

Drugs for hypertension

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Hypertension

- التشخيص ما بصير بقياس ضغط الدم لمرة واحدة، عادة بنقاس مرتين أو أكثر عشان نتأكد، لانه ممكن يكون ارتفع الضغط بشكل طبيعي لسبب ما
- عادة أكثر من مرتين بنفس الزيارة للطبيب وزيارتين أو أكثر

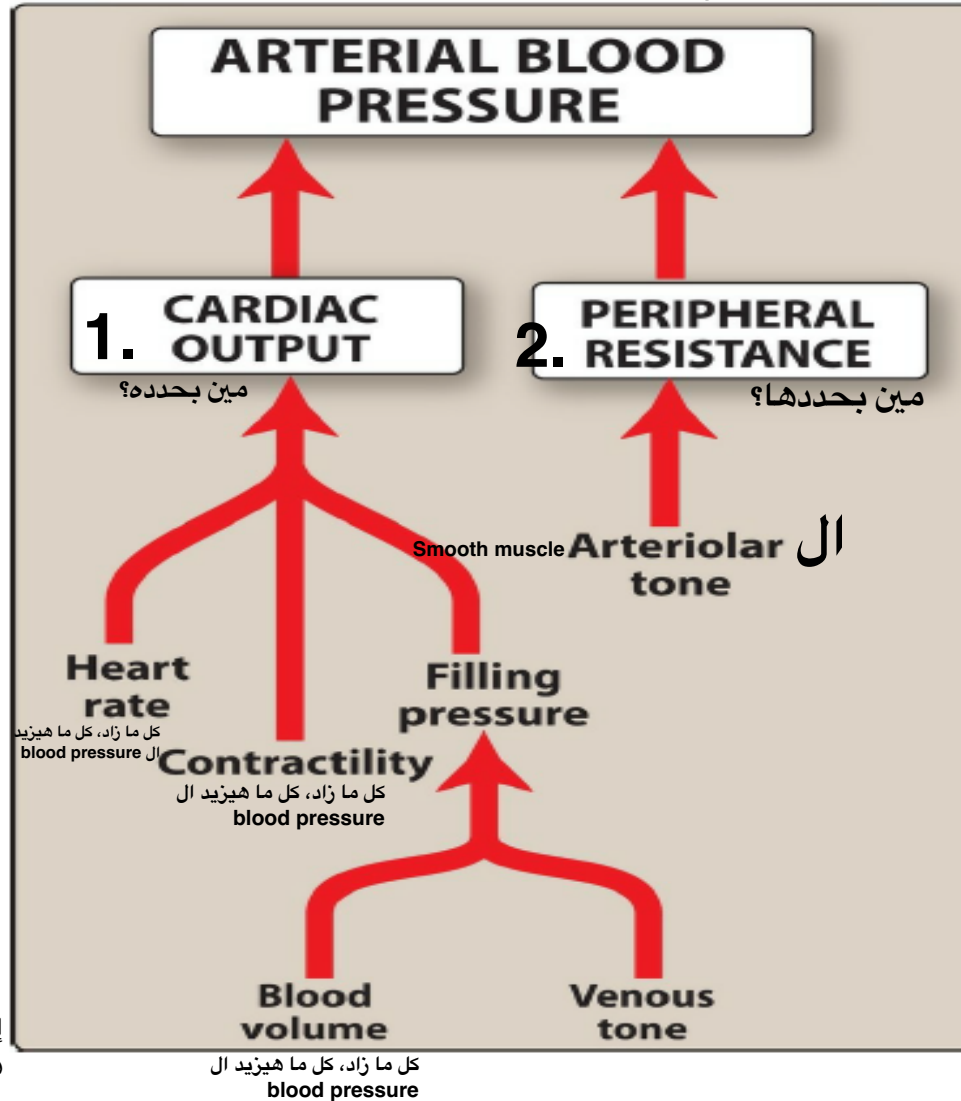
- It is a sustained elevation of systemic arterial blood pressure
- It is defined as systolic blood pressure more than or equals 140 mm Hg or diastolic blood pressure more than or equals 90 mm Hg
- Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous System
- chronic hypertension can lead to heart disease and stroke, the top two causes of death in the world.
- Hypertension is also an important risk factor in the development of chronic kidney disease and heart failure

- Vasoconstriction in the arteriolar smooth muscle will cause increasing in arteriolar resistance and venous resistance

- ال Hypertension بيؤثر على أعضاء الجسم، زي القلب فمممكن يعمل hheart disease، ممكن يؤدي لحدوث ischemic heart disease، ممكن يؤدي لحدوث heart faliure لأنه بزيد ال load على ال hard، ممكن يؤدي لحدوث stroke in the brain وتؤدي للموت

- الهدف الأساسي تبعها انها تحمي المريض من ال cardiovascular events الي ممكن تصير وانها تقلل ال morbidity and mortality الي ممكن تصير للمريض

میں بلع دور بال arterial blood pressure؟



إذاً احنا لما نعطي دواء ك anti-hypertensive
هيكون هدفه واحد من هدول الي بآثروا

Classification of blood pressure

	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

- عندي two mechanisms لإرتفاع ضغط الدم في الجسم، وهدول
هيكونوا الهدف تبع كثير من أدوية ال anti-hypertensive

- لما يصير decrease in blood pressure الجسم عنده two
mechanisms عشان يتعامل مع الموضوع:

- sympathetic activity
- Renal blood flow

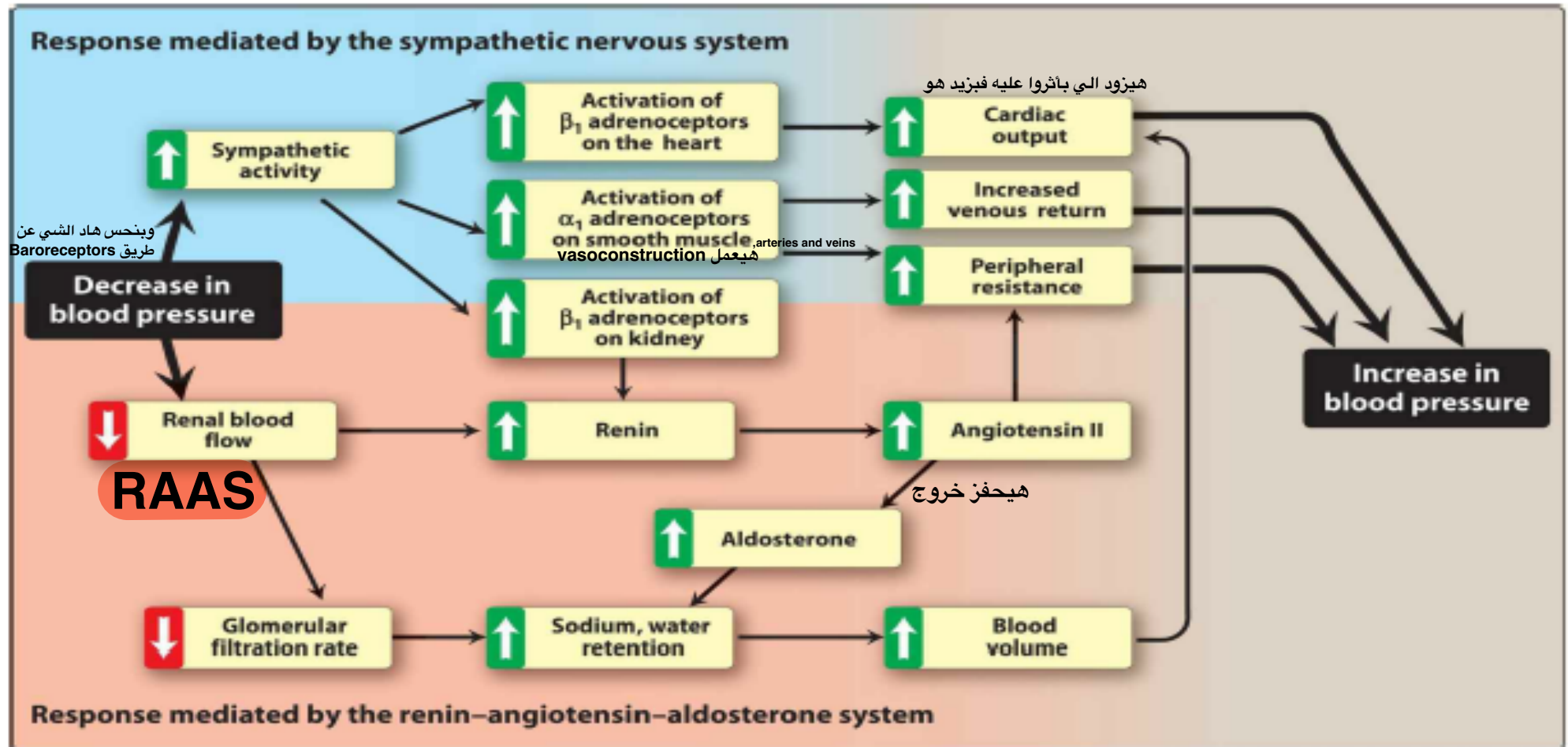


Figure 16.4 Response of the autonomic nervous system and the renin-angiotensin-aldosterone system to a decrease in blood pressure.

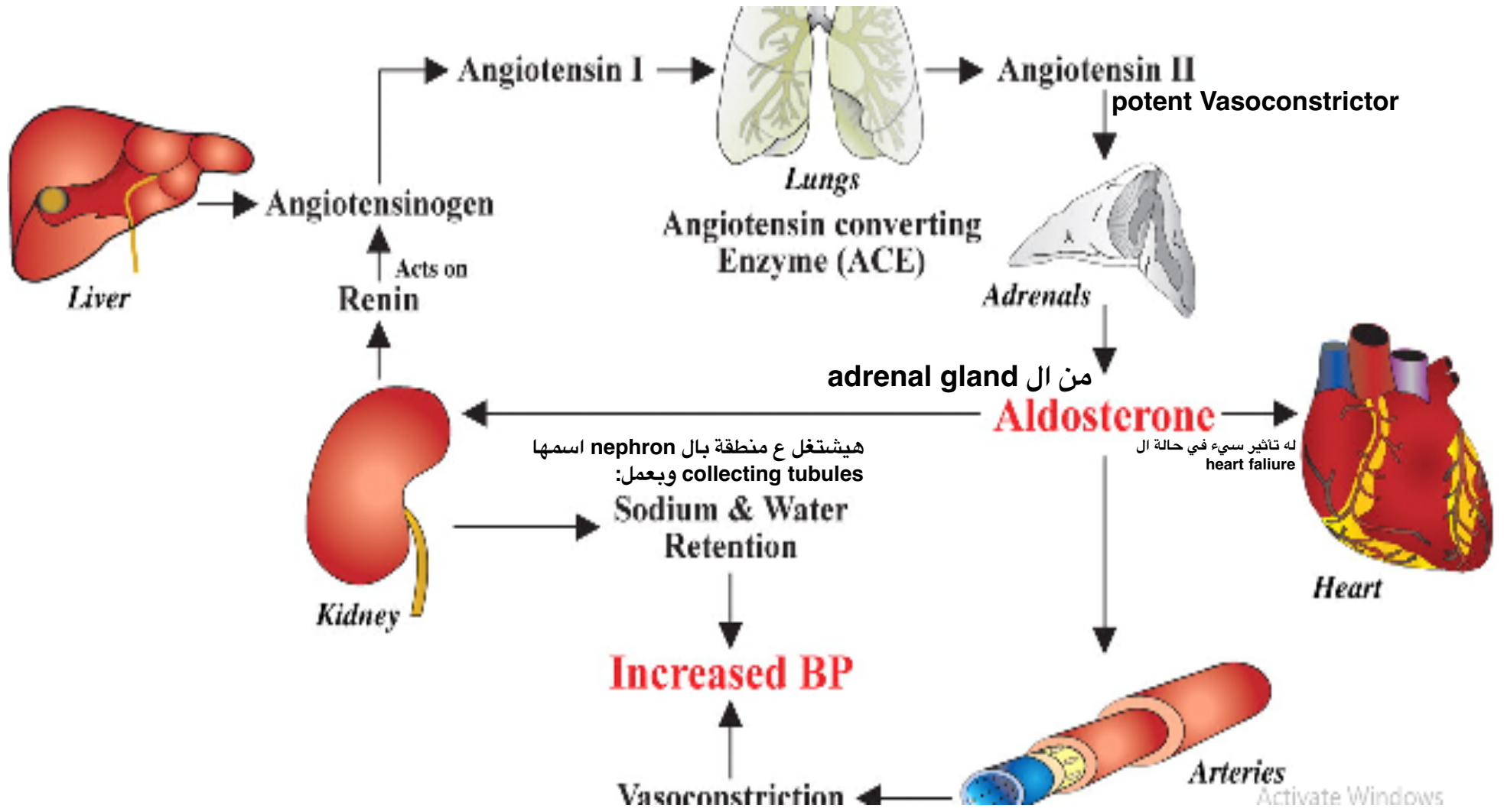
بيحسوا بأدق التغيرات في ال blood pressure

Baroreceptors and the sympathetic nervous system

- Baroreflexes act by changing the activity of the sympathetic and parasympathetic nervous system.
- They are responsible for the rapid, moment-to-moment regulation of blood pressure. 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

Renin–angiotensin–aldosterone system(RAAS)

- The kidney provides 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).
- عشان هيڪ هنلاقي أدوية ال **ACE inhibitors** وال **RCE** بتلعب دور مهم في ال **anti-hypertensive**

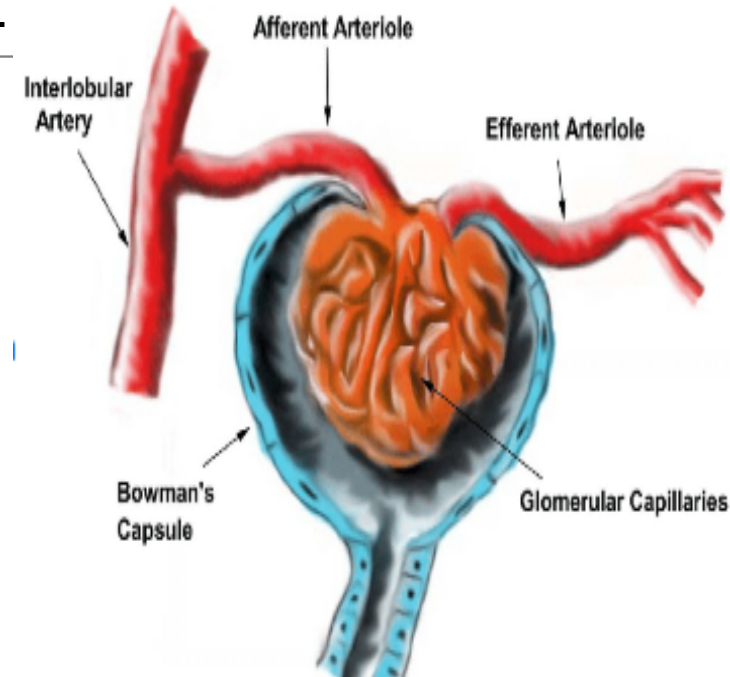


Prostaglandin

بعمل afferent ال vasodilation في ال

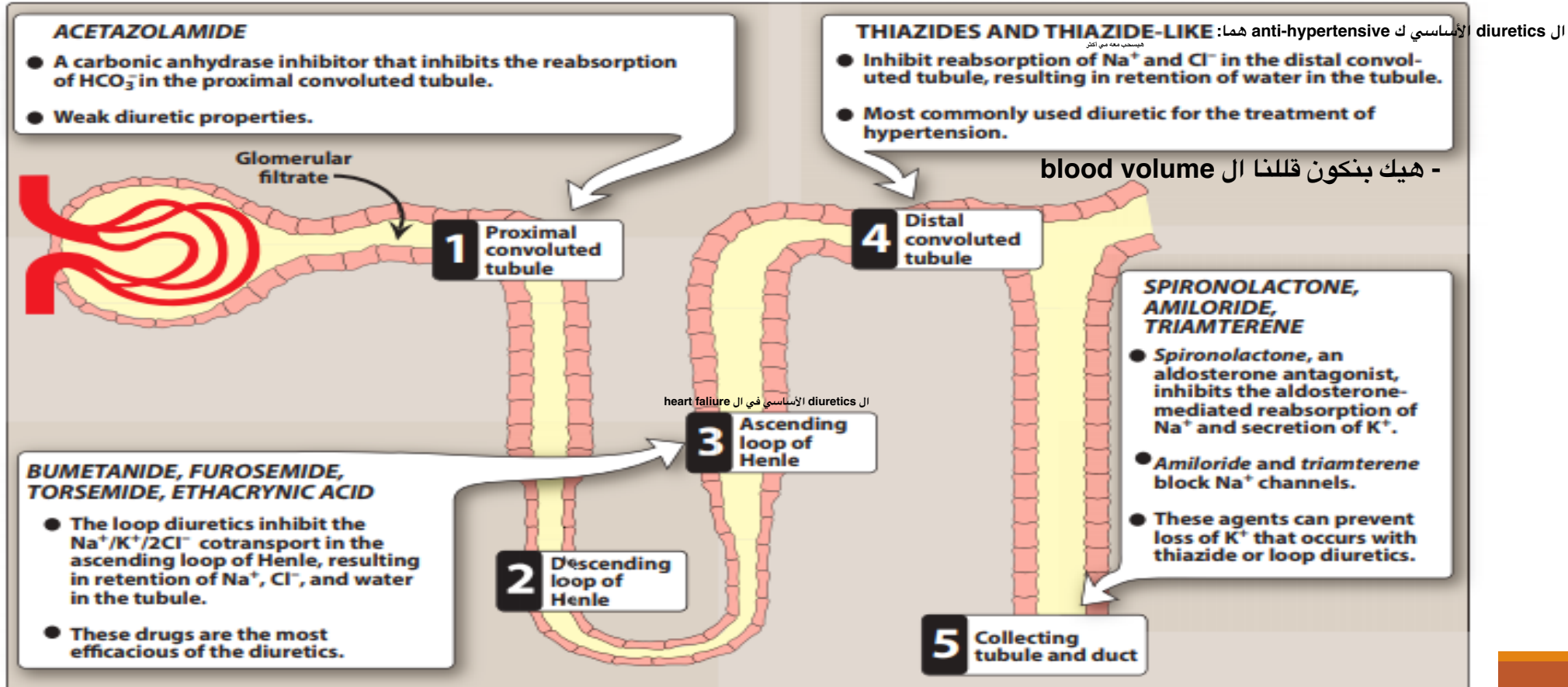
- والاثنين مع بعض بعملوا زيادة في ال glomerulus filtration rate (GFR)

- Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins, resulting in an increase in blood pressure.
- **Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration.**
- Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin II type 1 (AT1) receptors



مدرات البول

Diuretics antihypertensive drugs أول قروب هحكى عنه من ال



احنا بنحصل على ال full effect من كل ال anti-hypertensive medication
بعد فترة من الزمن، مش يوم ولا ثلاثة، أقل شي بدنا من 3 ل 4 أسابيع

Thiazide diuretics

- **hydrochlorothiazide and chlorthalidone**, lower blood pressure initially by increasing sodium and water excretion.
- This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow .
بعد 3-4 أسابيع شغلهم بصير أساسي عن طريق...
- With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a **decrease in peripheral resistance**.
- Thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate less than 30 mL/min/m²).. ال normal يكون أكثر من 90

DIURETICS	
Amiloride	MIDAMOR
Bumetanide	BUMEX
Chlorthalidone	GENERIC ONLY
Eplerenone	INSPIRA
Ethacrynic acid	EDECIN
Furosemide	LASIX
Hydrochlorothiazide	MICROZIDE
Indapamide	GENERIC ONLY
Metolazone	GENERIC ONLY
Spironolactone	ALDACTONE
Triamterene	DYRENIUM
Torsemide	DEMADEX

ال thiazide عشان يشتغل لازم يصير له secretion in the tubule، فلو ما صار له secretion في ال tubule بشكل جيد وتركيز جيد، مش هيشغل منيح

Actions

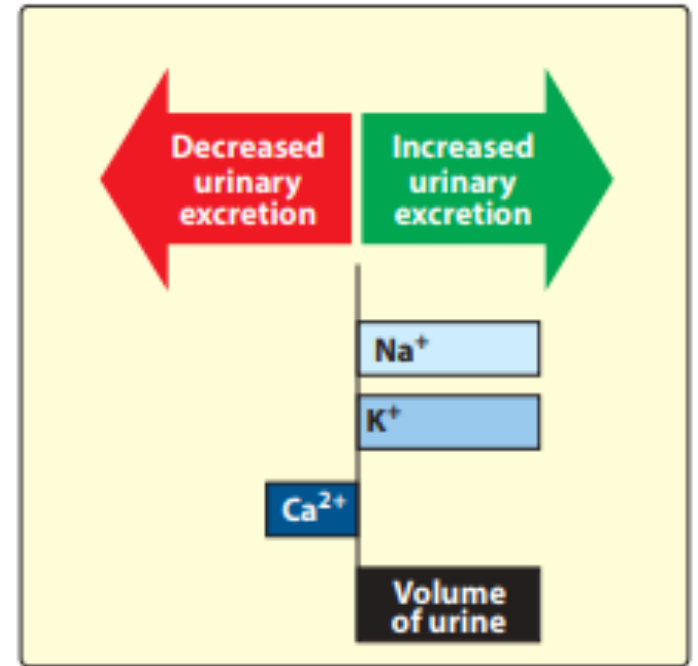
Increased excretion of Na^+ and Cl^-

Loss of K^+ هيطلع معهم

Loss of Mg^{2+} هيطلع معهم

Decreased urinary calcium excretion: فھيزود من الكالسيوم في الدم

Thiazide and thiazidlike diuretics



Adverse effects

Potassium depletion: the most frequent problem with the thiazide diuretics, and it can predispose patients who are taking digoxin to ventricular arrhythmias

hyperkalemia يعمل digoxin ال

مقوي لعضلة القلب

إذا المريض كان عنده hypokalemia وبيأخذ digoxin، ال hypokalemia بتحفز ال
toxicity of digoxin ويمكن تعرضهم ل ventricular arrhythmias

Anti-diuretic hormone

نقص منسوب الصوديوم

ويعملوا hyonatremia
أكثر بكثير من ال

Hyponatremia: Hyponatremia may develop due to elevation of ADH as a result of hypovolemia, as well as diminished diluting capacity of the kidney and increased thirst

FUROSEMIDE

Limiting water intake and lowering the diuretic dose can prevent hyponatremia

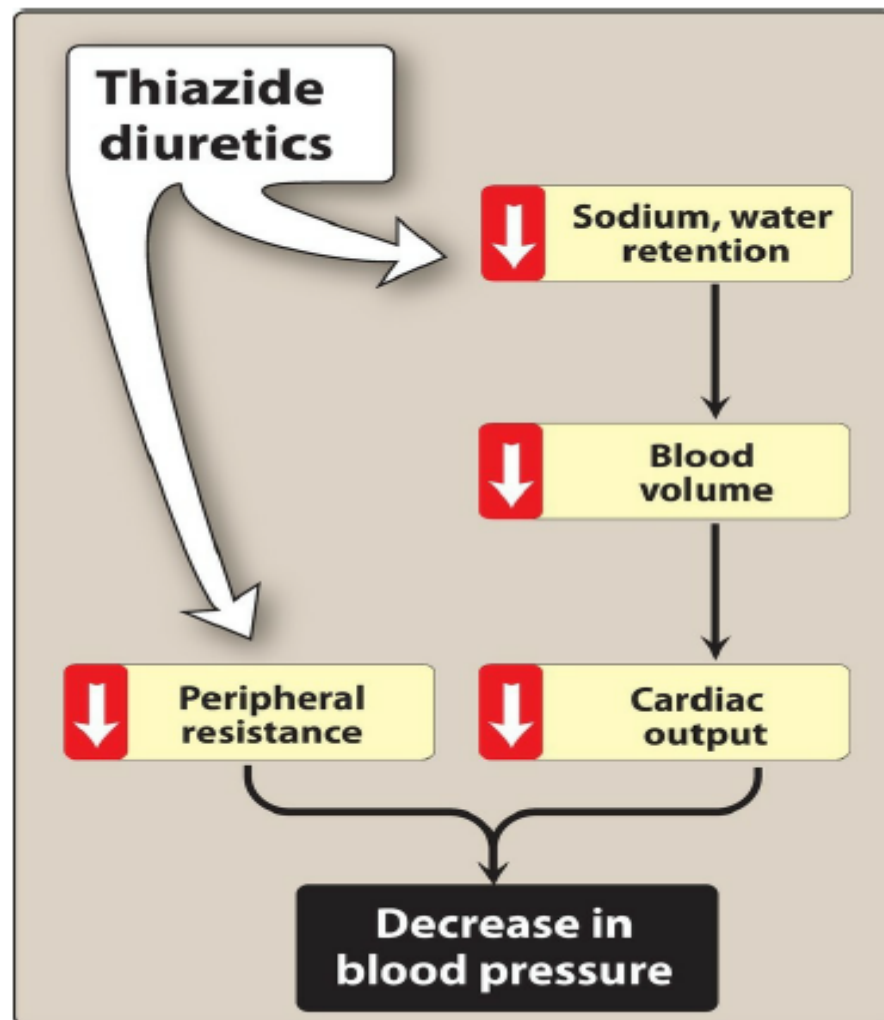
Hyperuricemia: Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system

Volume depletion

Hypercalcemia

Hyperglycemia: lead to glucose intolerance, possibly due to impaired release of insulin and tissue uptake of glucose. وذلك من خلال شغله على ال potassium receptors، الموجودة في ال

pancreatic cells ال release of insulin دور أساسي في ال



يمكن استخدامه للمرضى الذين يعانون من chronic renal disease والمرضى الذين يعانون من renal impairment

ما يستخدمهم ك Loop diuretics anti-hypertensive

- The loop diuretics (*furosemide, torsemide, bumetanide, and ethacrynic acid*) act promptly by
 - blocking sodium and chloride reabsorption in the kidneys, 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.
 - Like thiazides, they can cause hypokalemia.
 - However, unlike thiazides, loop diuretics increase the calcium content of urine, whereas thiazide diuretics decrease it.
- These agents are rarely used alone to treat hypertension, but they are commonly used to manage symptoms of heart failure and edema.

ممنوع استخدامه

من اسمهم هيحتفظوا بال potassium يزودوه في الجسم

Potassium-sparing diuretics

هيزود من الصوديوم في ال urin وبالمقابل
راح يزودوا ال potassium in the blood

- *Amiloride* and *triamterene* are inhibitors of epithelial sodium transport at the late distal and collecting ducts.

في ال heart failure

بالتالي هيمنعوا ال aldosterone انه يعمل sodium water retention

- *spironolactone* and *eplerenone* are aldosterone receptor antagonists.

- All of these agents reduce potassium loss in the urine. ‘

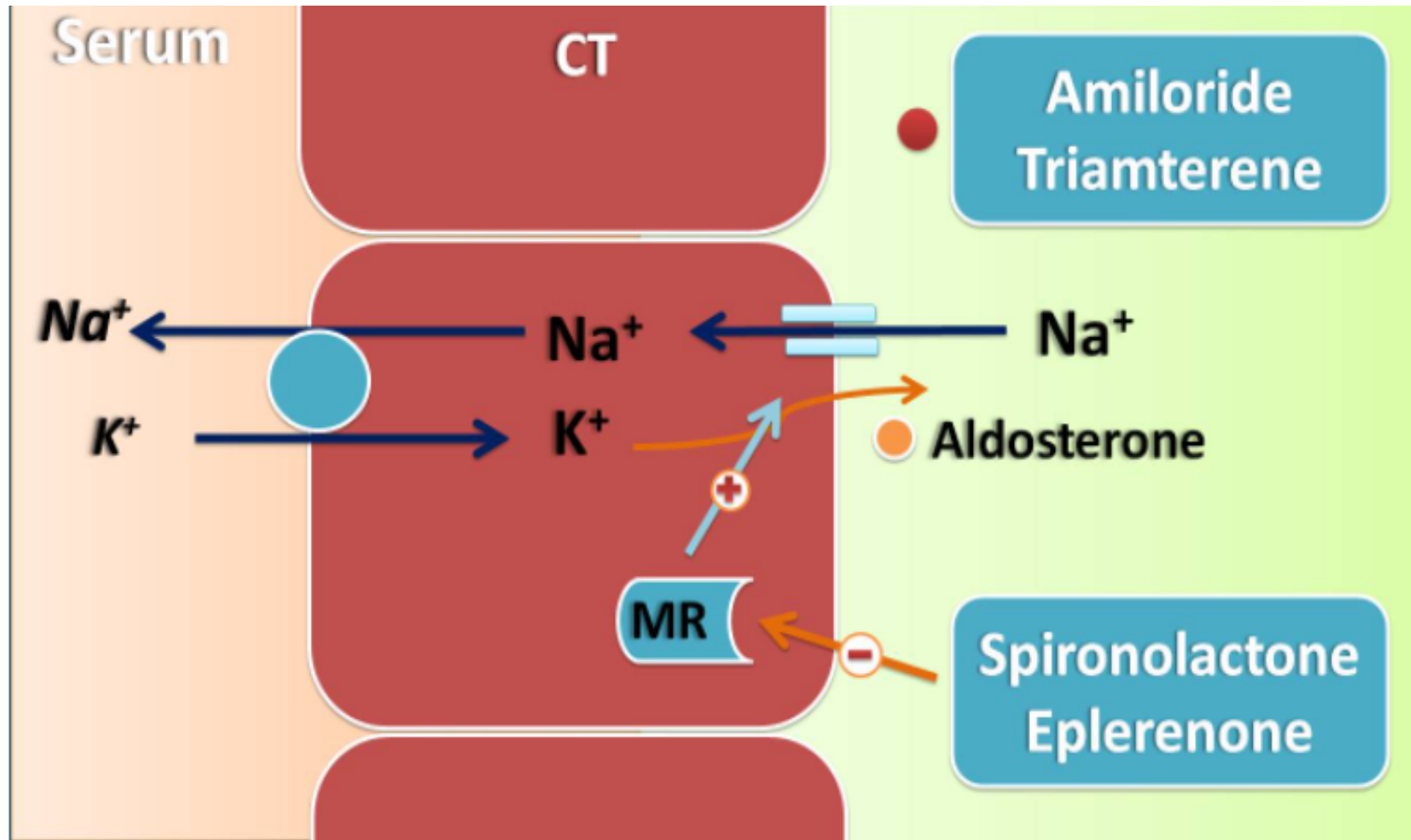
ال transporters الي بشتغلوا عليها بتكون linked، يعني هو بده يعمل inhibition excretion of potassium in the urin، بنفس الوقت هاد ال transport هيكون راكب عليه صوديوم وبوتاسيوم، يعني هيكون بينقل صوديوم وبوتاسيوم

- Aldosterone antagonists have the additional benefit of diminishing the cardiac remodeling that occurs in heart failure

- Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

-
- Sodium entry in these segments occur through aldosterone sensitive sodium channels
 - The reabsorption of cationic sodium without an anion creates a lumen negative electrical gradient that then favors the secretion of potassium and hydrogen ions.
 - Thus inhibition of sodium reabsorption at this site can lead to hyperkalemia and metabolic acidosis

Amiloride and triametrene are cations that directly block sodium channels but don't affect mineralocorticoid receptor.

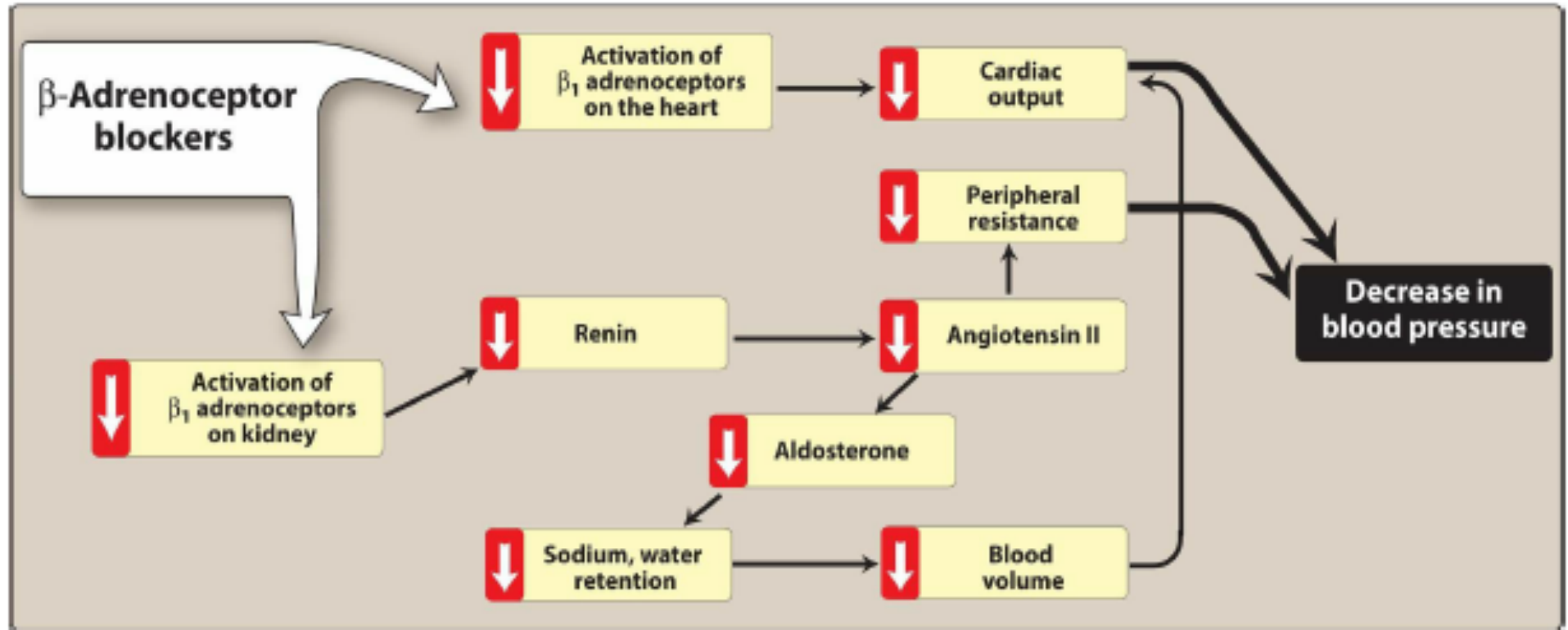


Spironolactone and eplerenone competitively inhibit the mineralocorticoid receptor

Eplerenone is better tolerated than spironolactone , as it has lower incidence of endocrine side effects (gynecomastia, menstrual abnormalities, impotence)

Spironolactone has non selective binding to estrogen and progesterone receptors.

β -Adrenoceptor-Blocking Agents



β -Adrenoceptor–Blocking Agents

β -BLOCKERS

Acebutolol GENERIC ONLY
Atenolol TENORMIN
Betaxolol GENERIC ONLY
Bisoprolol GENERIC ONLY
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Pindolol GENERIC ONLY
Propranolol INDERAL LA, INNOPRAN XL

Non-Selective β_1 & β_2

Nadolol
Propranolol
Timolol
Sotalol

Mixed α_1 , β_1 & β_2

Carvedilol
Labetalol

With ISA* RxKeySlides

Acebutolol
Pindolol

*Intrinsic Sympathomimetic Activity
Associated with LESS Resting Bradycardia

Cardio-Selective β_1

RxKeySlides

Atenolol
Betaxolol
Bisoprolol
Esmolol
Metoprolol
Nebivolol

Mortality Benefit in HFrEF

Bisoprolol
Carvedilol
Metoprolol Succinate

ال **thiazide diuretics** عبارة عن ال **first line**، أول خط من العلاجات نتسخدمها في مرضى الضغط، لقدام هنشوف ضغط وسكر ضغط و مشكلة بالكلية

هل ال **betablockers** تعتبر **first line**؟

لا، ال **betablockers** ما بيستخدموا لمريض عنده ضغط لحال

متى ال **betablockers** تعتبر **effective antihypertensive**؟

لما مريض الضغط يكون عنده مشاكل في القلب أيضاً

-
- The primary therapeutic benefits of β -blockers are seen in hypertensive patients with concomitant heart disease, such as supraventricular tachyarrhythmia (for example, atrial fibrillation), previous myocardial infarction, stable ischemic heart disease, and chronic heart failure.
 - Conditions that discourage the use of β -blockers include reversible bronchospastic disease such as asthma, second- and third-degree heart block, and severe peripheral vascular disease

- هنبعد عن ال non selective betablockers مثل Propapabonol الي
بشتغل ع ال beta one and beta two، ليش؟
عشان قصة ال beta two، لما اسكر ال beta two هعمل broncho
constriction

- المرضى الي عندهم مشاكل heart block، مشاكل في ال conduction،
مناطق مسكرة منها؟
أعطيهـم beta blockers واسكر عليهم ال rhythm of the heart

وفي مرضى يكون عندهم مشاكل بأطرافهم زي مثلاً ال leg يكون عنده مشكلة في ال venous capacitance، بال blood circulation، يكون عندهم resistance، طب لو انا رحت اعطيهم betablockers، خاصة ال non selective betablockers هاد هيزود ال vasoconstriction

- ال beta two receptors موجودين في ال blood vessels، لما انا اسكرهم هيك انا بعمل vasoconstriction

ال selective زي ال beta one ضررهم أقل بالذات لو استخدمهم بجرعات بسيطة يعني لو مريض عنده heart failure و peripheral vascular resistance، هل ممنوع استخدمله selective beta blockers for beta one؟

لا عادي بستخدمله بالذات لو بجرعات بسيطة

Adverse effects

مشكلة خاصة في ال non selective
males عند ال beta blockers



Sexual
dysfunction



Hypotension

■ Non cardioselective β -blockers may disturb lipid metabolism, decreasing **HDL** high-density lipoprotein cholesterol and increasing triglycerides.

وكل هاد بسبب ال beta two
وال beta three، لأنها non
selective، فهتشتغل عليهم



Bradycardia
heart rate ال

■ Hyperkalemia (minor elevation of less than 0.5 meq/L)

■ Lipophilic beta blockers (propranolol and metoprolol) >>> CNS effects

ممنوع نوقف ال beta blockers مرة وحدة، لازم بالتدريج Drug withdrawal

Abrupt withdrawal may induce severe hypertension, angina, myocardial infarction, and even sudden death in patients with ischemic heart disease.

Therefore, these drugs must be tapered over a few weeks in patients with hypertension and ischemic heart disease.



Fatigue
بسبب تقليل ال heart rate
وال contractility



Insomnia

- ليش؟

لأنه انت عندك دواء بعمل ك antagonist على ال beta adrenergic receptors،
فبالتالي انت سكرت ال beta receptors، فکرد فعل من الجسم هيزود عدد ال
receptors، فلو سحبت الدواء مرة وحدة هيكون عندك كمية receptors كثيرة فمثلاً
هيصير sympathetic activation فهيجي ال adrenalin or nor-adrenalin
يشتغلوا على ال beta receptors الي هان، فهايدي لزيادة في الشغل زيادة في ال
heart rate وال contractility وهاد ممكن يؤدي ل sever hypertensive

CONCOMITANT DISEASE

[Stable Angina]

STABLE ISCHEMIC
HEART DISEASE

β -Blockers

ACE inhibitors

ARBs

Ca²⁺ channel
blockers

DIABETES

Diuretics

ACE inhibitors

ARBs

Ca²⁺ channel
blockers

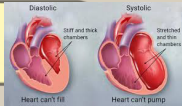
RECURRENT STROKE

Diuretics

ACE inhibitors

ARBs

HEART FAILURE



Diuretics

β -Blockers

ACE inhibitors

ARBs

Aldosterone-
receptor
antagonists

PREVIOUS MYO-
CARDIAL INFARCTION

β -Blockers

ACE inhibitors

Aldosterone-
receptor
antagonists

CHRONIC KIDNEY
DISEASE

ACE inhibitors

ARBs

DRUG CLASSES INDICATED IN TREATING HYPERTENSION

Figure 16.6

Treatment of hypertension in patients with concomitant diseases. [Note: Angiotensin receptor blockers (ARBs) are an alternative to angiotensin-converting enzyme (ACE) inhibitors.]

ACE Inhibitors / or ^{Angiotensin receptor blockers} ARBs →

يعتبر الخيار الذهبي لمريض hypertension وعنده أمراض أخرى

They are considered as **cardioprotective** that decrease heart disease mortality.

ACE inhibitors are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease or Ischemic heart disease

ACE INHIBITORS

Benazepril LOTENSIN

Captopril GENERIC ONLY

Enalapril VASOTEC

Fosinopril GENERIC ONLY

Lisinopril PRINIVIL, ZESTRIL

Moexipril GENERIC ONLY

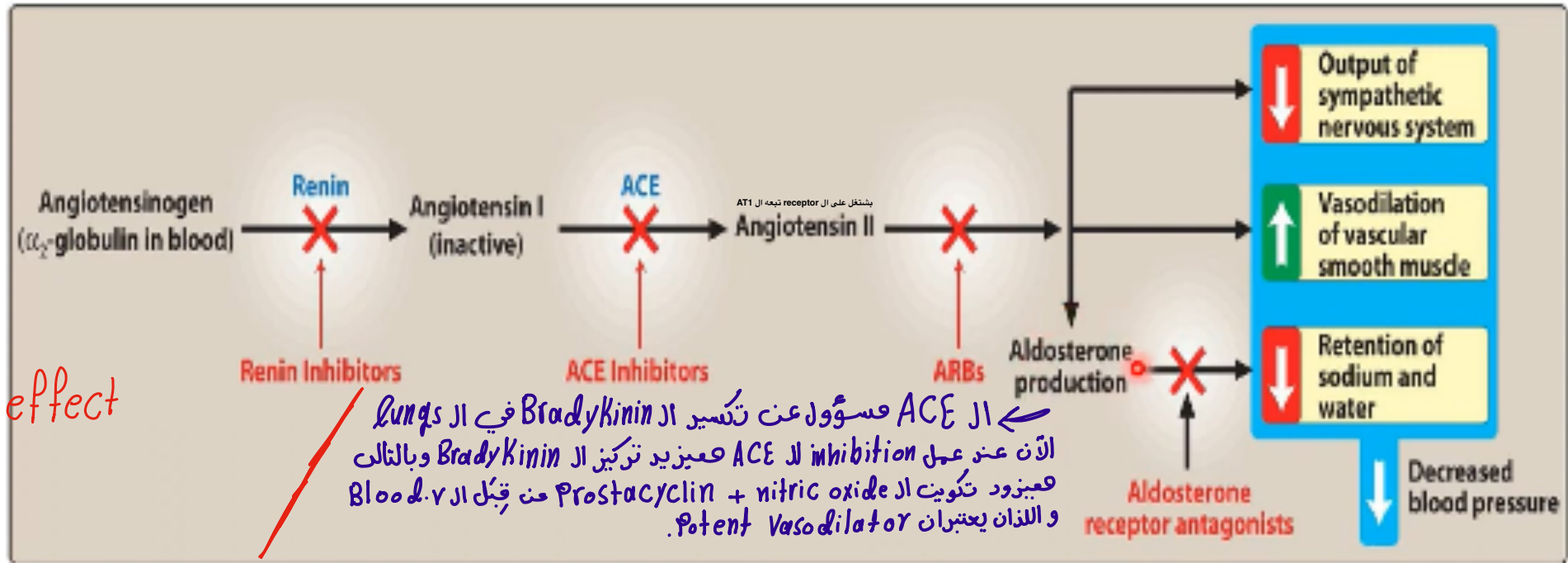
Quinapril ACCUPRIL

Perindopril GENERIC ONLY

Ramipril ALTACE

Trandolapril GENERIC ONLY

ACE Inhibitors



side effect

← ال ACE مسؤول عن تكسير ال Bradykinin في ال lungs
 الآن عند عمل inhibition ال ACE فعيزيد تركيز ال Bradykinin وبالتالي
 فعيزود تكوين ال Prostacyclin + nitric oxide من قبل ال Blood v.
 والذان يعتبران Potent Vasodilator.

↓
Angiotensin II

← موجودة في ال BV الموجودة في ال pulmonary tree.
Bradykinin it is a vasodilator.
 (nitric oxide and prostacyclin by the blood vessels)
 اه صحيح، انه زيادة ال Bradykinin يعتبر اشي لطيف ومفيد، ولكن ال side effects

Damage in filtration unit (Glomeruli) marked by the Proteinuria, HBP.

Therapeutic uses

عن طريق تقليل الـ protein urea، يعني بقللوا من الـ excretion of the protein (خروج البروتين عن طريق الـ glomerulus)، أول ما يبدأ الـ albumin أو الـ protein يطلع في الـ urin معناها عناء مشكلة

➤ Slow the progression of **diabetic nephropathy** and decrease albuminuria

في الجلطات

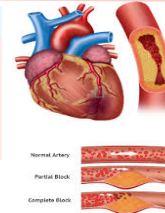
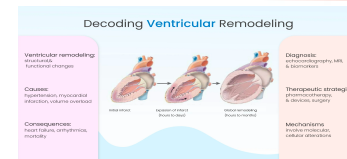
➤ Standard in the care of a patient following a **myocardial infarction** and first-line agents in the treatment of patients with systolic dysfunction

↳ [Heart attack], occurs when blood flow to a part of heart is blocked, typically occurs by blood clot

➤ Regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a **myocardial infarction** or block in coronary artery.

➤ Hypertensive patients with chronic kidney disease.

(Side effect of bradykinin high levels)
Angioedema: swelling of the deeper layers of the skin, often around the face, lips, eyes, throat, and in severe cases it obstruct airway so difficulty of breathing then ...



↳ ACE inhibitors + ARBs decrease All level so they:

1. Decrease glomerular pressure because NO All to vasoconstrict the efferent arteriole.
2. Decrease glomerular permeability so reducing protein like albumin leakage into urine.
3. Decrease inflammation and fibrosis + lowering B.P.

→ Edema: is swelling caused by accumulation of fluid.

→ High Bradykinin level causes Angioedema + Pulmonary edema.

Adverse effects

بتروح بعد ما الواحد يعمل discontinuation لن
drug. ممكن تروح خلال أول أيام ويمكن بعد أسابيع

سببها ال
Bradykinin in the lung
(pulmonary tree)

بنسبة 10% من الناس
dry cough

Angioedema

تقلل ARBs + ACE

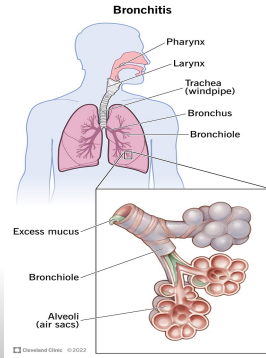
Hyperkalemia. → ال Aldosterone الذي يقوم ب
excut K⁺ in urin

أهم أشي ما تعلق أكثر من هيك لأنه هيدللي على مشاكل

Increase in serum creatinine of up to 30% above baseline

Fetal malformations in pregnant women

Teratogenic substances



← ذكرنا سابقاً أن ال Bradykinin هو
Vasodilator وهذا يتجلى في الآتي
BK accumulation vasodilation in
the lung and increase vascular
permeability so fluid leakage
and make Pulmonary edema.

← دور ال BK في ال Dry Cough

The accumulation of BK causes
irritation of bronchial mucosa
so this cause cough reflex.

← ضرباً لو كان
شخص فاعنده
مشاكل في الكلية
في تصريف ال K⁺
فهاد ال Adverse
فش خطير كتير...
لأن لو واحد مثلاً
عنده Kidney failure
أو بياخد دواء بيزيد
مستوى ال K⁺ في الدم
عنا بيصبح الأمر أخطر

Angiotensin II Receptor Blockers

لا يمكن أخذ
ARBs و ACE
مع بعض

- ARBs 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.
- They may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of 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.

ثآنه قصير عذري
severe side effect

ANGIOTENSIN II RECEPTOR BLOCKERS

Azilsartan EDARBI

Candesartan ATACAND

Eprosartan GENERIC ONLY

Irbesartan AVAPRO

Losartan COZAAR

Olmesartan BENICAR

Telmisartan MICARDIS

Valsartan DIOVAN

ثآنه ال Bradykinin مستويانه بتكون
أقل عند استخدام ال ARBs، ثآنه ال ACE
تم تكوينه في ال lung يعني تم تكسير
ال Bradykinin ...

Renin Inhibitor

Aliskiren , is available for the treatment of hypertension. الدواء الوحيد

Aliskiren directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs

→ it would cause hyperkalemia.

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

It also causes cough and angioedema but less often than ACE inhibitors.

As with ACE inhibitors and ARBs, **aliskiren** is contraindicated during pregnancy.

Aliskiren can cause diarrhea, especially at higher doses.

Aliskiren is metabolized by CYP3A4 and is subject to many drug interactions.

عموماً أنزيم من Cytochrome P450 family
موجود في ال intestine + liver وخصوصاً درراً
عموماً في metabolism of many drugs
← عادة أي دواء يصير به metabolism
من عوامل الأنزيمات بتأثر بعدد من ال
Drug-Drug interaction...

لأنه عننا drug كثير بتأثر على هذه الإنزيمات، ممكن تعملهم inhibition or induction

→ First line of Antihypertensive medication.

تأثيره على ضغط الدم
Hyper.T

First line تعتبر الـ Black Patients، ويستغفروا عند المرضى
لي عندهم SIHD / Diabetes + Hypertension
لو كان المريض Contraindicated لا ACE والـ ARBs

يمكن استخدامه البديل وهو الـ calcium channel broke blockers

CCBs

Classes of calcium channel blockers

مقسمة chemically

(Non dihydropyridines)

Ne-inotropic effect.
Ne-chronotropic effect.
Ne-Dromotropic effect.

Diphenylalkylamines

- Verapamil
- Acts on cardiac and vascular smooth muscle cells
- Used as anti-angina
- Anti arrhythmic

فيها Ca^{2+} Channels، ودخول الـ Ca^{2+} للعضلة يؤدي لـ contraction واحدنا بدنا Vasodilation، يفتح بدنا تمنع دخول الـ Ca^{2+} .

أكثرهم عنده negative inotropic effect. أكثرهم يقلل الـ contractility
- عشان هيك بنحاول نتفادي استخدامه في مرضى الـ heart failure

Benzothiazepines

- diltiazem
- both cardiac and vascular smooth muscle cells
- less pronounced negative inotropic effect on the heart compared to that of verapamil

هو أيضاً بيشتغل على الـ C.A. أكثر، الغرق بيه وبين الـ Verapamil هو أنه الـ diltiazem يعتبر / less negative inotropic effect

Dihydropyridines

- Nifedipine
- Amlodipine
- Isradipine
- Nicardipine

much greater affinity for vascular calcium channels than for calcium channels in the heart

لما أنه بيشتغل أكثر على الـ Vessels إذن هو يلبس استخدمه لعلاج الـ Hyper.T فضلاً على ذلك.

يؤثر على الـ smooth muscles في [Coronary artery and peripheral BV]
أكثر من الـ الـ Heart

هو أكثر واحد
يعمل Negative inotropic effect
لذلك لا يستخدم مع مرض الـ Heart Failure
الآن الـ Verapamil
بيشتغل أكثر على الـ Cardiac Affenety تبعته لا الـ C.A. لذلك هو يستخدم كـ Anti-angina Anti-arrhythmic

Digoxin is more effective in HR controlling at rest, while diltiazem or verapamil at physical activity is more effective...

Dihydropyridines

ولكن ال Verapamil و Diltiazem are more commonly used with warfarin and Digoxin. ولذا لازم يكون في monitoring لأنه ممكن يغير DDI

They are beneficial in treating hypertension.

١ Dihydro-group ا عندهم less Drug-Drug interaction than Non-Dihydro-group.

The dihydropyridines have the advantage in that they show little interaction with other cardiovascular drugs, such as digoxin or warfarin, which are often used concomitantly with calcium channel blockers.

مقارنة مع ال nondihydro

It slows the Heart rate by affecting electrical activity of Heart. (Ne-chronotropic effect)

٢ Has positive inotropic effect so it increases the heart contraction strength.

٣ It's Anticoagulant "blood thinner". It block vitamin K which is essential in blood clot.

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 mainly arterioles. Calcium channel blockers do not dilate veins. —> Arter* ال شلوم

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.

Amlodipine has a very long half-life and does not require a sustained-release formulation.

→ $HL = 30-60h$
→ once daily dosing

مثلاً الـ verapamil لو صعدو
فشن يصنع بطريقة أنه
يكون sustained إذن يحتاج
أخذه كل 8 ساعات مثلاً.
لكن لو صعد بطريقتة يكون
sustained-release
يبقى فقط مرة وحدة في اليوم
بأخذه ، وهذا أسهل على المريض.

Chronotropic effect الـ Chronotropic effect
Diltiazem تيج الـ Diltiazem
AV node بيكون عبر التأثير على الـ AV node
Verapamil يعني إياها
Ne-Dromotropic Effect
فعدا ممكن يؤدي إى الـ AV block ...

Verapamil relaxes smooth muscle including those in GI tract so this results (Peristalsis) slow movement of digestive muscles so this make stools passing is harder + verpamil decrease fluid secretion which hardening the stool.

Adverse effects

Heart block الـ Heart block
negative inotropic effect الـ negative inotropic effect

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 (force of cardiac muscle contraction) and dromotropic (velocity of conduction) effects.

Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines

Peripheral edema is another commonly reported side effect of this class.

Nifedipine and other dihydropyridines may cause gingival hyperplasia.

Diltiazem يعمل زيه
لكن بقوة أقل منه

سريعاً ينتج عنه
Slow heart rate

لأنه الـ Dihydro بتشتغل أكثر
Hypertension of vessels الـ



Peripheral edema

Gingival hyperplasia



Gingival Cells حدث لها Hyper Plasia [فرط نمو]

يعني كل
ما زودنا الـ
Dose
زاد الـ
effect

سرعة
انتقال الـ
impulses
في الـ
Heart's
Conduction
System

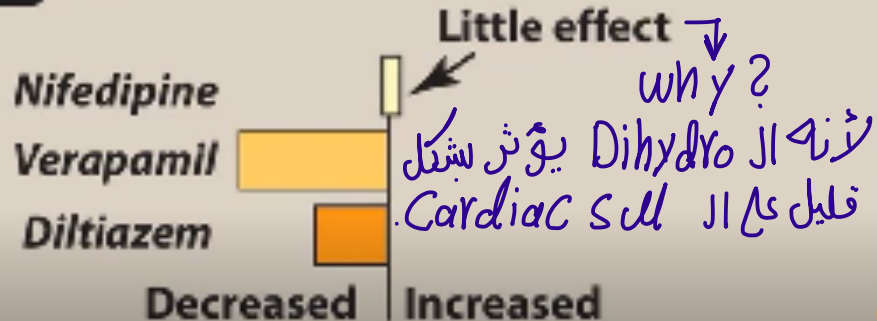
Dose dependant

لأنه الـ Ca^{2+} blockers بتشتغل على الـ arteries فقط فويسير عنزي فرق
ضغطيين الـ الرئيتين فعدا يؤدي لتضخم السوائل يعني edema

A Dilation of coronary vessels



B AV Conduction

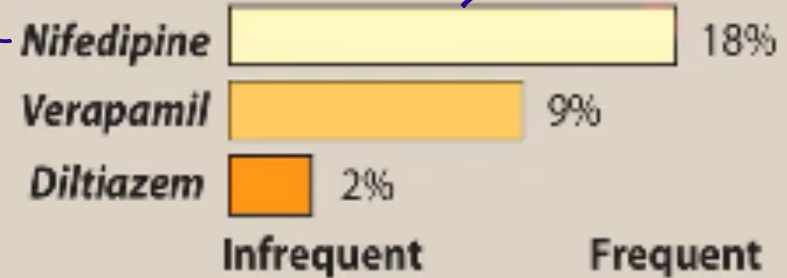


لو تم أخذه بطريقة أنه يصل
لبسرى الدم فيعمل Reflex tachycardia
لأنه ال BP فيقل جداً مرة وحدة وبالتالي
الجسم فيعمل reflex وعضو زيادة ال H.Rate
يعني Reflex Tachycardia، ولو المريض عنده
Angina و Re ischemia فيصير عندي

نجد أنه ال Nifedipine يتم
تصنيعه ليكون Sustained-release
ليكون مغطوط في Gouting
حتى يخرج ببطء إلى الدم ...

السبب

C Frequency of adverse effects



Peripheral edema
Dizziness
Gingival hyperplasia

موجودة في ال blood vessels

α -ADRENOCEPTOR-BLOCKING AGENTS

prazosin, doxazosin and terazosin.

These agents produce a competitive block of α_1 -adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.

Long-term tachycardia does not occur, but salt and water retention does.

Reflex tachycardia and postural hypotension often occur at the onset of treatment and with dose increases, requiring slow titration of the drug in divided doses.

لما يقوم المريض بحسن بدوخة.

لأنه في بداية العلاج
يبتزل الضغط بطريقتين
مستمرة يعني.

عشان هيك يتفول للمريض خد
الحبة عند النوم عشان ما يتعرض
لهادي الشفلات، وينتدأ بجرعات
صغيرة وشوي شوي تعلق

Because α -blockers
are potent hypertensive
treatments.

Due to weaker outcome data and their side effect profile, α -blockers are no longer recommended as initial treatment for hypertension but may be used for refractory cases.

(resistance hypertension)

Other α_1 -blockers with greater selectivity for the prostate are used in the treatment of benign prostatic hyperplasia

العالان يلي
جربت فعوا
أكثر من دواء
ولا يزال الضغط
مرتفع بالجرعة
للـ α -blockers

So
they are not
First line...

used in Hypertension Emergency
when BP (sys ≥ 180 or Diy ≥ 110) +
There is organ failur like heart attack,
impaired Kidney function, and So on...

IV

a-/b-Adrenoceptor-blocking Agents

➤ Labetalol and carvedilol block $\alpha 1$, $\beta 1$, and $\beta 2$ receptors.

يعتبر first line hypertensive medication للناس التي عندها heart failure and hypertension

➤ Carvedilol is indicated in the treatment of heart failure and hypertension. It has been shown to reduce morbidity and mortality associated with heart failure.

➤ Labetalol is used in the management of gestational hypertension and hypertensive emergencies.

يعني T Hyper أثناء ال pregnancy

→ it's used for
Pregnant women.

α_2 -receptors α Clonidine بيشتهل Directly
 لكن ال Methyldopa بيشتهل indirectly از آنه يتحول الى
 Methylnorepinephrine أي False N-T ثم يرتبط مع α_2 -R
 في ال Brain وعليها Norepi-inhibition for SNS



Centrally Acting Adrenergic Drugs

Clonidine
 Not a first line

الدماغ يأمر ال SNS بتقليل ال Nor Epi. Flow

- acts centrally as an α_2 agonist to produce inhibition of sympathetic vasomotor centers. decreasing sympathetic outflow to the periphery.
- Adverse effects includes sedation, dry mouth, and constipation
- used in refractory cases.
- like β -blockers, we should stop treatment step by step to avoid severe Hypertension.

يحدث inhibition ال enteric nervous sys
 وعليه slow intestinal muscle contraction
 ال SNS يعجز ال Salivary gland
 عن تليل نشاطه بقل ال Salivation

Methyldopa

Save for Pregnant women
 يوصى استخدامها للنساء الحوامل.

- α_2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS
- The most common side effects of methyldopa are sedation and drowsiness
- It is mainly used for management of hypertension in pregnancy

تقريباً كل 8 ساعات أو كل 6 ساعات Short half life

عن طريق زيادة ال nitric oxide الي يعتبر potent vasodilator

Vasodilators

قليل ما يتم استخدامها

less likely
to be used.

Potent.

Not First line.

- The direct-acting smooth muscle relaxants, such as hydralazine and minoxidil, are not used as primary drugs to treat hypertension.
- These vasodilators act by producing relaxation of vascular smooth muscle, primarily in arteries and arterioles. This results in decreased peripheral resistance and, therefore, blood pressure.

← ال Vasodilators حبيب Potent
يبقن عنري reflexes حقتير قتل $\uparrow$ HR عليها
عند أخذ ال Vasodilation نأخذ معه β -blocker
حتى يغلل ال HR و ال Contractility.

Side effects

- Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption.

These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals خاصة في المرضى ال cardiac الي معروف انه ischemic heart disease

- Vasodilators also increase plasma renin concentration, resulting in sodium and water retention

← لذلك أستخدم Diuretics
حتى أفتقد Na^+ و water عبر ال
urine.

Hydralazine is an accepted medication for controlling blood pressure in pregnancy-induced hypertension خاصة في حالات ال preeclampsia

Adverse effects of *hydralazine* include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina .

A lupus-like syndrome can occur with high dosages, but it is reversible upon discontinuation of the drug.

Minoxidil treatment causes hypertrichosis (the growth of body hair). This drug is used topically to treat male pattern baldness

استخدامه
ک Anti hyper. T
فعلياً غير موجود.

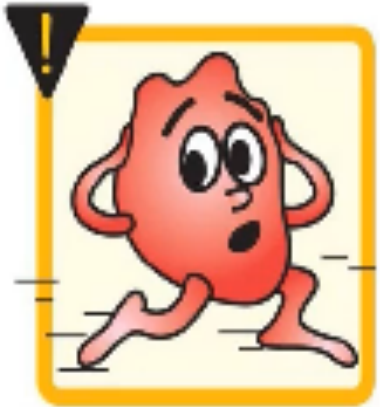


Headache



Palpitations

*lupus like syndrome
with high dosage*



Tachycardia



Angina



Nausea

Antiarrhythmic part 1

Atrial arrhythmia

This common arrhythmia involves multiple ectopic foci of atrial cells, creating a chaotic movement of impulses through the atria. The ventricular response may be rapid (100–150 beats per minute) and irregular. Cardiac output is decreased and exercise intolerance is common.

TYPE OF ARRHYTHMIA

Class I

ATRIAL
ARRHYTHMIAS

ATRIAL
FLUTTER

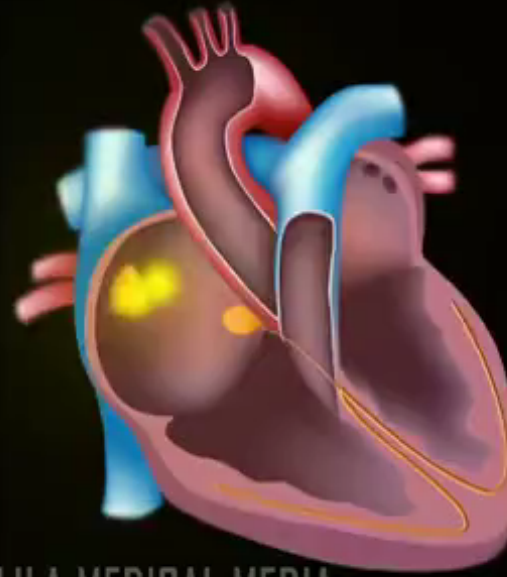
ATRIAL
FIBRILLATION

Propafenone

More common

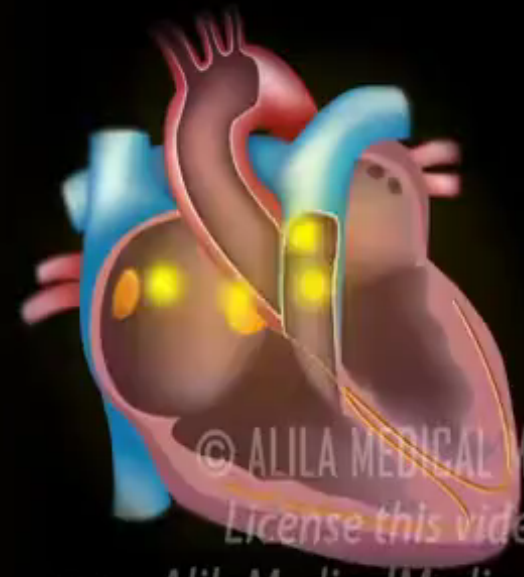
سببها ال ectopic signals من امكان اخرى في ال SA nodes بنقيا تطلع signals اسرع من ال SA node
Contraction in the atrium can reach 300 contraction

Normal



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A-Fib

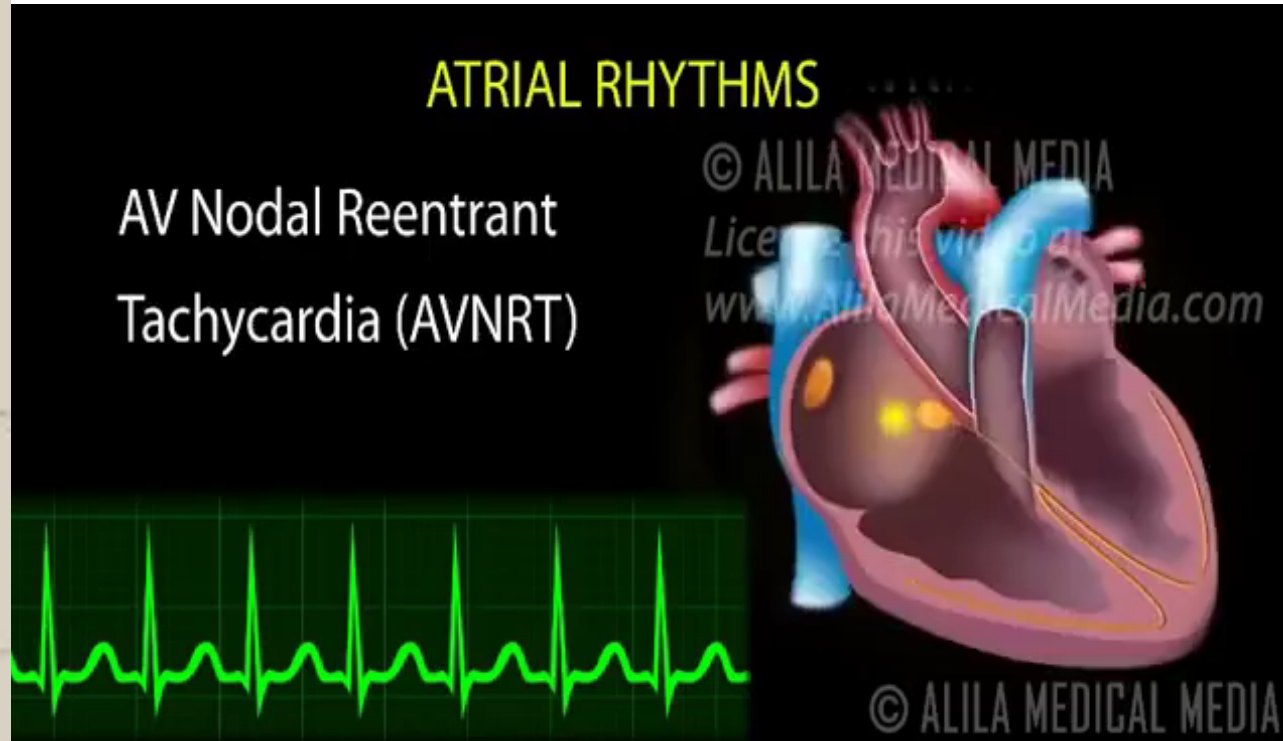
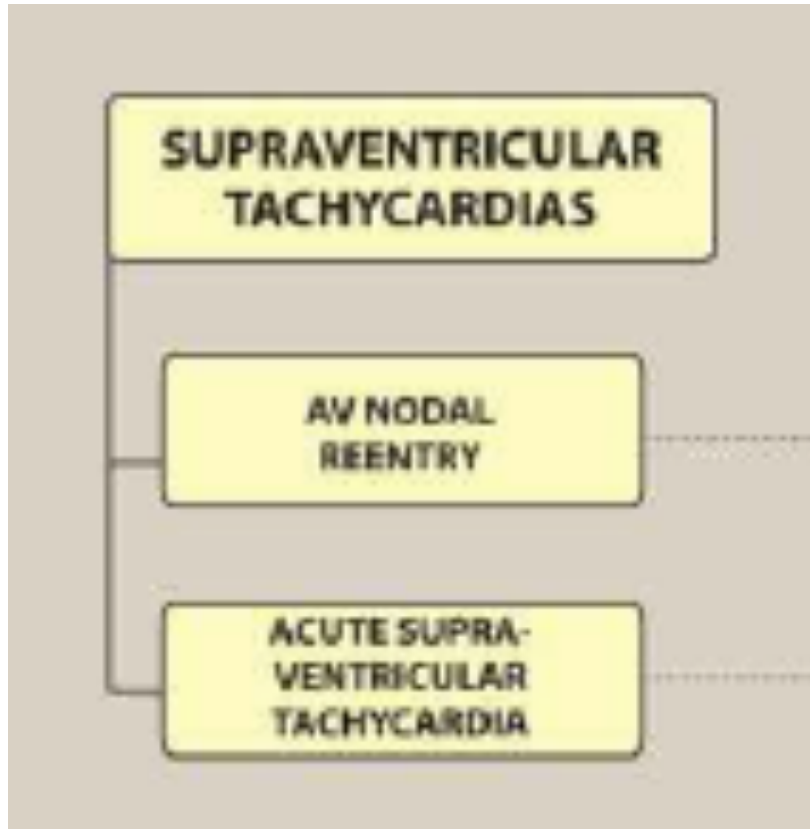


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- Atrial arrhythmia:

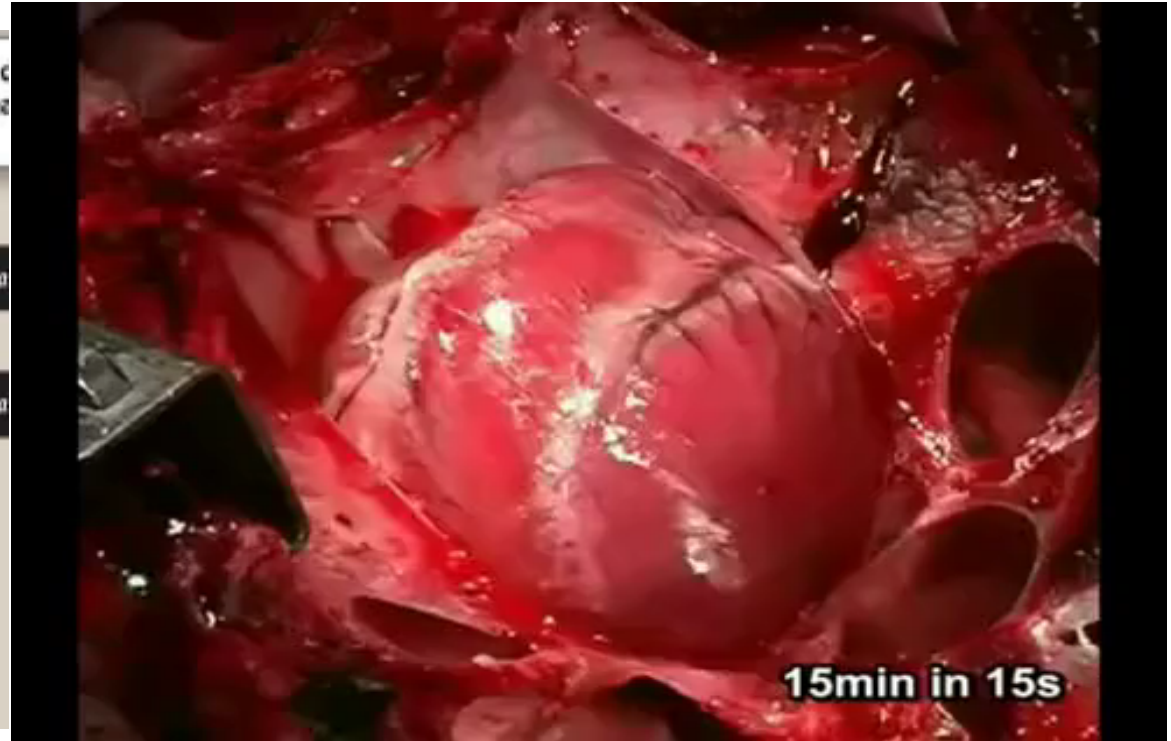
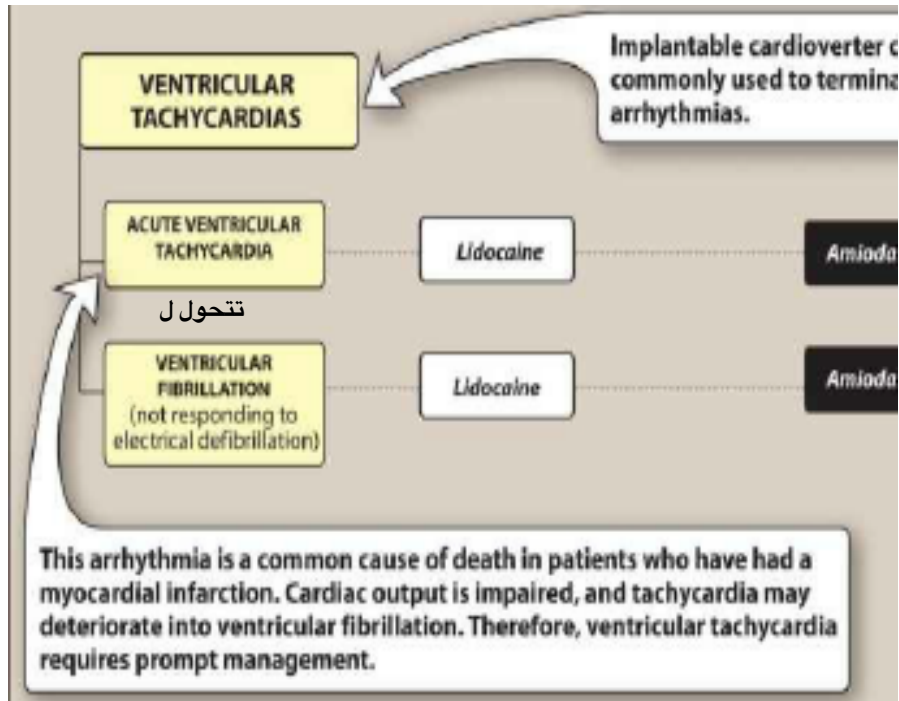
- صعب كل ال signals تصل لل AV node ولل ventricle، الي بقدر يلقطه ال AV node بدخله لل ventricle، عشان هيك بكون ال atrial contraction يكون أعلى بكثير من ال ventricular contraction، ولكن هيصبر برضو increase in HR، وهيكون ال ventricular response عالي
- ممكن يؤدي لل death، أو يؤدي لل ischemic stroke، وهذا لإنه ال atrium ما بيقدر يعمل contraction بالشكل الصحيح، فبؤدي لتجميع ال blood في ال atria، مش كل الدم بروح ع ال ventricle، وهذا ممكن يعمل thrombosis وتروح لأي مكان، أشهر مكان انها تروح لل brain

Supraventricular tachycardias



من أخطر أنواع ال Tachycardia

Ventricular tachycardia



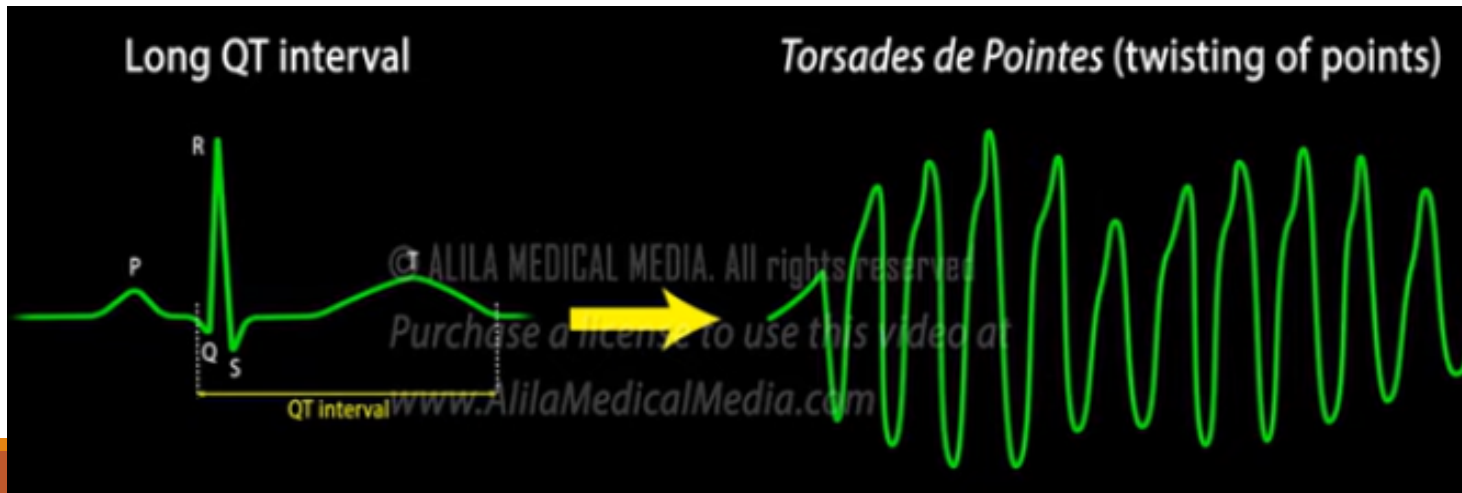
- ممكن يعملوا slowing of conduction, أزود فترة ال action potential
بالتالي أقلل من سرعة انتقالها من خلية لأخرى

Antiarrhythmic drugs

Many of the antiarrhythmic agents are known to have dangerous proarrhythmic actions—that is, to cause arrhythmias

Inhibition of K^+ channels widens the action potential and can, thus, prolong the QT interval. If prolongation is excessive, these drugs increase the risk of developing life threatening ventricular tachyarrhythmias (torsades de pointes).

Causes:: drug induced, ischemia and hypokalemia) and genetic abnormalities may contribute.



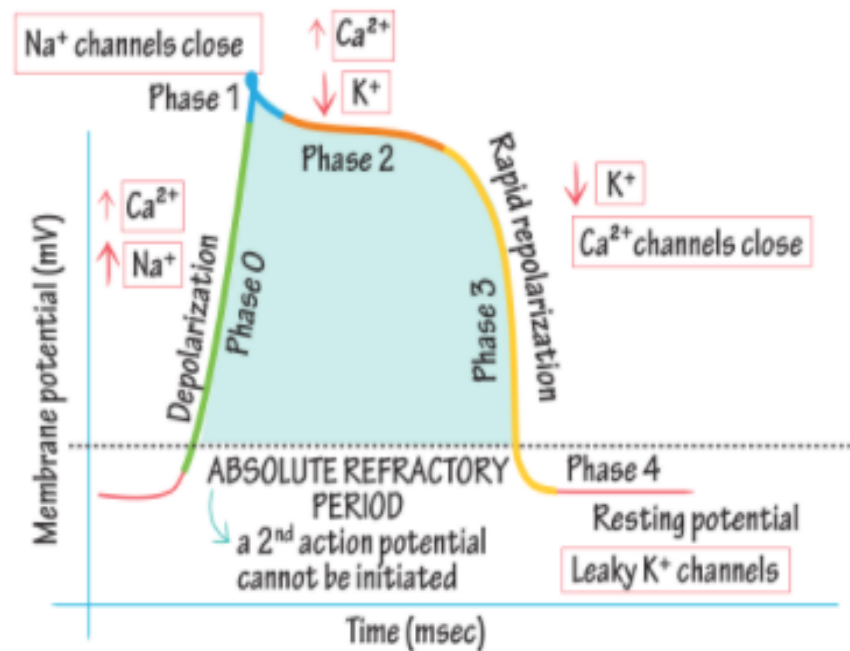
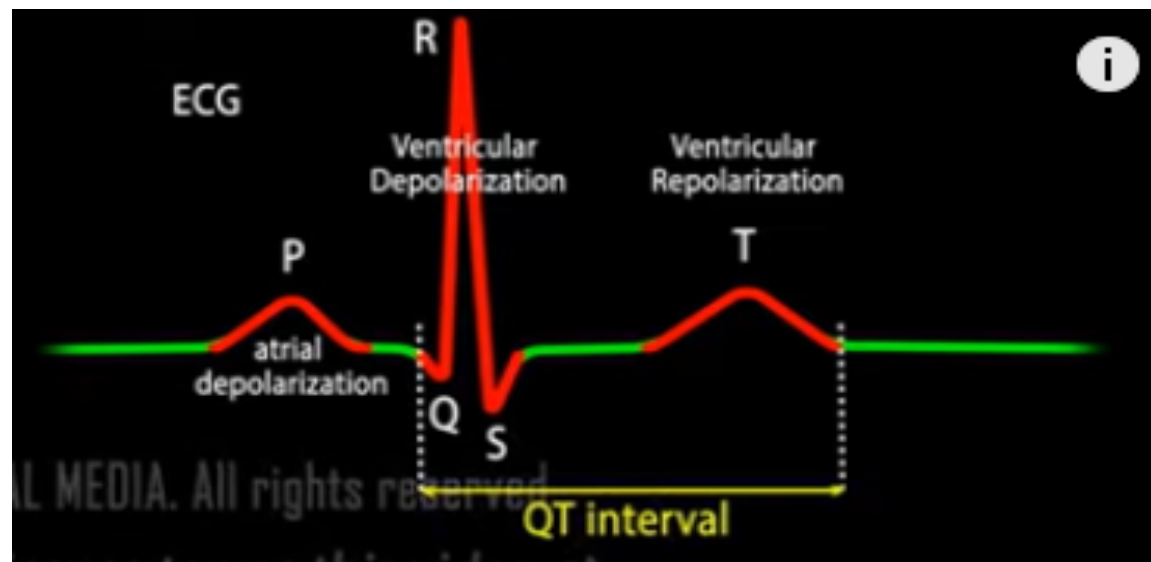
- واحدة من أهم ال side effect لهذه الأدوية هي انهم ممكن يعملوا dangerous
proarrhythmic actions

خاصة ال anti-arrhythmic medications، الي بتعمل inhibition of potassium channels، فهادي راح تطولي فترة ال action potential، وهتطول فترة ال refractory period، وراح تطول الفترة تبعت ال repolarization، فهيصير في abnormal beat and electrical impulse, reentry

وهتعطي فرصة انه يتكون نوع من أنواع ال tachyarrhythmia وهو ال torsade de
pointed

وعادة سببها ال drug induced

المريض ممكن يكون عنده prolongation لل QT interval ولكن يكون asymptomatic، ولكن ال
torsades de pointes بتكون symptomatic



تم تقسيمهم 4 classes

Anti-arrythmic classification

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na ⁺ channel blocker	فأنا هيك بعمل تثبيط لل firing الي يكون في ال tissues الي عندها abnormal rythim Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na ⁺ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na ⁺ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β -Adrenoreceptor blocker Beta one	Inhibits Phase 4 depolarization in SA and AV nodes موجود في ال SA node بنسبة محترمة، وموجود كمان في ال AV node
III	K ⁺ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers وهيك بطول ال refractory period
IV	Ca ²⁺ channel blocker	Inhibits action potential in SA and AV nodes

Class I

Mechanism of action :: blocking voltage-sensitive Na^+ channels.

They bind more rapidly to **open or inactivated** Na^+ channels than to channels that are fully repolarized. **repolarization** ال مرحلة التي في channels الصوديوم

Therefore, these drugs show a greater degree of blockade in tissues that frequently depolarizing. هان يكون تأثيرها أعلى.

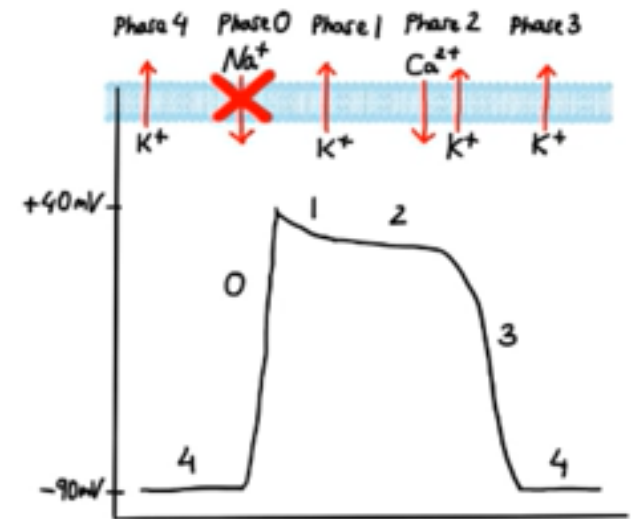
Use dependence (or state dependence):

It enables these drugs to block cells that are discharging at an abnormal high frequency, without interfering with the normal beating of the heart.

normal beating of the heart ال سيكون تأثير ضعيف جداً على

proarrhythmic
effects!!!!!!!!

المشكلة المرتبطة في class 1 drugs وختل
ال clinical practice الهم قليل، هو:



CLASS I (Na⁺-channel blockers)

A **Disopyramide** (IA) NORPACE

C **Flecainide** (IC) TAMBOCOR

B **Lidocaine** (IB) XYLOCAINE

Mexiletine (IB) GENERIC ONLY

Procainamide (IA) GENERIC ONLY

Propafenone (IC) RYTHMOL

Quinidine (IA) GENERIC ONLY

Class I

تختلف من ناحية ال action على ال Na channels، يعني في منهم potent Na channel blocker وفي منهم long Na channel blocker وفي منهم weak، وفي بينهم intermediate بين الاثنين، في منهم بعمل prolongation of action potential وفي بعمل shortening، في منهم ما بأثر على ال refractory period وفي بيأثر بإنه بيزيدها وفي بقللها

Class IA Intermediate	Moderate Na channel blocker (Slowing the rapid upstroke during phase) فهي عمل slowing لا انتقال ال action potential من خلية لخلية Prolong action potential and refractory period Slows conduction velocity يعمل block لل K channels ال هي مسؤولة عن phase 4 بالتالي هي يصير في increase في ال refractory period
Class IB sodium channel limited effect اله	Weak Na channel blocker shorten phase 3 repolarization and decrease the duration of the action potential
Class IC The strongest	Powerful and strong fast Na channel blockers Depress phase 0 depolarization Has limited effect on repolarization and refractory period more potent antiarrhythmics.

فالتقسيمة كانت بناءً على ال efficacy تبعتهم، وال mechanism of action، وتأثيرهم على ال refractory period وال repolarization وال depolarization

السلبي فيهم انه فيهم خصائص انهم يعملوا ،blocking of potassium channels
فهما مش مقتصرين على ال Na channels ، فتعمل prolongation repolarization

Class IA antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

proarrhythmia

❖ Because of their concomitant class III activity, they can precipitate arrhythmias that can progress to ventricular fibrillation. or torsade de point (death (ويمكن تؤدي مباشرة لل

❖ Mechanism of action:

Slowing the rapid upstroke during phase 0

It slows conduction velocity and increases refractoriness

المريض ممكن يعاني من dry mouth ، ممكن يعاني من
CNS effects ، constipation ، urinary retention واكيد في

Quinidine also has mild α -adrenergic blocking and anticholinergic actions.

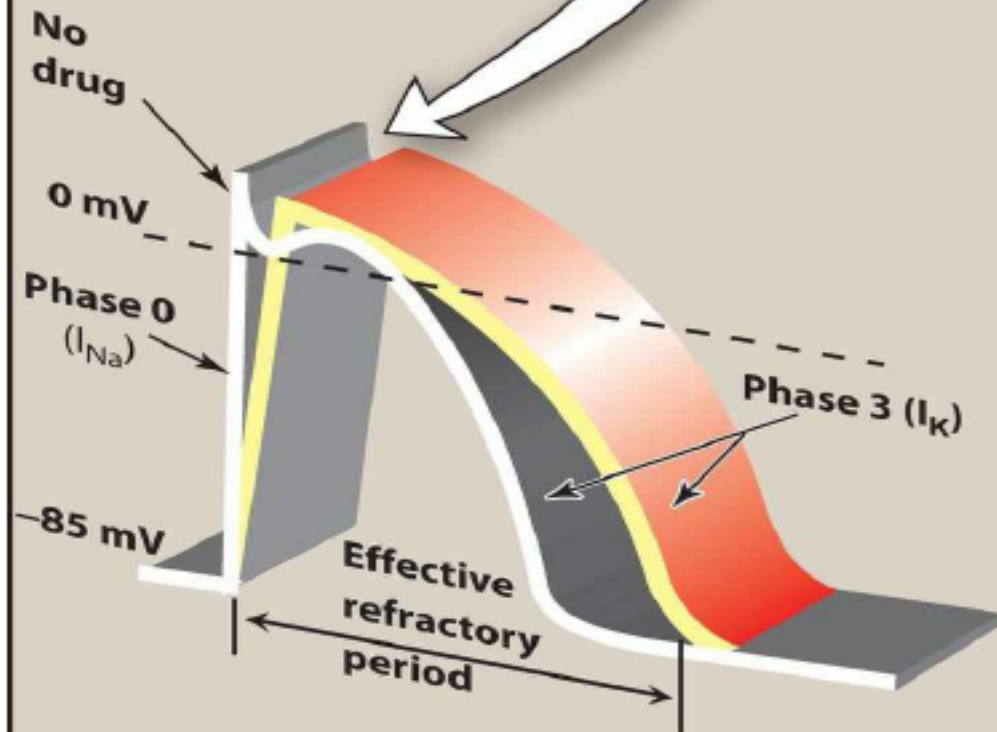
Neither *procainamide* nor *disopyramide* has α -blocking activity

less anticholinergic activity with *procainamide* and more with *disopyramide*

Disopyramide produces a greater negative inotropic effect, and unlike the other drugs, it causes peripheral vasoconstriction

فلازم ابعد عنه في المرضى الي عندهم left
ventricular dysfunction، herat failure

Class IA drugs slow Phase 0 depolarization. In addition, because of their Class III activity, these drugs prolong the action potential.



Therapeutic uses:

They are used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias

Adverse effects:

فلازم تبعد عنهم في مرضى ال heart failure, ischemic heart disease, atherosclerosis. او عامل قسطرة

- ❖ Enhanced proarrhythmic effects and ability to worsen heart failure symptoms,

Class IA drugs should not be used in patients with atherosclerotic heart disease or systolic heart failure

- ❖ Large doses of *quinidine* may induce the symptoms of **cinchonism** (for example, blurred vision, tinnitus, headache, disorientation, and psychosis)

- ❖ Intravenous administration of *procainamide* may cause hypotension.

- ❖ *Disopyramide* has the most anticholinergic adverse effects of the class IA drugs (for example, dry mouth, urinary retention, blurred vision, and constipation)

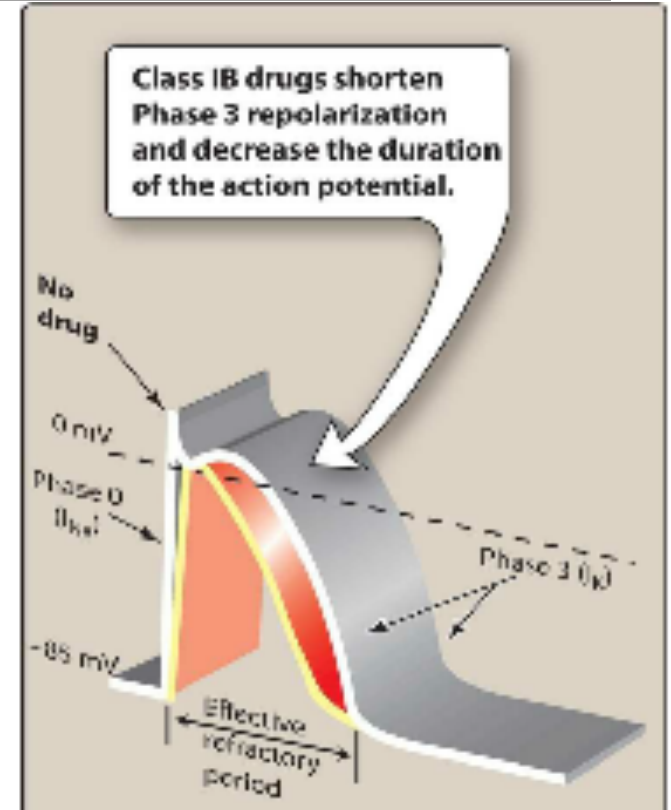
Class IB antiarrhythmic drugs: Lidocaine and mexiletine

- They are useful in treating ventricular arrhythmias
- They have little effect on atrial or AV junction arrhythmias
- Neither drug contributes to negative inotropy

Mechanism of action:

In addition to Na⁺ channel blockade, *lidocaine* and *mexiletine* shorten phase 3 repolarization and decrease the duration of the action potential

Adverse effects:



Adverse effects

Lidocaine has a **fairly wide therapeutic index**.

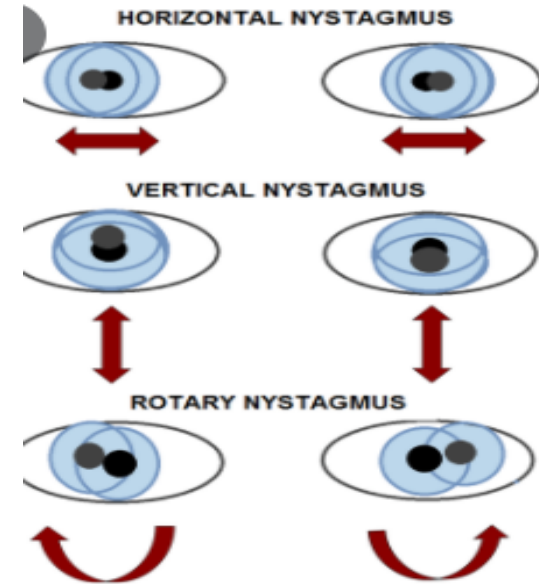
لكن الجرعات العالية منه تسبب

Central nervous system (CNS) effects include nystagmus (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions, which often limit the duration of continuous infusions.

استخدامه في ال clinical practice as antiarrhythmic drug is very rare

Mexiletine has **a narrow therapeutic**. Nausea, vomiting, and dyspepsia are the most common adverse effects.

Uncontrolled and repetitive
movement of the eye



they will slowly **bind to Na channels and they will slowly deassociate from resting Na channel** يتميزوا بال slow pharmacokinetics، يعني

Class IC antiarrhythmic drugs: Flecainide and propafenone

These drugs **slowly dissociate from resting Na⁺ channels** and show prominent effects even at normal heart rates.
هاد يؤدي على انهم بقدروا يشتغلوا على ال normal heart rate وهاد عكس الباقيين، الي يكون تأثيرهم في حالة ال abnormal heart rhythm
- أما ال class 1C راح يبطء ال normal heart rate يعني they will cause arrhythmia

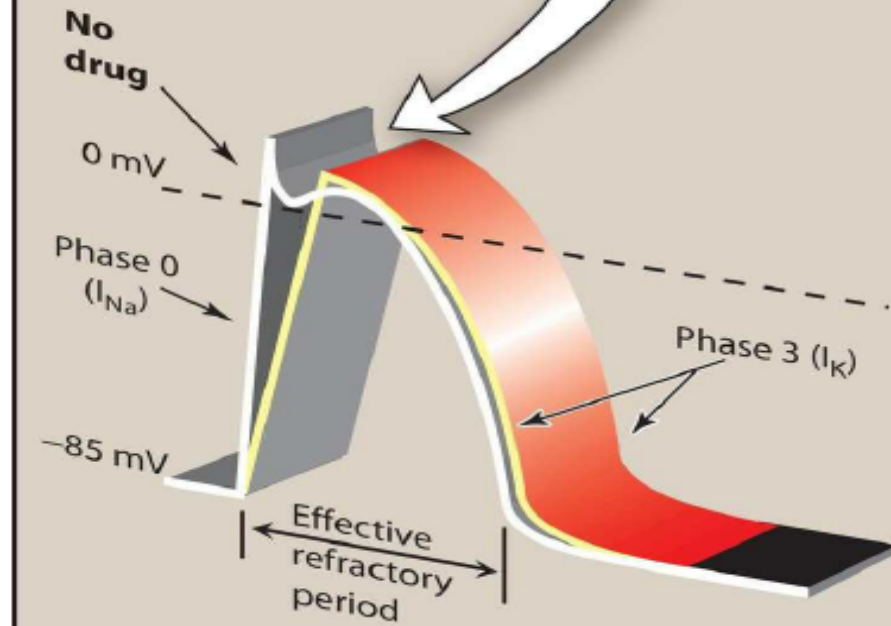
Due to **their negative inotropic and proarrhythmic effects!!!!!!**

The use of these agents is avoided in patients with structural heart disease (left ventricular hypertrophy, heart failure, atherosclerotic heart disease). **dysfunction**

Mechanism of action::

- ❖ They suppress phase 0 upstroke in Purkinje and myocardial fibers
- ❖ *Flecainide* also **blocks K⁺ channels**, leading to increased duration of the action potential.
- ❖ *Propafenone*, like *flecainide*, slows conduction in all cardiac tissues but does not block K⁺ channels.
- ❖ propafenone possesses weak β -blocking properties.

**Class IC drugs markedly
slow Phase 0
depolarization.**



Therapeutic uses

بس في ال clinical practice ما بنستخدمه عشان هيك

Flecainide is useful in the maintenance of sinus rhythm in atrial flutter or fibrillation in patients without structural heart disease and in treating refractory ventricular arrhythmias. ممكن بنستخدمه في .

Use of *propafenone* is restricted mostly to atrial arrhythmias: rhythm control of atrial fibrillation or flutter and paroxysmal supraventricular tachycardia prophylaxis in patients with AV reentrant tachycardias

Adverse effects

Flecainide is generally well tolerated, with blurred vision, dizziness, and nausea occurring most frequently.

Propafenone has a similar side effect profile, but may cause bronchospasm and should be avoided in patients with asthma.

broncho constriction
بيعمل

Class IA	Moderate Na channel blocker Prolong action potential and refractory period Slows conduction velocity
Class IB	Weak Na channel blocker shorten phase 3 repolarization and decrease the duration of the action potential
Class IC	Powerful and strong fast Na channel blockers Depress phase 0 depolarization Has limited effect on repolarization and refractory period more potent antiarrhythmics.

Anti-arryhthmic part 2

YASMINE Z AL SHORAF

- بنبعد عن ال non selective beta blocker، لأنه الها side effect أكثر، مثلاً ال
Propranolol يفضل انه to be avoided to people who have asthma لأنه
ممکن بعملوا bronchospasm

Class II Antiarrhythmic Drugs

β-blockers.

احنا قصدنا عن beta one
selective beta blocker يعني

عادة ينعطيه IV، مثلاً خلال surgery معينة.
فصار فيها arrhythmia او في حالات ال
antiarrhythmic medication ك emergency

من أشهر ال beta blocker الي
يتم استخدامها ك
antiarrhythmic medication

CLASS II (β-adrenoreceptor blockers)

Atenolol TENORMIN

Esmolol BREVIBLOC Short and rapid acting beta blocker

Metoprolol LOPRESSOR, TOPROL-XL

Bisoprolol برضو مشهور

أشهر أنواع ال atrial arrhythmia الي
يستخدم ال beta blocker عشانها

They are also used for atrial flutter and fibrillation
AV nodal reentrant tachycardia.

Prevent life-threatening ventricular arrhythmias following a
myocardial infarction.

عشان يعمل prevent لحدوث ventricular arrhythmia

هلقيت من أسباب موت المرضى الي بصير
معهم myocardial infarction هو أنهم
بفوتوا ب ventricular arrhythmia ثم
death ثم ventricular fibrillation

They will block beta one blocker so they will suppress the action potential

Class II Antiarrhythmic Drugs

Mechanism of action :

1- Diminish phase 4 depolarization

2-Depress automaticity,

3-Prolong AV conduction زودنا الفترة

4-Decrease heart rate and contractility

Common adverse effects:

include bradycardia, hypotension, and fatigue

Class III Antiarrhythmic Drugs

- Class III agents block K^+ channels and, thus, diminish the outward K^+ current during repolarization of cardiac cells.
- These agents prolong the duration of the action potential without altering phase 0 of depolarization or the resting membrane potential
- They prolong the effective refractory period, increasing refractoriness.
- > All class III drugs have the potential to induce arrhythmias.

CLASS III (K^+ channel blockers)

Amiodarone CORDARONE, PACERONE

Dofetilide TIKOSYN

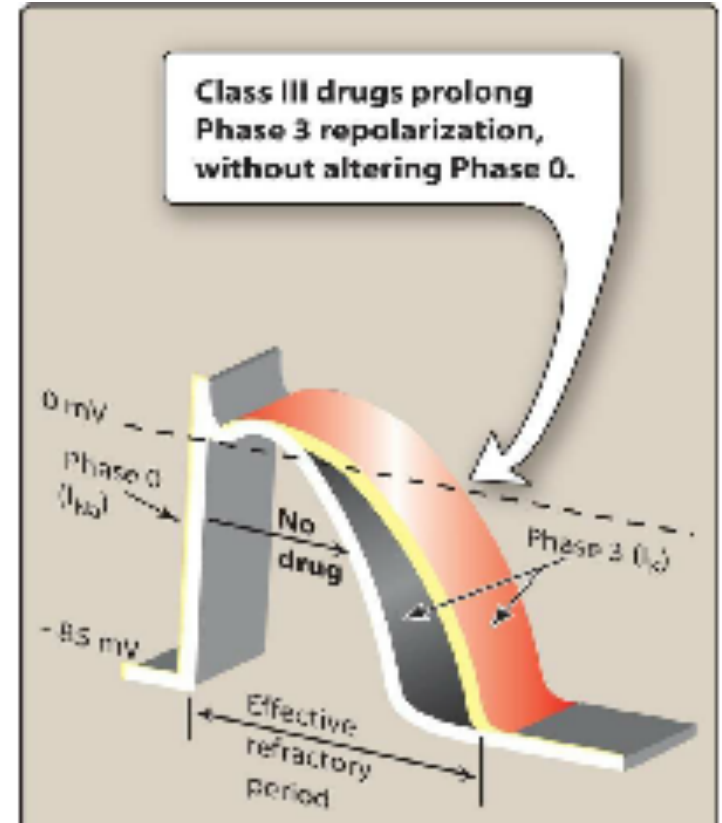
Dronedarone MULTAQ

Ibutilide CORVERT

Sotalol BETAPACE, SORINE

أشهر واحد وموجود IV or oral

موجود في الصيدليات orlay



Amiodarone

King of the group, very effective, used in emergency

Iodine groups

- *Amiodarone* contains iodine and is related structurally to thyroxine.
- Its dominant effect is prolongation of the action potential duration and the refractory period by blocking K⁺ channels
- It has complex effects, showing class I, II, III, and IV actions, as well as α -blocking activity.

Therapeutic uses

Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias.

عادة يستخدم لهم class 2

Amiodarone has been a mainstay of therapy for the rhythm management of atrial fibrillation or flutter.

Despite its adverse effect profile, *amiodarone* is thought to be the least proarrhythmic of the class I and III antiarrhythmic drugs.

The drug is unusual in having a prolonged half-life of several weeks (25-100 days), and it distributes extensively in tissues. **التالي بصيرله Accumulation في ال tissues**
بالتالي أي مريض بصير معاه side effect منه، ما نتوقع انها تروح بسرعة أول ما نوقفه

Full clinical effects may not be achieved until months after initiation of treatment, unless loading doses are employed.

Adverse effects::

reversible بعد استخدام طويل، عادة

قرنية

pulmonary fibrosis, neuropathy, hepatotoxicity, corneal deposits,

optic neuritis, blue-gray skin discoloration, and hypo- or hyperthyroidism

unilateral or bilateral fission ممكن يؤدي ل
blindness loss، لكن rarley ما تؤدي لحدوث

face خاصة في منطقة ال

بأثر ع كثير ادوية وادوية كثير بتأثر عليه
Drug drug interaction

Numerous DDIs ::: since it is metabolized by CYP3A4 and

serves as an inhibitor of CYP1A2, CYP2C9, CYP2D6, and P glycoprotein

عبارة عن بروتين يعمل efflux
لل drugs out of the cells





مشتق من ال structure of amiodarone

Dronedarone

- It has a shorter half-life than *amiodarone*.
- It does not have the iodine moieties that are responsible for thyroid dysfunction associated with *amiodarone*.
- *Dronedarone* has a better adverse effect profile than does *amiodarone* but may still cause liver failure.
- It is used to maintain sinus rhythm in atrial fibrillation or flutter, but it is less effective than *amiodarone*.
- The drug is contraindicated in those with symptomatic heart failure or permanent atrial fibrillation due to an increased risk of death
لأنه الدراسات وجدت ان هاستخدامه لهدول الناس بزيد ال **risk of death**

Sotalol

- Nonselective β -blocker activity
- *Sotalol* blocks a rapid outward K^+ current. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period
- Therapeutic use**: *Sotalol* is used for maintenance of sinus rhythm in patients with atrial fibrillation, atrial flutter, or refractory paroxysmal supraventricular tachycardia and in the treatment of ventricular arrhythmias
- It has a low rate of adverse effects when compared to other antiarrhythmic agents
- To reduce the risk of proarrhythmic effects, *sotalol* should be initiated in the hospital to monitor QT interval.

Dofetilide Orally

It can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease.

Because of the risk of proarrhythmia, *dofetilide* initiation is limited to the inpatient setting.

The half-life of this oral drug is 10 hours.

Ibutilide

Ibutilide is a K⁺ channel blocker that also activates the slow inward Na⁺ current (mixed class III and IA actions).

Ibutilide is the drug of choice for chemical conversion of atrial flutter.

It is not used orally. Initiation is also limited to the inpatient setting due to the risk of arrhythmia.

Class IV Antiarrhythmic Drugs

Nondihydropyridine Ca²⁺ channel blockers ^{يعمل constipation} **verapamil and diltiazem**

Both drugs show greater action on the heart than on vascular smooth muscle, but more so with *verapamil*

In the heart, *verapamil* and *diltiazem* bind only to open depolarized voltage-sensitive channels, thus decreasing the inward current ^{يعني يرتبطوا وقت ال plateau phase}

They slow conduction in tissues that are dependent on Ca²⁺ currents, such as the AV and SA nodes ^{خاصة في}

These agents are more effective against atrial than against ventricular arrhythmias, in treating reentrant supraventricular tachycardia

Common adverse effects include bradycardia, hypotension, and peripheral edema

Other Antiarrhythmic Drugs

Narrow therapeutic index

Digoxin Na k ATPase pump inhibitor

Prolonging the effective refractory period and diminishing conduction velocity in the AV node, while shortening the refractory period in atrial and ventricular myocardial cells

IV *Digoxin* is used to control ventricular response rate in atrial fibrillation and flutter

At toxic concentrations, *digoxin* causes ectopic ventricular beats that may result in VT and fibrillation. Ventricular arrhythmia

لو زاد عن هيك ممكن نفوت ب toxicity

Note: Serum trough concentrations of 1.0 to 2.0 ng/mL are desirable for atrial fibrillation or flutter

مهم نعمل **adjustment** لل **dose** في مرضى ال **kidney**، لأنه مرضى ال **renal impairment** بتزيد عندهم جرعات ال **digoxin**، بصير **accumulation** أكثر لل **digoxin**

Trough concentration : هو أقل **concentration** ممكن يصله اي دواء بالدم

Adenosine

- *Adenosine* is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node.
- Intravenous *adenosine* is the drug of choice for converting acute supraventricular tachycardias.
- It has low toxicity but causes flushing, chest pain, and hypotension.
- *Adenosine* has an extremely short duration of action (approximately 10 to 15 seconds) due to rapid uptake by erythrocytes and endothelial cells.

لأنه يصير له تكسير سريع

Magnesium sulfate

Magnesium is necessary for the transport of Na^+ , Ca^{2+} , and K^+ across cell membranes.

It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue.

Intravenous *magnesium sulfate* is the salt used to treat arrhythmias, as oral *magnesium* is not effective in the setting of arrhythmia.

Most notably, *magnesium* is the drug of choice for treating the potentially fatal arrhythmia torsades de pointes and *digoxin*-induced arrhythmias.

Ranolazine

Ranolazine is an antianginal drug with antiarrhythmic properties similar to *amiodarone*

Its main effect is to shorten repolarization and decrease the action potential duration similar to *mexiletine*.

It is used to treat refractory atrial and ventricular arrhythmias, often in combination with other antiarrhythmic drugs.

dizziness and constipation as the most common adverse effects



Drugs for Heart Failure

YASMINE AL SHORAF

للأسف المرض هاد بتطور من مرحلة لأخرى، وكل ما مر الوقت كل ما زادت الحالة سوء، خصوصاً لو المريض مش ملتزم بعلاجه

Heart failure (HF)

- It is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.
- Its cardinal symptoms are dyspnea, fatigue, and fluid retention.
- HF is due to an impaired ability of the heart to adequately fill with and/or eject blood.
- It is often accompanied by abnormal increases in blood volume and interstitial fluid.
- Underlying causes of HF include, but are not limited to, atherosclerotic heart disease, hypertensive heart disease, valvular heart disease, and congenital heart disease.

أسبابه كثير، مثلاً ال **ischmeic heart disease** بالتالي ممكن يؤدي ل **HF**،
مريض صار معاه **myocardial infarction** فممكن يصير عنده **HF**



مش بتاخر بسبب ال pulmonary congestion
بسبب انه الدم ما يتحرك بشكل جيد للصدر وبالتالي
يجمع الدم ويجمع ال fluids في ال lung في
هذه الحالة المريض يحتاج مررتين على ال اسبوع فقط
ال fluids الزيادة من جسم المريض

رجليه منفخين وعنده edema

بصيرلهم ترشيع

هو في أكثر من نوع، لكن أكثر نوعين مشهورين:

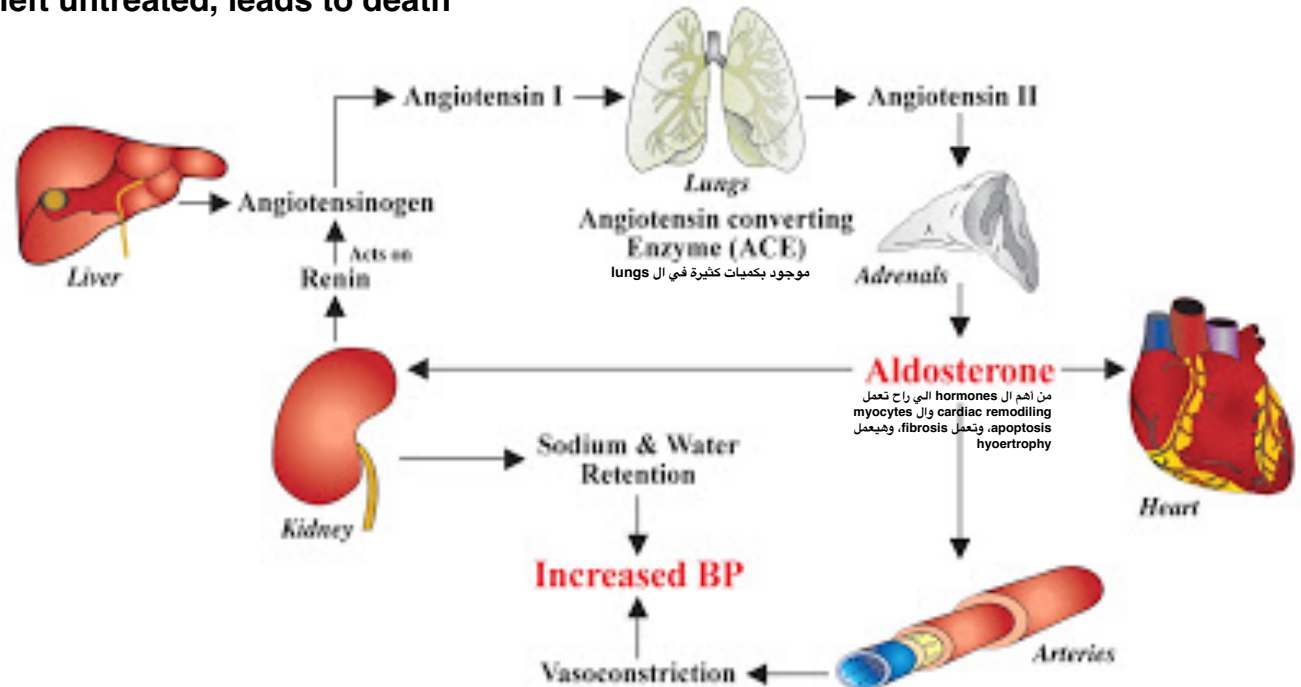
- انه القلب مش قادر يعمل pump to blood وهاد بنسميه heart failure with reduced ejection fraction

- أو ال HF is unable to relax فمش قادر يستقبل blood وهاد بنسميه HF with preserved ejection fraction

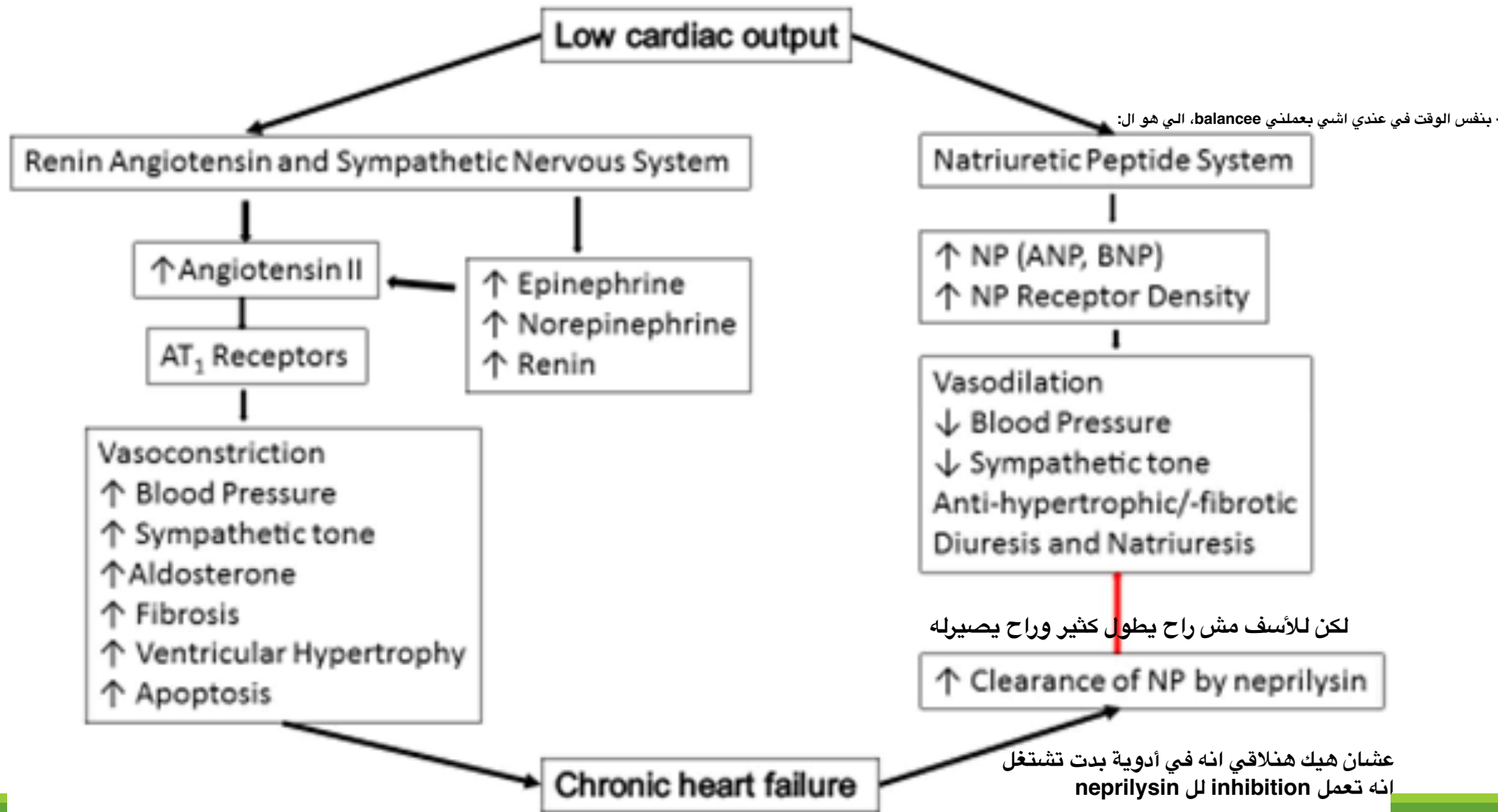
لكن هدول ال mechanism مع انه الهدف منهم انه يرجع ال blood ويزجع ال cardiac output
normal pressure لي ويحسن التروية و لكن هما السبب في ال progression of heart failure

Role of physiologic compensatory mechanisms in the progression of HF

1. Chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS) is associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis. This prompts additional neurohormonal activation, creating a vicious cycle that, **if left untreated, leads to death**



فالأدوية تبعت ال HF عادة بتكون موجهة against these two compensatory mechanisms



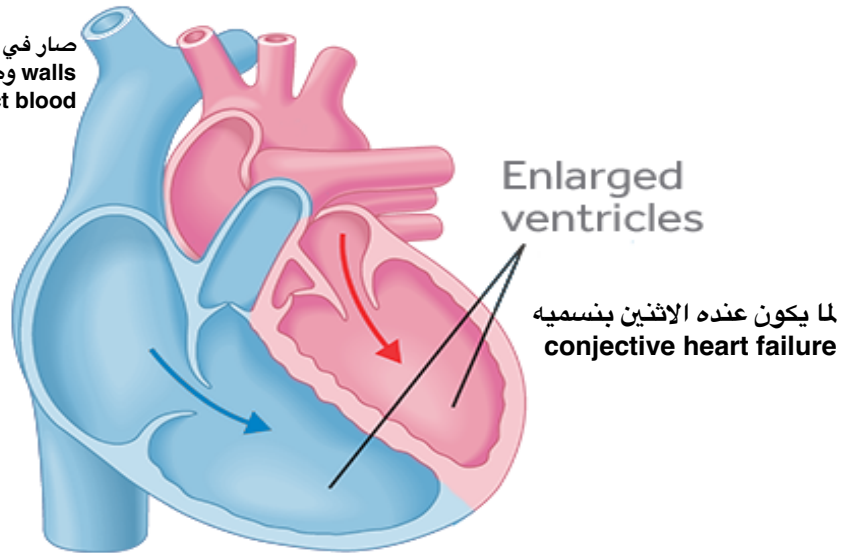
كل ال compensatory mechanisms الي ذكرناهم هيعملوا stretching لل
heart muscle وهيعملوا more and strong contraction to the heart

Types of HF

Heart failure(HF) with reduced ejection fraction (Systolic HF)

كل ما صار strong contraction to the heart وتل
صار excessive elongation لل fibers تديت ال
heart، مرة ع مرة فيصير weaker contraction
وهيصير diminished ability to eject blood

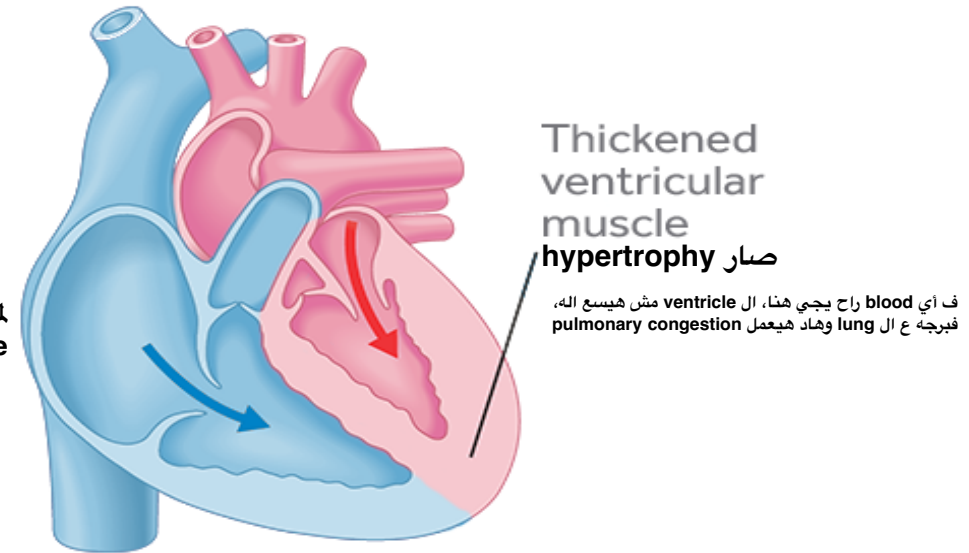
صار في weakining بال ventricle
diminshed ability to eject blood



This results from reduced contraction of the left ventricle such that not enough blood is pumped into the circulation.

لما ال ability of the ventricle to relax and to accept blood is impaired, this is called diastolic heart failure

Heart failure with preserved ejection fraction (Diastolic HF)



The left ventricle becomes stiff and does not relax normally. As a result, it cannot fill properly, and pressure begins to increase in the left heart chambers and in the lungs.

Types of HF

If the compensatory mechanisms adequately restore cardiac output, HF is said to be compensated.

If the compensatory mechanisms fail to maintain cardiac output, HF is decompensated and the patient develops worsening HF signs and symptoms.

Typical HF signs and symptoms include:

Dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and peripheral edema.

تمارين، أو ممكن لما يطلع الدرج أو لما
يروح من غرفته للحمام، أو حتى
at rest
وخذته تعتبر آخر مراحل ال
heart
failure
في تقسيم لأنواع ال HF according
activity التي يفتر يعملها للمريض

انقطاع في النفس وصعوبة في
التففس لما المريض
lying flat

بصحي فجأة مخنوق



Goals of pharmacologic intervention in HF

مش راح نعالجه ولا نوقفه، بل:

”

alleviate symptoms

slow disease
progression

Improve survival

أهم اشئ هو ال compliance تتبع المريض، يعني نعمل
pateint education للمريض بأهمية انه ياخذ كل علاجاته

Therapeutic strategies in HF

Non pharmacological therapeutic strategy

1-Fluid limitations (less than 1.5 to 2 L daily)

2-Low dietary intake of sodium (less than 2000 mg/d

3-Treatment of comorbid conditions يعني لو عنده diabetes بدنا نعالجه لأنه هيعمل progression لل HF

4- judicious use of diuretics.

5- inhibitors of the RAAS,

6- inhibitors of the sympathetic nervous system

7-drugs that enhance activity of natriuretic peptides

تزيد ال contractility

8- Inotropic agents are reserved for acute signs and symptoms of HF and are used mostly in the inpatient setting. بستخدمه في decompensated heart failure، الي يكون عندهم acute signs and symptoms

عاده يستخدموه للمرضى في المستشفيات. زي التروفين، الديكلوفين، مسكنات الألم من مجموعة ال NSAIDs لأنه بتعمل fluid and Na retention

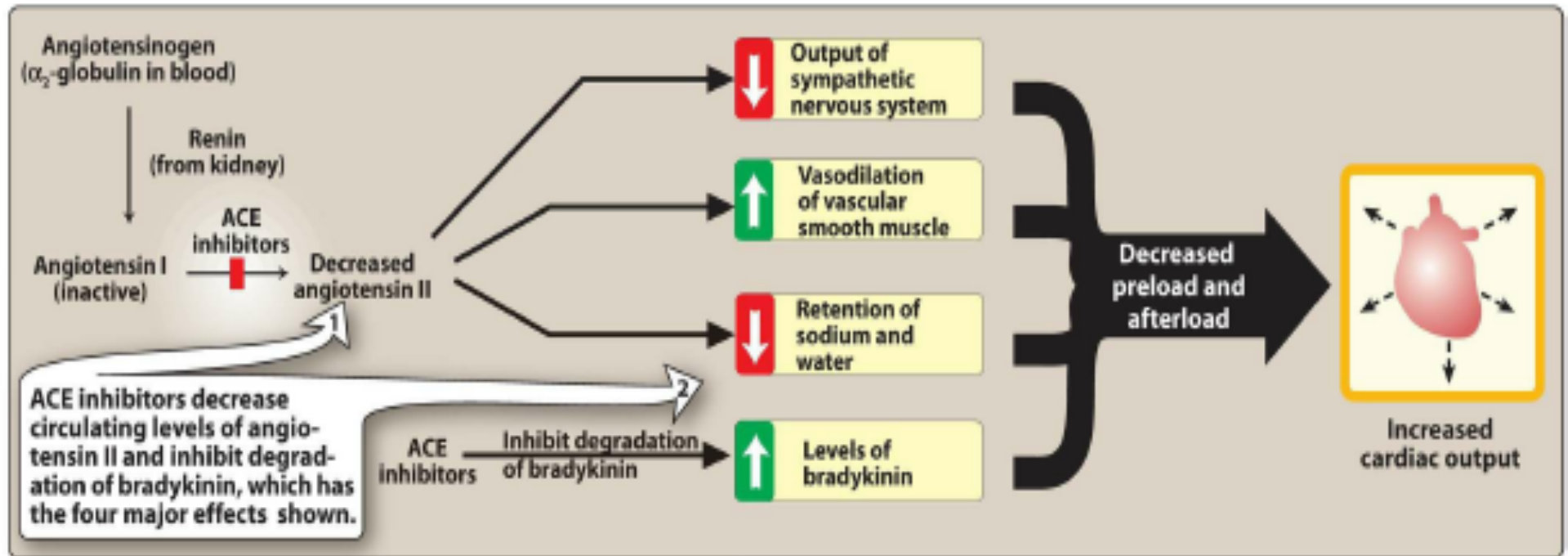
9-Avoid nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nondihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible

لأنه عندهم negative inotropic effect، يعني يقللوا ال contractility



Inhibitors of the Renin–Angiotensin–Aldosterone System

Angiotensin-converting enzyme inhibitors:



Inhibitors of the Renin–Angiotensin–Aldosterone System

ANGIOTENSIN RECEPTOR BLOCKERS

Candesartan ATACAND

Losartan COZAAR

Telmisartan MICARDIS

Valsartan DIOVAN

ACE INHIBITORS

Captopril GENERIC ONLY

Enalapril VASOTEC

Fosinopril GENERIC ONLY

Lisinopril PRINIVIL, ZESTRIL

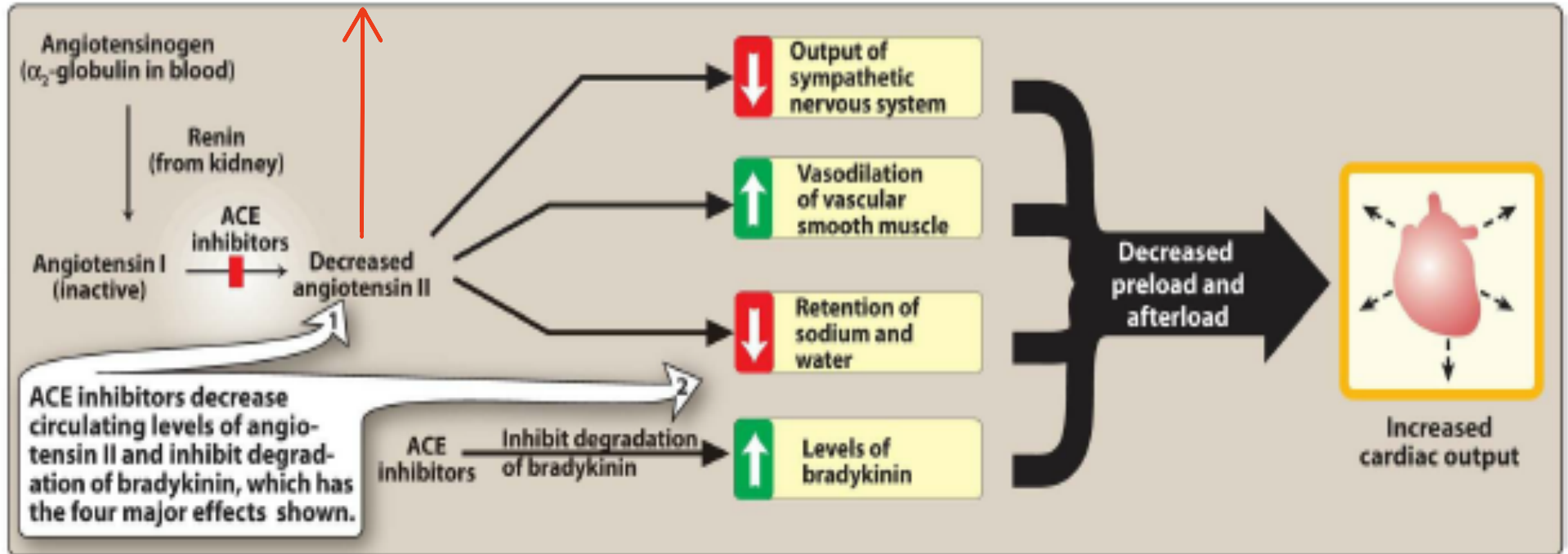
Quinapril ACCUPRIL

Ramipril ALTACE

- هو بنفسه برضو (غير ال Aldosterone)، بشتغل على receptors موجودة في ال heart، برضو يزود موضوع ال cardiac remodeling، بزود ال hypertrophy، ال apoptosis and loss of myocytes

- بحفز من خروج pinephrine and norepinephrine من ال adrenal glands، الي بعملوا على تزويد ال cardiac remodeling and hypertrophy، يؤدوا لحدوث ال cell apoptosis and loss of myocytes

- بحفز ال sympathetic nervous system



Actions of ACEIs

- ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output.
- ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF. ^{and norepinephrine}
- ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF.

ACE INHIBITORS

Captopril GENERIC ONLY

Enalapril VASOTEC

Fosinopril GENERIC ONLY

Lisinopril PRINIVIL, ZESTRIL

Quinapril ACCUPRIL

Ramipril ALTACE

Therapeutic use

- ACE inhibitors may be considered for patients with asymptomatic and symptomatic HFrEF. ACE inhibitors or ARBs أول ما المريض نحس انه عنده heart failure ل risk factor برقعته
- ACE inhibitors are indicated for patients with all stages of left ventricular failure.
- These agents should be started at low doses and titrated to target or maximally tolerated doses in the management of HFrEF.
- ACE inhibitors are also used in the treatment of hypertension .
لأنه بعد ما يصير معاه، يكون معرض انه يصير معاه cardiac remodeling, hypertrophh ومشاكل في ال heart
- Patients who have had a recent myocardial infarction or are at high risk for a cardiovascular event also benefit from long-term ACE inhibitor therapy.

ACEIs

Pharmacokinetics

Food may decrease the absorption of *captopril*, so it should be taken on an empty stomach.

Except for *captopril* and injectable *enalaprilat*, ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes active form of oral enalapril ^{oral} بنعطيهِ IV

هلقيت في استخدام خاطيء بصير لل enalapril، انه بيتم استخدامه في حالات ال hypertensive emergency، بنعطي حبة تحت اللسان، هل هاد صح؟
طبعاً لا لأنه مش راح يصير اله activation هيك

Adverse effects:

➤ postural hypotension, if used concomitantly with a diuretic ولو تم استخدامه بجرعات كبيرة
يرضو هاد هيعمل hypotension

➤ Renal insufficiency, . Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease من ال side effects المشهورة، خاصة بعد 3 ل 5
أيام من استخدام ال ACE inhibitors

➤ Hyperkalemia, the risk of hyperkalemia, potassium levels must be monitored, particularly with concurrent use of potassium supplements, potassium-sparing diuretics, or aldosterone antagonists

➤ Persistent dry cough, and angioedema هي fatal ولكنها rare، وقت ما بتصير ممنوع يتم استخدام ال ACE inhibitor
لهاد المريض ويندور على يدلي ثاني والأفضل في هذه الحالة هو ال ARBs، لأنهم وجدوا أنه بتصير معها cross reactivity مع ال ACE تاحية ال angioedema قليلة،
يعني نسبة أنه يصير معاه angioedema من ال ARBs قليلة

سببها ارتفاع ال bradykinin في الجسم وال lungs
تقريباً 20% من الناس بتصير معهم، ممكن
يصير بعد استخدام ال 4 أيام وممكن بعد 6 شهور
- وقت ما تولف العلاج، ال cough is reversible
ويمكن تختفي بعد 4 ل 7 من
التوقف ويمكن تأخذ وقت أطول عند بعض
الناس وتقدر ل 4 أسابيع

ACE inhibitors are teratogenic and should not be used in pregnant women.

- كيف أعرف انه لازم أوقف استخدام ال ACE inhibitor؟
أي ارتفاع في ال serum creatinine أكثر من أو يساوي 30% من ال
base line، لازم توقفه (الكلام هاد بملشي برضو على ال ARBs)
يعني لو كان ال base line serum createnine هو 0.8 وارتفع بعد 3 ل 5
أيام من استخدام ال ACE أو ال ARBs ل 1.2، المفروض أوقف ال ACE أو
ال ARBs وأبدا أدور على المشكلة الي موجودة عم المريض، لأنه على
الأغلب عنده مشكلة في ال kidney
تدور على ال bilateral renal aretery stenosis، أو يمكن يكون عنده أي
underlying renal disease ثانية

Dysgeusia:: more with captopril >>> reversible loss or alteration of taste sensation

Angiotensin receptor blockers

- Competitive antagonists of the angiotensin II type 1 receptor
- ARBs have the advantage of more complete blockade of the actions of angiotensin II. هلقيت وجدوا انه ال ACE inhibitors هيعملولي inhibition فقط لل ACE، وجدوا انه في طرق ثانية. التفاقية لتصنيع ال angiotensin 2
- ARBs do not affect bradykinin levels
- ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical.
- ARBs are a substitute for patients who cannot tolerate ACE inhibitors.

Actions

- Their actions on preload and afterload are similar to ACEis **cardiac output** بالتالي هيزودوا
- Their use in HF is mainly as a substitute in patients who cannot tolerate ACE inhibitors due to cough or angioedema.
- Hypertension

Adverse effects

ARBs have an adverse effect and drug interaction profile similar to that of ACE inhibitors.

ARBs have a lower incidence of cough and angioedema.

Like ACE inhibitors, ARBs are contraindicated in pregnancy.

ال receptors الي بشتغل عليها عبارة عن steroid receptors، معنى هاد الكلام هي عبارة عن intracellular receptors، يرتبط فيها وبدخل بشتغل على ال Nucleus وعلى عملية تصنيع ال porin channels

Aldosterone receptor antagonists

Patients with HF have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone.

يعني سبب ارتفاع ال aldosterone هو
reduction of ال RAAS system

نephrones
collecting duct في ال

عشان مرضى ال HF يكون عادة في congestion حوالين ال liver، فما يكون بشتغل بشكل 100%، يكون في reduction in hepatic function وبالتالي reduction in hepatic clearance to aldosterone hormone

steriod receptors عبارة عن

Spironolactone and eplerenone are antagonists of aldosterone at the mineralocorticoid receptor, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia.

يعني اله تأثير سلبي بموضوع الهرمونات

لأنه ال structure تبعه
steriod بال تشبيه

Spironolactone also has affinity for androgen and progesterone receptors, and is associated with

غدد صماء

كبر يحجم الثدي عن ال males ويكون painful

لخبطة في Menstrual period للنساء

endocrine-related adverse effects such as gynecomastia and dysmenorrhea.

Aldosterone antagonists are indicated in patients with symptomatic HFrEF or HFrEF and recent myocardial infarction.

بالتالي ما في affinity لل androgen and progesterone receptor

Eplerenone is more selective for aldosterone receptors and causes less endocrine effects (gynecomastia) than spironolactone, which also binds to progesterone and androgen receptors.

β-Blockers

These agents improved systolic function and reverse cardiac remodeling .

How???

- Their ability to prevent the changes that occur because of chronic activation of the sympathetic nervous system.

يعني هتعمل inhibition of RAAS system

- These agents decrease heart rate and inhibit release of renin in the kidneys.

يسبب انها هتعمل inhibition لل sympathetic nervous system
system وكمان يسبب ال inhibition لل RAAS system

- β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.

Beta one selective
Non selective
Bishtagl'aly beta one and two and alpha one
Selective
Beta one selective

β-ADRENORECEPTOR BLOCKERS

Bisoprolol GENERIC ONLY

Carvedilol COREG, COREG CR

Metoprolol succinate TOPROL XL

Metoprolol tartrate LOPRESSOR

> Negative inotropic effect

طب ها كيف حسنت من ال **systolic function** وعملت **reversing to cardiac remodeling**؟

الدراسات وجدت انه ال **Beta blockers** قللت ال mortality and morbidity in heart failure patients

عندهم قدرة انهم يعملوا **reversing** لل **actions** تبعت ال **sympathetic nervous system**، لانهم راح يقللوا من ال **chronic activation** لل **sympathetic nervous system** بسكروا على ال **sympathetic nervous system** بشغلها على ال **beta one receptor**، واحنا قلنا انه ال **sympathetic nervous system** وحدة من ال **compensatory system** الي بتعمل **progression of heart failure**

يعني مش موجود هلاقيت في المستشفى وتعبان كثير

- β -Blockade is recommended for all patients with chronic, stable HFrEF
- *Carvedilol* is a nonselective β -adrenoreceptor antagonist that also blocks α -adrenoreceptors, whereas *bisoprolol* and *metoprolol succinate* are β_1 -selective antagonists. فيعمل hypotension
- *Bisoprolol*, *carvedilol*, and *metoprolol succinate* reduce morbidity and mortality associated with HFrEF.
- Treatment should be started at low doses and gradually titrated to target doses based on patient tolerance and vital signs

لأنه ممكن يصير heart block

- **β -Blockers should also be used with caution with other drugs that slow AV conduction, such as *amiodarone*, *verapamil*, and *diltiazem***

عندهم ngative inotropic effect

used for symptomatic relief ما بأثروا لا على mortality ولا على morbidity، هما بس

Diuretics

Loop diuretics are the most commonly used diuretics in HF.

Diuretics reduce signs and symptoms of volume overload, such as dyspnea on exertion, orthopnea, and peripheral edema. **pulmonary edema** ونمنع انه المريض يصير معاه

Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure.

Diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess

Loop diuretics

Bumetanide , furosemide, torsemide , and ethacrynic acid
أشهر واحد
اسمه التجاري: lasix

All of them act on ascending limb of the loop of Henle

These agents have the greatest diuretic effect of all the diuretic drugs (25% to 30% of filtered NaCl)

The most commonly used is furosemide

The most potent Bumetanide & torsemide

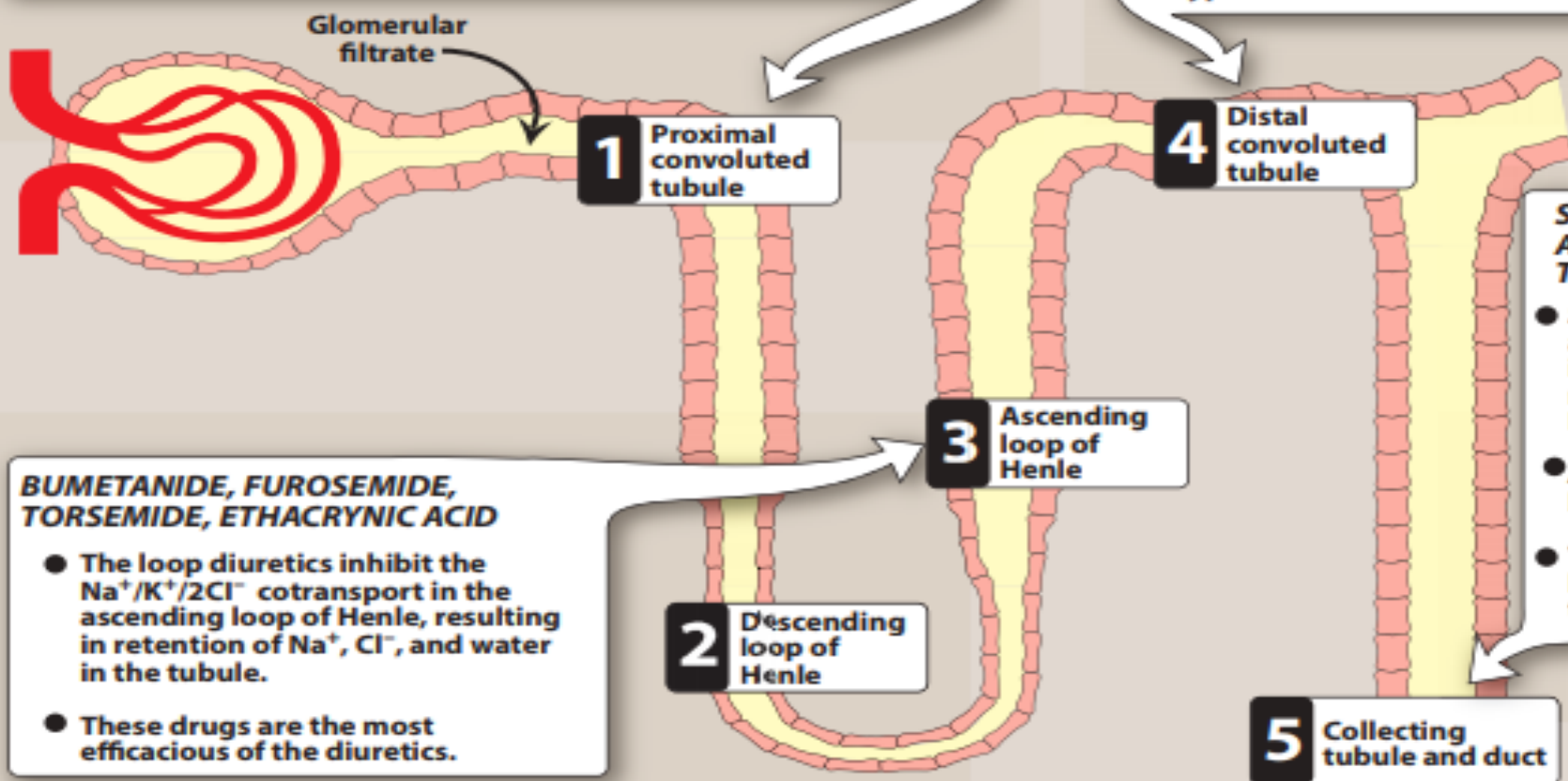
Ethacrynic acid is not used frequently due to its side effects >>> most likely to cause deafness
فقدان سماع

ACETAZOLAMIDE

- A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
- Weak diuretic properties.

THIAZIDES AND THIAZIDE-LIKE

- Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
- Most commonly used diuretic for the treatment of hypertension.



BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID

- The loop diuretics inhibit the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+ , Cl^- , and water in the tubule.
- These drugs are the most efficacious of the diuretics.

SPIRONOLACTONE, AMILORIDE, TRIAMTERENE

- Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+ .
- Amiloride and triamterene block Na^+ channels.
- These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.

Adverse effects:

أو استخدمته مع **other ototoxic drug** هاد بصير لو استخدمناه بجرعات كبيرة

Ototoxicity: Reversible or permanent hearing loss may occur with loop diuretics, particularly when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics)

Hyperuricemia: Furosemide and ethacrynic acid compete with uric acid for the renal secretory systems causing or exacerbating gouty attacks **gaout attack** فمثلاً مرضى النقرس ممكن هيك أعمللهم

Acute hypovolemia

Potassium depletion: The heavy load of Na^+ presented to the collecting tubule results in increased exchange of tubular Na^+ for K^+ , leading to the possibility of hypokalemia. The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis.

Hypomagnesemia:

Chronic use of loop diuretics combined with low dietary intake of Mg^{2+} can lead to hypomagnesemia, particularly in the elderly

عبارة عن إنزيم مسؤول عن تكسير بعض ال
peptides في الجسم، بعض ال vasoactive peptide
peptide زي:

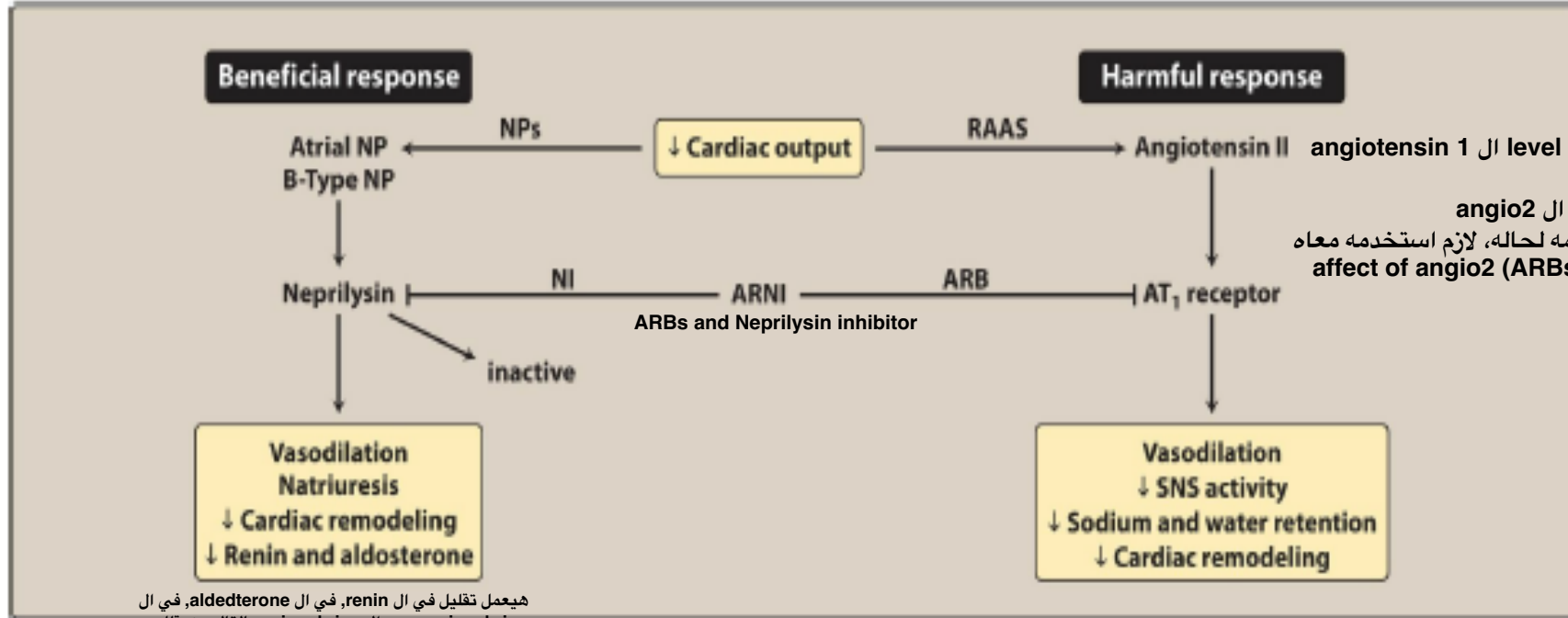
- angiotensin 1
- angiotensin 2
- bradykinin
- Natriuretic Peptide

Angiotensin Receptor–Neprilysin Inhibitor

ففي زيادة من
استخدامه وفي ضرر



جديدة بس داخلة بقوة



لما عمله inhibition هيرتفع ال level ال angiotensin 1
bradykinin وال and 2
طب هادي مشكلة، خصوصاً ال angio2
عشان هيك بنفعش استخدامه لحاله، لازم استخدمه معاه
دواء تاني يعمل block لل (ARBs) affect of angio2

هيعمل تقليل في ال renin, في ال aldosterone, في ال
norepinephrine و ال epinephrine بالتالي هيقفل
من ال heart remodeling و ال heart hypertrophy

(بنحكي عن Natriuretic Peptide system)

بسببهم قل استخدام ال digoxin

Sacubitril/valsartan

- *Sacubitril/valsartan* combines the actions of an ARB with neprilysin inhibition.
- Inhibition of neprilysin results in increased concentration of vasoactive peptides, leading to natriuresis, diuresis, vasodilation, and inhibition of fibrosis.
- Together, the combination decreases afterload, preload, and myocardial fibrosis.
- An ARNI improves survival and clinical signs and symptoms of HF, as compared to therapy with an ACE inhibitor
- *Sacubitril/valsartan* is orally active, administered with or without food, and quickly breaks down into the separate components. *Sacubitril* is transformed to active drug by plasma esterases.

Intresto

Prodrug

Adverse effects

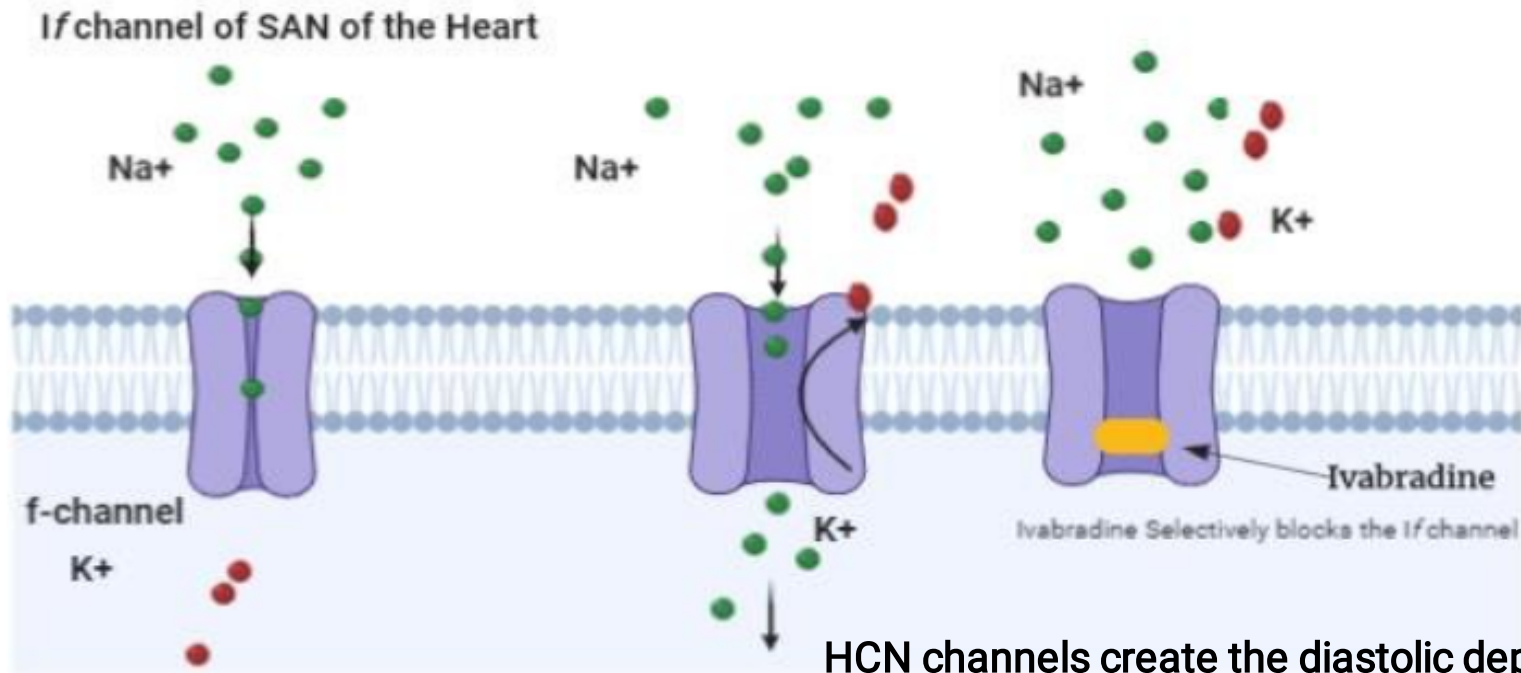
- similar to that of an ACE inhibitor or ARB.
- Hypotension is more common with an ARNI.
- Due to inhibition of neprilysin with *sacubitril*, bradykinin levels may increase and angioedema may occur.
- Therefore, the combination is contraindicated in patients with a history of hereditary angioedema or angiodema associated with an ACE inhibitor or ARB. To minimize risk of angioedema
- An ACE inhibitor must be stopped at least 36 hours prior to starting *sacubitril/valsartan*.

تعتمد anaphylactic reaction، يصعب face swelling،
واللـ limbs والـ pharynx والـ larynx ويمكن تؤدي لحدوث
انقطاع في التنفس وينتفخ ويموت المريض

عشان الـ levels الي رفعلي ياها من الـ bradykinin تلحق تنزل، قبل ما أضيف الـ compination تبع الـ ARNI

هدول ال HACN blockers موجودين في ال SA node، فتحهم مسؤول عن ال diastolic depolarization، عن بداية حدوث ال depolarization وال action potential الي بصير

Hyperpolarization-Activated Cyclic Nucleotide–Gated Channel Blocker



HCN channels create the diastolic depolarization or “funny pacemaker current (I_f) of the sinoatrial node, so termed because it is uniquely activated by the membrane hyperpolarization that follows systolic depolarization

Ivabradine يعمل slowing لل depolarization تبع ال SA node، بالتالي هينزل ال HR

Actions

By selectively slowing the If current in the SA node, reduction of heart rate occurs without a reduction in contractility, AV conduction, ventricular repolarization, or blood pressure.

In patients with HFrEF, a slower heart rate increases stroke volume and improves symptoms of HF.
هتحسن ال contractility

Therapeutic use

Ivabradine is utilized in HFrEF to improve symptoms in patients who are in sinus rhythm with a heart rate above 70 beats per minute and are on optimized HF pharmacotherapy.

Specifically, patients should be on an optimal dose of β -blocker or have a contraindication to β -blockers.

Pharmacokinetics

كمان بضيفه للمرضى الي مشبههم على كل أدويتهم تبع ال HF و still عنده signs و symptoms. و Still مش قادر اسيطر على ال HR تبعته و لسا عالية

Ivabradine should be administered with meals to increase absorption.

Adverse effects

- Bradycardia may occur with *ivabradine*, which may improve with dose reduction.
- It has been shown to increase the risk of atrial fibrillation.
- *Ivabradine* inhibits similar channels in the eye, and luminous phenomena may occur early in therapy. This enhanced brightness may be ameliorated by dose reduction.
- *Ivabradine* should not be used in pregnancy or breast-feeding, with more advanced heart block, or with potent 3A4 inhibitors.

Drugs for heart failure part 2

YASMINE ZOHAIR AL SHORAF

شغلهم mainly على ال peripheral vessels

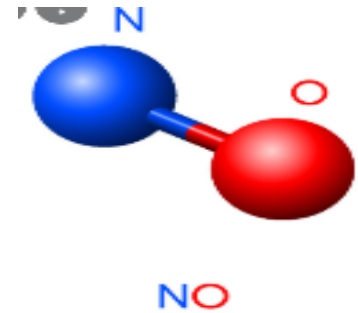
Vaso- and Venodilators

- Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance.

Potent vasodilator

شغلها أكثر على ال veins أكثر
من ال artery، ف يتقلل ال
preload أكثر من ال afterload

- **Nitrates** are commonly used venous dilators to reduce preload for patients with chronic HF. **potent vasodilator** عبارة عن Nitric oxide **metabolism** تبعتها **Nitric oxide** وهو عبارة عن



بالتالي ينزل ضغط
أكثر من ال Nitrates

- Arterial dilators, such as **hydralazine**, reduce systemic arteriolar resistance and decrease afterload. **يستخدم في حالات ال hypertensive emergency**

- If the patient is intolerant of ACE inhibitors or ARBs, or if additional vasodilator response is required, combination of *hydralazine* and *isosorbide dinitrate* may be used. **مثال على ال Nitrate**

- A fixed-dose combination of these agents has been shown to improve symptoms and survival in black patients with HFrEF on standard HF treatment (β - blocker plus ACE inhibitor or ARB).

أي دواء بعلمي **vasodilation**، أكيد راح يعمل **hypotension, headache, dizziness**

- Headache, dizziness, and hypotension are common adverse effects with this combination. **Rarely**, *hydralazine* has been associated with drug-induced lupus **الذئبة الحمراء**

بس مجرد ما ننزع ال **hydralazine**، بتروح ال **symptomes**

بسبب ال **hydralazine**، في **antibodies** هتظهر في الدم، وهي الي هتسبب ال **lupus symptoms**

positive inotropic effects يعني الهم

Inotropic Drugs

- Positive inotropic agents enhance cardiac contractility and, thus, increase cardiac output. heart ال هو منيح اه بزود ال contractility، بس انا هيك برهق ال **output**.
- Although these drugs act by different mechanisms, the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.
- All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival, especially in patients with HFrEF.
mortality ال بزود ال
- For this reason, these agents, with the exception of *digoxin*, are only used for a short period mainly in the inpatient setting.

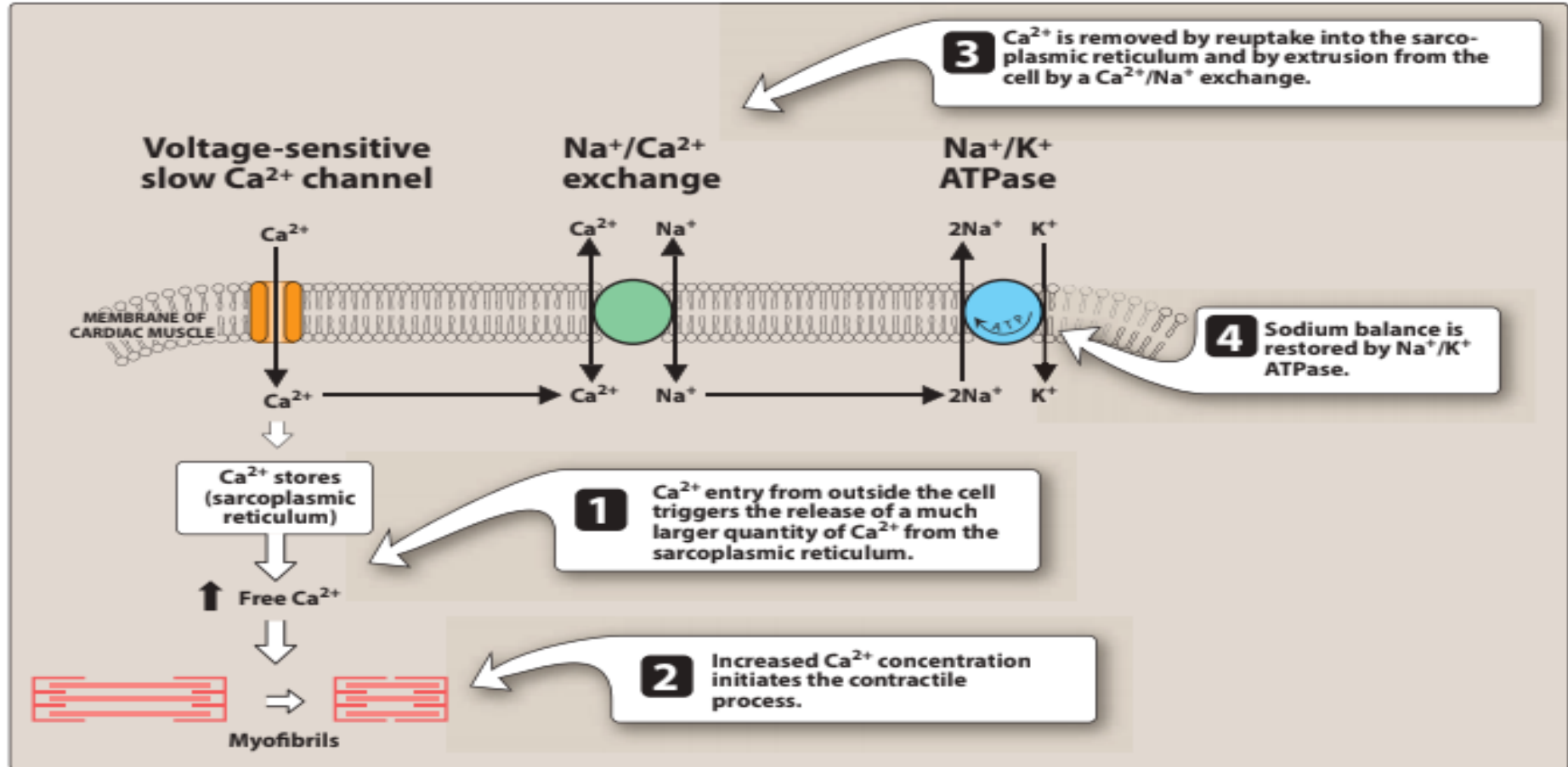
مجموعة من المركبات الكيميائية، نستخلصها من نبات ال foxglove

Digitalis glycosides

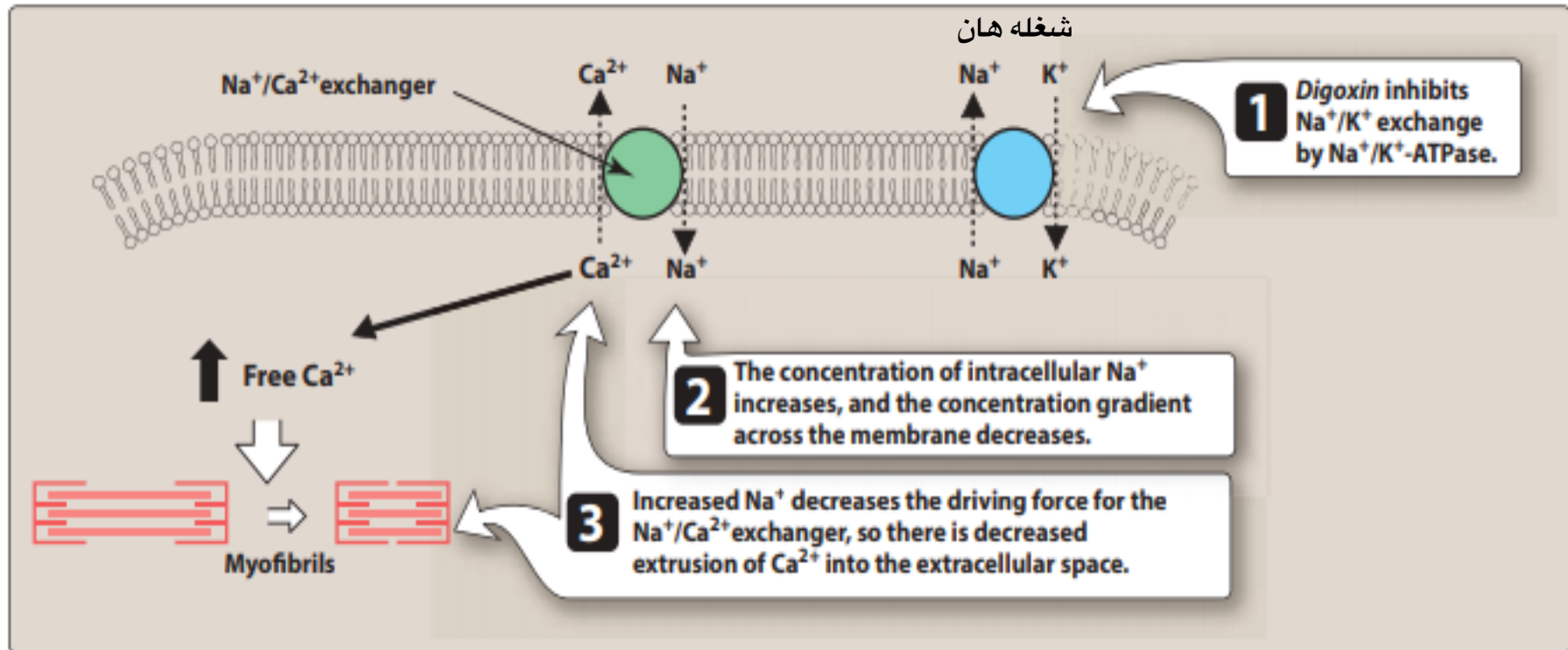
- ❖ The drugs come from the digitalis (foxglove) plant
- ❖ The digitalis glycosides have a low therapeutic index
يعني بنفعش تخريط بالجرعة
- ❖ The most widely used agent is digoxin. Digitoxin is seldom used due to its considerable duration of action
كثير طويلة



Ion movements during the contraction of cardiac muscle.



Mechanism of action of digoxin



Increased contractility of the cardiac muscle:

Increases the force of cardiac contraction, thereby cardiac output

Increasing cardiac output, improves circulation. It has **vagomimetic** action so heart rate and myocardial oxygen demand decrease

يعني ال vagus nerve (الذي يعمل تنبيط لل conduction تتبع ال heart)، فهو يزيد ال action تبعه، فيثبط ال HR وال conduction

Digoxin slows conduction velocity through the AV node, making it useful for atrial fibrillation

Neurohormonal inhibition:

low-dose digoxin inhibits sympathetic activation with minimal effects on contractility

لأنه التأثير الأساسي زي ما حكينا هو زيادة ال ca

❖ Therapeutic uses

Digoxin therapy is indicated in patients with severe HFrEF after initiation of ACE inhibitor, β -blocker, and diuretic therapy

Atrial fibrillation

❖ Pharmacokinetics

❖ Digoxin is available in oral and injectable formulations ^{IV}

❖ inotropic effect of digitalis takes hours to develop, even after i.v. administration. ^{خصوصاً ال orally}

❖ large volume of distribution, because it accumulates in muscle <sup>بدخل بكل ال tissues ويتراكم هناك،
وهاد الي بخلي اله long half life
بوصل من 30 ل 40 ساعة</sup>

❖ The dosage is based on lean body weight

❖ Digoxin has a long half-life of 30 to 40 hours

❖ requiring dose adjustment in renal dysfunction as it is excreted unchanged in urine by glomerular filtration ^{ما بصيرله metabolism، بنزل زي ما هو، لا بصيرله inactivation ولا اشبي}

أول adverse effect اله، هي ال GIT

Adverse effects

- ❖ very narrow therapeutic index, and digoxin toxicity is one of the most common adverse drug reactions leading to hospitalization
- ❖ Anorexia, nausea, and vomiting may be initial indicators of toxicity
- ❖ Patients may also experience blurred vision, yellowish vision (xanthopsia)
- ❖ cardiac arrhythmias due to hyperkalemia (increase extracellular potassium)
- ❖ Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to digoxin (digoxin immune Fab), which bind and inactivate the drug

بحفزوا ال Beta one and two receptors

β -Adrenergic agonists عبارة عن positive inotropic effect

هو الي mainly يعمل vasodilation

Dobutamine and *Dopamine*, improve cardiac performance by causing positive inotropic effects and vasodilation. ليش vasodilation؟
لأنهم هما يشتغلوا كمان على ال beta two

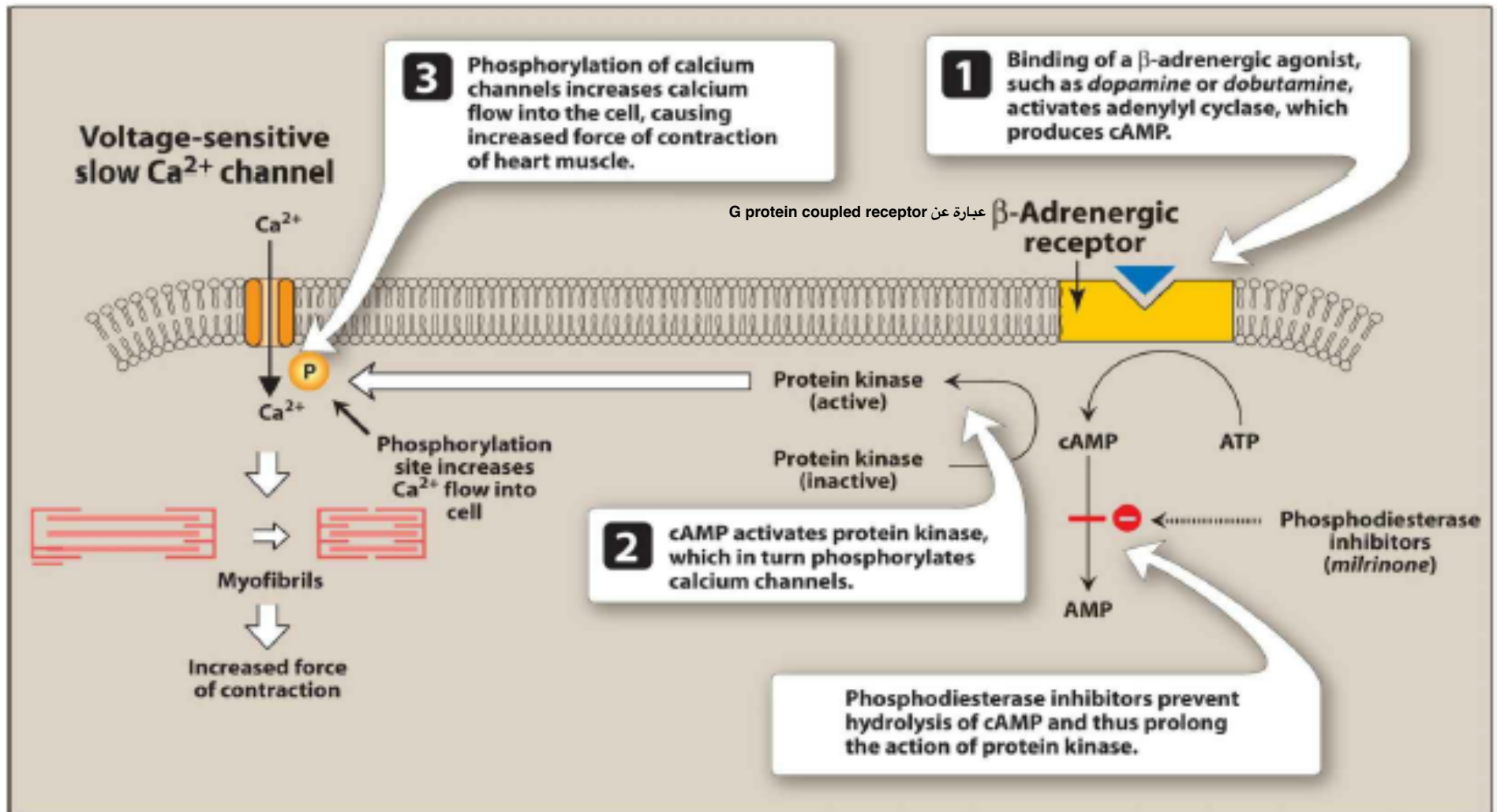
β -Adrenergic agonists ultimately lead to increased entry of calcium ions into myocardial cells and enhanced contraction .

Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting

- ال dopamine يشتغل بناءً على ال dose، يعني لو عندي جرعة صغيرة، وجدوا انها بتعمل vasodilation لل renal vessels، فهتحسن من ال renal perfusion

- الجرعة المتوسطة بتعمل ال positive inotropic effect

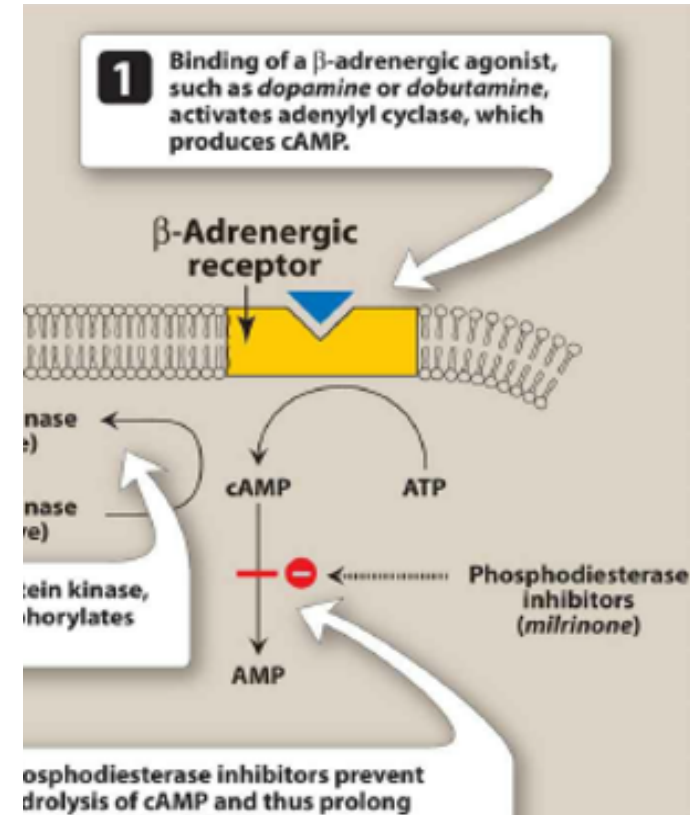
- الجرعة العالية بتشتغل على ال alpha receptors، يعني كل ما زودنا الجرعة هتشتغل على ال alpha receptor وهتعمل vasoconstriction



هو عبارة عن إنزيم موجود داخل الخلايا، يحفز من تحول ال cAMP ل AMP

Phosphodiesterase inhibitors

- ❖ Milrinone is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP .
- ❖ Like β -adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility.
- ❖ Long-term, milrinone therapy may be associated with a substantial increased risk of mortality. يستخدم في المستشفى خصوصاً لو كان عنده مشاكل في القلب
- ❖ However, short-term use of intravenous milrinone is not associated with increased mortality in patients without a history of coronary artery disease.



مش موجود بالمستشفيات عنا، من الأدوية الجديدة

Recombinant B-type Natriuretic Peptide

صنعوا مركب شبيهه بال natriuretic peptide يتشغل على ال receptor تبعه

- In acute decompensated congestive HF, drugs that reduce preload result in improvement in HF symptoms such as dyspnea.
- When IV diuretics are minimally effective, a recombinant B-type natriuretic peptide (BNP), or *nesiritide*, can be used as an alternative.
- Through binding to natriuretic peptide receptors, *nesiritide* stimulates natriuresis and diuresis and reduces preload and afterload.

جرعة أولية

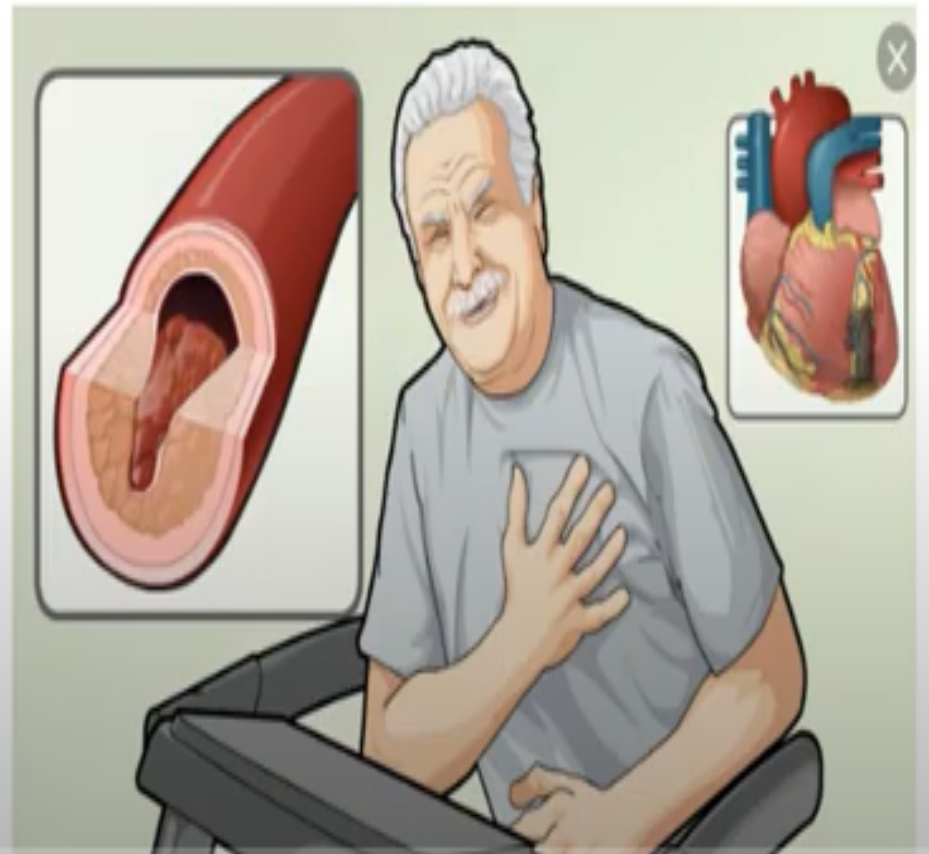
Nesiritide is administered intravenously as a bolus (most often) and continuous infusion.

Like endogenous BNP, *nesiritide* has a short half-life of 20 minutes and is cleared by renal filtration, cleavage by endopeptidases and through internalization after binding to natriuretic peptide receptors.

The most common adverse effects are hypotension and dizziness, and like diuretics, *nesiritide* can worsen renal function.

dehydration, intravascular يمكن يعمل
acute kidney وهاد ممكن يعمل demolition
injury

Antianginal Drugs



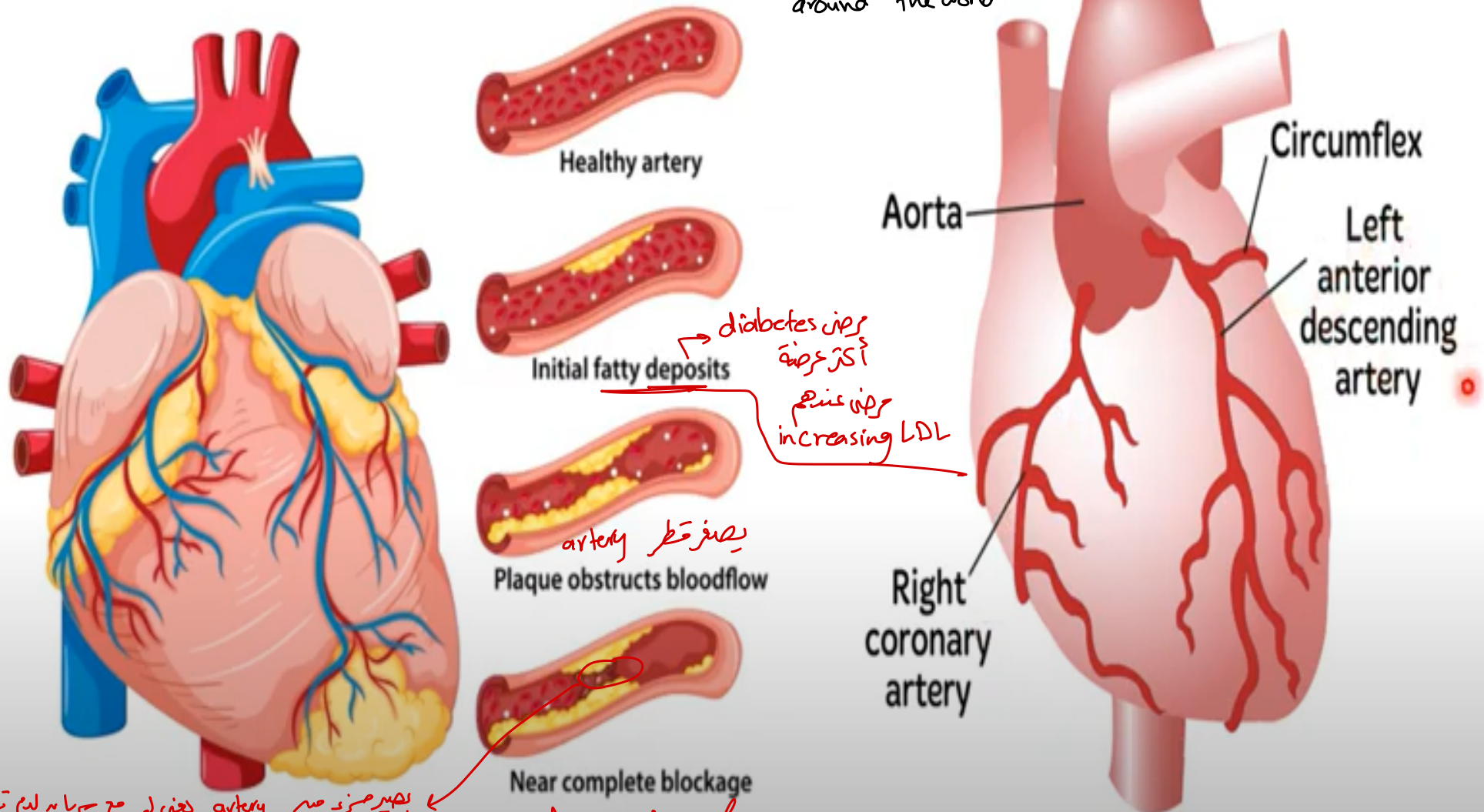
heart muscle has its own blood supply

atherosclerosis → deposition of fat in the wall of arteries

کاهش contractility و کمبود
blood supply تachycardia
oxygen demand زیاد

CORONARY ARTERY DISEASE

The most common
cause of death
around the world



destruction of
blood flow

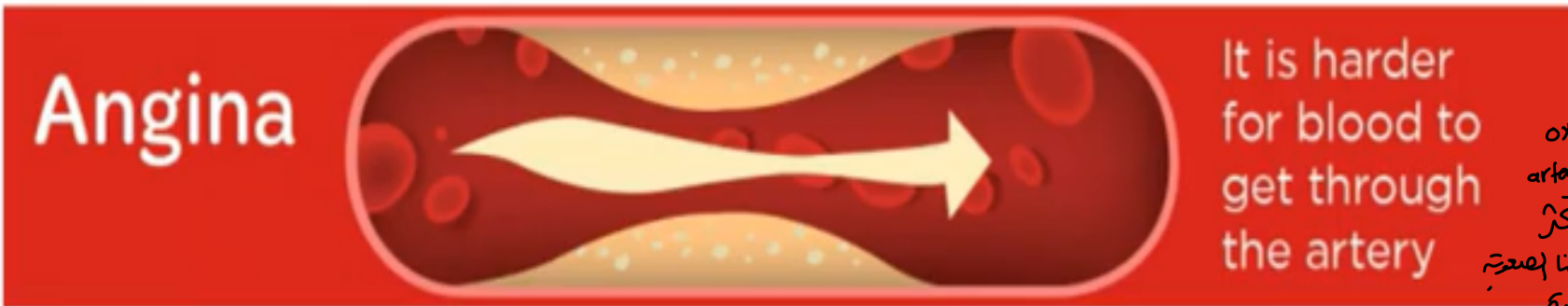
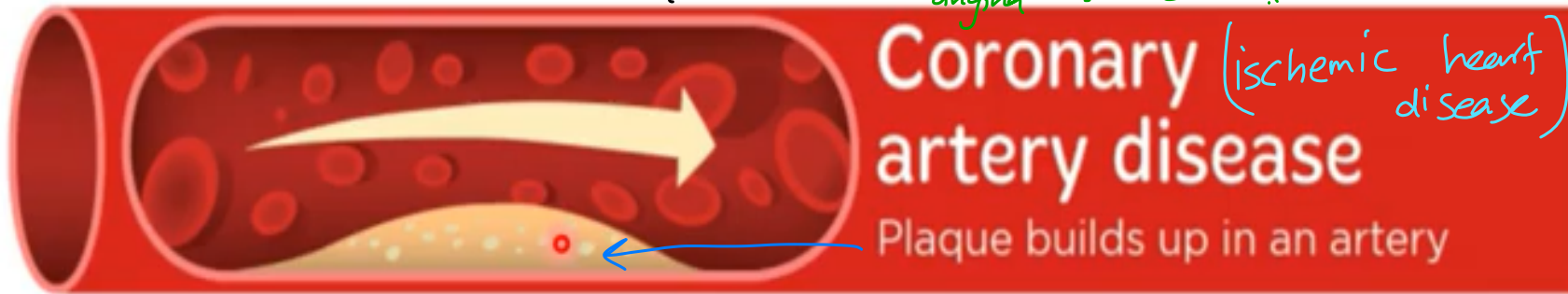
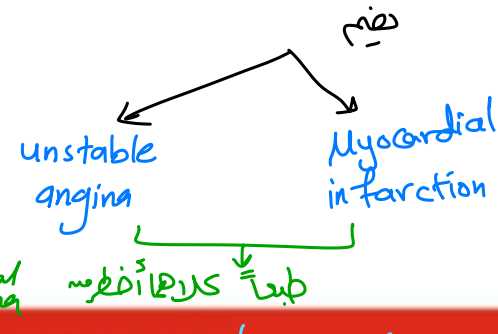
بصیرمیزد سر artery خوندار مع سرابه بدم تکر
خوندار مع سرابه بدم تکر
(التهاب مع سرابه بدم تکر injury خوندار)

↓
 Platelet فَيَسْجِي
 blood clot خثرة / خضاد
 near complete obstruction

Angina مِلِيْر
 ويمكن تصل إلى

Myocardial infarction → توقف سريان الدم للمنطقة
 معنية في القلب ما يؤدي لموت خلايا هذه المنطقة
 ويمكن يؤدي إلى death / hypertrophy

Acute Coronary syndrome

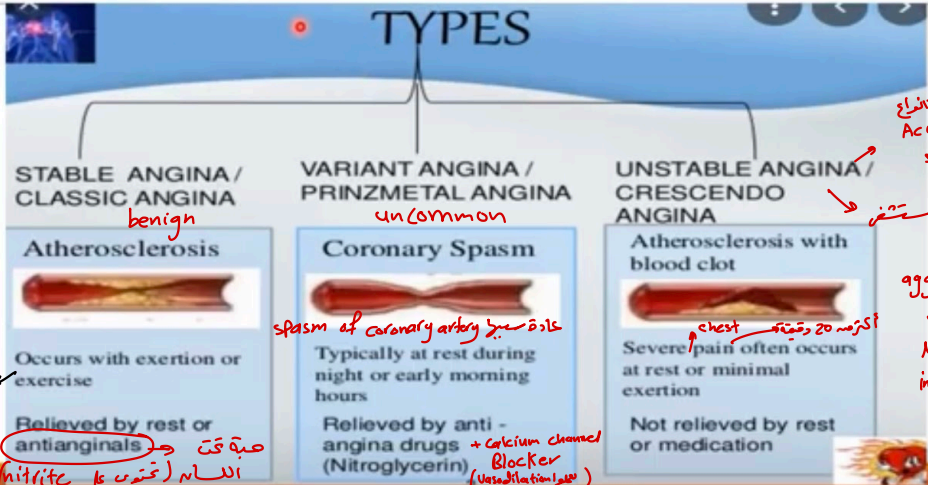


لما المرض بيجي
 أي exercise
 عيش حاج oxygen demand
 أكثر ← ضغط artery
 بيجري محتاج لblood أكثر
 حتى يفرغ القلب زحوا يصعب
 أنه ما يقدر يرضل كمية
 دم كافية تقنيه

Platelet aggregation →

لذلك من أهم الأدوية التي بلاصتها مرض
 Acute coronary syndrome & Myocardial infarction
 → anti platelet & anti coagulant

Types of angina



من أو زعل

حبة قوت و
الناله (تحتوي على nitrite)

عادة سبب spasm of coronary artery

+ Calcium channel Blocker
(Vasodilation)

نفع من داء
Acute coronary syndrome

لازم يرفع عال مستقر
ونظيره

aggressive therapy
حتى تمنع تحولها إلى
Myocardial infarction.

chest أكثر من 20 دقيقة

symptoms of Angina :-

- ① fatigue
- ② diaphoresis ^{پیشانی}
- ③ burning sensation of chest
- ④ heaviness
- ⑤ shortness of breath

Anti-anginal Drugs

للمهم منهم هو تقليل العمل على القلب

→ selective β_1

β -BLOCKERS

Atenolol TENORMIN

Bisoprolol GENERIC ONLY

Metoprolol LOPRESSOR, TOPROL XL

Propranolol INDERAL, INNOPRAN XL

CALCIUM CHANNEL BLOCKERS (DIHYDROPYRIDINES)

Amlodipine NORVASC

Felodipine PLENDIL

Nifedipine ADALAT, PROCARDIA

CALCIUM CHANNEL BLOCKERS (NONDIHYDROPYRIDINE)

Diltiazem CARDIZEM, CARTIA, TIAZAC

Verapamil CALAN, VERELAN

NITRATES

Nitroglycerin MINITRAN, NITRO-DUR,
NITROSTAT

Isosorbide dinitrate DILATRATE-SR,
ISORDIL

Isosorbide mononitrate GENERIC ONLY

SODIUM CHANNEL BLOCKER

Ranolazine RANEXA

عملية
vasodilation

CLASSIFICATION

1. *Nitrates*

- (a) *Short acting*: Glyceryl trinitrate (GTN, Nitroglycerine)
- (b) *Long acting*: Isosorbide dinitrate (short acting by sublingual route), Isosorbide mononitrate (orally)

2. *β Blockers* Propranolol, Metoprolol, Atenolol and others.

3. *Calcium channel blockers*

- (a) *Phenyl alkylamine*: Verapamil
- (b) *Benzothiazepine*: Diltiazem
- (c) *Dihydropyridines*: Nifedipine, Felodipine, Amlodipine, Nitrendipine, Nimodipine, Lacidipine, Lercanidipine, Benidipine

4. *Potassium channel opener* Nicorandil

Nitrates

- ❖ All organic nitrates share the same action; differ only in time course.
- ❖ Preload reduction : It is through their action on peripheral veins that nitrates exert major beneficial effects in classical angina. Nitrates dilate veins more than arteries
stable
- ❖ Afterload reduction: Nitrates also produce some arteriolar dilatation → slightly decrease total peripheral resistance (t.p.r.) or afterload on heart; BP falls.
→ decrease blood pressure
- ❖ With usual doses there is no reflex tachycardia
- ❖ With high doses, reflex tachycardia occurs and this would exacerbate angina
→ potent hypertensive effect
ردة فعل من تقطع على نزول BP انخفاض

Mechanism of Action of Nitrovasodilators

Nitrates become denitrated by glutathione S-transferase

to release

Nitric Oxide

activates

Guanylate Cyclase*

converts

GTP

cGMP

activates

cGMP-dependent protein kinase

Dephosphorylation of
MLCK

Activation of PKG results in dephosphorylation
of several proteins that reduce intracellular calcium
causing smooth muscle relaxation

Smooth muscle cells
دافند

Clip slide

X

Nitrates

Venodilators
(systemic
vasodilation)

Coronary
vasodilators

Modest
arteriolar
dilators

X

- Venodilation >>> lowers preload (left ventricular end diastolic pressure) >>> reduces wall stress >>> decrease myocardial oxygen demand
- Coronary vasodilator>>> relieve ischemia
- Vasospastic angina>>> reduce or reverse coronary vasospasm

Mechanism of relief of angina: due to the relaxant effect on large coronary vessels and thereby increasing blood supply to the ischemic heart

vasodilatation & relaxation of coronary vessels

By decreasing the work on heart

Mechanism of action::

Organic nitrates are rapidly denitrated enzymatically in the smooth muscle cell to release the reactive free radical nitric oxide (NO)

All nitrates share the same action but differs pharmacokinetically



Nitrates

- Nitrates in the form of sublingual preparation are the first line therapy for the treatment of acute anginal symptoms
- Patients should be instructed to use them at the onset of the attack
- Longer acting nitrates are added to beta blockers or calcium channel blockers to control angina.

Pharmacokinetics

الامتصاصات بينهم ممكن تكون بـ duration of / onset action

- ❖ Nitrates are lipid soluble; well absorbed from buccal mucosa, intestines and skin orally
- ❖ Hepatic metabolism is extensive for nitroglycerin (GTN) transdermal patch
- ❖ Isosorbide mononitrates has the highest bioavailability and the least first pass metabolism تتفكك وبعطي isosorbide mononitrate & iso sorbide mononitrate.
- ❖ GTN short-acting from sublingual but isosorbide dinitrate longer-acting from oral route

	GTN	ISDN	ISMN
Half life	2 min	40 min	4-6 h
Bioavailability	<1 %	20%	100%
Route of administration	SL 2 min/transdermal/oral sustained release / IV / spray	SL 5 min /oral sustained ↓ Sublingual	Oral extended release

كمية الدواء التي تصل للدور
متشغل
→ كما كانت Bioavailability أعلى كلما كانت
metabolism in liver أقل

sublingual route تجاوزت سرعة liver بروجع على طول على الدم

headache
tolerance effect
تسبب headache عادة بسبب tolerance of action of nitrate
نتنعمه بجعل مقرر (طوبل ليم) ارج يؤدي الى
desensitization of action of nitric oxide
تسبب أنه الجسم يعمل
tolerance effect

Adverse effects

ممكن يغير في الخلايا signal transduction (تبع الكلية لا nitrite أقل) ← ن drug effect ارج يقل

Headache is the most common adverse effect of nitrates

Fullness in head, throbbing headache; some degree of tolerance develops on continued use.

Flushing, weakness, sweating, palpitation, dizziness and fainting; these are mitigated by lying down

↓
hypotension ارج يعمل

← بالتالي له استخدام مع nitrite ممكن يعمل potent hypotensive effect

Drug Drug interactions >>>>>> with phosphodiesterase type 5 inhibitors such as sildenafil (viagra) (vasodilator) له استخدام في بعض حالات severe pulmonary hypertension

Tolerance::::
صنف

- ❖ Attenuation of haemodynamic and anti-ischaemic effect of nitrates occurs in a dose and duration of exposure dependent manner if they are continuously present in the body
- ❖ Tolerance weans off rapidly (within hours) when the body is free of the drug
- ❖ To prevent nitrate tolerance is to provide nitrate free intervals everyday

up to 12 hours → nitrite طلع خلاص بجوده

بدل صبة مرتين في اليوم ← صبة ساعة 8 صباحاً وصبة ساعة 3 مساءً
هناك رجة فصل سه بعد 3 أيام ساعة ارجي ثاني يوم ماغي nitrite في الجسم (nitrite free interval)

← desensitization حاسل مدبره لجرعة صلبة مدبره

Sodium channel blocker

Ranolazine inhibits the late phase of the sodium current, improving the oxygen supply and demand.

Inhibition of depolarization

Its considered anti angina and anti arrhythmic

It has many drug drug interactions, also it prolongs QT interval



لذلك مفرص ما يتخذ مع
أدوية ثانية سيجل أيضاً
prolong QT interval



Nicorandil

- Potassium channel activator
- It has an arterial and venous dilator and improves coronary blood flow due to potassium channel opening and nitrate effect
- Can protect the heart from subsequent ischemic attacks

مش بس الي عندهم Hyperlipidemia بياخدوا هذه الأدوية، برضو زي مرضى ال diabetes، خصوصاً المتوقعين معه ان يصير cardiovascular disease، ممكن نحطله antilipidemic agent، أهم مجموعة هي مجموعة ال statins

Drugs for Hyperlipidemia

تلعب دور في زيادة ال risk لل angina،
لل acute coronary syndrome

elevation in cholesterol level

عبارة عن increasing of one or more plasma lipids (triglycerides, cholesterol, LDL , VLDL)

من أهم ال risk factors الي بتعمل cardiovascular diseases

Hypercholesterolemia: زيادة في ال cholesterol leve

Hypertriglyceridemia: زيادة في الدهون الثلاثية

الها فوائد أخرى وبنسبها agent عندها pleotropic effect، يعني مش
بس الها ال effect الأساسي انها تقلل ال lipid، ولكن عندها other effects

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors

مجموعة ال statins بتقلل ال lipid (triglyceride, cholesterol,..)، وكمان الها فوائد أخرى **Statins** متخصصة في ال LDL

First-line treatment for patients with elevated risk of ASCVD **Atherosclerosis cardiovascular disease**

Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity

يتمنع حدوث ال cracking الها
هلقية ال Arteriosclerosis عبارة عن complex process، عملية ال depozition لل plaque تبعث ال cholesterol في arterial wall، هاد نفسه بحفر عملية من ال inflammation وال oxidation

Atorvastatin, lovastatin, simvastatin, pravastatin, Fluvastatin, pitavastatin, rosuvastatin

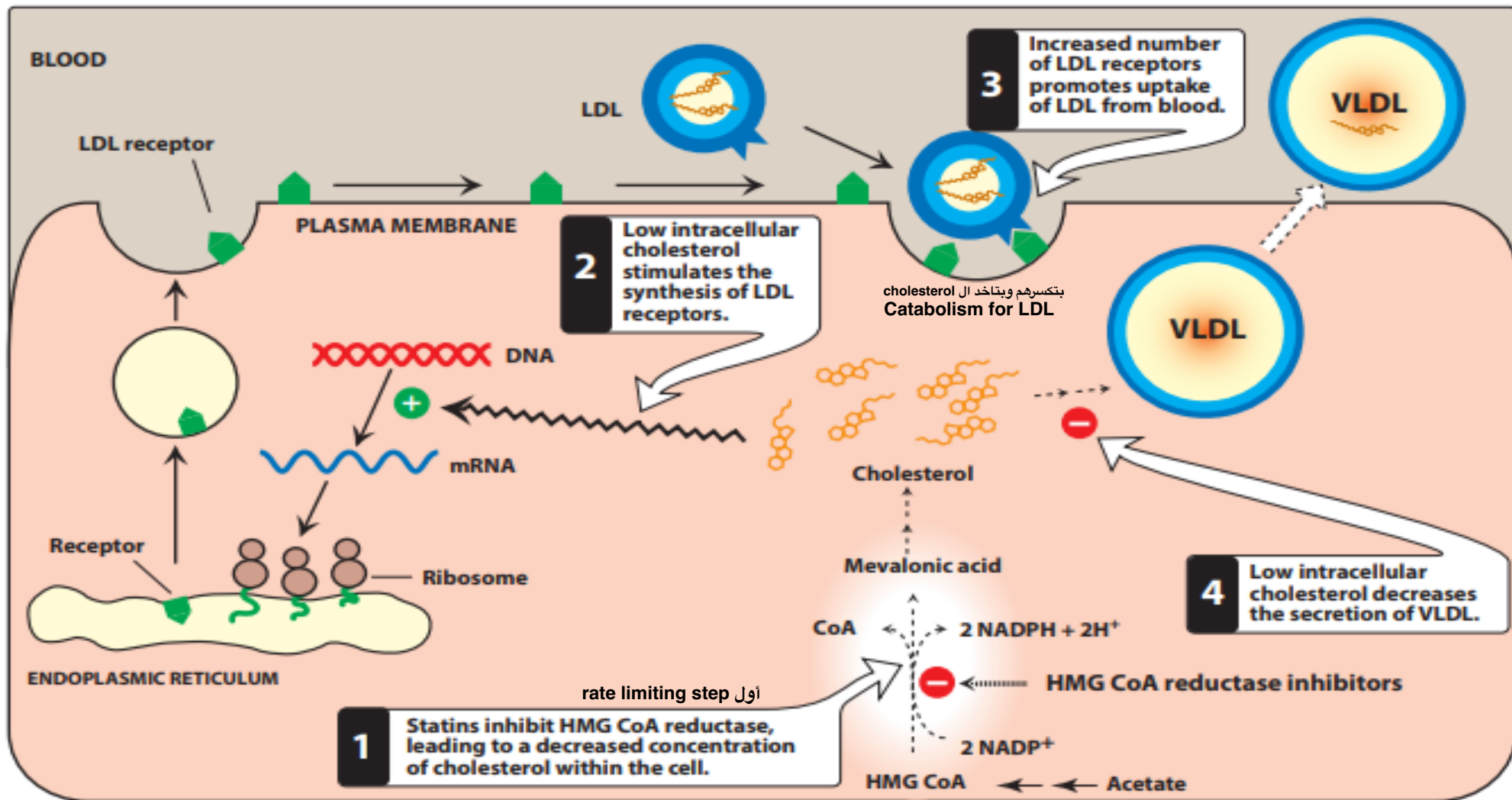
Mechanism of action

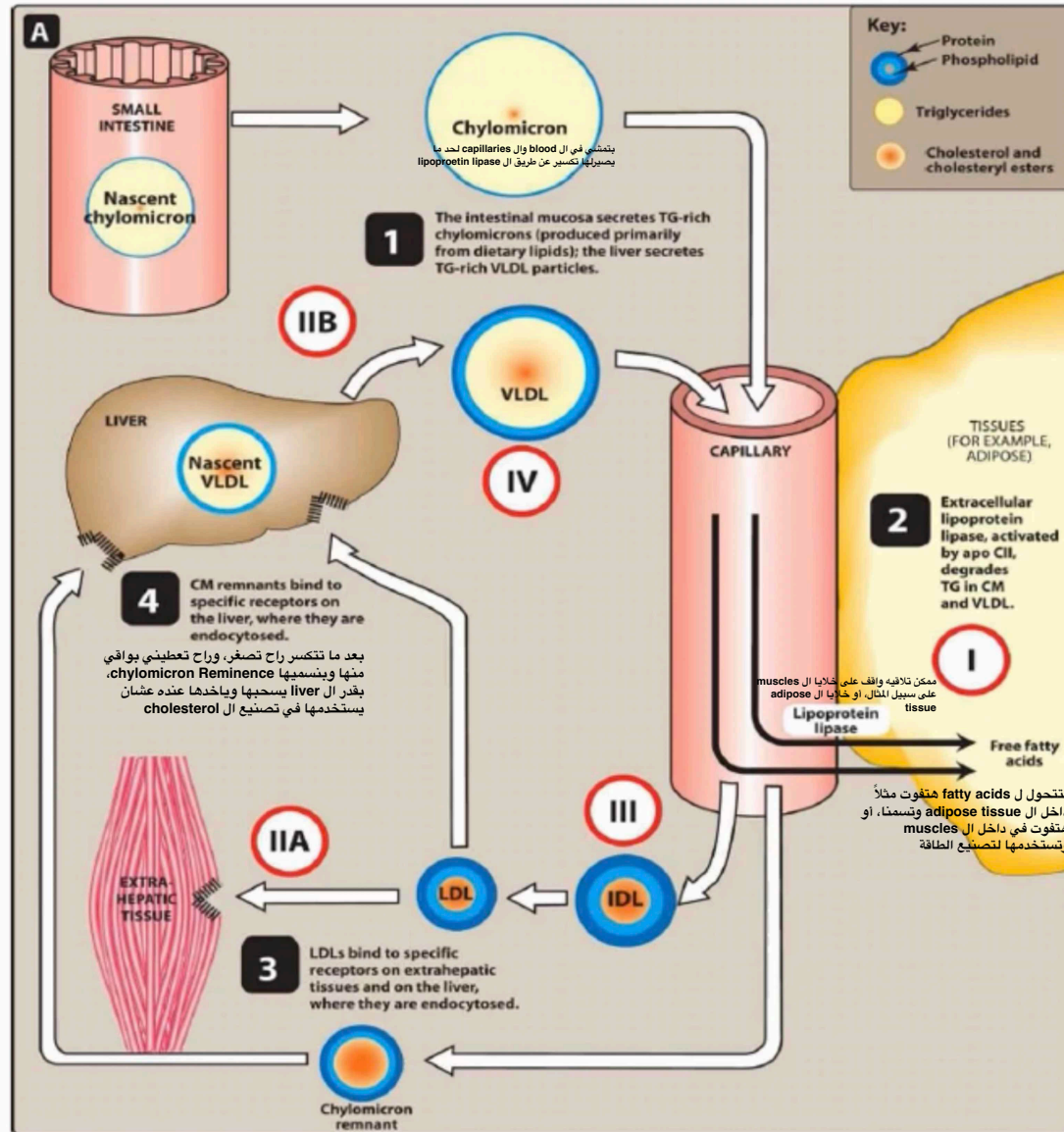
competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis

Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDLs

In the liver

plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL catabolism





القصة بتبدأ من ال lipoprotein، وهو عبارة عن molecule جزء منه lipid وجزء منه protein

- ال lipid هاد ممكن يكون triglyceride، cholesterol، cholesterol esters
- ال protein هاد فيه منه أنواع، عادة بنسميه apolipoprotein، لما تشوف apo بتعرف انه هاد protein، في عنا apo B,C,E,D في أنواع مختلفة بتكون على سطح هذا ال lipoprotein

- هلقيت ال lipid مش هتقدر تمشي بال blood ك lipid لأنها hydrophobic، لازم تكون محاطة بدائرة محبة للماء، بالتالي البروتينات بتكون عاملة covering وال lipid جوا متخبي
- ع ال cover بكون عنا protein و phospholipid

VLDL = very low density lipoprotein، لأنه هو mainly مكون من
cholesterol وفي **triglyceride**، مين الي أكثر **density**؟ البروتين، مين الي أقل
density؟ ال **lipid**

- كل ما كان هذا ال **molecule** بيحتوي على **lipid** أكثر، كل ما كانت ال **density**
تبعته أقل

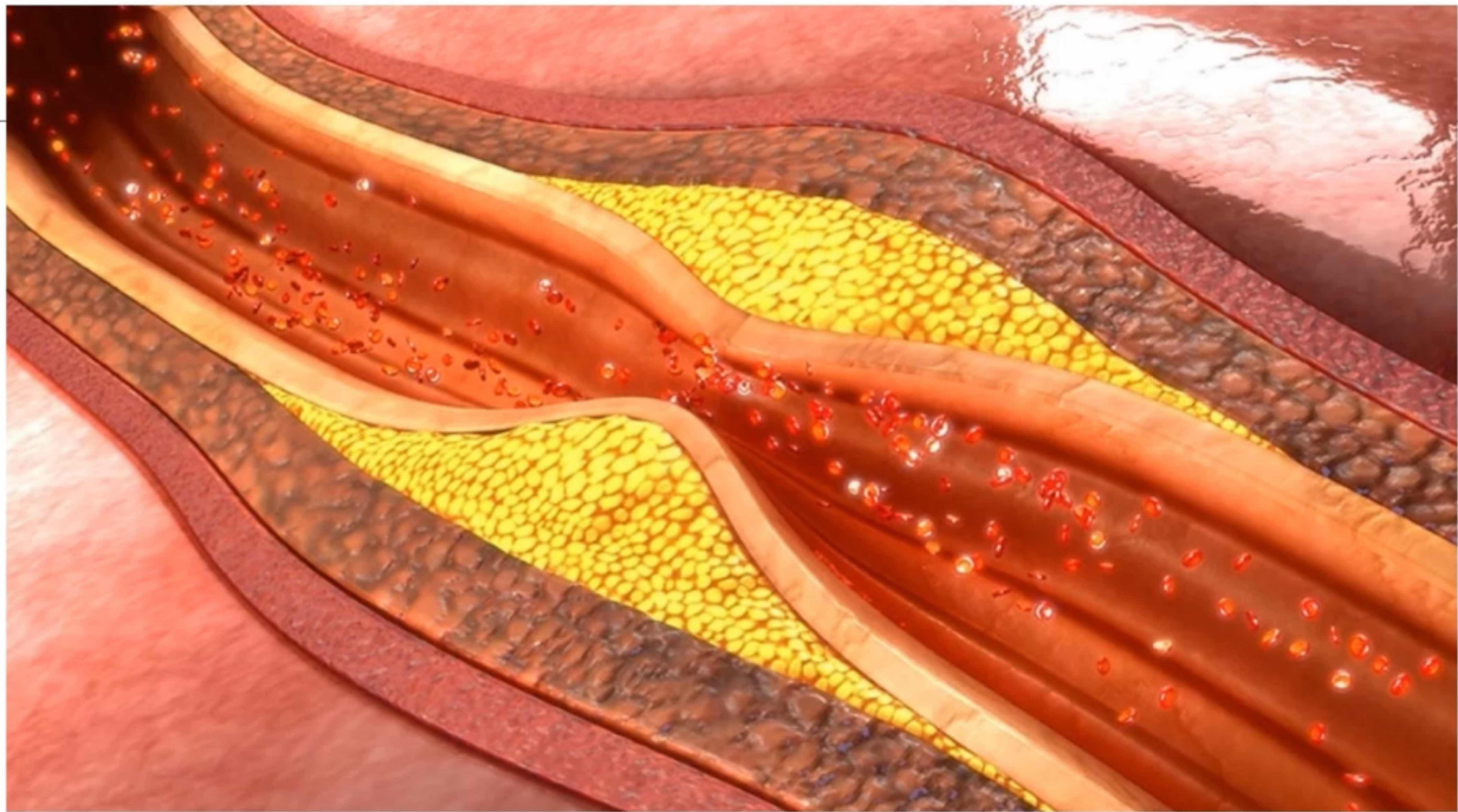
- ال **VLDL** بيتتم تصنيعه عن طريق ال **liver** و ال **liver** بطلعه على ال **blood**

وهو بتمشى هيك، بلاقي ال **lipoprotein lipase** واقفله 🦊، وبيتتم عملية تكسيره
وبنستفيد من ال ال **cholesterol** وال **triglyceride**، بيعطينا **free fatty acid**، يا
بنستخدمها بالطاقة، يا بتتخزن (بتسمن)

- بعد ما تتكسر هتعطينا بواقياها وبتكون عبارة عن **intermediate density**

lipoprotein (IDL) وبعديها بيعطيني ال **LDL**

- هلقيت على سطح ال **cells**، في **receptors** بتاخذ ال **LDL** وبتشفطه، زي ال
muscles الي بتستخدمه عشان الطاقة، كمان ال **liver**



مشكلة ال LDL، انه ممكن يترسب في جدار الأوعية الدموية، بس راح يصيرله oxidation و يعطيني oxidised LDL، فهاد هيخلي ال microphages تنط وتيجي و كمان هتيجي ال Platelet وكلهم هدول هيتجمعوا ويعملوا تجمع بلزق بالجدار و يؤدي لقصة ال atherosclerosis ومن بعدها ال acute coronary syndrome

Pharmacological actions:

Mainly decrease LDL , decrease TG, and may increase HDL

The most potent : atorvastatin, rosuvastatin, pitavastatin

يعني يحتاج جرعات أكبر عشوائياً
the same effect

Less potent; simvastatin, pravastatin, Fluvastatin, lovastatin

Therapeutic uses:

All types of hyperlipidemias

Familial hypercholesterolemia lack LDL receptors

genetic هادي مشكلة

Pharmacokinetics:

Lovastatin and simvastatin are prodrugs

All statins are metabolized in the liver, with some metabolites retaining activity.
Excretion takes place principally through bile and feces, but some urinary elimination

عشان هيك في كثير أدوية بنقدر نستخدمهم في ال renal dysfunction، بدون ما نعمل adjustment لل dose

The best

Characteristic	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Serum LDL cholesterol reduction produced (%)	55	24	34	43	34	60	41
Serum triglyceride reduction produced (%)	29	10	16	18	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	8	12	8	12
Plasma half-life (h)	14	1–2	2	12	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	15	20	10	13

بنزلوه بنسبة أقل
من ال LDL

هدول المرضى الي يكون عندهم **acute و cardiovascular diseases** **coronary syndrome**، احنا بنحتاج انه نقلل ال **LDL** كثير عشان نقلل ال **risk** عندهم ل **ischemia** جديدة و **angina** جديدة - بنحتاج انه نقلل ال **LDL**، لدرجة أقل من 70، وإذا صحلنا نوصله ل 50 يكون ممتاز و رائع

Adverse effects:

Elevated liver enzymes

تفسير في ال skeletal muscles يعمل وهن ووجع بالعضلات

Myopathy and rhabdomyolysis (disintegration of skeletal muscle;

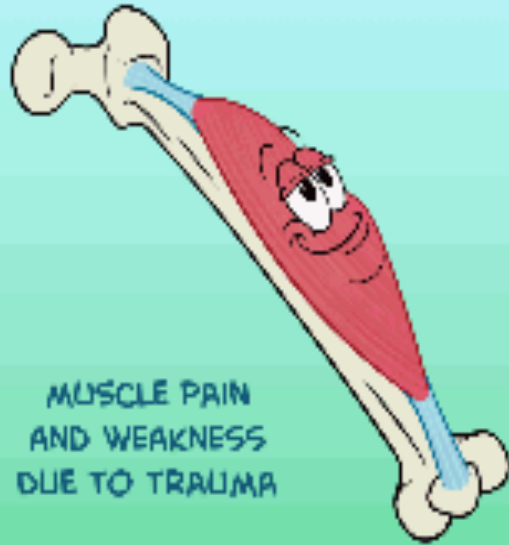
أكثر واحد بسبب هذه ال risk factors

Simvastatin is metabolized by cytochrome P450 3A4, and inhibitors of this enzyme may increase the risk of rhabdomyolysis (Creatine kinase levels) ^{CK levels} rhabdomyolysis and myopathy يكون عالي في المرضى الي عندهم

These drugs are contraindicated during pregnancy and lactation

RHABDOMYOLYSIS

MUSCLE TISSUE BREAKDOWN WITH
RELEASE OF INTRACELLULAR CONTENTS
(MYOGLOBIN) INTO CIRCULATION



MUSCLE PAIN
AND WEAKNESS
DUE TO TRAUMA

ELEVATED CREATINE
KINASE (CK) LEVELS



DARK, REDDISH
BROWN URINE DUE
TO MYOGLOBINURIA
وَحْلَهُ هُوَ very good hydration

MYOGLOBIN MAY OCCLUDE THE STRUCTURES OF THE KIDNEY
AND BREAK DOWN INTO TOXIC COMPOUNDS LEADING TO
ACUTE TUBULAR NECROSIS OR ACUTE RENAL FAILURE

Niacin (nicotinic acid): Vitamin B3

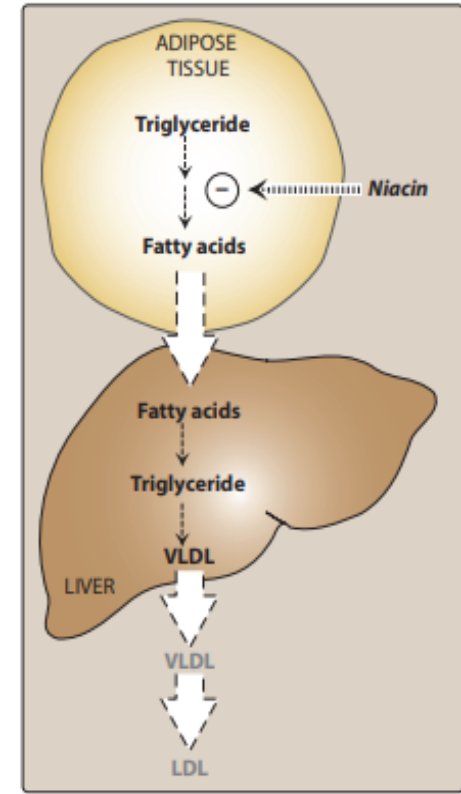
Reduce LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C
lowers triglycerides by 20% to 35%

Mechanism of action: inhibits lipolysis in adipose tissue,
thereby reducing production of free fatty acids

Reduce VLDL production & therefore LDL levels

Therapeutic uses: familial hyperlipidemias, Hypertriglyceridemia

Pharmacokinetics: It is converted in the body to nicotinamide,
which is incorporated into the cofactor nicotinamide adenine dinucleotide
(NAD+)



Adverse effects:

The most common side effects of niacin are an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus

Aspirin??? **side effects** ال بقلل ال niacin، لو استخدمه مع ال

Nausea, abdominal pain

Sustained-release formulation of niacin reduces bothersome initial adverse effects.

Niacin inhibits tubular secretion of uric acid and, thus, predisposes to hyperuricemia and gout.

Impaired glucose tolerance and hepatotoxicity have also been reported.

The drug should be avoided in hepatic disease.

Fibrates

متخصصة في ال triglycerides

Fenofibrate and gemfibrozil are derivatives of fibric acid that lower serum triglycerides and increase HDL levels.

Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels.

Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AIII

بلعبوا بدور في عملية تصنيع ال HDL

MOA:

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family that regulates lipid metabolism

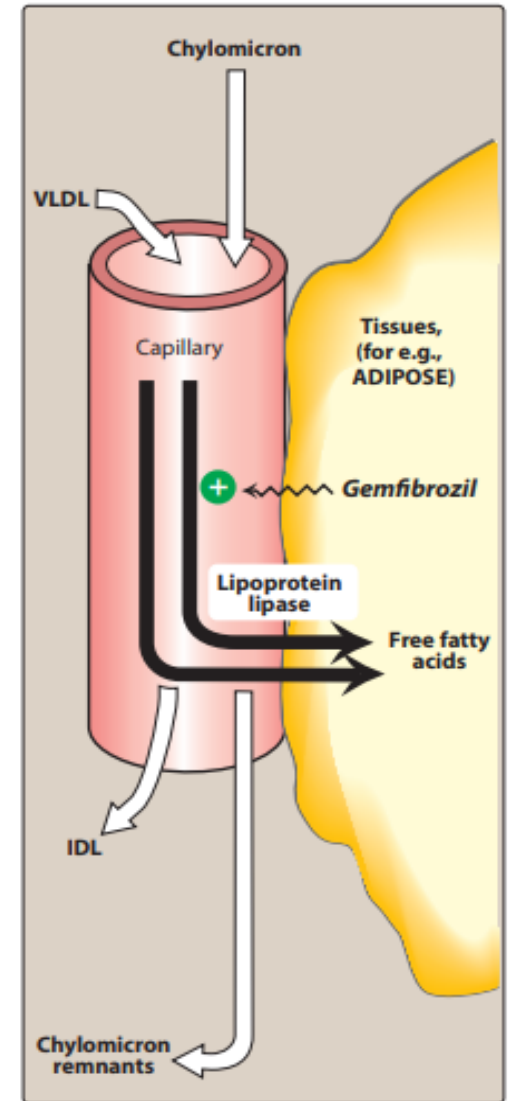
مجموعة كبيرة من ال receptors شغلها يكون بشكل أساسي على ال DNA، انها تعمل regulation لبعض ال gene expression، يتشتغل على أجزاء في ال DNA، اما يتعمل زيادة في gene expression معين او يتعمل inhibition ل gene expression معين

Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs, PPARs are activated

increased expression of lipoprotein lipase and decrease expression of apo CIII

وهيك بنقل من نسبة ال triglyceride، الي يكون موجود بنسبة كبيرة في ال VLDL وال Chylomicron وبنسبة أقل في ال LDL

بلعب دور في تقليل ال level تبع ال triglyceride



Therapeutic uses

Hypertriglyceridemias

Hyperlipidemia

Pharmacokinetics

Fenofibrate is a prodrug, which is converted to the active moiety fenofibric acid
undergo extensive biotransformation and are excreted in the urine

Adverse effects

gastrointestinal (GI) disturbances (most common)

Gallstones...Myositis

Myopathy and rhabdomyolysis have been reported in patients taking gemfibrozil and statins together **ولو زودوا ال effect تبع ال warfarin**

The use of gemfibrozil is contraindicated with simvastatin. **أكثر تزيين بعملوا ال myopathy وال rhabdomyolysis.**

Both fibrates may increase the effects of warfarin. عبرة عن anticoagulant. كثير ال drug drug interaction INR should, therefore, be monitored more frequently when a patient is taking both drugs.

Fibrates should not be used in patients with severe hepatic or renal dysfunction or in patients with preexisting gallbladder disease

اشي بمسك بال cholesterol وبروح بنزله بالفضلات وما بخلي يصيرله امتصاص

Bile acid-binding resins

❖ significant LDL cholesterol- lowering effects<<< statins

❖ Cholestyramine, colestipol , and colesevelam

❖ Mechanism of action::

في ال Small intestine

❖ Anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine

❖ resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration

❖ Hepatocytes then increase conversion of cholesterol to bile acids, which are essential components of the bile

بعد ما يسحب ال LDL الي في الدم

Therapeutic uses::

The bile acid-binding resins are useful often in combination with diet or niacin for treating type type IIA and type IIB hyperlipidemias

Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis.

بسبب زيادة ال bile acid في الدم

Colesevelam is also indicated for type 2 diabetes due to its glucose-lowering effects.

صراحة ما بنستخدمه Clinically

Pharmacokinetics

Bile acid sequestrants are insoluble in water and have large molecular weights

Neither absorbed Nor metabolized ,,,, totally excreted in feces

Adverse effects:

GI disturbances, such as constipation, nausea, and flatulence

Colesevelam has fewer GI side effects

They impair the absorption of the fat-soluble vitamins يروحوا ماسكين بشغلات تانية بالغلط

They interfere with the absorption of many drugs (for example, digoxin, warfarin, and thyroid hormone) ?????

These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (≥ 400 mg/dL)

بالتالي ال liver راح يسحب ال LDL

Cholesterol absorption inhibitor

Ezetimibe selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver.

This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

Ezetimibe lowers LDL cholesterol by approximately 17%.

Patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe.

Adverse effects are uncommon with use of ezetimibe
عادة بنستخدمه لما بنستخدم جرعات عالية من ال statin وما بنصل لل effect الي بدنا ياه

يمكن استخدامه مع ال statin

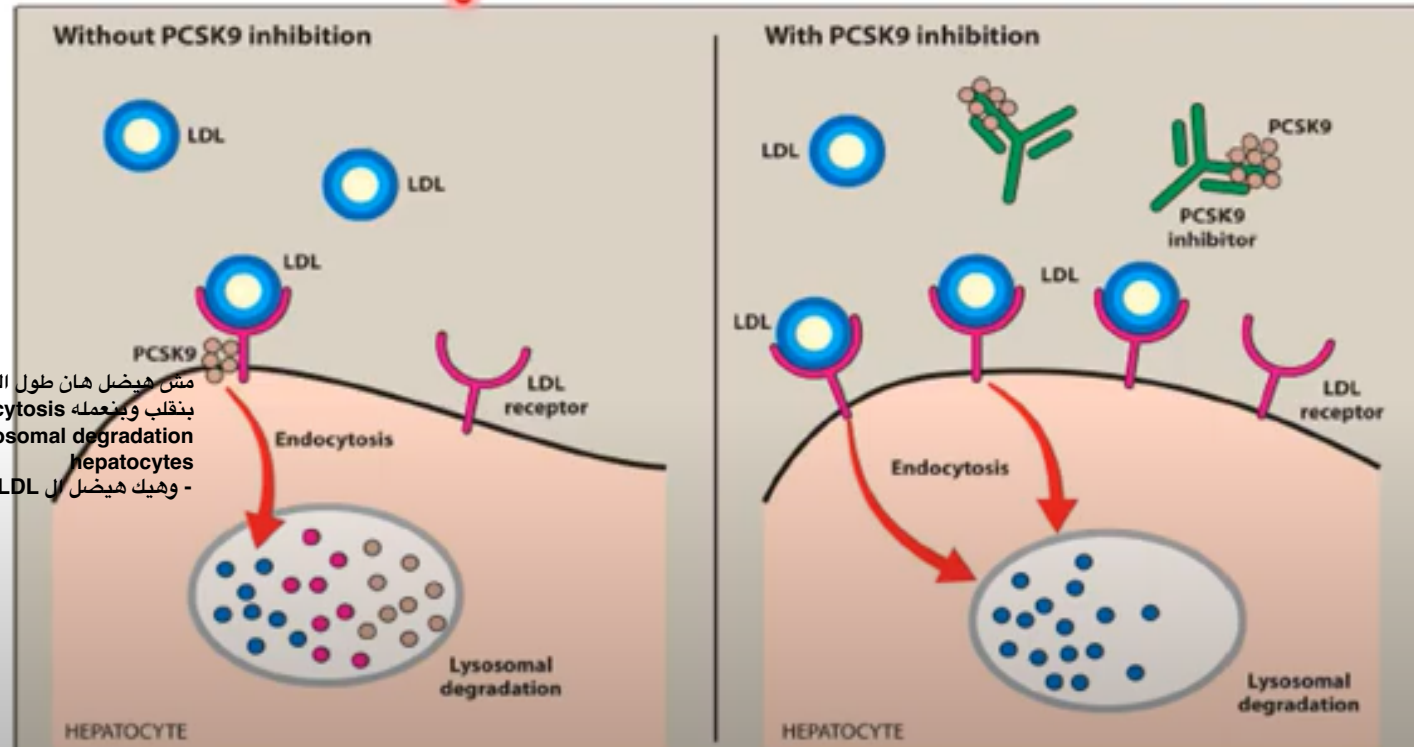
PCSK9 inhibitors (Proprotein convertase subtilisin kexin type 9 inhibitors)

Monoclonal antibodies

Evolocumab

Alirocumab

مس هبضل هان طول الوقت، في وقت من الأوقات
بنقلب وينعمله endocytosis ويصيرله
lysosomal degradation ويتخلص منه ال
hepatocytes
- وهيك هبضل ال LDL في الدم
الإنزيم هاد يساعد في هذه العملية



When combined with statin therapy, PCSK9 inhibitors provide potent LDL-C lowering (50% to 70%).

They may also be considered for patients with high ASCVD risk and statin intolerance.

PCSK9 inhibitors are only available as subcutaneous injections and are administered every two to four weeks.

The most common adverse drug reactions are injection site reactions, immunologic or allergic reactions, nasopharyngitis, and upper respiratory tract infections.

اشي طبيعي بصير مع معظم ال monoclonal antibodies