

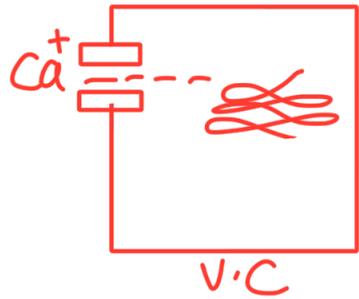
تفريغ فارما 1

اسم الموضوع: CVS/HTN

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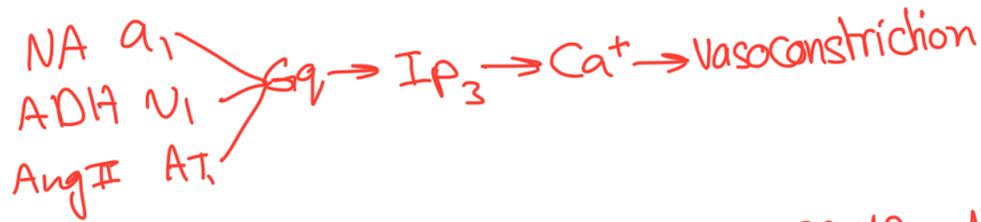
CCBs



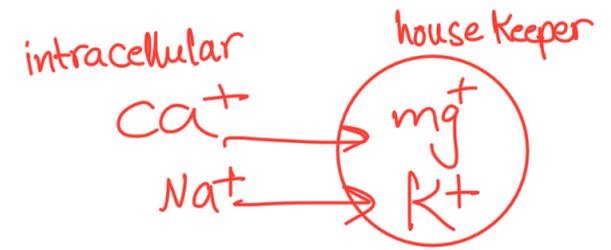
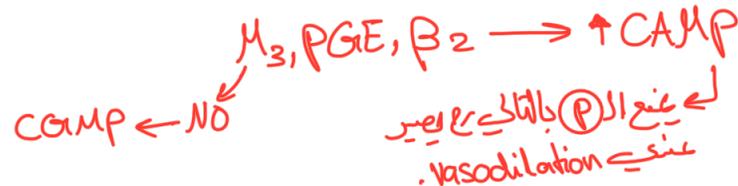
Cardiovascular System

Hypertension

normal $\frac{120}{80} = \frac{(90-140)}{(60-90)}$

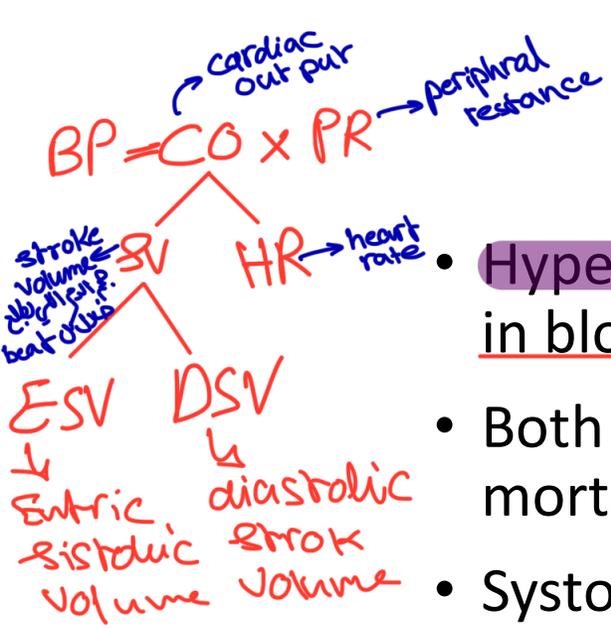


in smooth muscle



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


poor function of the kidneys that may be due to a reduction in blood-flow to the kidneys caused by renal artery disease.



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

blood vessels compliance / عند كبار السن
 ↓ elasticity of blood vessels
 ↑ resistance as peripheral.
 (diastolic near normal)

يعني الارتفاع في
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 الارتفاع في الـ

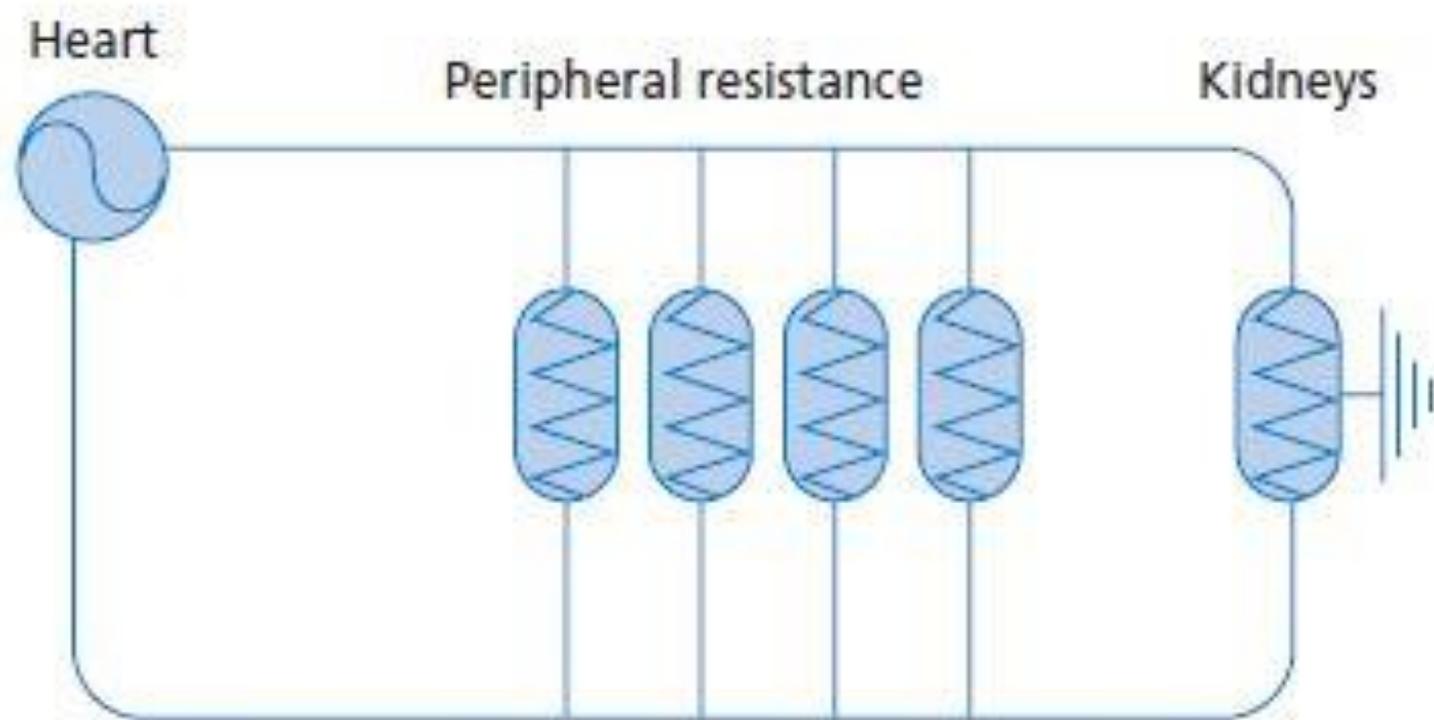


Figure 28.2: Arterial blood pressure is controlled by the force of contraction of the heart and the peripheral resistance (resistances in parallel though various vascular beds). The fullness of the circulation is controlled by the kidneys, which play a critical role in essential hypertension.

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

انسداد

180/120 hypertensive crises.

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

التهديد
 emergency and urgency
 180/120 180/120
 organ damage no organ damage.
 يجب أخذ حذرك
 على الضغط وبعدها
 لازم يشوف الدكتور

gradually on
 ischemic organ عند
 عشانك مايسر

The risk of cardiovascular disease, is increased markedly by:

Smoking

Diabetes

Elevated low-density lipoprotein LDL

Genetic factor

Male gender

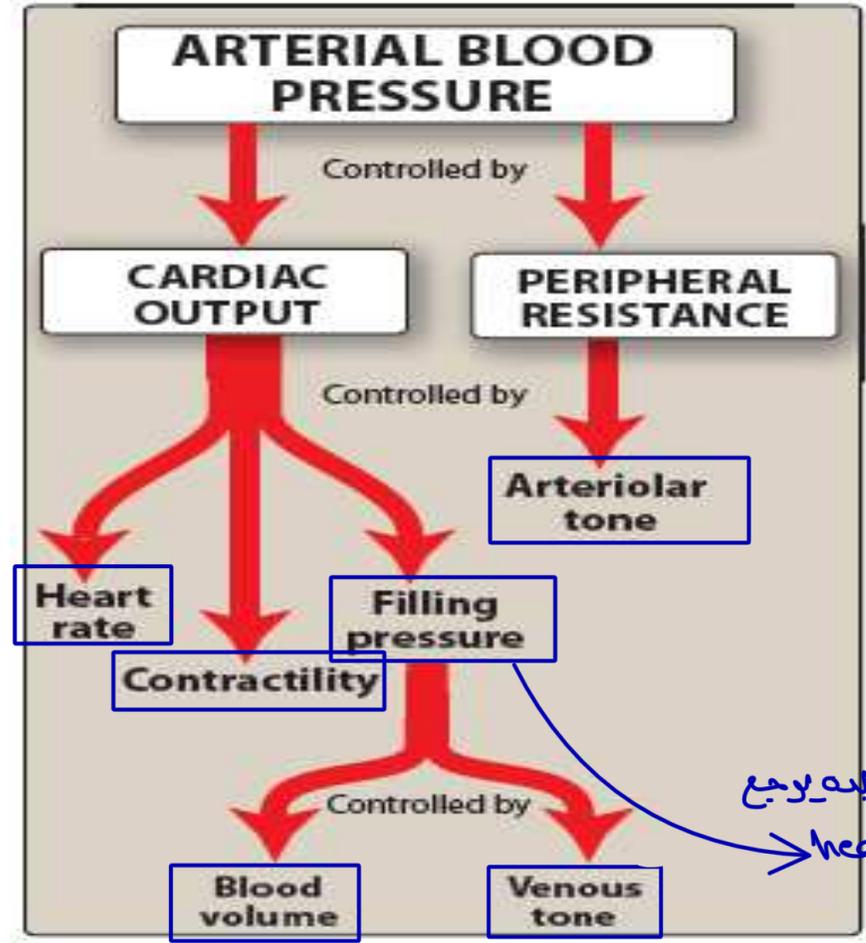
Obesity

Stressful life style

	Systolic mm Hg		Diastolic mm Hg
Normal	<120 <i>+20</i>	and	<80 <i>+10</i>
<u>Prehyper-</u> <u>tension</u>	120– 139	or	80–89
<u>Stage I</u>	140– 159	or	90–99
<u>Stage II</u>	≥160	or	≥100

emergency *≥180* *≥120*

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).



حجم الدم الذي يجمع على القلب

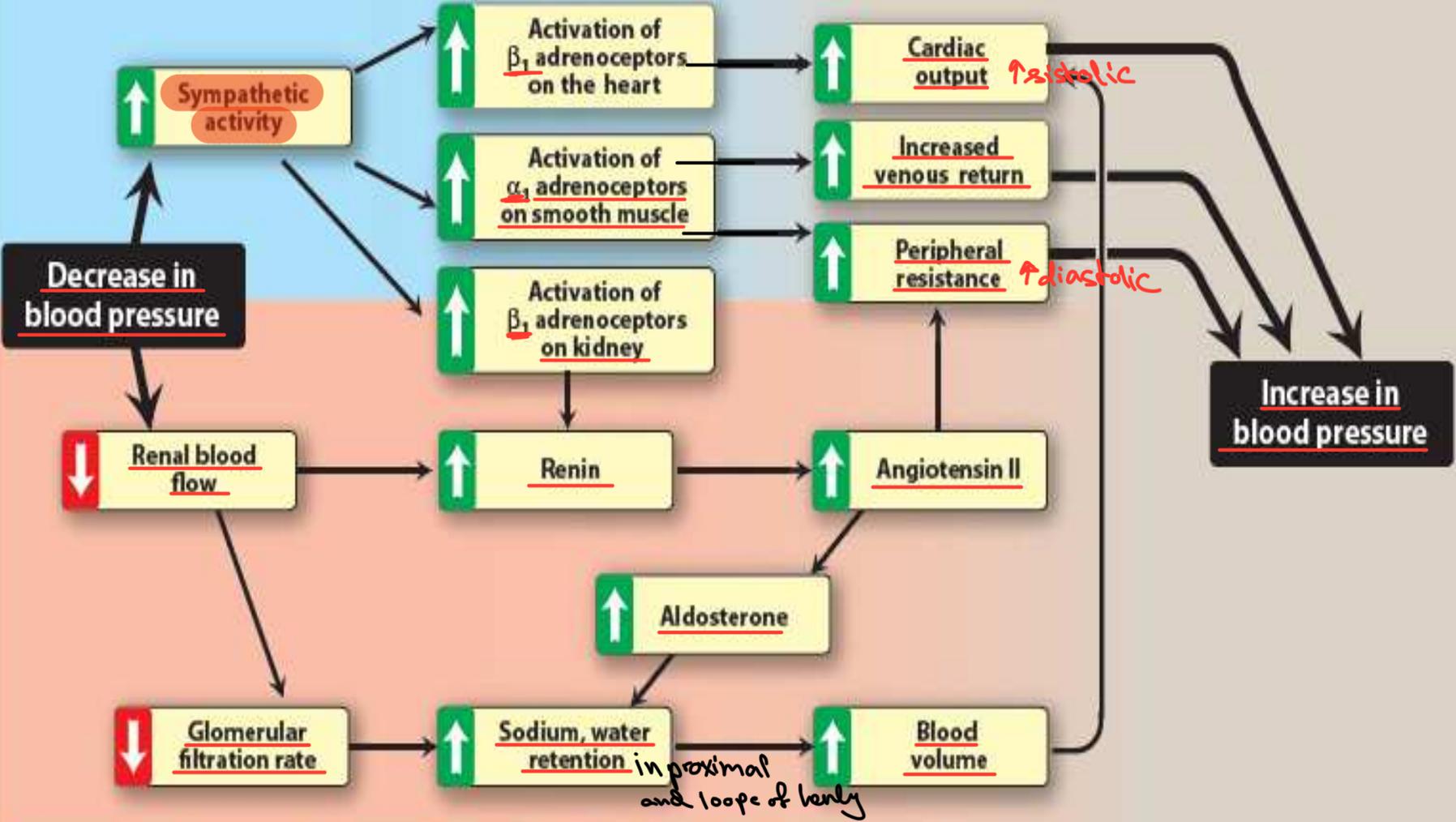
Figure 19.3
Major factors influencing blood pressure.

BP control

- 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** *renin-angiotensin-aldosterone system*



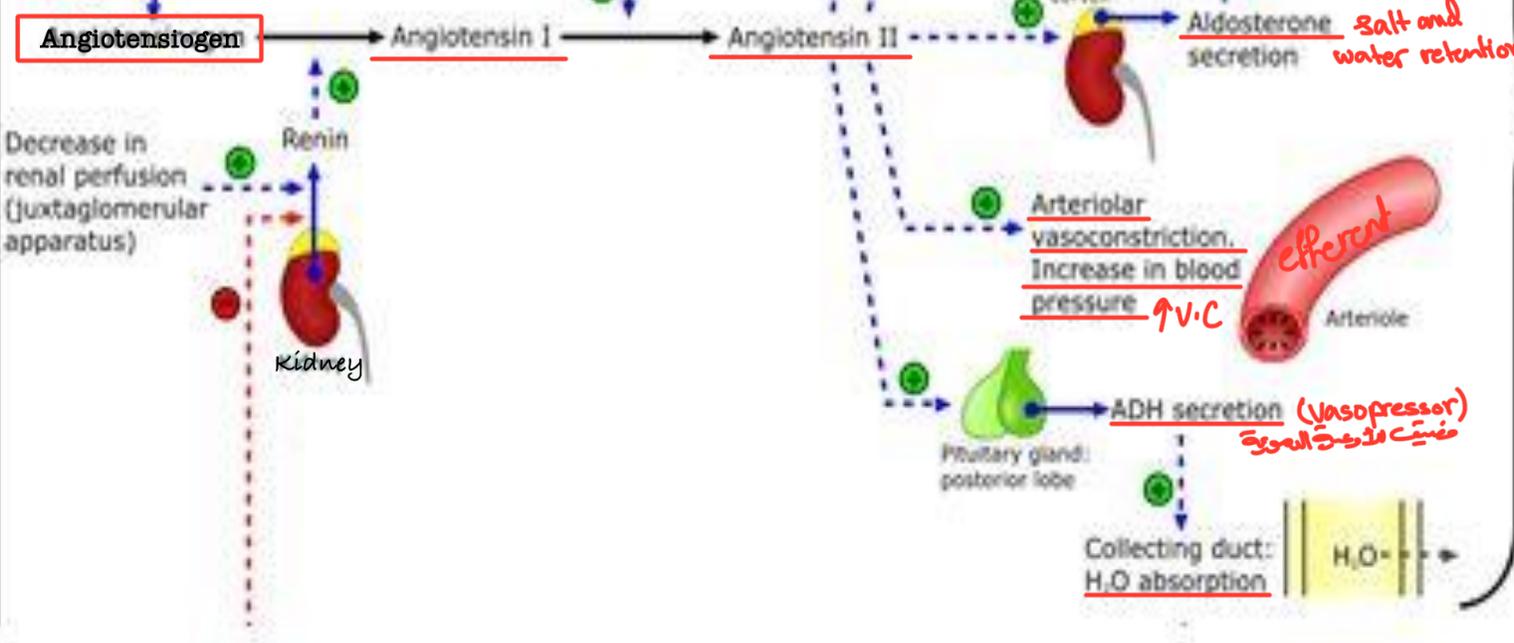
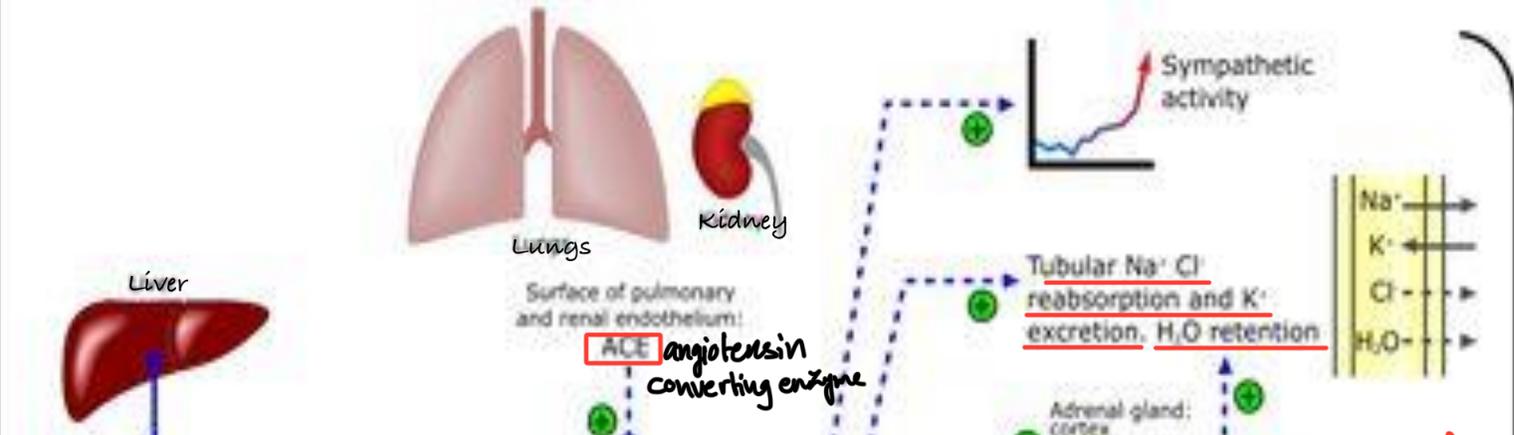
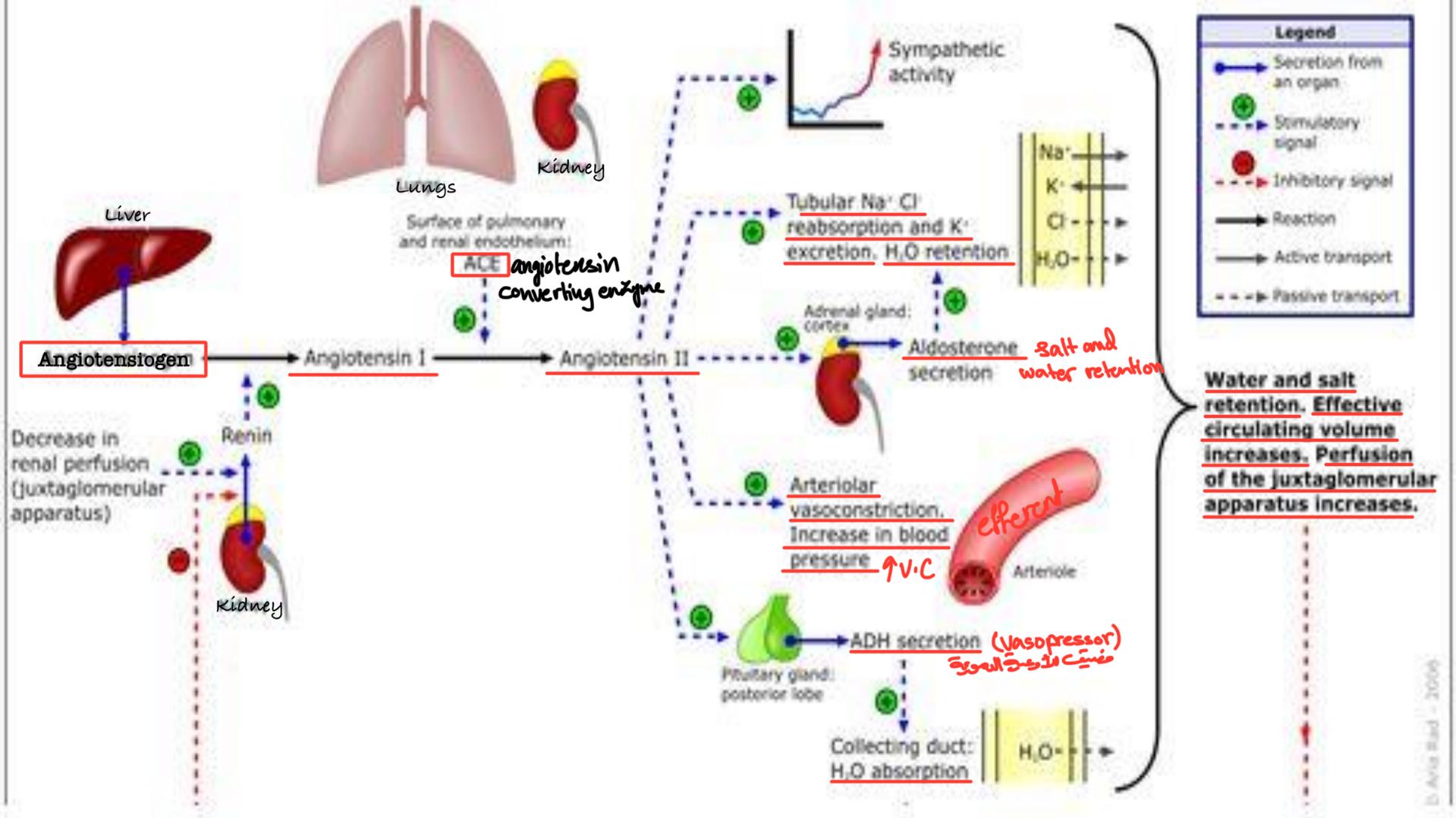
Response mediated by the sympathetic nervous system



Response mediated by the renin-angiotensin-aldosterone system

Figure 10.4

Renin-angiotensin-aldosterone system



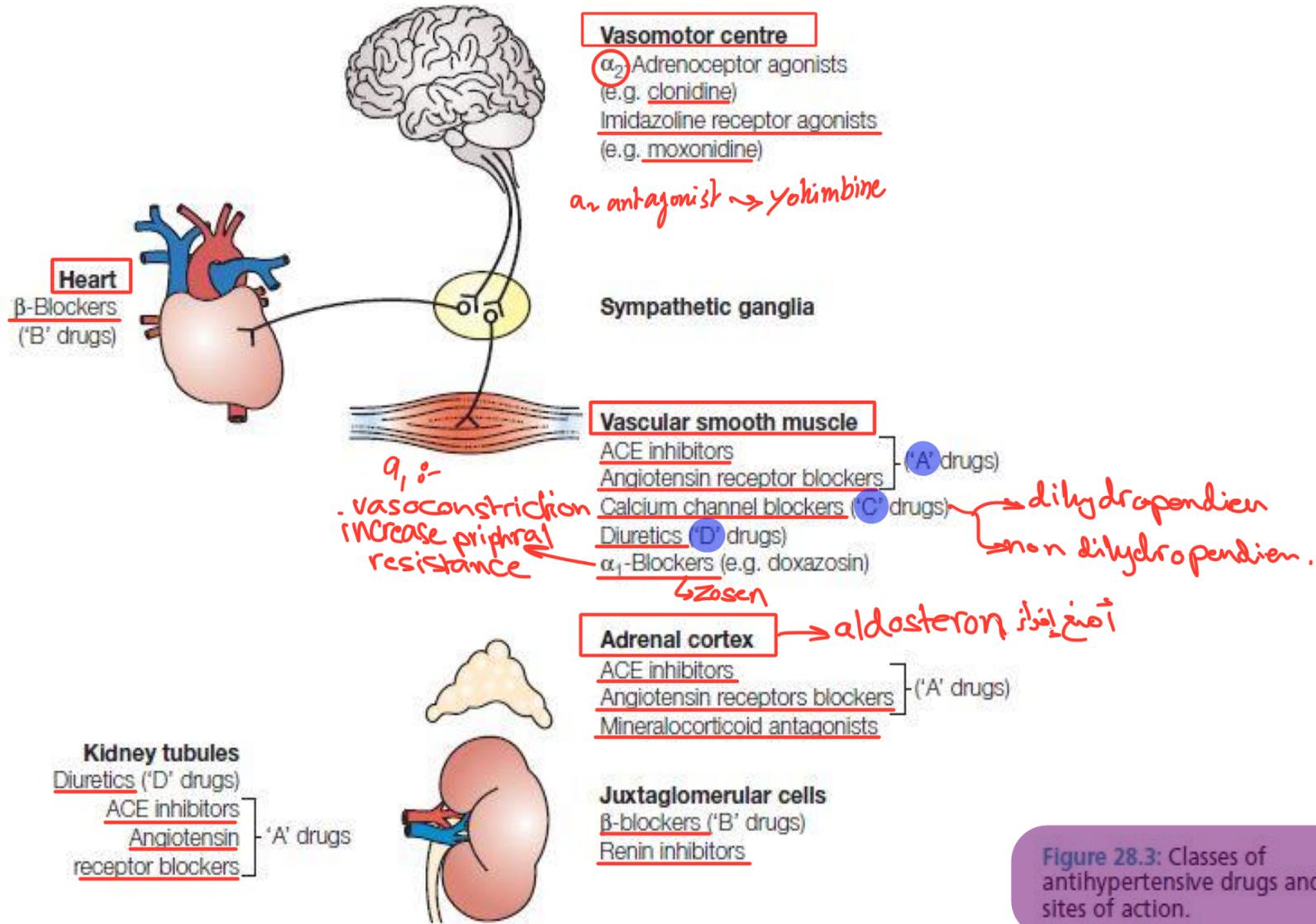


Figure 28.3: Classes of antihypertensive drugs and their sites of action.

Anti-hypertensive drugs

ABCD

- A:** Angiotensin-converting enzyme inhibitors (ACEI) and Angiotensin AT1 receptor antagonists (Sartans) ARB's
- B:** β -adrenoceptor antagonists / \downarrow CO, \downarrow Renin, \downarrow NA, NO, PGE
- C:** Calcium channel antagonists
- D:** Diuretics. \downarrow hypovolemia, \downarrow Na

\nrightarrow α_1 blocker

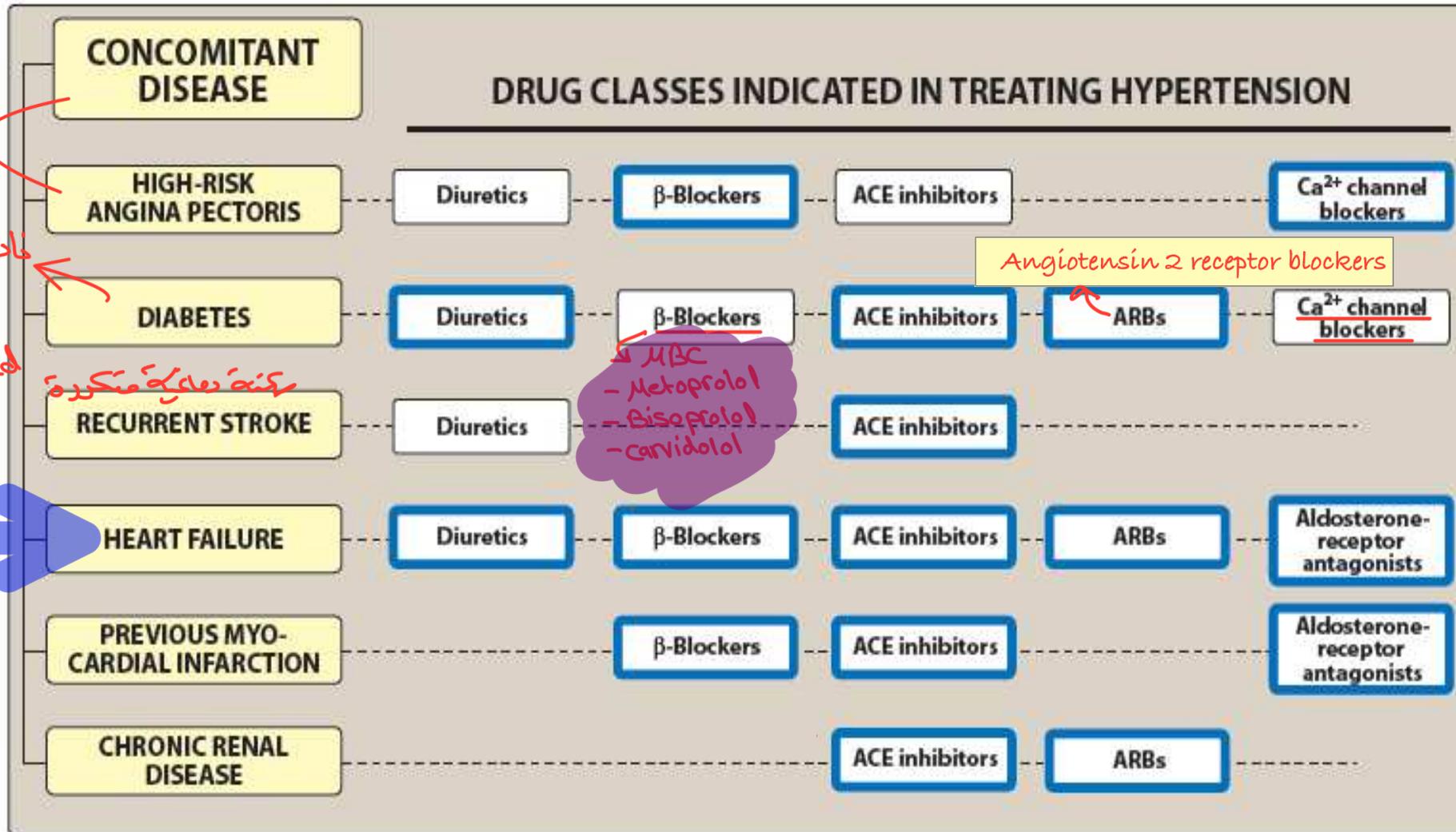


Figure 19.5

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

• يفضل إنني ما أبلس بدواء ضغط وبعدين اذا حسيت الضغط
 not controlled أمير أبلس أعالي بال dose معي ما أوصل لل maximum
 رتبه معي هل ثانيه اني أعطي دواء ثانيه معي .
 • إزني أذا قد احيي خيارين إما اني أعلي ال dose
 أم اني أختار دواء ثانيه ولكن من different family .
 • إزني من الخطأ اني أبلس أعالي حلاله ضغط ب ثلاثه أدويه مثلا
 لزم maximum يكون معاشيه .
 • الخطوة الثانيه إذا ما سيطر على الضغط بعلي ال dose بن جابون
 maximum
 • إذا كان لما الضغط من سيطر عليه من أعلي حسب دواء ثانيه أو ثالثه .

• في حال رفعت ال dose وبتبها أتمت دواء وبتبها ما سيطرت
 على الضغط لازم ارجع أسوف شو سبب الضغط أتمت .
 • "adherence" من ملتزم بالدواء | ما بيوفده على الوقت
 | ما بيوفده الجرعات لصبح | قبل الأكل بعد الأكل .
 • و أمانه الضروريه (تأكد المريض كيف بيوفده الدواء متى بيافذه وجرعة
 اللي بيوفدها .

- Addition of a second drug is often needed.
- 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.

drug-drug interaction
 مش شرط يكون ماخذ دواء ضغط
 يمكن ماخذ في وقت واحد
 - Enzyme induction
 or
 - Enzyme inhibition
 or

interaction
 يمكن ان يكون نوع interaction
 drug food interaction

حاي الأذوية يمنع
 synthesis of prostaglandin
 وبالتالي مع زيادة sodium
 water retention.

ضعف
 يقلب
 blood flow يقل عند
 وبالتالي مع زيادة blood pressure

من الضروري للمريض ضغط
 في أعين السبب قبل وأثناء
 الضغط

DRUGS USED TO TREAT HYPERTENSION

(A) DRUGS:

Angiotensin II
inactivates I →

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE I & ARPs →

ACEI له مختلف عن ال
side effect أيضا أقل
رديت أعلى تكلفه.

Ramipril 2.5-20 mg /day

Trandolapril, 1-4 mg

Fosinopril :10-40mg

lisinopril :

Captopril →

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
- They slow the progression of diabetic nephropathy.

و دائما مرضى diabetic يمرضون عندهم
micro vascular diabetes
neuropathy, Retinopathy, nephropathy
و ايضا يمرضون عندهم
macro vascular diabetes
MI, stroke.

كيف أدوية ال ACE I وبتعالج مرض ال
nephropathy عند diabetic
و هاي الأدوية بتعمل على ال afferent و efferent
arterials

(nephroprotective agent)

تعاظف أنه ما تنهوي أمور ال kidneys لتتأخر
glomerulus بتأخر
Vasodilation بتأخر
efferent و mainly ال afferent
arterials

once daily
اللم ياخذ
معدا دواء
والبراهون
CNS
prodrug

ACE MOA

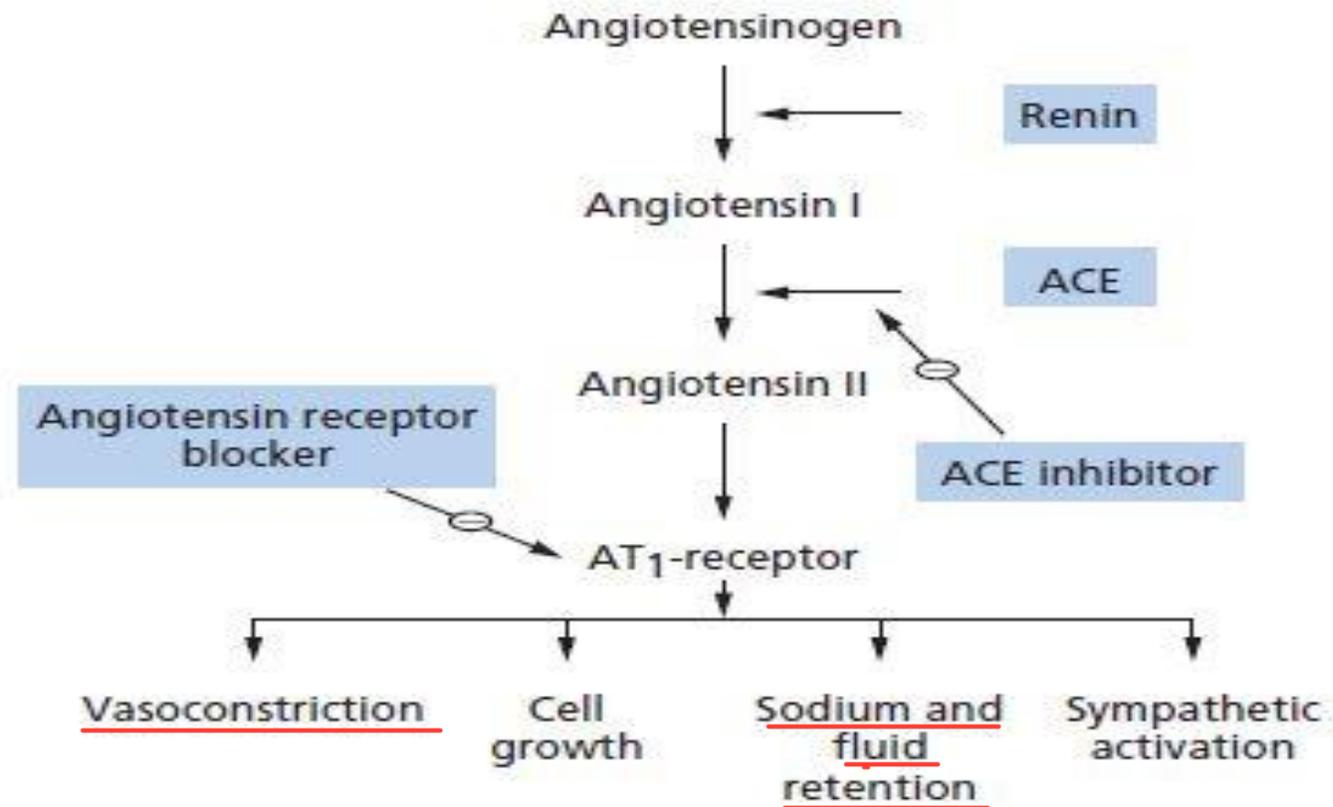


Figure 28.4: Generation of angiotensin II, and mode of action of ACE inhibitors and of angiotensin receptor blockers.

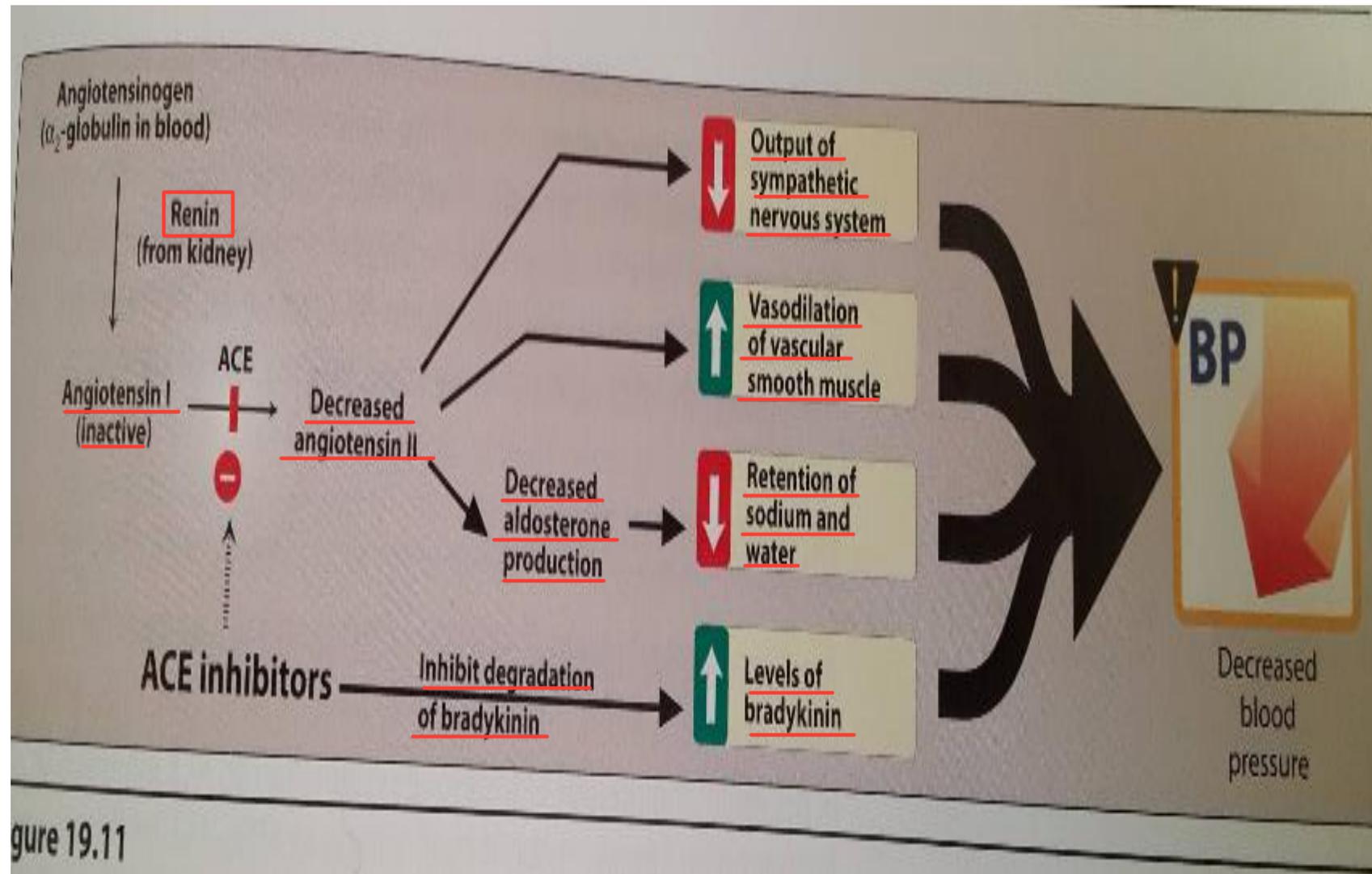


Figure 19.11

- Possibility of first-dose hypotension.
- 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 degradation of bradykinin which is (a vasodilator peptide). ↓ BP

angiotensin I → هي عبارة عن Decapeptide يعني مكونة من 10 amino acids من ACE مستول عن تكبير هذه ال amino acids وتحويله لـ angiotensin II (active form) بال ACEI يمنع هائي العملية بالتالي خارج يمين عنده vasoconstriction و stimulation of SNS.

هل كل مريض إذا كان عنده ارتفاع في ال Creatinine هاد دليل أنه عنده مشاكل في الكلى؟؟؟

لا، يعني الشخص يكون شرب رجهه يعني هبار عنده muscle lysis يعني الحالة يكون عنده ال creatinine عالي.

لا فأننا مشاك أناكد أنه عنده مشاكل في ال kidneys لازم يكون عنده ارتفاع في ال creatinine و uria في الدم.

How does ACEIs contribute to Renal failure 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

metabolic effect سواء كانت ACEI أو ARB's

الاشخاص اللي عندهم hyperkalemia لازم يبعدوا عن أكل العوز تماماً لأنه full of K⁺.

Renin inhibitor أهم برج يعملوا hyperkalemia وهذا الاشياء ما خوفوا الا الشخص اللي معده hyperkalemia والي هه الاشخاص اللي يكون عندهم مشاكل بال kidneys اللي بوجاي الحالة برج فإثر مباشره على heart ويبر عندهم irregular heart arrhythmia. و برهنه بعض ال K⁺ ال narrow range.

Pharmacokinetics

- active when administered orally, but are highly polar and are eliminated in the urine.
*لا يمكن البقاء في الدم في الأنواع CNS، والتمثيل الغذائي في الكلى، ومنه التخلص من الجسم في البول.
CNS side effect، في حالات الـ epilepsy*
- A number of these drugs (e.g. captopril, lisinopril) are active
→ no CNS side effect
- 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 of these agents have long half-lives permitting once daily dosing; captopril is an exception.

Drug interactions

- ✓ Beneficial combination with thiazides because :
 - ACEIs enhance thiazides efficacy (since it blocks RAS loop)
 - Decrease thiazide- induced hypokalemia

لأنه يمنع ACEI من جعل hyperkalemia

- ❖ ACEIs not preferred with potassium sparing diuretics
due to hyperkalemia induction

جنب

warning

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

inhibition of PG → vasoconstriction.

mainly thiazide diuretics
eg:- hydrochlorothiazide .
مما يمتد إلى على distal loop of hili
ويعتاد إلى Na and water retention
من إفراز إلى excretion of Na & water
التي مع تقلص blood volume
في تقلص cardiac output
blood pressure
و بالأخص أن thiazide
يقل hypokalemia و ACEI
بمعلي hyperkalemia التي مع تبادل
الأموه .

Therapeutic Indications of ACEIs

- Essential HTN, +- DM *D. nephropathy / albumin uria.*
- Left ventricular dysfunction
- Post MI
- IHD *Ischemic heart disease*

ANGIOTENSIN RECEPTOR BLOCKERS “SARTANS”

ARB's

- ✓ 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. *لا يوجد ما يستعمله براديكينين*
- ✓ Useful in HTN patients with complication as Heart Failure or post MI, and diabetic (same as ACEIs)
- ✓ Binds with AT1 receptor in a stable complex

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/>

یعنی آریٹھ! حکایت ال
angiotensin 2
دالتالی خارج بیس عنی
vasoconstriction
بیس هو antagonists

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

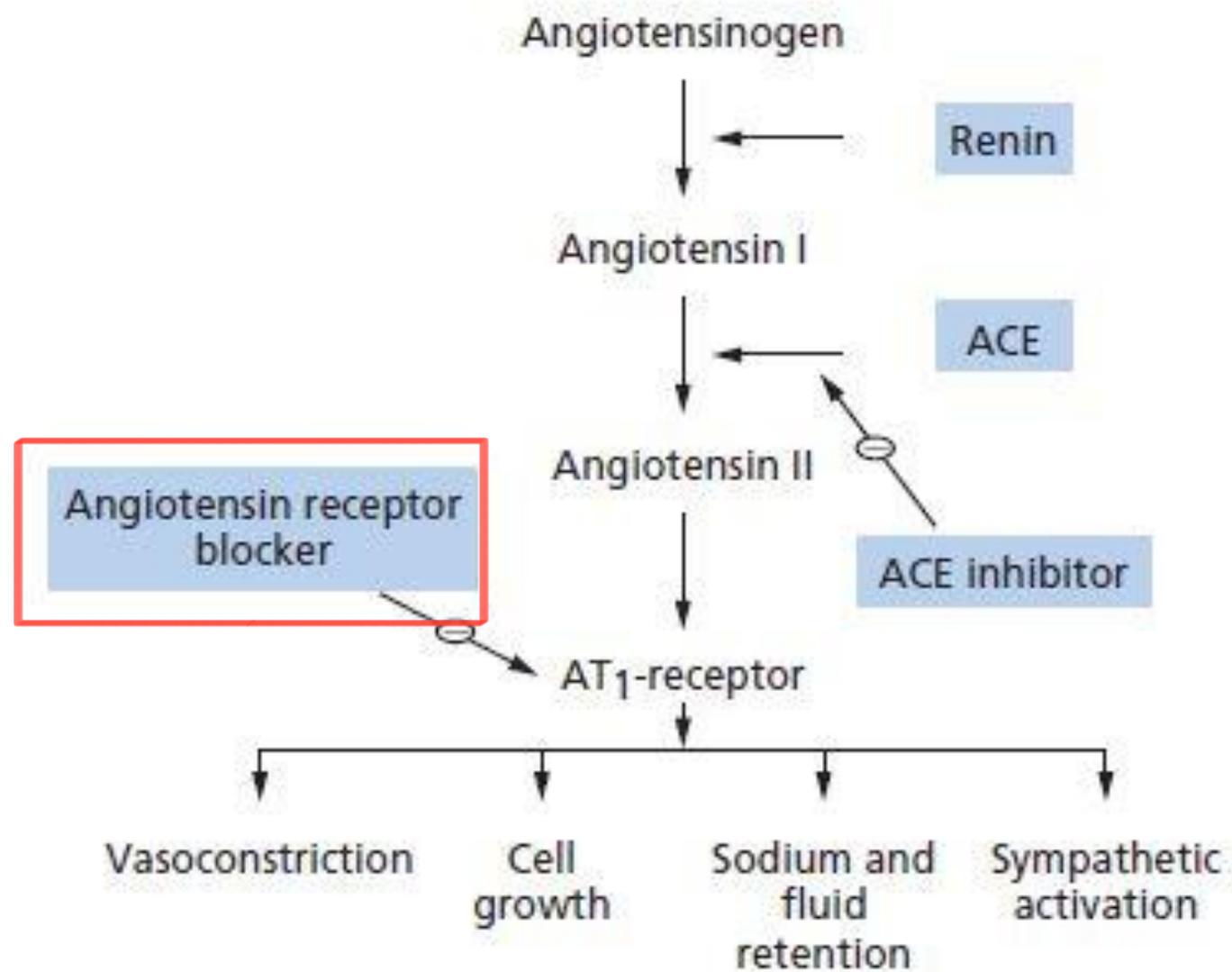


Figure 28.4: Generation of angiotensin II, and mode of action of ACE inhibitors and of angiotensin receptor blockers.

Pharmacokinetics

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

Drug interactions

No rational to combine ACEIs with Sartans.

Favourable Sartan combinations as in ACEIs combination

Adverse effects

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

Aliskiren

- Direct renin inhibitor (DRI) *on active site* \longrightarrow *angiotensinogen* $\not\rightarrow$ *angiotensin I*
- 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



نهاية مادة السكند يعطيك الف عافية 🎉