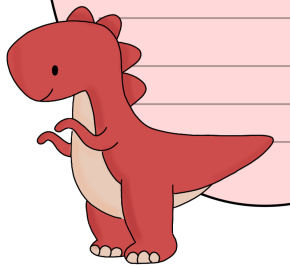
Cardiovascular System

يشمل القلب، والأوعية الدموية، والدم وكل الأمراض اللي بتأثر عليهم وشو هي الأدوية اللي رح نستخدمها بهاي الحالات

Hypertension

التفريغ شامل الـnotes

AT:angiotensin
BV:blood volume
SE: side effect
SR: susatained release
VD: vasodilator



- Hypertension is the most common cardiovascular disease. The prevalence of hypertension increases with advancing age.

- About 50% of people between the ages of 60 and 69 years old have hypertension

complication

- Hypertension is the principal cause of:
  - stroke
  - coronary artery disease
  - myocardial infarction
  - sudden cardiac death
  - cardiac failure
  - renal insufficiency

مشكلتنا في الـhtn مش المرض بحد ذاته و إنما الـcomplications الناتجة عنه، نفس مبدأ الـdiabetes

بنسميه الـsilent killer, لأنه أعراضه مش واضحة مثل الصداع وما يخطر ببالهم الضغط،

ارتفاع ثابت

- Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mm Hg.

Systolic / diastolic = 140 / 90

- Both systolic and diastolic measurements contribute to mortality – morbidity.
- Systolic blood pressure tends to rise disproportionately greater in the elderly due to decreased compliance in blood vessels associated with aging and atherosclerosis.
- Isolated systolic hypertension (sometimes defined as systolic BP >140 to 160 mm Hg with diastolic BP <90 mm Hg) is largely confined to people >60 years of age

هو كمرض لحد الآن غير معروف المسبب الرئيسي اله، بس المشكلة الأساسية هي الـ peripheral resistance,
وهو عبارة عن تضيّق بالشرايين بتقلل وصول الدم blood perfusion لباقي الـorgans مثل القلب، الكلى وبتأثر عليها مثلًا يصير في renal failure
فهذا بعطيني تلميح إنه كل الأدوية المستخدمة لعلاجه رح تكون vasodilating effect

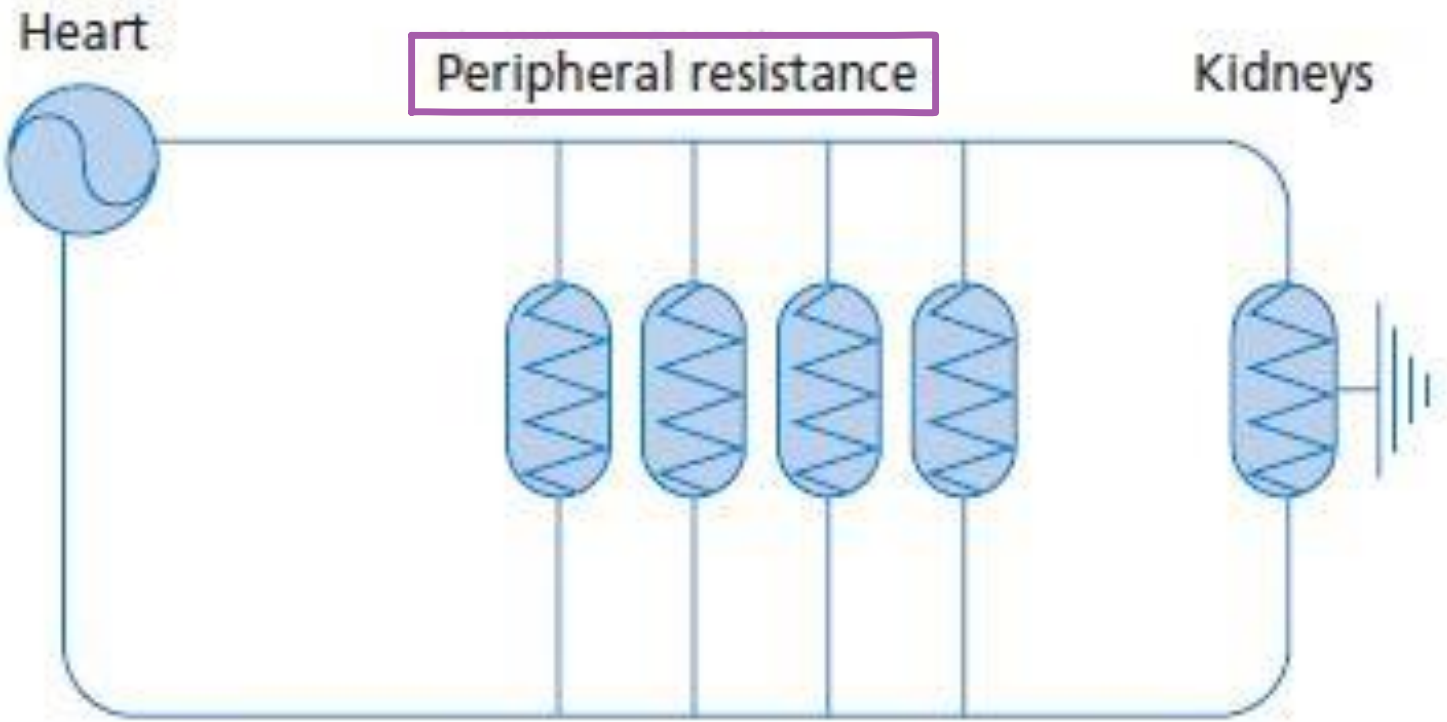


Figure 28.2: Arterial blood pressure is controlled by the force of contraction of the heart and the peripheral resistance (resistances in parallel though various vascular beds). The fullness of the circulation is controlled by the kidneys, which play a critical role in essential hypertension.

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- Associated with rapidly progressive microvascular occlusive disease in the kidney (with renal failure), brain (hypertensive encephalopathy), congestive heart failure, and pulmonary edema.

- Hospital management on an emergency basis for prompt lowering of blood pressure.

أكثر عرضة للإصابة، risk factors

The risk of cardiovascular disease, is increased markedly by:

- ✔ Smoking
- ✔ Diabetes
- ✔ Elevated low-density lipoprotein LDL
- ✔ Genetic factor
- ✔ Male gender 😌
- ✔ Obesity
- ✔ Stressful life style

عنا نوعين من الـhtn,

الـprimary : أو بنسميه essintial htn, سببه غير معروف وبشكل نسبة ٩٠-٩٥٪ من حالات الضغط

الـsecondary سببه معروف وفترته مرتبطة بالسبب، مشاكل بالـكلى أو مثلًا بالـthyroid gland يصير عنده hyperthyroidism ويزيد التايروسين فلما أعالجه برجع الضغط طبيعي

هون مقسم الـprimary لـstages وهذا مهم للـhtn managment
وأحافظ عليه ما ينتقل للمرحلة الأخطر ونقلل المشاكل

	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

لسا ما صار عنده HTN بس معرض للإصابة

Figure 19.2
Classification of blood pressure, based on report of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

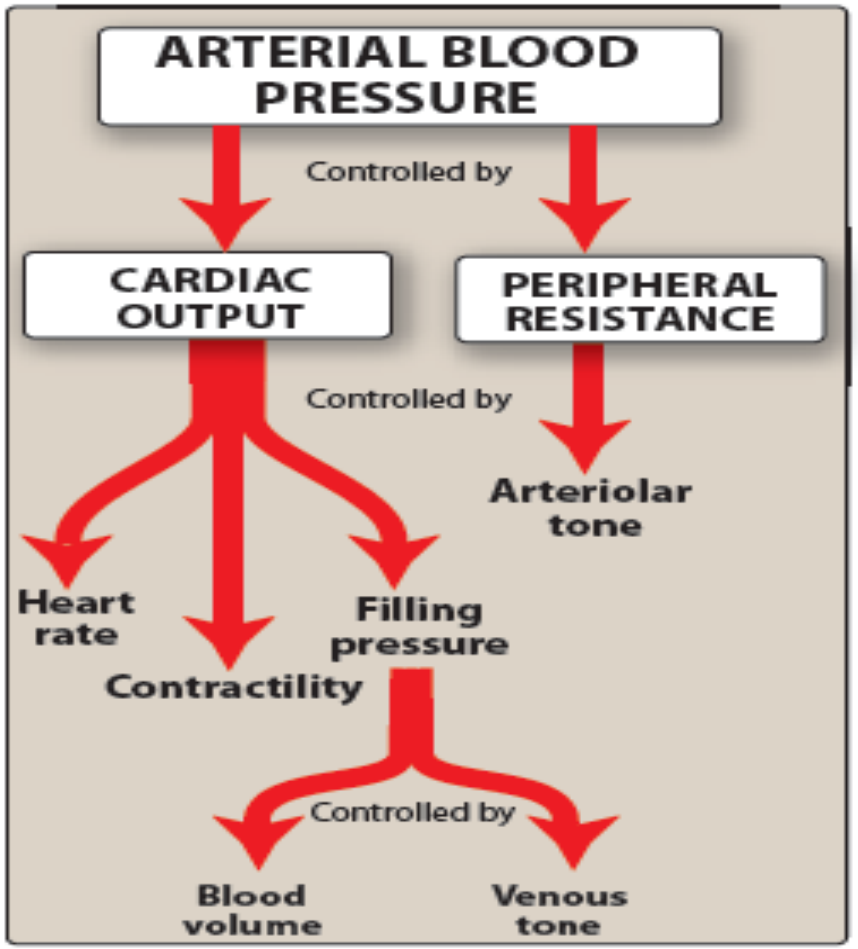


Figure 19.3
Major factors influencing blood pressure.

خلينا نحكي عن الـpathophysiology للـHTN

عنا الـRAAS هو أكثر system بتحكم بالـblood pressure,

Renin:جاي من الـjuxtaglomerular apparatus والمسؤول عن إفرازه الـB1 receptors الموجودة كمان على القلب، وبروح للـliver اللي فياته **angiotensinogen**, فبحوله لـ **angiotensin 1** اللي بتحول بعدين لـ **angiotensin 2** عن طريق الـ**ACE**

تأثيرات ارتفاع الـangiotensin 2:

-vasoconstriction

-بزيد انتاج الـaldosterone المسؤول عن الـsodium and water retention/reabsorption, هيك بزيد الـblood volume وبزيد ضغط الدم

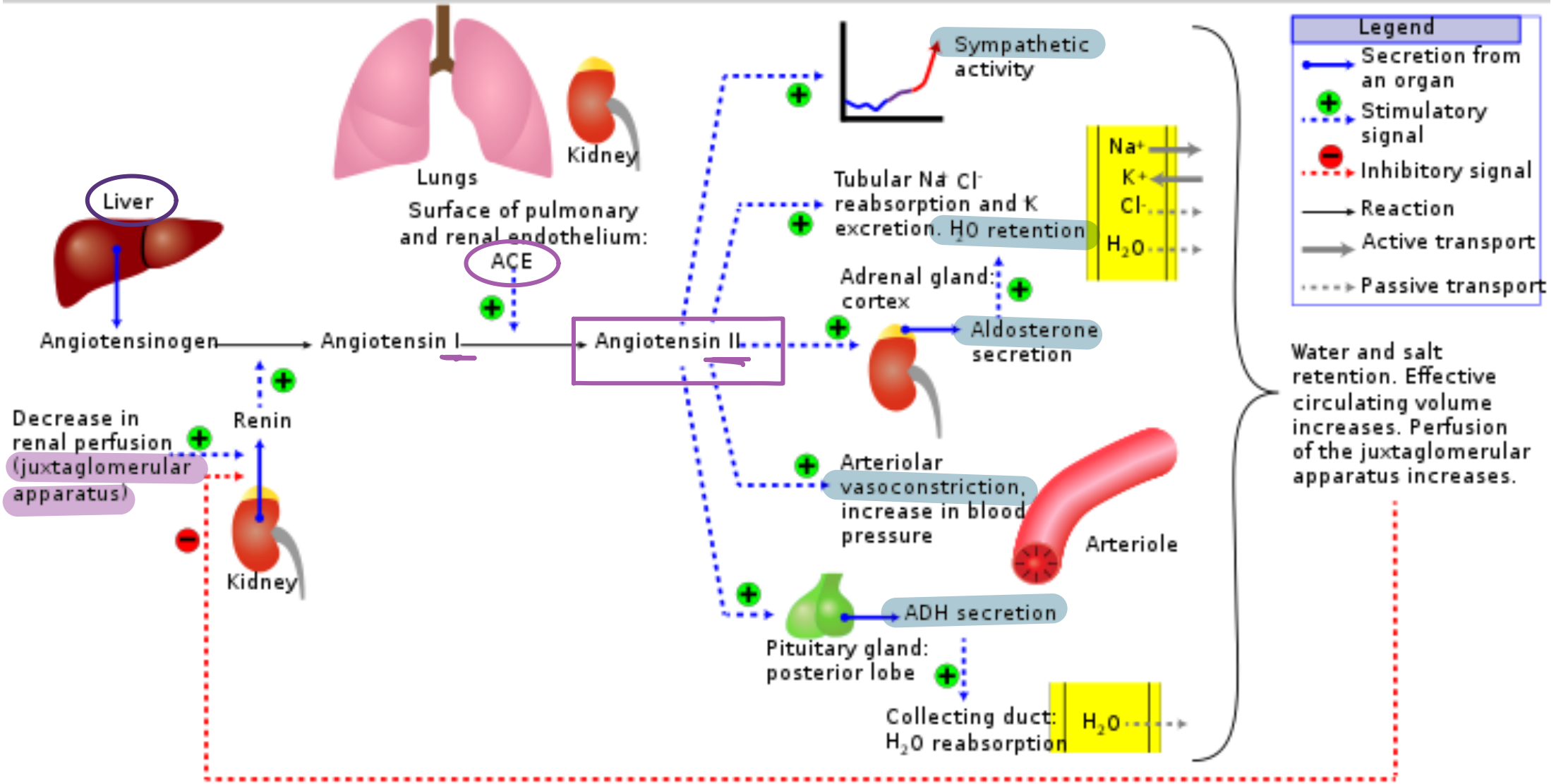
-بزيد الـADH بقلل الـurine secretion

-بزيد الإحساس بالعطش thirst

عنا كمان الـA1 receptor اللي بتعمل vasoconstriction، ففي تأثير للـsympathetic على الـHTN

وهاي التأثيرات كلها بالنهاية بتزيد ضغط الدم، فعرفنا بالتالي وين كل دوا رح يشتغل وشو رح نستهدف

Renin–angiotensin–aldosterone system



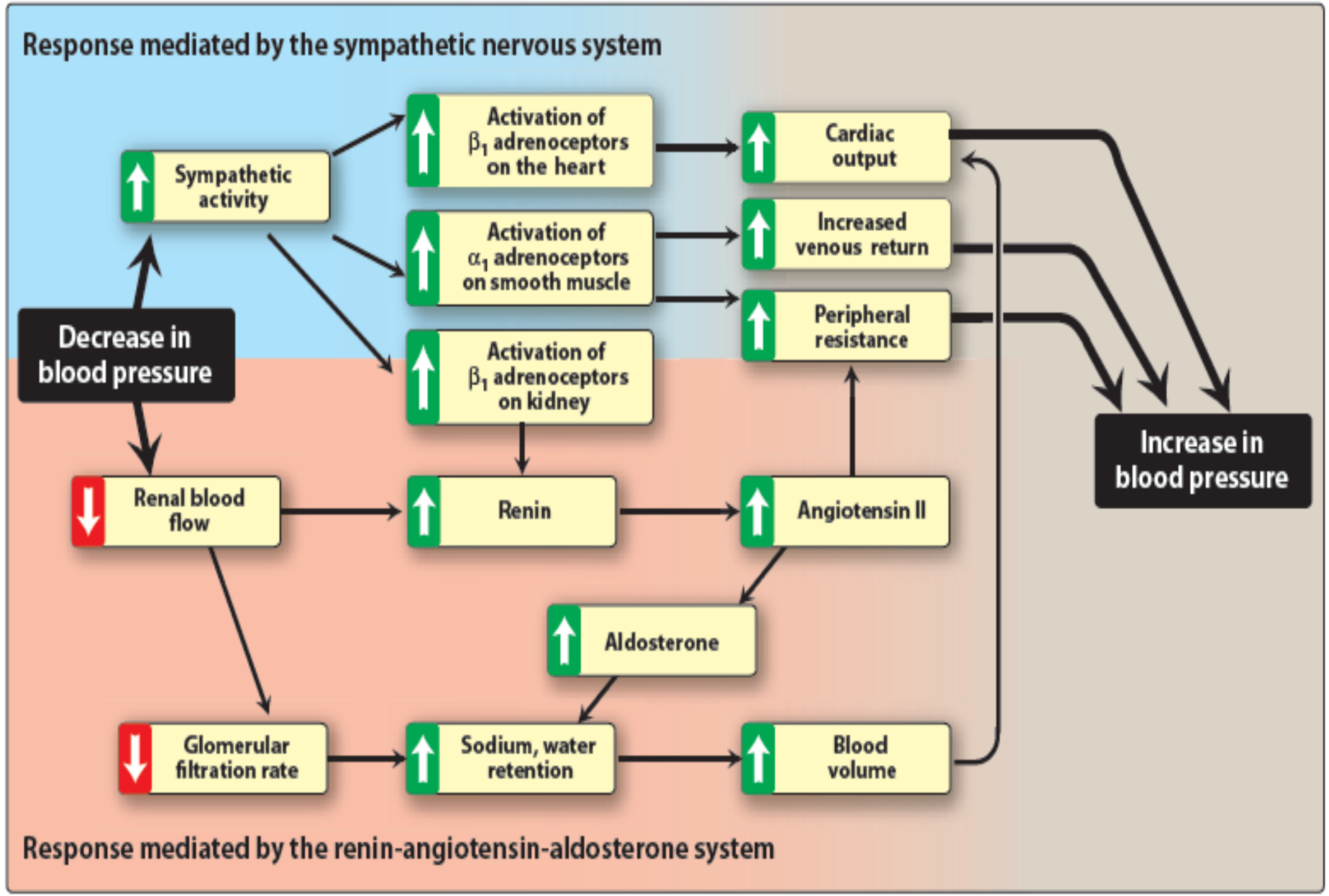
BP control

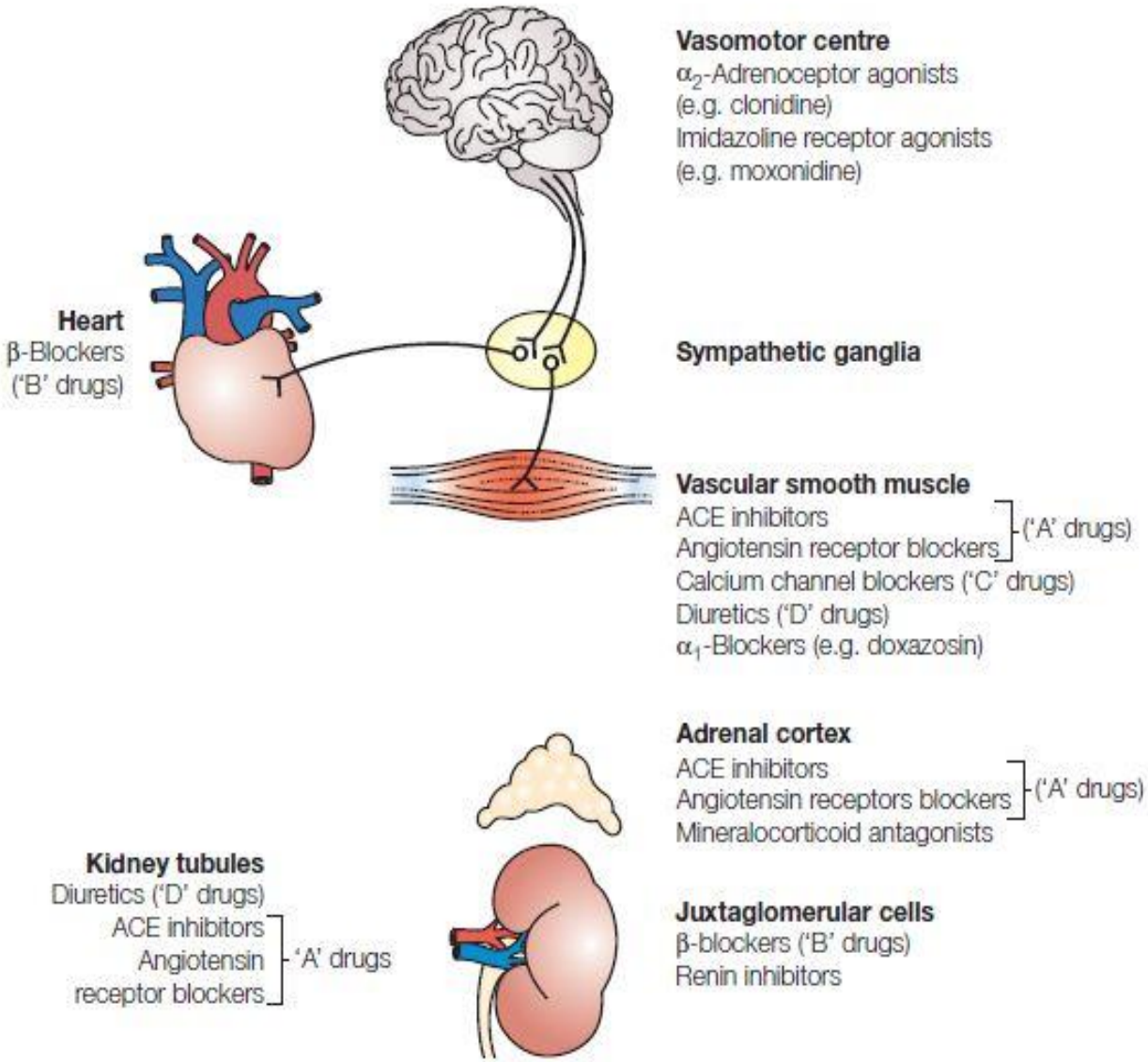
(NS)

- **The sympathetic nervous** system is important in the control of blood pressure(**Baroreceptors** in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord.

- **α receptor** mediated vasoconstrictor tone and β receptor-mediated cardiac stimulation.
- A vasoconstrictor peptide, **endothelin**, released by the endothelium contributes to vasoconstrictor tone.

- Conversely , **endothelium-derived nitric oxide** provides background active vasodilator tone.
- RAAS


Response mediated by the sympathetic nervous system
Sympathetic activity
Activation of β_1 adrenoceptors on the heart
Activation of α_1 adrenoceptors on smooth muscle
Activation of β_1 adrenoceptors on kidney
Cardiac output
Increased venous return
Peripheral resistance
Decrease in blood pressure
Increase in blood pressure
Renal blood flow
Renin
Angiotensin II
Aldosterone
Glomerular filtration rate
Sodium, water retention
Blood volume
Response mediated by the renin-angiotensin-aldosterone system



Mineralocorticoid/ aldosterone antagonists: Spiranolactone

Figure 28.3: Classes of antihypertensive drugs and their sites of action.

Anti-hypertensive drugs

مقسمينهم لأربع مجموعات حسب الأحرف:

A: Angiotensin-converting enzyme inhibitors (ACEI) and

Angiotensin AT1 receptor antagonists (Sartans)

B : β-adrenoceptor antagonists

C : Calcium channel antagonists

D : Diuretics.

وظيفته الكالسيوم للـcontraction, لما أعمله inhibition رح يصير عندي dilation وهذا بسبب إنه smooth muscle cells of the heart and blood vessels رح تضل في حالة relaxation

هون بعطيني guidelines لأعرف شو الأدوية اللي لازم أعطيها لكل مريض بحسب المشاكل الثانية المرتبطة غالبًا بـ الـhtn

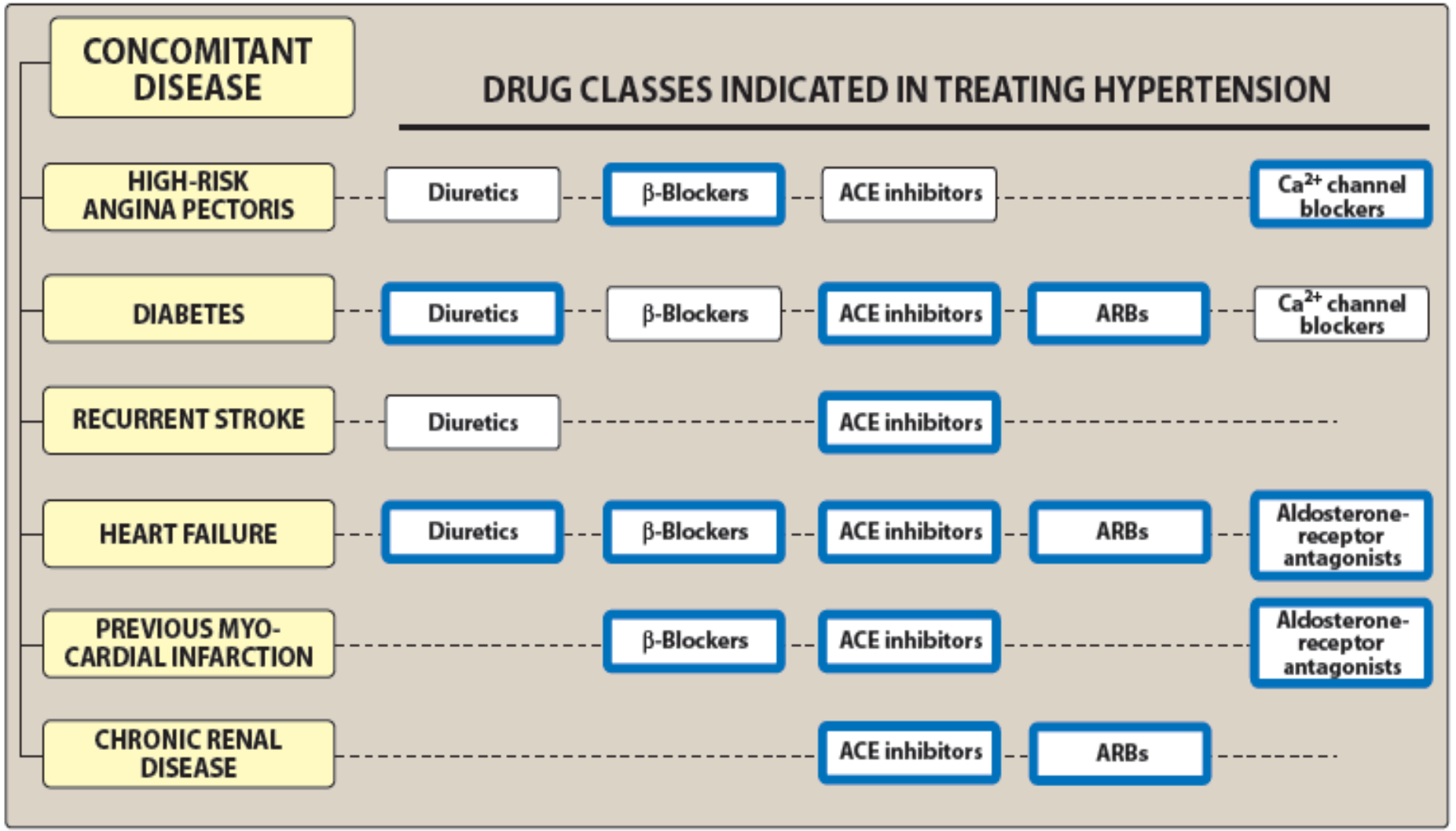


Figure 19.5

Treatment of hypertension in patients with concomitant diseases. Drug classes shown in blue boxes provide improvement in outcome (for example diabetes or renal disease) independent of blood pressure. [Note: Angiotensin-receptor blockers (ARBs) are an alternative to angiotensin-converting enzyme (ACE) inhibitors.] ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

- The ‘ABCD’ rule provides a useful basis for starting drug treatment.
- A (and B) drugs inhibit the renin–angiotensin–aldosterone axis and are effective
- Old people and people of Afro-Caribbean ethnicity often have a low plasma renin and in these patients a class C or D drug is preferred.

ما رح يستفيدوا لأنه AB بشتغلوا على RAAS وهو أصلا الـrenin قليل عندهم

- Use a low dose and, except in emergency situations, titrate this upward gradually.

- Addition of a second drug is often needed. بنعمل combination بين أكثر من مجموعة حتى نوصل للـeffect المطلوب أفضل من زيادة الجرعات
- It is better to use such combinations than to use very high doses of single drugs: this seldom works and often causes adverse effects.
- Loss of control – if blood pressure control, having been

well established, is lost, there are several possibilities to be

considered:

- non-adherence;
- drug interaction – e.g. with non-steroidal antiinflammatory

drugs (NSAIDs)

- intercurrent disease – e.g. renal impairment,

atheromatous renal artery stenosis.

Atheromatous: accumulation of macrophages and debris in the artery wall.

DRUGS USED TO TREAT HYPERTENSION

خلص مالكم ما بتتقبلوا مزح

(A) DRUGS:

1 **ANGIOTENSIN-CONVERTING ENZYME INHIBITORS** ACE I

الأكثر استعمالاً-first line لأنه عندهم beyond anti htn effect

Ramipril 2.5-20 mg /day

Trandolapril, 1-4 mg

Fosinopril :10-40mg

lisinopril :

Captopril 3 times / Day

Enalapril :

- differ in their duration of action.
- They are given once daily and produce good 24-hour control.
- Patients with heart failure or following myocardial infarction

لأنهم بعملوا حماية للقلب، cardioprotective effect

- They slow the progression of diabetic nephropathy.

الهم كمان diuretic effect وحماية للـkidneys

ACE MOA

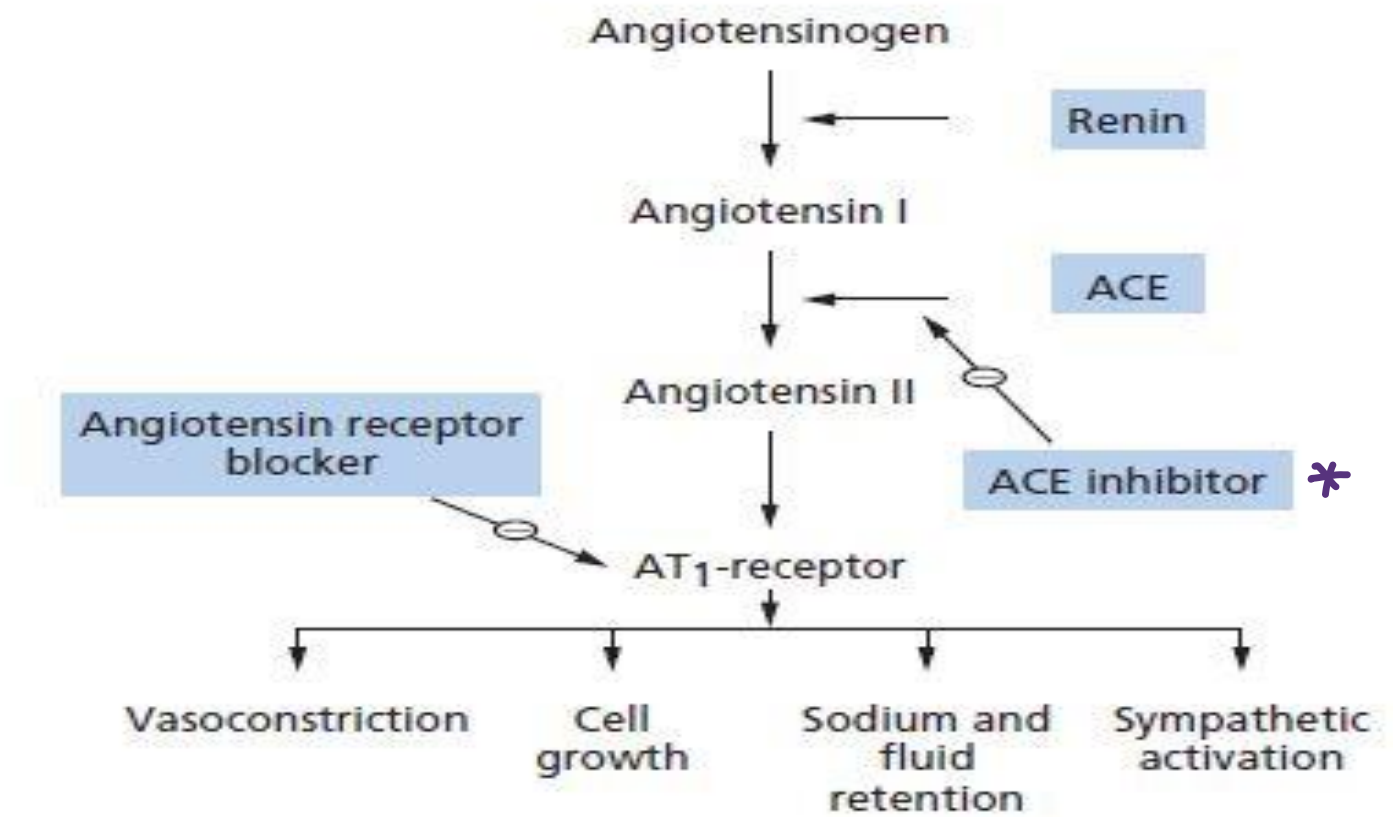
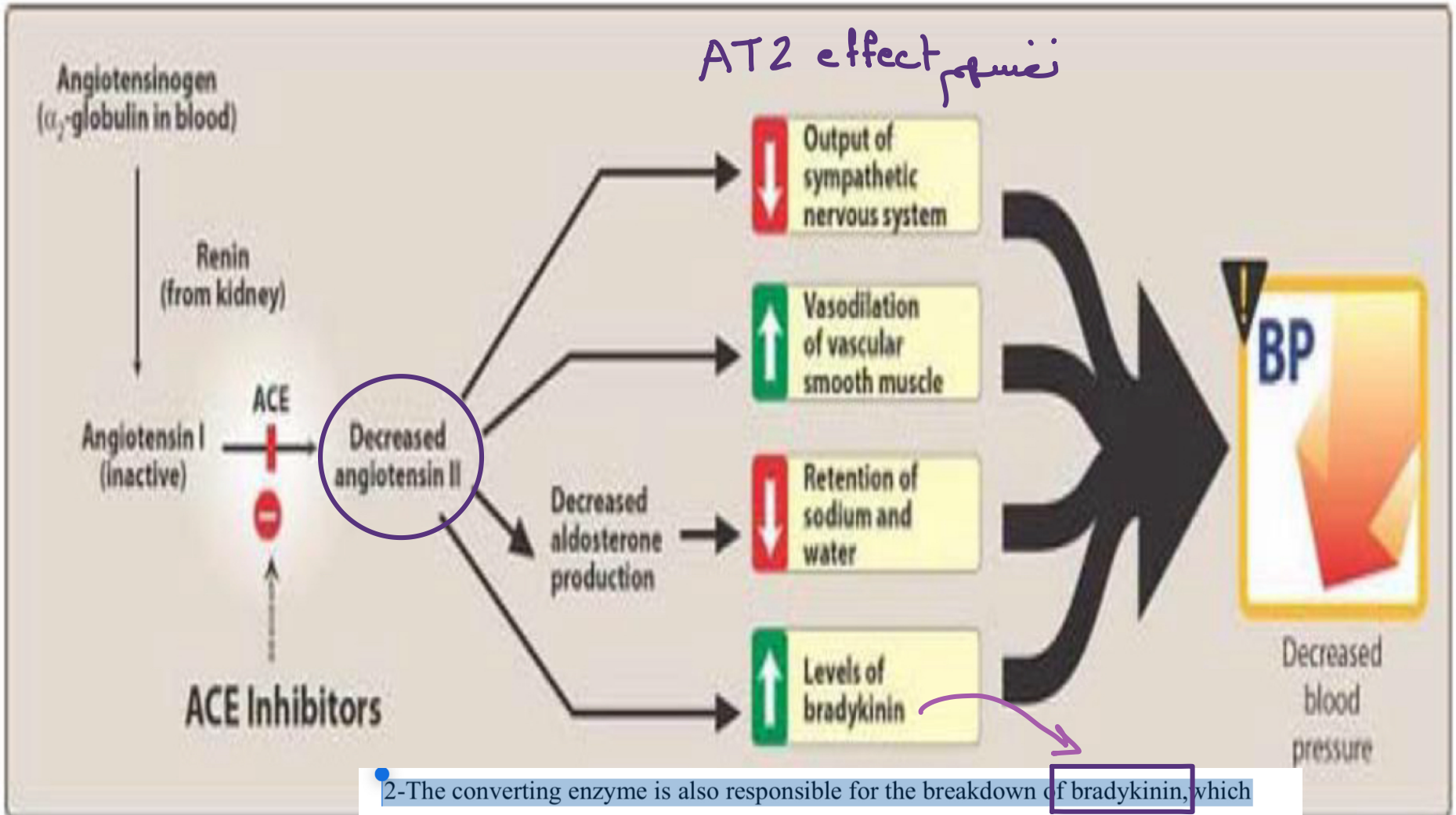


Figure 28.4: Generation of angiotensin II, and mode of action of ACE inhibitors and of angiotensin receptor blockers.

* هون بمنع تحول AT1 لـAT2 بالتالي بقلل نسبته بالجسم وبقلل كل التأثيرات الناتجة عنه



2-The converting enzyme is also responsible for the breakdown of bradykinin, which increases the production of nitric oxide and of prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators(arterioles and veins) .

- Possibility of first-dose hypotension. لو أول مرة بياخذه، انصحه ياخذه بالليل أو قبل النوم

- The dose is subsequently usually given in the morning and increased gradually if necessary, while monitoring the blood-pressure response

Mechanism of action

- 1. ACE catalyses the cleavage of a pair of amino acids from short peptides, thereby ‘converting’ the inactive decapeptide angiotensin I to the potent vasoconstrictor angiotensin II

- 2.It also inhibits the degredation of bradykinin which is (a vasodilator peptide).

- **Metabolic effects**

ACEI cause a mild increase in plasma potassium which is usually unimportant, (significant in RF) Renal Failure

- **Adverse effects**

ACE inhibitors are generally well tolerated. Adverse effects include:

- First-dose hypotension.
- Dry cough – this is the most frequent symptom (5–30% of cases) during chronic dosing (due to bradykinin accumulation)
- Renal Faliure in Bilateral Renal artery stenosis. (therefore contraindicated)
- Contraindicated in pregnancy
- Angiodema بحالات نادرة جدًا، ممكن يعمل عندي edema حول العين والفم برضو بسبب bradykinin

لو استمرت لازم تغيره

ارتفاعه بالجسم بعمل زي أعراض الحساسية inflammatory mediator أخو الـhistamine-، فالجسم بكسره وبخليه inactive عن طريق ACE

How does ACEI s contribute to Renal faliure in some patients?

- Glomerular filtration in these patients is critically

  dependent on angiotensin-II-mediated **efferent** arteriolar vasoconstriction, and when angiotensin II synthesis is

  inhibited, glomerular capillary pressure falls and

  glomerular filtration ceases

تعتمد filtration بشكل رئيسي على الـvasoconstriction
للـefferent عن طريقAT1 . فلما يقل، بتوقف الـfiltration

Pharmacokinetics

- active when administered orally, but are highly polar and are eliminated in the urine.
- A number of these drugs (e.g. **captopril, lisinopril) are active**
- others (e.g. **enalapril) are prodrugs and require**

  metabolic conversion to active metabolites (e.g. **enalaprilat, prendoprilat, ramiprilat)**
- ACEI penetrate the central nervous system.
- Many ofthese agents have long half-lives permitting once daily dosing; **captopril is an exception.**

3 times

Drug interactions

diuretic

✓ Benficial combination with thiazides because :

- ACEIs enhance thiazides efficacy (since it blocks RAS loop)

غالبًا بكونوا بنفس الدوا موجودين، مثلاً fisinopril مع hydrochlorothiazide

- Decrease thiazide- induced hypokalemia

كونه الـACEI بعملوا mild hyperkalemia هالشي مفيد

❖ ACEIs not prefered with potassium sparing diuretics due to hyperkalemia induction

الاثنين بعملوا hyperkalemia، فبقلل كفاءة عضلة القلب

❖**NSAIDs increase BP with ACEIs as well as other agents!!!**

ياخذ باراسيتامول✨
لأنه الـnsaids بزيدوا الضغط ورح يعملوا RF acute بشكل مباشر

Notes

NSAIDs inhibit prostaglandin-mediated vasodilation and promote salt and water retention. Both of these mechanisms may contribute to NSAIDs partially reversing the effects of hypotensive drugs, particularly those agents whose mechanism depends on modulating prostaglandins, renin, or sodium and water balance

Therapeutic Indications of ACEIs

- Essential HTN, +- DM
- Left ventricular dysfaunction لأنه حكينا عنده cardioprotective effect
- Post MI
- IHD

2 ANGIOTENSIN RECEPTOR BLOCKERS "SARTANS"

هذول الأدوية متطورة بشكل أكبر من الـACEI لأنه الـAT اله أكثر من مكان فـ إني أمنع ارتباطه بالـreceptor بكون أفضل وأشمل
يعني بضل الـAT موجود بالجسم بس لعدم ارتباطه بالـreceptor فما بعمل التأثيرات

- ✓**losartan, candesartan, irbesartan, valsartan**
- ✓Sartans are pharmacologically distinct from ACEI, but clinically similar in hypotensive efficacy.
- ✓lack the common ACEI adverse effect of dry cough.
- ✓ Useful in HTN patients with complication as Heart Faluire or post MI, and diabetic (same as ACEIs)
- ✓Binds with AT1 receptor in a stable complex

طيب مين أختار؟
الـACEI كونه الها مدة أكبر موجودة وعليها دراسة أكبر لفعاليتها وللـSE المكنة، ثاني سبب لأنه ARBS أغلى سعرًا
بس بنفضل الـARBs في حالة الـdry cough

Mechanism of action

- Most of the effects of angiotensin II, including vasoconstriction and aldosterone release, are mediated by the angiotensin II subtype 1 (AT1) receptor. (blocked by sartans).

http://pharmacologycorner.com/mechanism-of-action-video-animation-ace-inhibitors-angiotensin-ii-receptor-blockers-arbs-and-the-renin-angiotensin-aldosterone-system/

- Sartans are 10000 times more selective on AT1 receptors than Angiotensin 2!!!

Competitive antagonist reversible

بس عندهم affinity عالية حدًا بتعطيهم efficacy كثير عالية

- The pharmacology of sartans differs predictably from that of ACEI, since they do not inhibit the degradation of bradykinin

- This difference probably explains the lack of cough with sartans

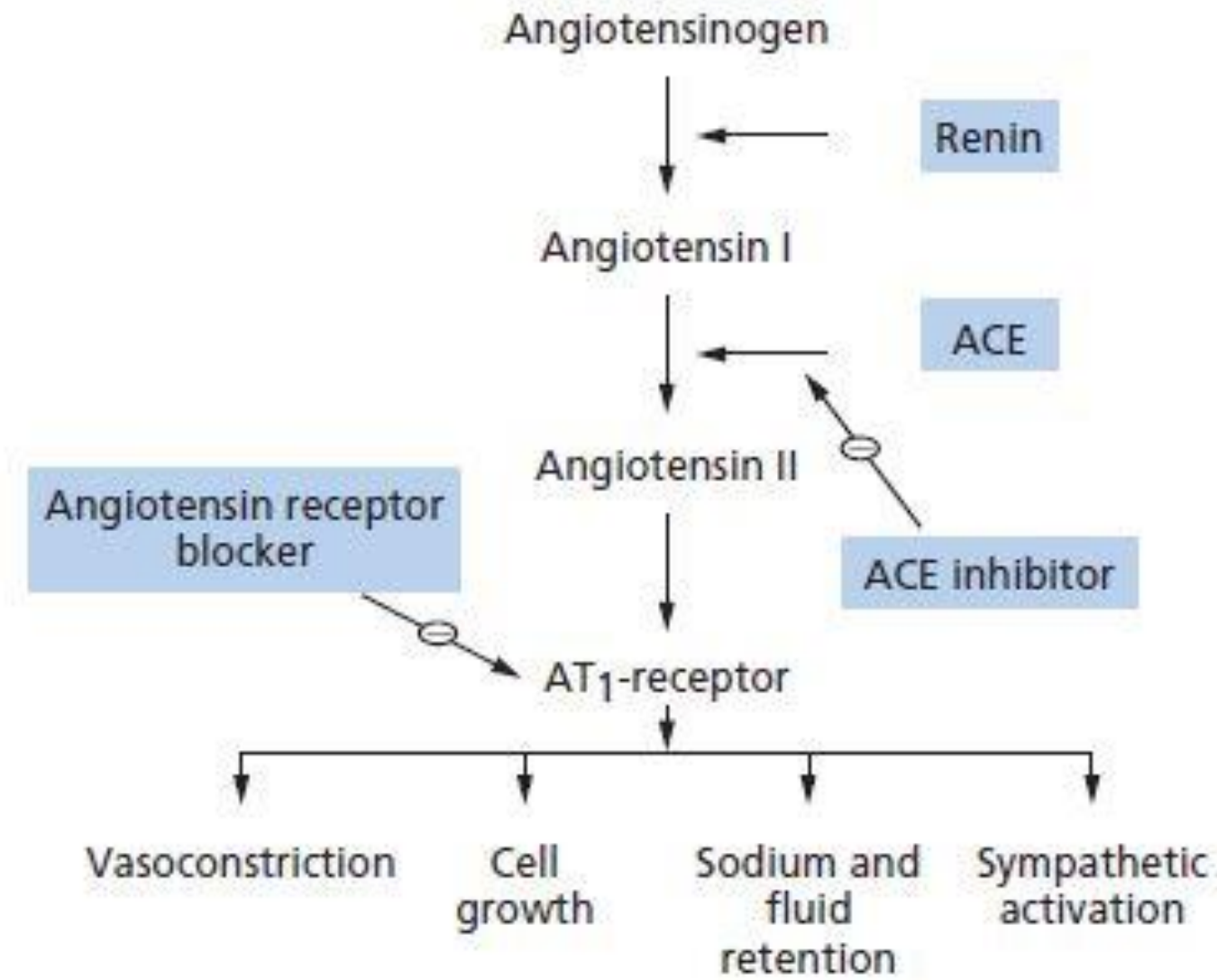


Figure 28.4: Generation of angiotensin II, and mode of action of ACE inhibitors and of angiotensin receptor blockers.

Pharmacokinetics

- Half-lives of most marketed ARB are long enough to permit once daily dosing.

Drug interactions

غير منطقي

No rational to combine ACEIs with Sartans.

Favourable Sartan combinations as in ACEIs combination + CCB / Diuretics

Adverse effects

- Adverse effects on renal function in patients with bilateral renal artery stenosis are similar to an ACEI.
- Hyperkalaemia and fetal renal toxicity.
- Angio-oedema is much less common than with ACEI

Aliskiren

حنمن الـA group وبكن استخدامه قليل جدًا

- Direct renin inhibitor (DRI)
- FDA approved in 2007
- Aliskiren binds to the binding pocket of renin, essential for its activity. Binding to this pocket prevents the conversion of angiotensinogen to angiotensin I.
- Aliskiren is also available as combination therapy with hydrochlorothiazide.
- Side effects include : hyperkalemia, angioedema

اللهم ارزقنا نجاحًا في كلّ أمر، ونيلاً لكلّ مقصد، وارزقنا القمة في درجات العلم💗
لينة سلامة