Diuretics

• يستخدم لما تكون المشكلة volume overload
يعني المريض عنده اعراض الـ congestion
• Pulmonary congestion: dyspnea, orthopnea.
• Leg edema, cynosis
• مشاكل بالهضم كونه عنده edema بال GIT

- **Among First-line therapy of heart failure**
- **Role in HF:**
- 1- Remove the signs and symptoms of volume overload (pulmonary congestion/ peripheral edema).

← يعني بعالج أو بخفف من الأعراض المذكورات فوق.

- 2- Reduce salt and water retention (Natriuresis)→↓ventricular preload and venous pressure.

excretion of Na, water → ↓ Blood volume
↓ preload.

- 3- Reduction of cardiac size →improve cardiac performance

كونها تعمل على ال loop of Henel

- Loop diuretics – **furosemide:** most powerful and used for most patients (Called high ceiling diuretics) ذات السقف العالي.
- Thiazide Diuretics- less effective but indicated in patients with hypertension and mild fluid retention chlorthiazide, hydrochlorthiazide
- **Side effects of diuretics**: metabolic alkalosis, electrolyte imbalance (hypokalemia) and hypovolemia

* من خلال الحفاظ إلي بالحالة إلي قبل ال diuretics ما إلهم علاقة بال Mortality Rate

- **N.B. Diuretics do not improve the mortality rate in patients**

/ Survival Rate / elongivity.

K^+ Sparing Diuretics (aldosterone antagonists: MRA)

is one of Mineralocorticoid (naturally occuring one) found in our bodies

هذا النوع التالت من ال diuretics ، ويحافظ على ال K^+ حيث ما بعمل إله hypokalemia Side effect ، بالتالي تخلص من ال water مع ال Na^+ excretion

Mineralocorticoid receptor antagonist.

- Spironolactone, triamterene, amiloride are weak diuretics-for achieving volume reduction with minimal K^+ loss

يعني لو ودي diuretic ما بعطيه لحاله effect

هدفي منه K^+ sparing

- **Advantages of spironolactone**:
- 1- Preserve K: prevents hypokalemia
- 2- Decreases mortality in cases of sever HF
- 3- Reverse aldosterone-induced remodeling
- **Dose**: one tablet lasilactone (furosemide and spironolactone) 50 mg in the morning 5 days a week.

as potent diuretic

لبه بعطيه (5) أيام وبومين ما بعطيه عشان يخاف من ال hypovolemia

- **Side effects**: **gynecomastia**

enlargement of Breast tissue in male.

بقعد على ال receptor تاعه وما بخليه يشتغل شغل

لبه ؟ لأن ال spironolactone ال structure تاعه يشابه ال testosteron ،

so antagonize action of Androgens

Drugs That Increase Contractility

Called:

Inotropic Drugs

- **Cardiac glycosides:**
- Digoxin, digitoxin
- **Phosphodiesterase inhibitors:**
- Amrinone , milrinone

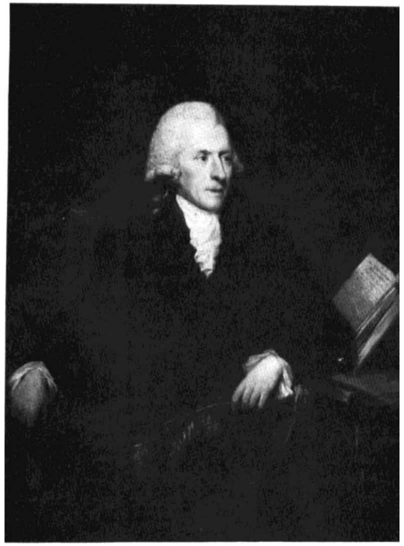
Inotropic Drugs

* قديمًا كان ال digitalis هو ال first line treatment.
لكن هلأ لا cuz of its toxicity.

* كونه الفرق بين ال therapeutic level وال toxic قليل بالتالي لازم اكون منتبه لهذا الاشي.

- **Cardiac glycosides: Digoxin**

كونه تركيبه الكيميائي فيه سكر.



William Withering 1785

Foxglove plant

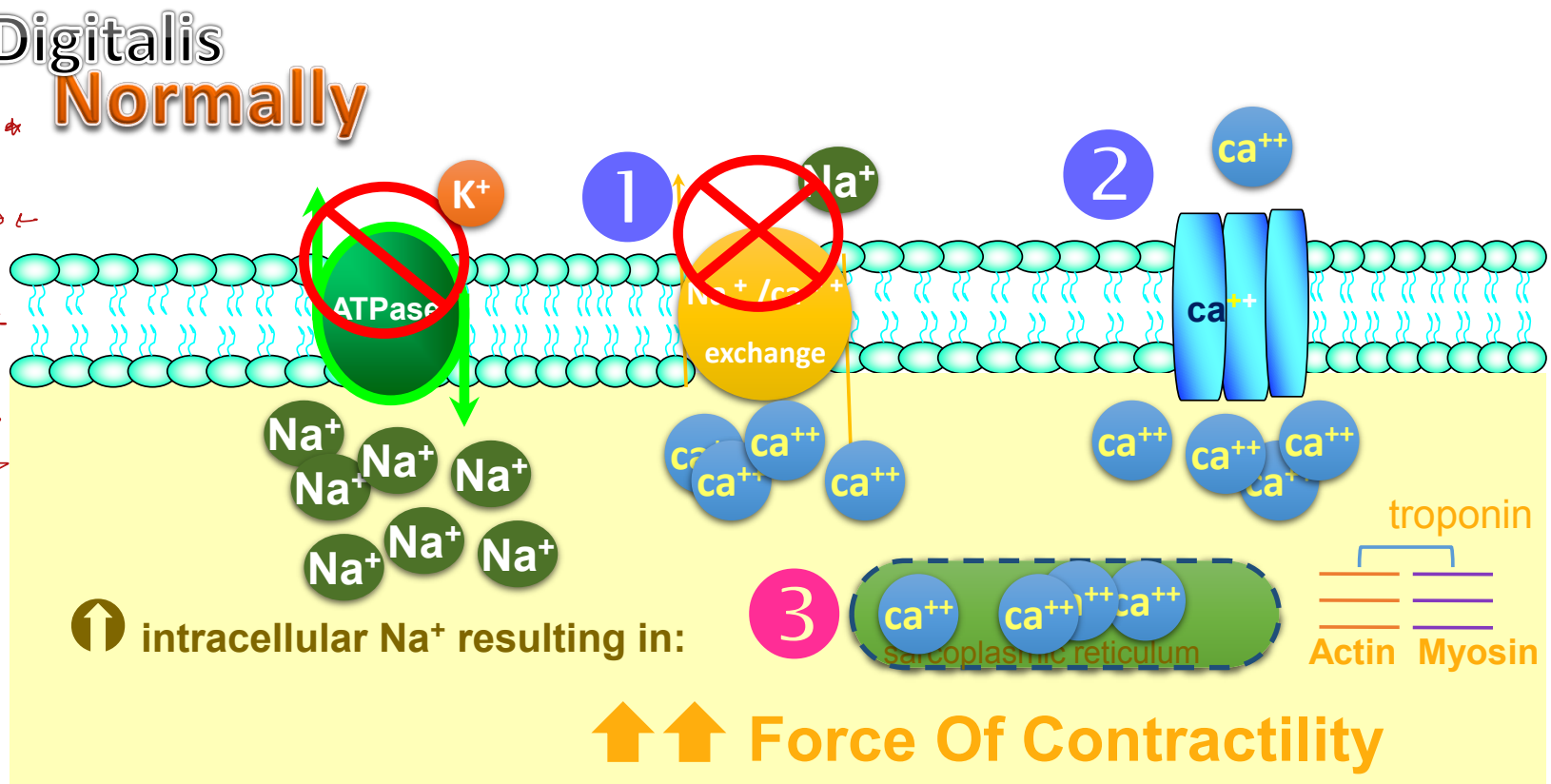
كف الثعلب لشكله.

Beneficial Effects Of Digoxin In HF

- **(Increasing the contractile force of the cardiac muscles)**
- **This effect is manifested in patients with heart failure, this results in:**
- 1- **Increased C.O.P**: **increasing renal blood flow**
- (inhibition of RAAS): decreasing systemic & pulmonary congestion
- Diuresis: relief of edema
- **Inhibition of central sympathetic stimulation**: normalization of BP
- **Improving tissue hypoxia**
- 2- **Bradycardia:** diminishing tachycardia: increasing filling time: ↑ COP
- 3- **Decreased heart size**

Mechanism Of Action Of Digitalis

Digitalis concentrated in myocardium 15 folds more than in other tissues



Digitalis Mechanism Of Action

- **Digitalis increase intracellular free Ca+2 in CARDIAC CELL**, during systole .
- **Ca+2 inhibits troponin (relaxing protein):**
- Facilitates excitation -contraction coupling between actin and myosin leading to increased cardiac contractility.
- N.B. Digitalis inhibit Na+/K+ ATPase by competition **with K+** , So **hypokalemia increase Digitalis toxicity** , while K+ administration improve toxicity of digitalis.

antagonize digitalis .

عشان هيك لازم اتفقد ال K+ level بيزول [?] المرضى وحتى احفف ال toxicity .

- In therapeutic dose leads to **partial inhibition** of Na^+/K^+ ATPase enzyme

due to K^+ ions

Digitalis increase intracellular free Ca+2 in cardiac cells by :

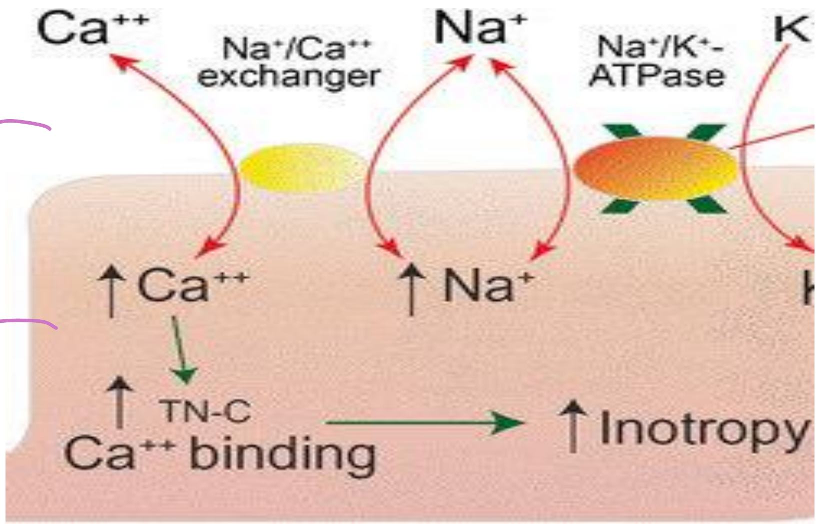
- 1- **Inhibition of membrane bound** **Na+ K+ Atpase enzyme**: ↑increasing intracellular Na+ ⟹ ↑increasing free intracellular Ca+2
- **2- Digitalis may directly facilitate the entry of Ca+2 into cardiac cells during the plateau of the action potential.**
- **3- Digitalis may increase the release of stored Ca +2 from the sarcoplasmic reticulum.**

So the end result is high Ca^{+2} intracellular.

قلبك رح يكمل ويعمل شغله بال Contraction.

↑K^+

↑Ca^{+2}, ↑Na^+



Pharmacological actions

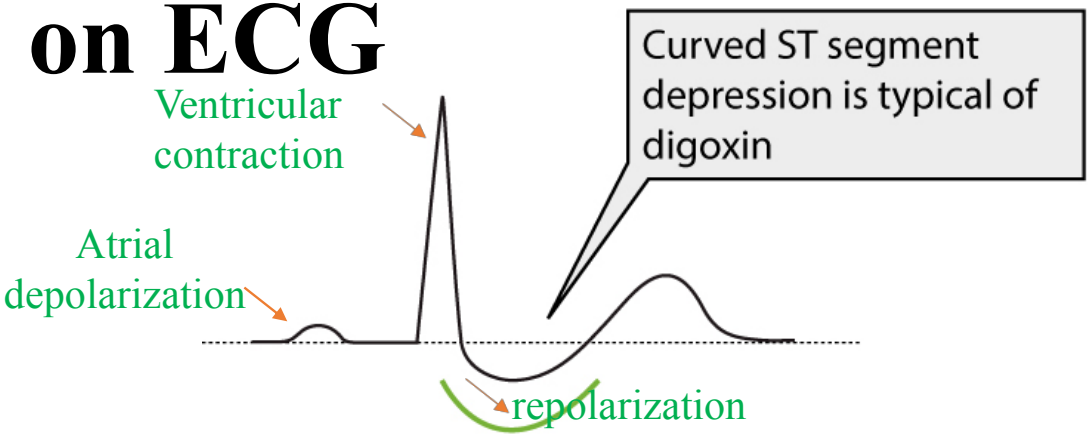
CARDIAC

- Contractility: ↑force of contraction & Cardiac Output: +ve inotropic
- ↓ Heart rate : - ve chronotropic: vagal stimulation: by direct and indirect mechanisms
- Conductivity: - ve dromotropic↓ CV in AV node
- Increased automaticity: ectopic foci
- Increased excitability: arrhythmia
  - Rhythmicity: disturbed

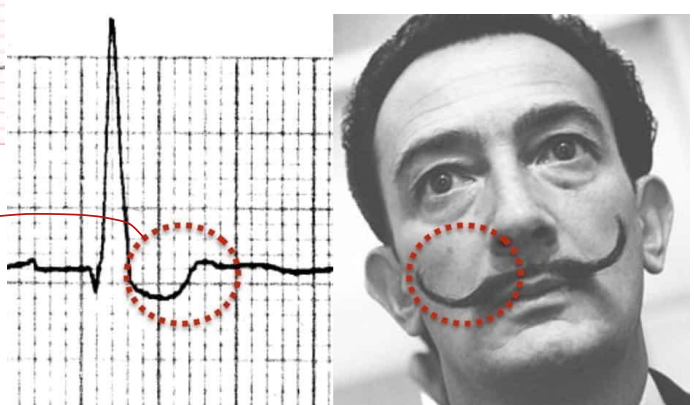
EXTRA CARDIAC

- Kidney:
- Due to improvement in circulation and renal perfusion
- Retained salt and water is gradually excreted
- CNS:
- Nausea, vomiting

Digitalis effects on ECG



- ECG: not indicator of toxicity but indicates treatment with digitalis.
- 1- Prolongation of P-R interval
- 2- High R wave
- 3- Depressed S-T segment
- 4- Inverted T- wave
- 5- Bradycardia
- 6- Any type of ahrrythmia: pulsus bigemini or trigemini



Clinical Uses Of Digoxin

- **1- Congestive heart failure: mild to moderated cases of HFrEF (less than 40%) who do not respond to other medications.**

- **2-CHF associated with Cardiac arrhythmias:**
  - Atrial fibrillation
  - Atrial flutter
  - Paroxysmal supraventricular tachycardia

- **DOSE**: Lanoxin tablet 0.25 mg once in the morning after breakfast 5 days/ week

- **Sever HF**:
- **Loading dose**: **2 tab. Twice daily for 2 days** or **2 tab, thrice daily for 1 day**
- **Then maintenance dose**
  0.25

Contraindications

Absolute

إطلاقًا

- 1- Heart block
- 2- WPW syndrome
- 3- Hypertrophic obstructive cardiomyopathy
- 4- Ventricular arrythmia

Relative

غير مستحب ، لكن اذا أعطيته بدي انتبه

- 1- Bradycardia: beta blockers, verapamil, myxedema, sick sinus syndrome.
- 2- Systemic or pulmonary hypertension
- 3- Renal and hepatic impairment
- 4- DC cardioversion
- 5- MI
- 6- Acute myocarditis of rheumatic fever

Drug interactions of digitalis

- **1- Antacids, cholystramine**: decrease digitalis absorption
- **2- Atropine**: increases digitalis absorption while metoclopramide decrease
- **3- Quinidine**: decreases digitalis clearance
- **4- K- losing diuretics**: increase digitalis toxicity

Toxicity of digoxin

Van goph

كان يعاني من epilepsy وعلاجو وقتهم كانو يعالجوها بال digitalis . لهيك بنلاحظ برسماته اللون الأصفر كثير .

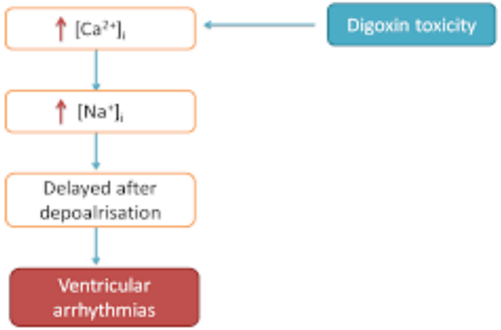
Extra-Cardiac

- **GIT**: Nausea & vomiting, anorexia (**first to appear**)
- **CNS**: convulsions
- **Vision**: visual disturbances: halos, scotoma, sudden loss of vision, yellow vision

  زي كأنك بتطل من انبوب.
- **Endocrine:** Gynaecomastia

Cardiac

- Bradycardia (first cardiac toxic sign)
- Pulsus bigemini — due to ectopic focus .
- Atrial flutter → fibrillation
- Ventricular extra-systole → tachycardia → fibrillation
- Partial heart block → complete block



Factors Increase Digitalis Toxicity

- **Small (Lean) body mass**
- **Old age**
- **Renal diseases**
- **Hypokalemia**
- **Hypercalemia**
- **Drug interactions:**
- **Diuretics → hypokalemia (arrhythmia)**

كونه قللنا بقلل الـ Clearance

- **Quinidine : ↑plasma level of digitalis**

Treatment Of Digitalis Toxicity

* Therapeutic level of digoxin: 0.5 – 2
. toxicity يبدأ من 2.1 فما فوق

- **1- Stop digitalis**
- **2- Oral or parenteral potassium supplements**
- **3- For ventricular arrhythmias:**
- Lidocaine IV drug of choice
- **4- For supraventricular arrhythmia:**
- Propranolol may be given IV or orally
- **5- For AV block and bradycardia**
- Atropine IM
- **6- Digoxin antibodies**: (digibind) **FAB fragment life saving: most spesific**

Fractionated Ab.
ترتبط فيه

Ivabredine

- **The First Selective and Specific I_f Inhibitor**
- Blocks the channel responsible for the cardiac pacemaker spontaneous firing (funny channel), I(f), which regulates heart rate. → ↓HR, brady.
- Without affecting any other cardiac ionic channels (including calcium or potassium).
- This results in reduced heart rate.
- Indicated in patients of CHF not responding or intolerant to B blockers
- **Adverse effects:**
- Bradycardia, atrial fibrillation and phosphenes (vision disorder).

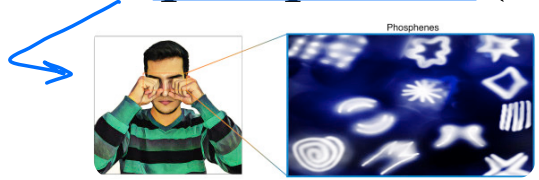
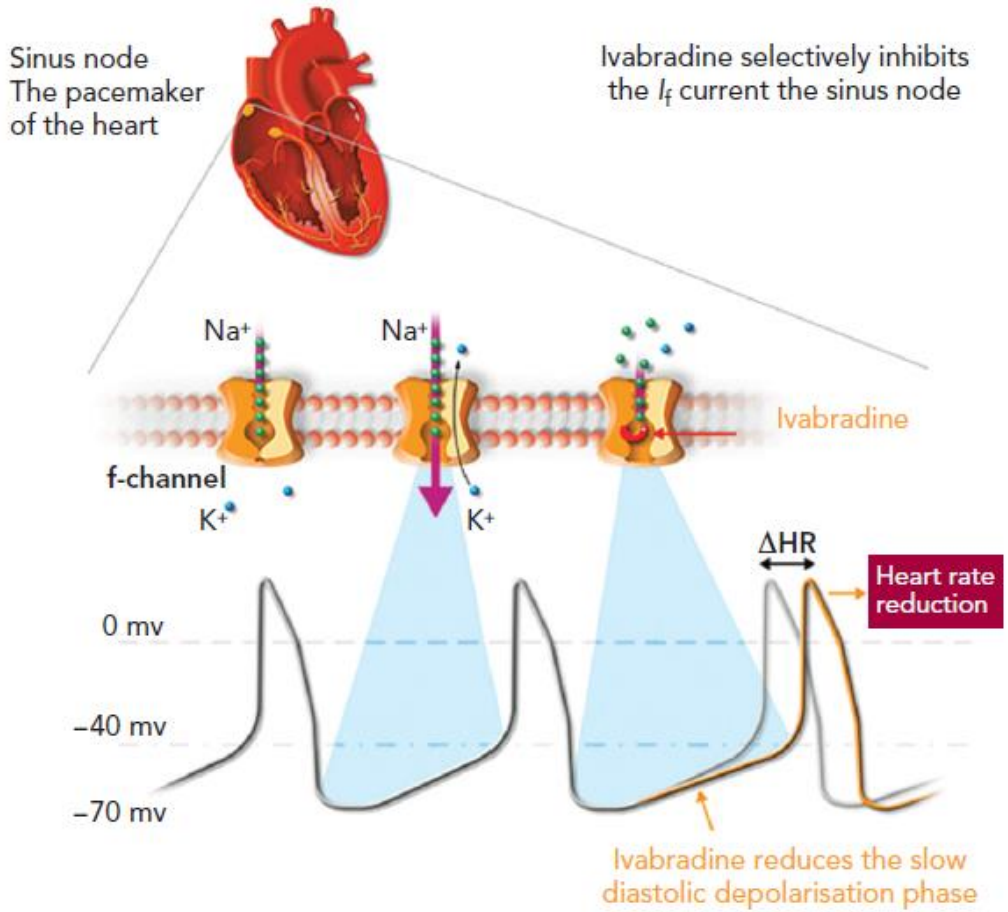


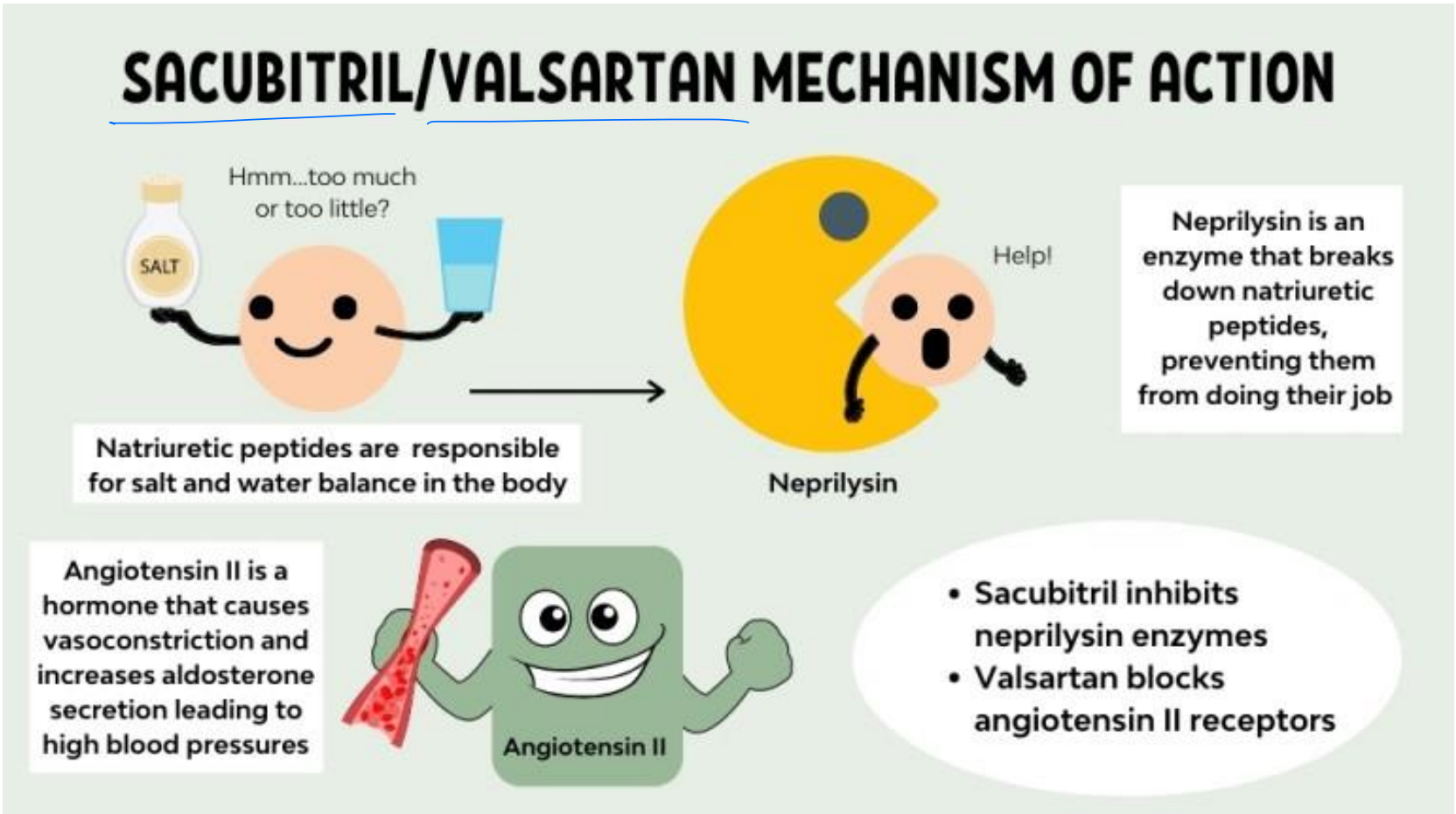
Figure 1: Mechanism of Action of Ivabradine



Source: http://www.shift-study.com/ivrabradine/mode-of-action/ Reproduced with the permission of Servier © 2016.

عرفنا شو دورهم بالمحاضرة الماضية. ← كونه بكسر الـ natreumbtic

ARNI (angiotensin receptor/neprilysin inhibitor)

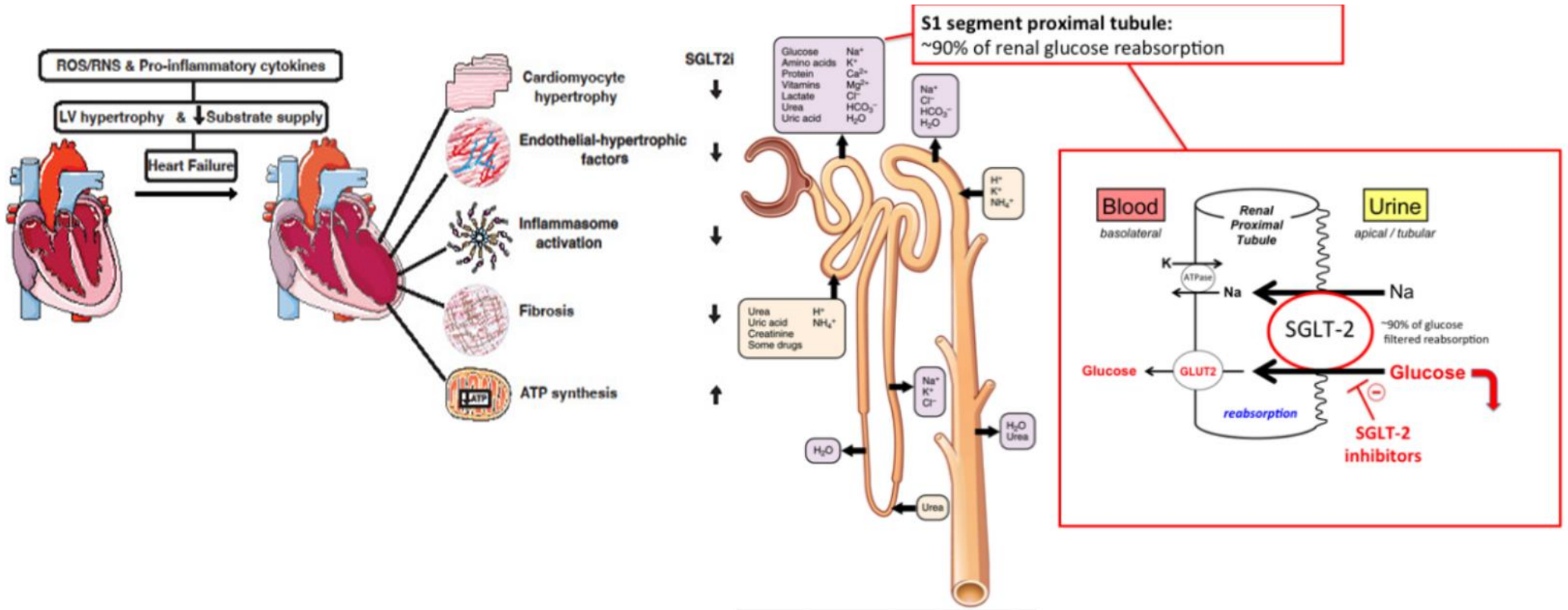


- **Adverse effects of Sacubitril-valsartan:**
- Hypotension, hyperkalemia and renal failure
- **Indications**:
- ARNI new class of drugs indicated in patients not responding to ACEIs or B blockers

SGLT-2 Inhibitors
Canagliflozin

- **Mechanism of Action:**
- **Inhibits the Na-glucose co-transporter 2 (SGLT-2)** in the kidney to reduce glucose reabsorption, resulting in increased urinary glucose excretion, and lower plasma glucose.
- **SGLT-2** is expressed in the proximal tubule and **mediates reabsorption of ~90% of filtered glucose** .
- **SGLT2 inhibition appears to underlie the ability of "gliflozins" to produce additional effects in the reduction of mortality and CV events in patients with heart failure.**

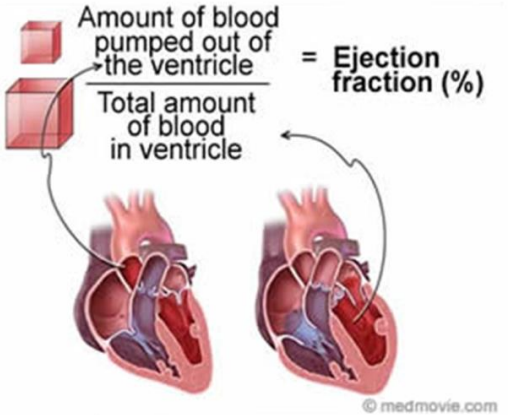
Mechanism of action& bebecicial effects of gliflozins in HF



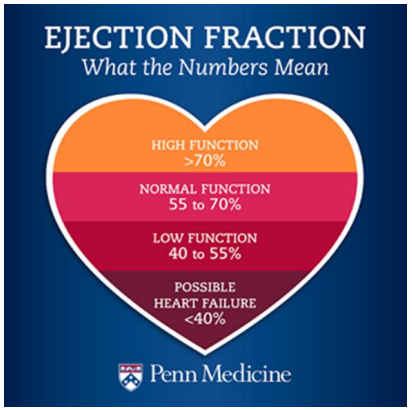
Management Of Chronic Heart Failure

- Lifestyle changes
- Drug therapy
- Surgery for correctable problems
- Implantable devices
- Heart transplant
- **Diet and lifestyle measures**
- Moderate physical activity, when symptoms are mild or moderate; or bed rest when symptoms are severe.
- Weight reduction
- Sodium restriction – excessive sodium intake may precipitate or exacerbate heart failure, thus a "no added salt" diet (60–100 mmol total daily intake) is recommended for patients with CHF.
- Stop smoking

Approach to the Patient with HFrEF



Assessment of LV function (echocardiogram)



EF < 40%

Assessment of volume status

Signs and symptoms of fluid retention

Diuretic

± digoxin

No signs and symptoms of fluid retention

ACE Inhibitor

β-blocker

Digoxin

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Thank you