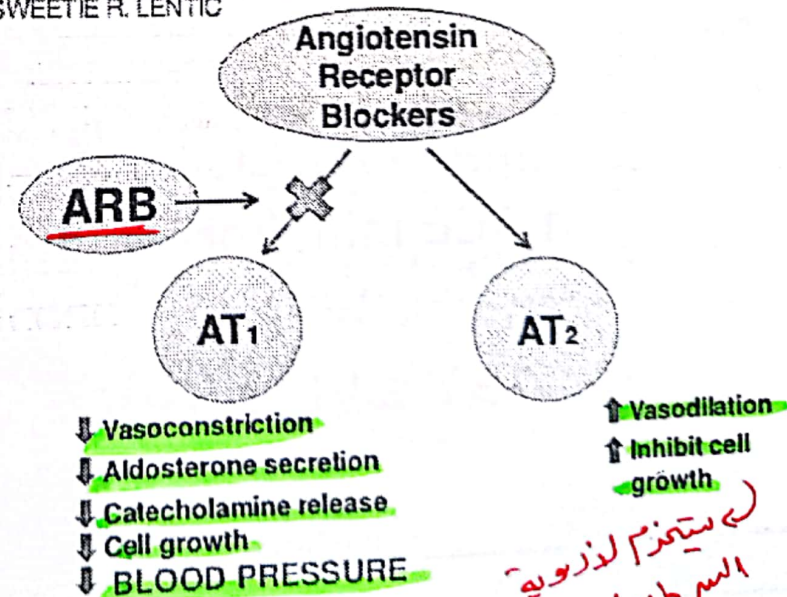
* لأنه يعمل للحرارة الكامل لأنه قاتل وسام الجنين.

B. Angiotensin Receptor Blockers (ARBs)

- * تمنع ارتباط angiotensin مع مستقبلاته وبناتاي تمنع تأثيره. ^{الإنساني}
- Losartan is the prototype drug. Other drugs are candesartan, valsartan and irbesartan.
- ARBs are extremely potent competitive antagonists of the angiotensin type 1 (AT₁) receptor.
- Like ACEIs, ^①produce vasodilation and ^②blocks aldosterone secretion, but have no effect on bradykinin.

ANGIOTENSIN RECEPTOR BLOCKERS
SWEETIE R. LENTIC

* اذوية قوية جداً ، تتنافس مع angiotensin على مستقبله (AT₁) فينبط من عمله وارتباطه مع المستقبل .



B. Angiotensin Receptor Blockers (ARBs)

- ▶ ARBs are orally active and require only once-a-day dosing.
- ▶ Little morbidity and mortality data → ARBs are a substitute ^{بدائل} for ACE inhibitors in those patients who cannot tolerate ^{لا يتحملونها} the ACEIs.
- ▶ ARBs have an adverse effect profile similar to that of ACE inhibitors. However, cough and angioedema can occur but are less common.
- ▶ As with ACE inhibitors, ARBs are contraindicated in pregnancy.

* توضع كدواء بديل عن ACEIs للأشخاص الذين لا يتحملون مع أدوية ACEIs.

C. Renin Inhibitor

لا يعمل في مراحل إنتاج Renin الأولى.

- ▶ A selective renin inhibitor, **aliskiren**.
- ▶ Aliskiren directly inhibits renin and, thus, acts earlier in the renin-angiotensin-aldosterone system than do ACE inhibitors or ARBs.
- ▶ It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- ▶ It can also be combined with other antihypertensives, such as diuretics, ACE inhibitors, ARBs, and calcium-channel blockers.
- ▶ **Hyperkalemia** is significantly more common in patients who received both valsartan and aliskiren.
- ▶ **Adverse effects:**
 - ▶ Diarrhea, especially at higher doses.
 - ▶ Cough and angioedema but less often than ACE inhibitors.
 - ▶ As with ACE inhibitors and ARBs, **aliskiren is contraindicated during pregnancy.**

side effect

لا أدوية تمنع إنتاج Renin فتتلف تأثيره في زيادة ضغط الدم.