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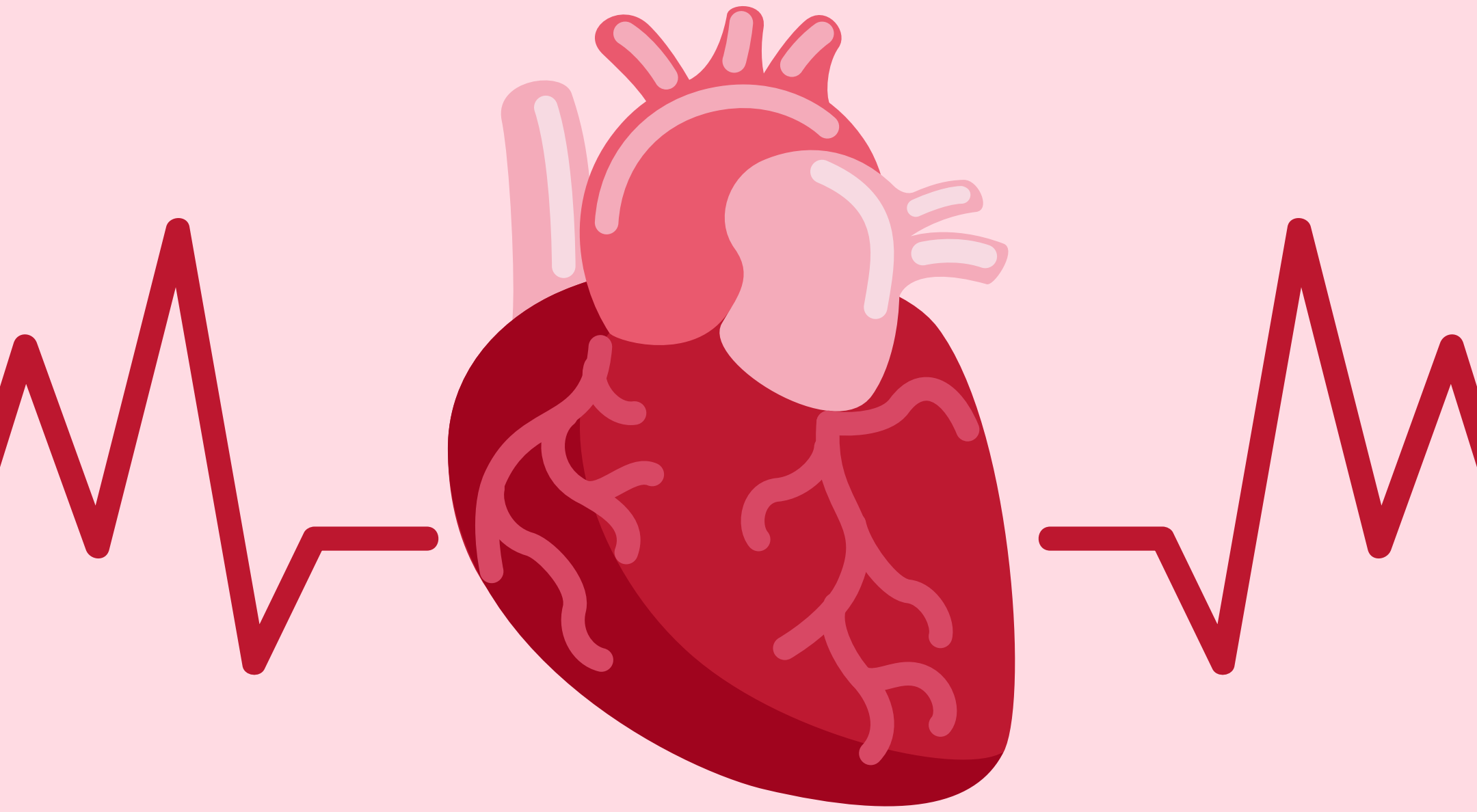

SUB: *Pharmacology*

LEC no: 7

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CVS- Pharmacology 7
Antihypertensive2

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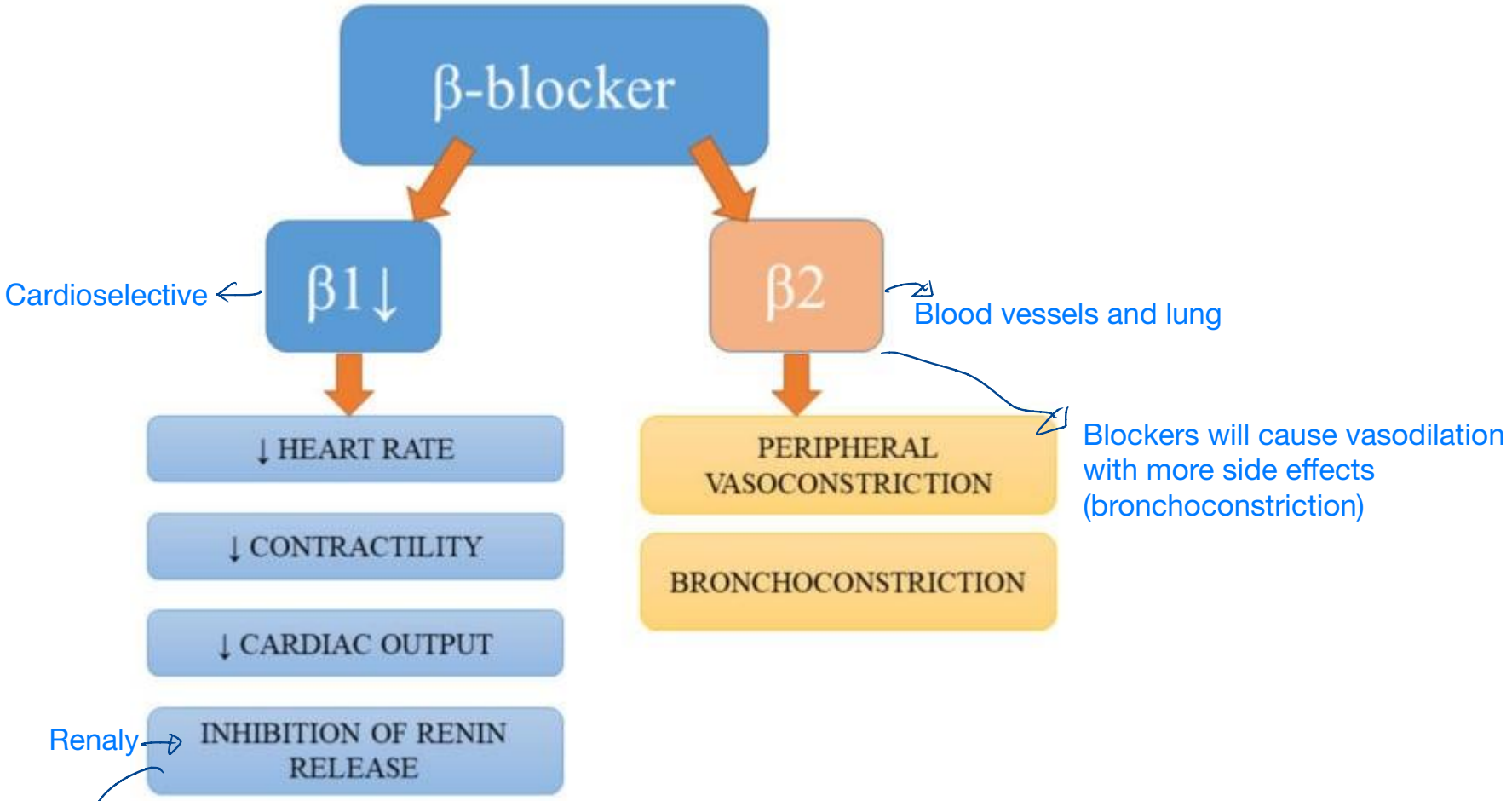
Beta-adrenergic blocking agents

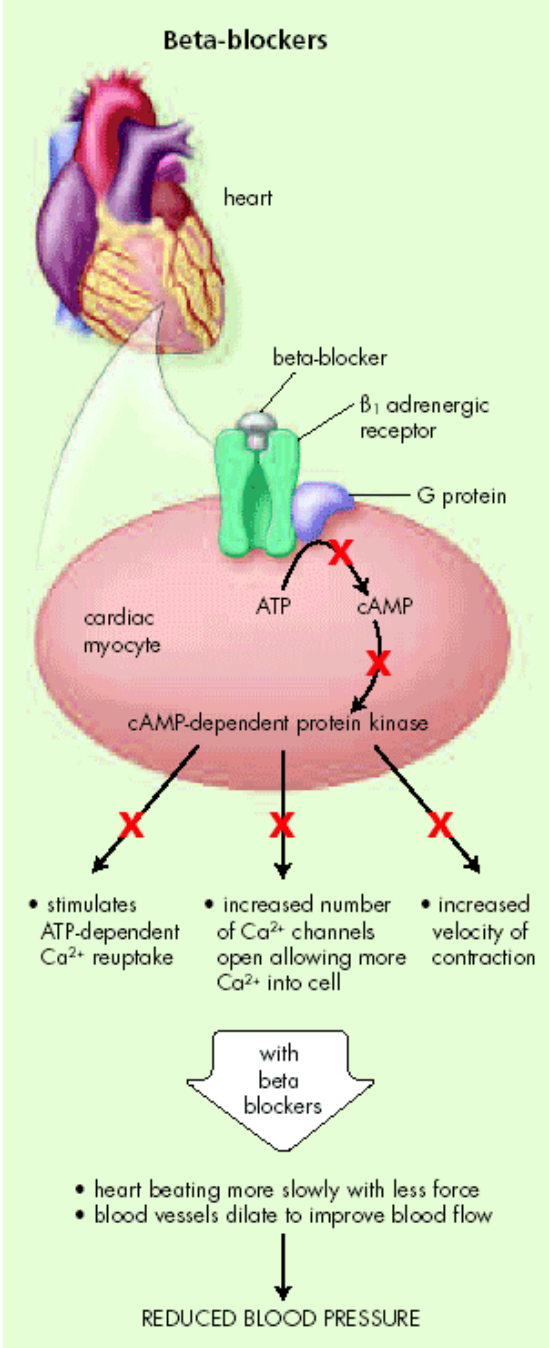
بدنا نعرف شو التاثير تبعهم على ال HTN؟



Beta-adrenergic blocking agents

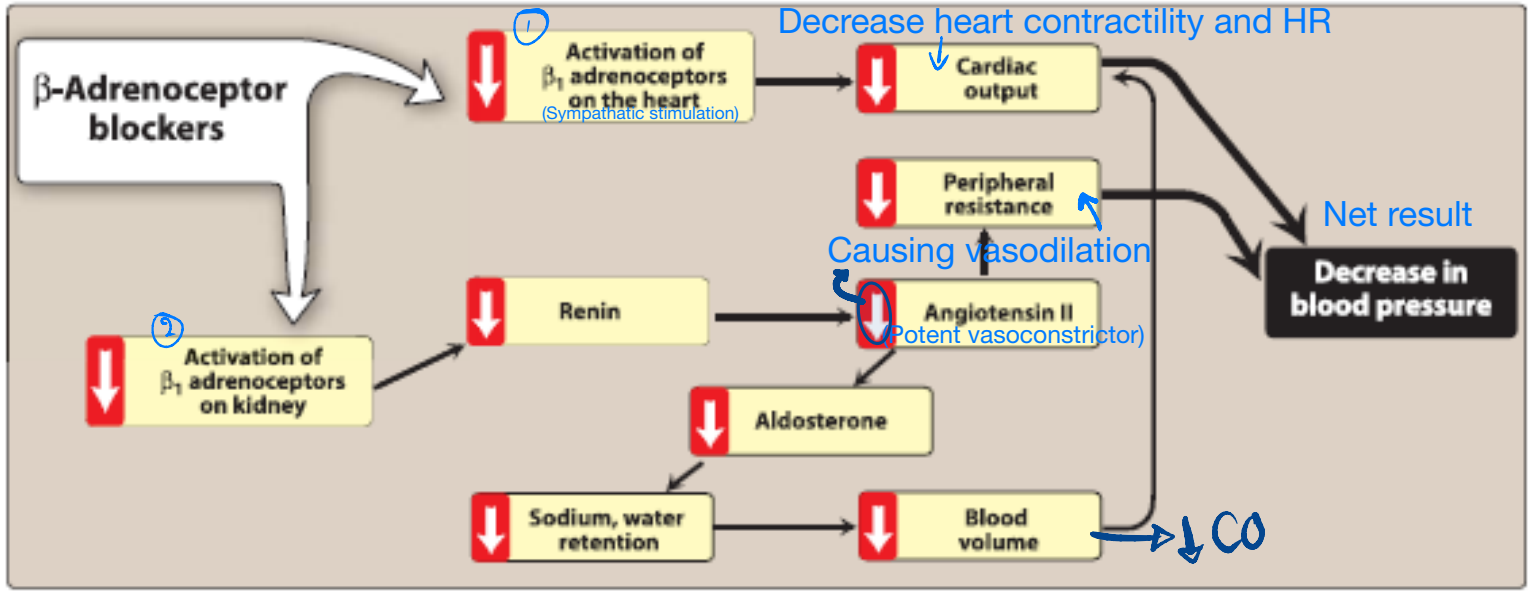
Affect is that they work on G protein coupled receptors
And the net result is the activation of cAMP will stimulate the calcium amplitude thus an increase in the heart contractions + increase in CO

So beta blockers will decrease the contractility of the heart and CO -> decrease in BP



Beta-adrenergic blocking agents

Means by which beta blockers agents reduce BP are :



- The beta-blockers reduce blood pressure primarily by decreasing cardiac output.
- They may also decrease sympathetic outflow from the central nervous system (CNS).
- They inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone. → ↓water retention → ↓ Blood volume → ↓ BP

Beta-adrenergic blocking agents

- Nonselective β- antagonists: propranolol (Prototype of betablocker)
- Selective β1- antagonists: Atenolol, metoprolol and Nebivolol.
- Nebivolol is a selective blocker of β1- receptors, which also increases the production of nitric oxide, leading to vasodilation. (Induction of endogenous nitric oxide that causes vasodilatation (decreasing BP))
- Partial β- agonists: Pindolol
- Antagonists of both α and β-adrenoreceptors: Carvedilol

Beta-adrenergic blocking agents

Beta blockers are used as anti arrhythmic drugs and in angina chronic HF and in HTN

Therapeutic uses:

The primary therapeutic benefits of Beta-blockers are seen in hypertensive patients with heart disease, such as : BETA BLOCKERS ARE BENEFICIAL IN THOSE PATIENTS

هون منكون عم نشتغل على ال both arrhythmias and HTN

- **Supraventricular tachyarrhythmia** {for example, atrial fibrillation)
- Previous **myocardial infarction or stable ischemic heart** disease
- **Chronic heart failure.** Remodeling and promotes contraction

Morality and promote survival

Conditions that discourage the use of Beta-blockers include: Due to Relative or absolute side effects

-Asthma Use with caution ⚠️ and only the cardio selective ones because increasing the dose will lead to its losing is selectivity so it will work on all beta receptors (beta II -> brochoconstriction) worsening of symptoms

-Second- and third-degree heart block Because beta blockers will increase the heart block

-Diabetes Because it will mask the hypoglycemic symptoms and might cause hypoglycemia also

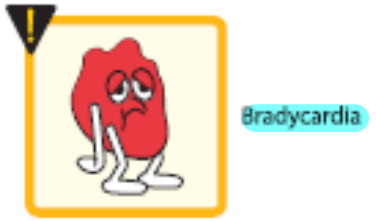
- Severe peripheral vascular disease??

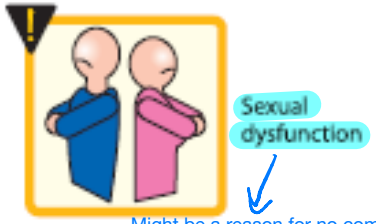
Controversial : some say it is contraindicated
But recent studies shows that there is no effect

Idea behind it is that people with peripheral vascular diseases(intermitted claudication in legs) have pain in their calf due to decreased perfusion and it was thought that beta blockers will further decrease the perfusion resulting in more pain and symptoms
But recent studies shows no difference between those who use it and those who does not

Beta-adrenergic blocking agents

Side effects:





Might be a reason for no compliance

Slightly

Alterations in serum lipid patterns: Noncardioselective Beta-blockers may disturb lipid metabolism: **decreasing HDL and increasing triglycerides.**

HDL يعني مش ممنوع عالاخر بس انه ممكن يزيد الدهون غير المرغوبه ويقلل الدهون المنيحه TAG

Drug withdrawal: Must be tapered over a few weeks in patients with hypertension and ischemic heart disease. Abrupt withdrawal may induce severe hypertension, angina, myocardial infarction, and even sudden death in patients with ischemic heart disease.

Patients who chronically take beta blockers , their body will compensate by increasing number of these receptors (up-regulation)

So if you want the patient to stop beta blockers it must be gradually

angina, myocardial infarction, ب و الضغط بشكل فجأه و يدخل المريض Heart rate .ال ويزيد عندي Beta agonist .عشان ما يصير زي كانه اعطيته

and even sudden death

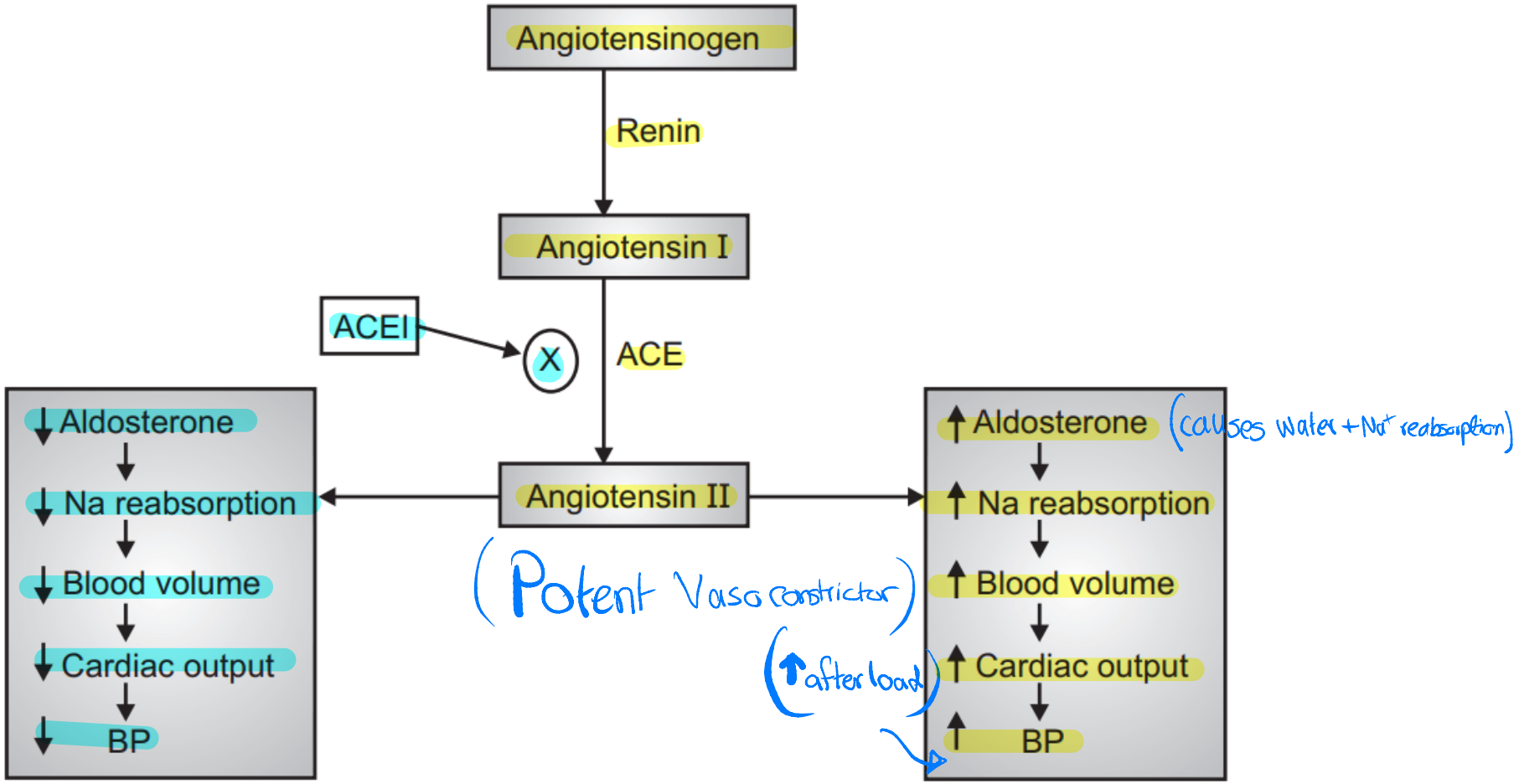
ACE inhibitors

Captopril, enalapril and lisinopril.

- The ACE inhibitors **lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility.**

- These drugs **block the enzyme ACE**, which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II And stimulate aldosterone secretions

ACE inhibitors



ACE inhibitors

ACE function:

1. Cleavage of angiotensin I to form the potent vasoconstrictor angiotensin II
2. Breakdown of **bradykinin (a peptide that increases the production of nitric oxide and prostacyclin)** → vasodilator
   So if we inhibited ACE no breakdown of bradykinin will occur so it can perform its function (vasodilation) ⬇️BP
3. Increasing secretion of aldosterone

   Angiotensin II will indirectly increase the secretion of aldosterone

Both nitric oxide and prostacyclin are potent vasodilators.

Inhibiting ACE will lead to

⬇️angiotensin II

⬇️aldosterone ➡️ ⬇️Na and water retention ⬇️blood volume

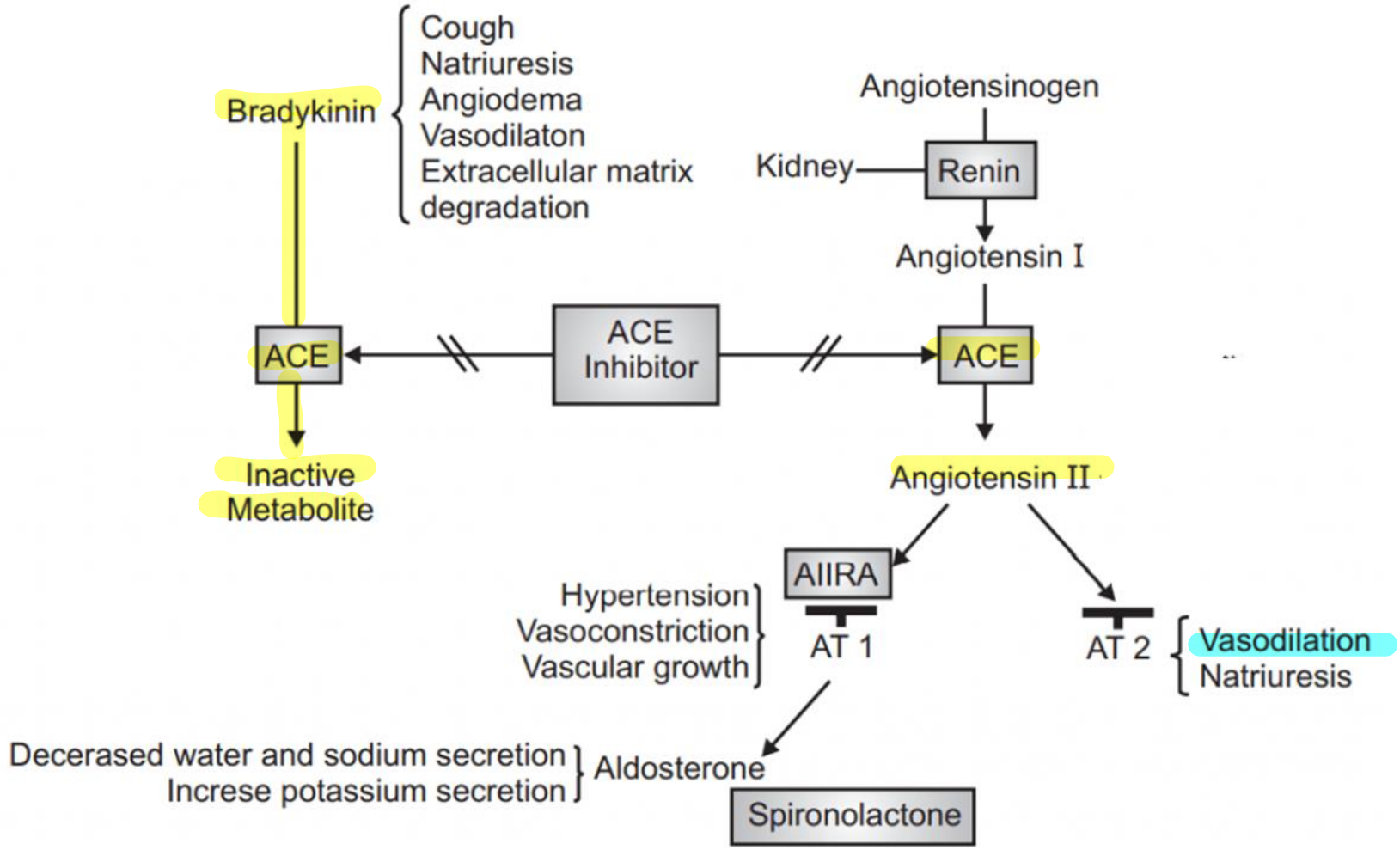
⬇️ ⬆️potassium secretion ➡️ hyperkalemia

⬇️ breakdown of bradykinin ➡️ (⬇️inactive metabolites) ⬆️bradykinin ➡️ vasodilation

D. ⬇️ side effect (cough, angioedema

⬇️BP(net result)

ACE inhibitors



ACE inhibitors

1- **ACE inhibitors induce vasodilation o**f both arterioles and veins as a result of:

A. Decreased vasoconstriction (from diminished levels of angiotensin II)

B. Enhanced vasodilation (from increased bradykinin).

2- **ACE inhibitors decrease the secretion of aldosterone,** resulting in decreased sodium and water retention.

ACE inhibitors decrease both cardiac preload and afterload, thereby decreasing workload on the heart. ↓BP

ACE inhibitors

- **Therapeutic uses:**

1. Diabetic nephropathy : slow the progression of diabetic nephropathy and decrease albuminuria Beneficial in diabetic patients
2. Chronic kidney disease : beneficial effects on renal function Promote rental function
3. Myocardial infarction: prevent ventricular remodeling after a myocardial infarction. After MI ➡️ the damaged tissue (myocytes) will be replaced by fibrous tissue ➡️ ⬇️ heart contractility
   So the ACE inhibitors preserve heart function
4. Systolic dysfunction → (Heart failure) (Remodeling لانه برضه بمنع ال) → Thus improving the function
5. Hypertension ⬇️BP
6. Regression of left ventricular hypertrophy → why? ↓Pressure → ↓resistance
   hypertrophy لتصير اكبر leftventricle ال بتضطر to ←
   ↓↓ Afterload → no Resistance → no need to ↑ work → ↓work
   ↓
   no hypertrophy

ACE inhibitors

- Recommended as first-line treatment of hypertension in patients with:
- **High coronary disease risk**
- **History of diabetes**
- **History of stroke**
- **History of heart failure,**
- **History of myocardial infarction**
- **Chronic kidney disease**

ACE inhibitors

ال cough بالعادة بتتحسن اذا وقفناه

Adverse effect:

Responsible for cough 😁

Dry cough: due to increased levels of bradykinin and substance P in the pulmonary tree, and it occurs more frequently in women. The cough resolves within a few days of discontinuation.

Angioedema is a rare but potentially life-threatening reaction that may also be due to increased levels of bradykinin.

Hyperkalemia :Potassium levels must be monitored while on ACE inhibitors.

↓ Aldosterone → ↓ the secreation of K^+ → ↑ K^+ in blood

ACE inhibitors can induce fetal malformations and should not be used by pregnant women. → Contraindicated

Angiotensin II receptor blockers(ARBs)

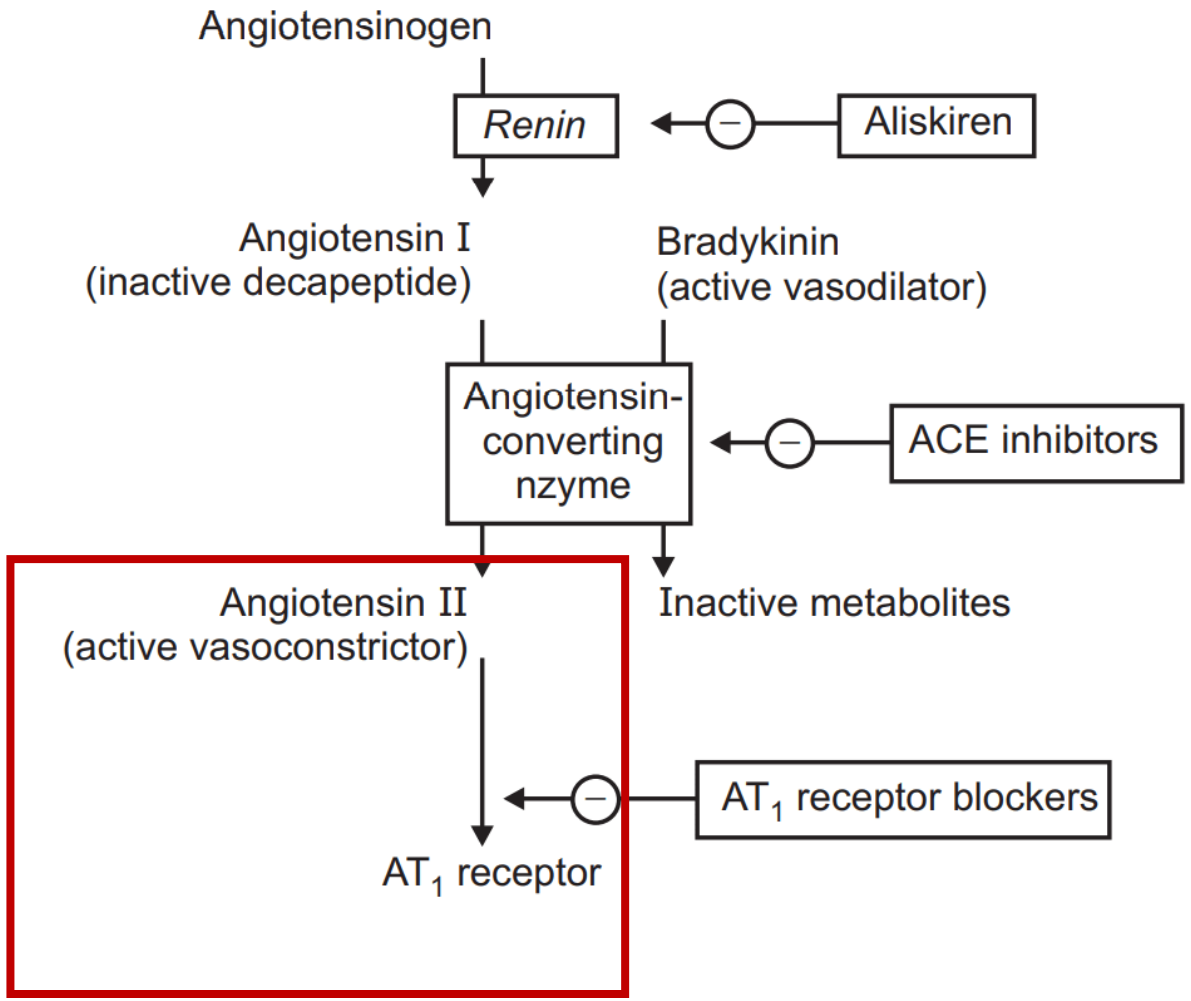
Work the same as ACE inhibitors but with no effect of bradykinin
So if the pt suffered from ACE inhibitors we can replace it with ARBs

- **Losartan and Irbesartan**

⬇️Effect of angiotensin (vasoconstriction , ⬆️aldosterone secretion)➡️➡️ resulting in vasodilation and ⬇️aldosterone secretion

- Block the AT1 receptors, decreasing the activation of AT1 receptors by angiotensin II.
- Their pharmacologic effects are similar to those of ACE inhibitors in that they **produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention .**
- **ARBs do not increase bradykinin levels.**

Angiotensin II receptor blockers(ARBs)



Angiotensin II receptor blockers(ARBs)

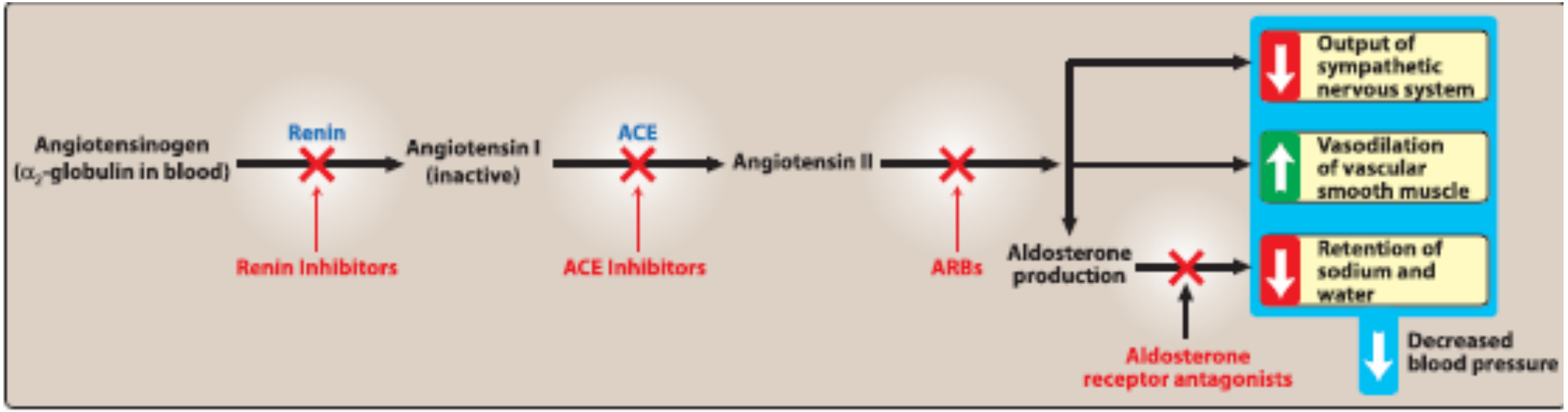
- They may be used as first-line agents **for the treatment hypertension, especially in patients with diabetes, heart failure, or chronic kidney disease**
- **Adverse effects** are **similar to those of ACE inhibitors**, although the risks of cough and angioedema are significantly decreased.
- **ARBs should not be combined with an ACE inhibitor** for the treatment of hypertension due to similar mechanisms and adverse effects.
- These agents are also teratogenic and should not be used by pregnant women.

If the pt couldn't tolerate ACE inhibitors cough side effect ARBs would replace it

Renin inhibitor

Cuts the cycle earlier than the previous drugs

- **Aliskiren**
- Selective renin inhibitor. → ⬇angiotensin I , ⬇angiotensin II, ⬇aldosterone



Renin inhibitor

- Aliskiren should not be combined with an ACE inhibitor or ARB in the treatment of hypertension.

- Aliskiren can **cause diarrhea, especially at higher doses. It also causes cough and angioedema but less often than ACE inhibitors**.

- Contraindicated during pregnancy.

Calcium channel blockers

Anti arrhythmic + for angina + HTN

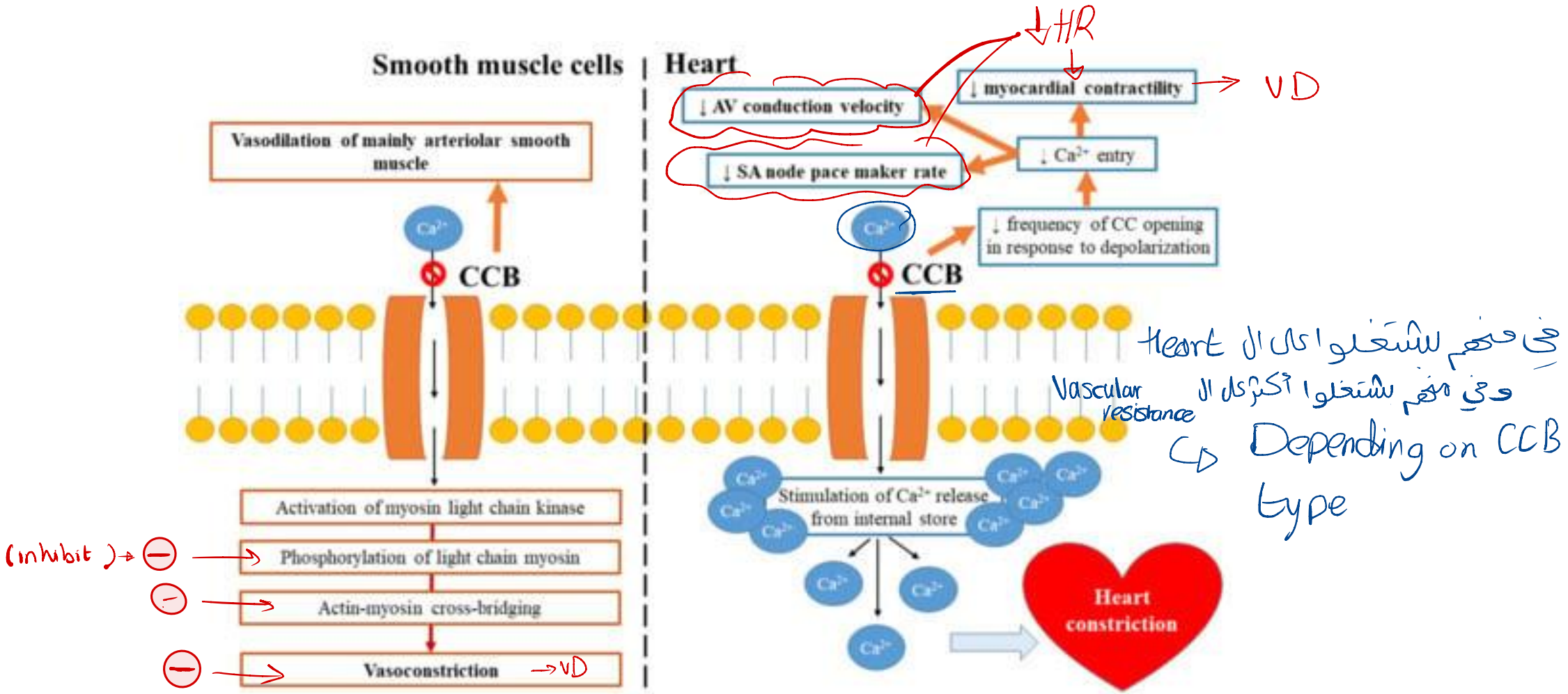
The intracellular concentration of calcium plays an important role in **maintaining the tone of smooth muscle and in the contraction of the myocardium.** ↓ Ca^{+2} intracellular → ↓VC → ↓HR

Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature.

This causes vascular smooth muscle to relax, dilating VD mainly arterioles.

Calcium channel blockers do not dilate veins.

Calcium channel blockers



Calcium channel blockers

1- Verapamil:

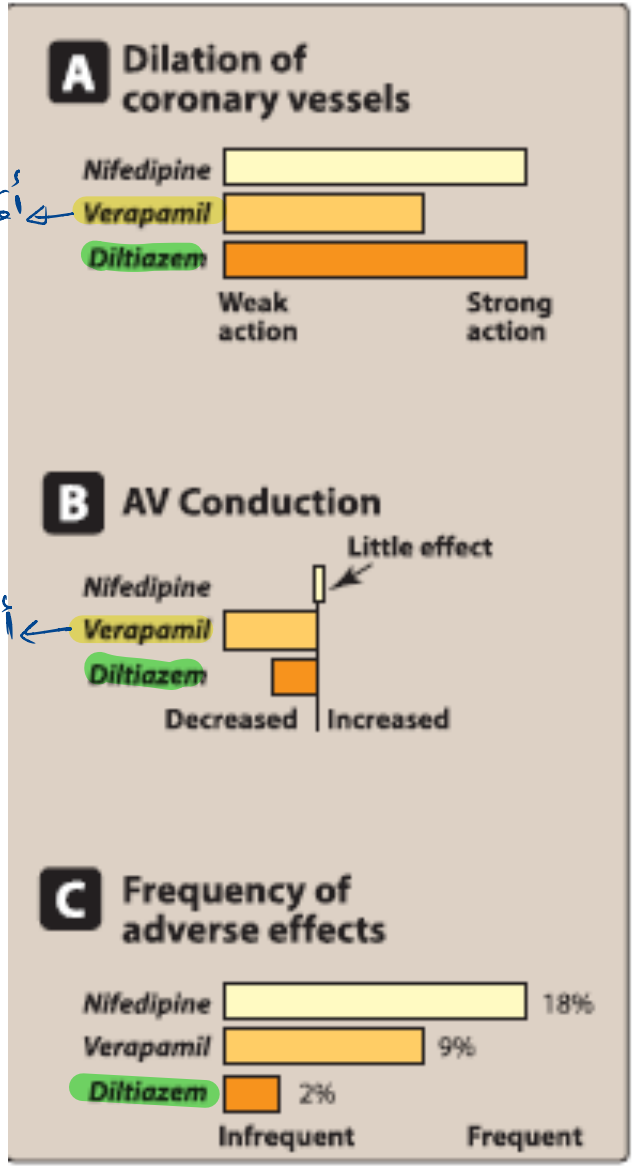
Effects are mainly on the heart ➡️⬇️ contractility +⬇️HR

- Has significant effects on both cardiac and vascular smooth muscle cells.
- Used to treat angina and supraventricular tachyarrhythmias and to prevent migraine and cluster headaches.

2- Diltiazem:

Intermediate action

- Affects both cardiac and vascular smooth muscle cells, but it has a less pronounced negative inotropic effect on the heart compared to that of verapamil.
- Diltiazem has a favorable side effect profile.



Calcium channel blockers

3- **Dihydropyridines:** Mainly on the vessels causing VD

Nifedipine, amlodipine

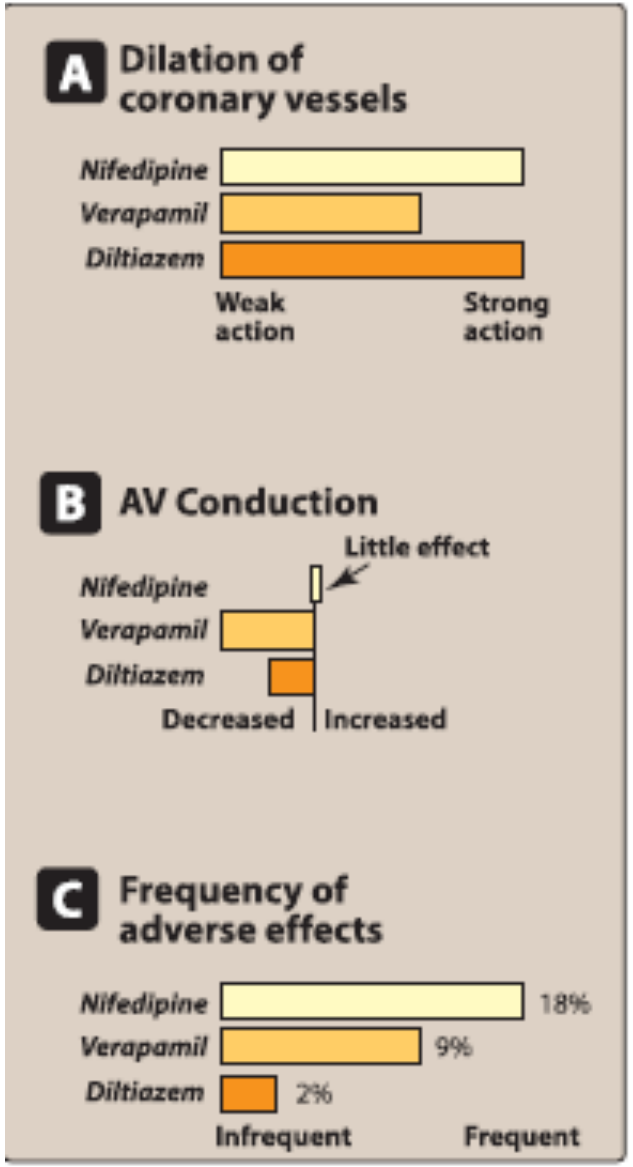
- Have a much greater affinity for vascular calcium channels than for calcium channels in the heart.

↓BP + ↑promote coronary blood flow

- Particularly beneficial in treating hypertension.

Safe

- Show little interaction with other cardiovascular drugs, such as digoxin (For Heart Failure) or warfarin (قميع), which are often used concomitantly with calcium channel blockers.



Calcium channel blockers

- Calcium channel blockers are a recommended first-line treatment option in black patients.
- They may also be useful in **hypertensive patients with diabetes or stable ischemic heart disease.**
- High doses of short-acting calcium channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation. → reflex tachycardia
- **In the management of hypertension, CCBs may be used as an initial therapy or as add-on therapy.** + contractility

High doses will cause vasodilatation sympathetic stimulation by Baroreceptors→ ⬆️HR and contractility → increase oxygen consumption
And the oxygen demand will also increase → causing ischemia and myocardial al infarction

Calcium channel blockers

Most of these agents have short half-lives (3 to 8 hours} following an oral dose. Sustained-release preparations are available and permit once-daily dosing

High doses may cause toxic effects → that's why we give sustained release formulas to avoid toxicity

Adverse effects

Dizziness, headache, and a feeling of fatigue, peripheral edema and gingival hyperplasia.

Gum hypertrophy

Most dangerous side effect

Dose dependent

First-degree atrioventricular block and constipation are common dose-dependent side effects of verapamil.

Verapamil and diltiazem should be avoided in patients with heart failure or with atrioventricular block due to their negative inotropic (1) dromotropic (velocity of conduction) (2) effect.

16.2 A 59-year-old non-Hispanic white patient presents for treatment of hypertension. His past medical history also includes diabetes, hyperlipidemia, and hypertension. The patient's blood pressure is 150/93 (both today and at the last visit). Which is a recommended initial therapy to treat hypertension in this patient?

A. Enalapril
B. Hydralazine
C. Verapamil
D. Metoprolol

Correct answer = A. Enalapril is an ACE inhibitor and is recommended for first-line therapy in various patient populations, including those who have a compelling indication such as diabetes. The other therapies are not considered first-line therapy.

16.3 A 45-year-old male complains of constipation. He was recently started on two antihypertensives due to elevated systolic blood pressure (greater than 20 mm Hg above goal). His current medications include lisinopril, chlorthalidone, verapamil, rosuvastatin, and aspirin. Which is most likely contributing to his constipation?

A. Chlorthalidone
B. Verapamil
C. Aspirin
D. Lisinopril

Correct answer = B. Common side effects specific for verapamil include constipation and first-degree atrioventricular block, which typically are dose-dependent. Electrolyte disturbances are often associated with both diuretics (chlorthalidone) and ACE inhibitors (lisinopril).

16.4 Which antihypertensive medication can cause the rare side effect of angioedema?

A. Amlodipine
B. Fosinopril
C. Prazosin
D. Propranolol

Correct answer = B. ACE inhibitors (fosinopril), ARBs (for example, losartan), and renin inhibitors (aliskiren) can cause angioedema. The occurrence of angioedema is more common with ACE inhibitors. Amlodipine can cause dizziness, headache, and peripheral edema. Prazosin can cause reflex tachycardia and postural hypotension. Propranolol can cause insomnia, decreased libido, fatigue, and bradycardia.

16.5 A 52-year-old female has uncontrolled hypertension (blood pressure 154/82 mm Hg) on treatment with lisinopril. She recently had a myocardial infarction and her past medical history includes diabetes, hypertension, hyperlipidemia, and osteoarthritis. Considering her compelling indications, which agent may be appropriate to add to her antihypertensive therapy?

A. Clonidine
B. Olmesartan
C. Furosemide
D. Metoprolol

Correct answer = D. Individual patient care is warranted particularly in the case of a compelling indication for certain medication. Considering her recent myocardial infarction, the best choice is a β_1-blocker (metoprolol). It is not appropriate to combine an ACE inhibitor (lisinopril) and ARB (olmesartan). The other agents are not considered first-line therapy and do not have a compelling indication for addition to the regimen.

16.6 The blood pressure of a patient with essential hypertension is at goal on treatment with enalapril. Since initiation of enalapril, the serum creatinine has increased 25% above baseline. What is the appropriate next step for the enalapril therapy?

A. Discontinue enalapril.
B. Reduce dose of enalapril.
C. Continue current dose of enalapril.
D. Increase dose of enalapril.

Correct answer = C. The blood pressure is at goal. Electrolytes (such as potassium) and serum creatinine should be monitored in patients who initiate ACE inhibitors. Increases in serum creatinine up to 30% above baseline are acceptable and do not warrant discontinuation or reduction of treatment. Since the blood pressure is at goal, increasing the enalapril is not necessary.

16.7 Which of the following correctly outlines a major difference in electrolyte disturbances associated with thiazide and loop diuretics?

A. Thiazide diuretics decrease potassium and loop diuretics increase potassium.
B. Thiazide diuretics increase potassium and loop diuretics decrease potassium.
C. Thiazide diuretics decrease calcium and loop diuretics increase calcium.
D. Thiazide diuretics increase calcium and loop diuretics decrease calcium.

Correct answer = D. Thiazide and loop diuretics decrease potassium, sodium and magnesium. However, thiazide diuretics increase calcium (through reduced urinary excretion), while loop diuretics reduce calcium (through enhanced urinary excretion).

16.9 Which of the following is a dihydropyridine calcium channel blocker?

A. Amlodipine
B. Metoprolol
C. Verapamil
D. Lisinopril

Correct answer = A. There are three classes of calcium channel blockers: nondihydropyridines (benzothiazepines, diphenylalkylamines) and dihydropyridines. Amlodipine is a member of the dihydropyridine class of calcium channel blockers, which also includes nifedipine and felodipine. Verapamil is a benzothiazepine calcium channel blocker, metoprolol is a β-blocker, and lisinopril is an ACE inhibitor.

16.10 A 45-year-old man was started on therapy for hypertension and developed a persistent, dry cough. Which is most likely responsible for this side effect?

A. Lisinopril
B. Losartan
C. Nifedipine
D. Atenolol

Correct answer = A. The cough is most likely an adverse effect of the ACE inhibitor lisinopril. Losartan is an ARB that has the same beneficial effects as an ACE inhibitor but is less likely to produce a cough. Nifedipine and atenolol do not cause this side effect.