CVS
PHARMACOLOGY

Modified NO:

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Color code
slides
Doctor
important
Additional information

Newer antianginal drugs

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- Those agents were developed after the 2000s, meaning they were approved by the FDA (both the American FDA and the European equivalent) by 2006 or around that time.
- We will discuss four drugs in general. Three of them are particularly important, while the fourth will only be briefly mentioned, as it is not widely used. However, the three key drugs have significant applications in the treatment of angina. Some of these drugs are also used in heart failure (HF) and as antianginal agents.
- Angina is a type of chest pain caused by reduced blood flow to the heart. Angina is a symptom of coronary artery disease.

🤗The flow of information in this lecture:

We are going to talk about 4 Newer antianginal drugs:

1. **Ivabradine**
2. **Ranolazine**
3. **Trimetazidine**
4. **Nicorandil**

Don’t worry it's an easy lecture😊

بسم الله نبدأ

HR : Heart Rate
HF : Heart Failure

1. Ivabradine

Check next slide plz for the explanation of point 2 and 3 😁

- Ivabradine selectively inhibits the I_f current, an important current involved in generating the early phase of spontaneous diastolic depolarization in sino-atrial cells, reducing the frequency of action potential initiation and lowering heart rate.

Simply, we are closing the sodium channel. That closed sodium channel is going to produce a reduction in heart rate, so our target is the SA node. Whenever we talk about the SA node, we are really talking about the chrono phrenic activity of the heart. So, what we really want to produce when we use Ivabradine is reducing HR

- It decreases the body's demand for myocardial oxygen, without any effect on blood pressure (increasing or decreasing) or myocardial contractility or conduction times, and results in a reduction in angina symptoms
- Ivabradine is metabolized by CYP3A4, there is drug interaction with CYP3A4 inhibitors and inducers.
- It is contraindicated to be used with verapamil and diltiazem.
- Used in HF especially when the ejection fraction less than 35%

Ejection fraction (EF) is a measure of how well the heart is pumping blood. It represents the percentage of blood ejected from the heart's left ventricle during each contraction compared to the total amount of blood in the ventricle before contraction.

Little explanation of I_f current:

- The I_f current, also known as the funny current, is a pacemaker current that plays a crucial role in regulating heart rate, particularly in the sinoatrial (SA) node.

- It allows a **slow influx of sodium (Na^+)** and a smaller efflux of **potassium (K^+)**. This mixed ion flow contributes to the gradual depolarization of the cell membrane during the **diastolic phase**.

- The I_f current is the main driver of the **diastolic depolarization** phase, helping pacemaker cells reach the threshold to generate an action potential. This regular depolarization establishes the heart's natural rhythm.

- **Diastolic depolarization** refers to the gradual increase in the membrane potential of pacemaker cells (such as those in the SA node) during diastole (the heart's resting phase), leading up to the threshold that triggers an action potential. This process is crucial for controlling the heart's rhythm.

- Ivabradine decreases the body's demand for myocardial oxygen, which we need in angina. So, remember, when we are treating angina pectoris, the demand for oxygen is greater than the supply. Therefore, we want to reduce the demand, and ivabradine helps in doing that.

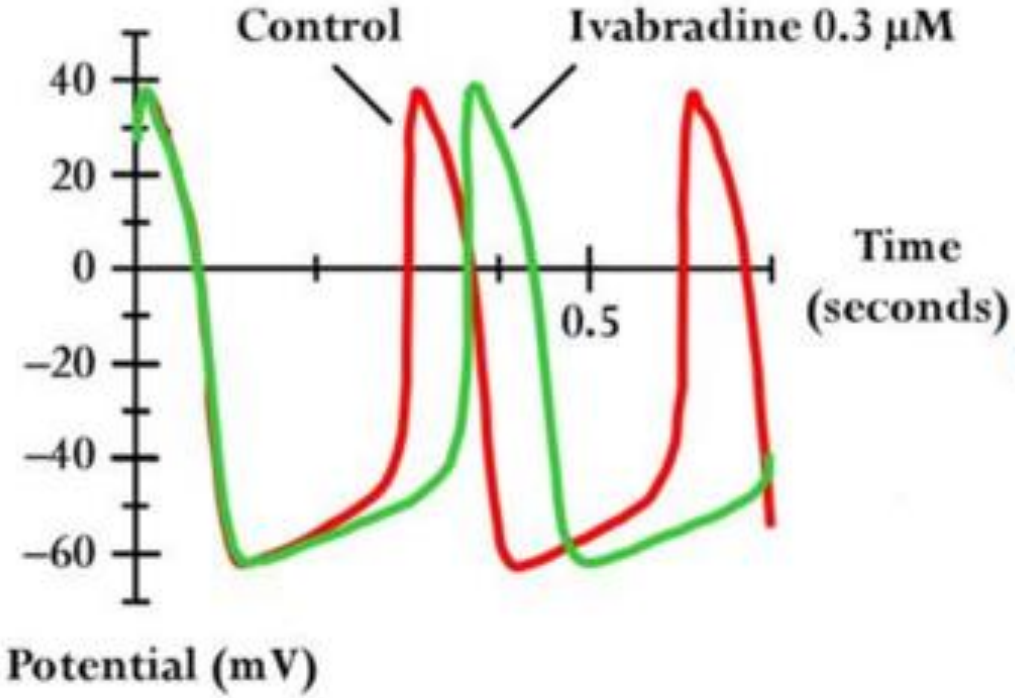
- Ivabradine is metabolized by CYP3A4, so there is a drug interaction with CYP3A4 inhibitors and inducers, which will affect ivabradine's pharmacokinetics. HLS final choice if u remember xD
- So:
- inhibitors of CYP3A4 like antifungal agents that inhibit CYP3A4 (like ketoconazole) --> increase Ivabradine level
- Inducers (like rifampicin) of CYP3A4 --> decreasing Ivabradine level

- Generally speaking, ivabradine has a profound effect on the SA node, so it can interact with other medications. It can be used in combination with a beta blocker.

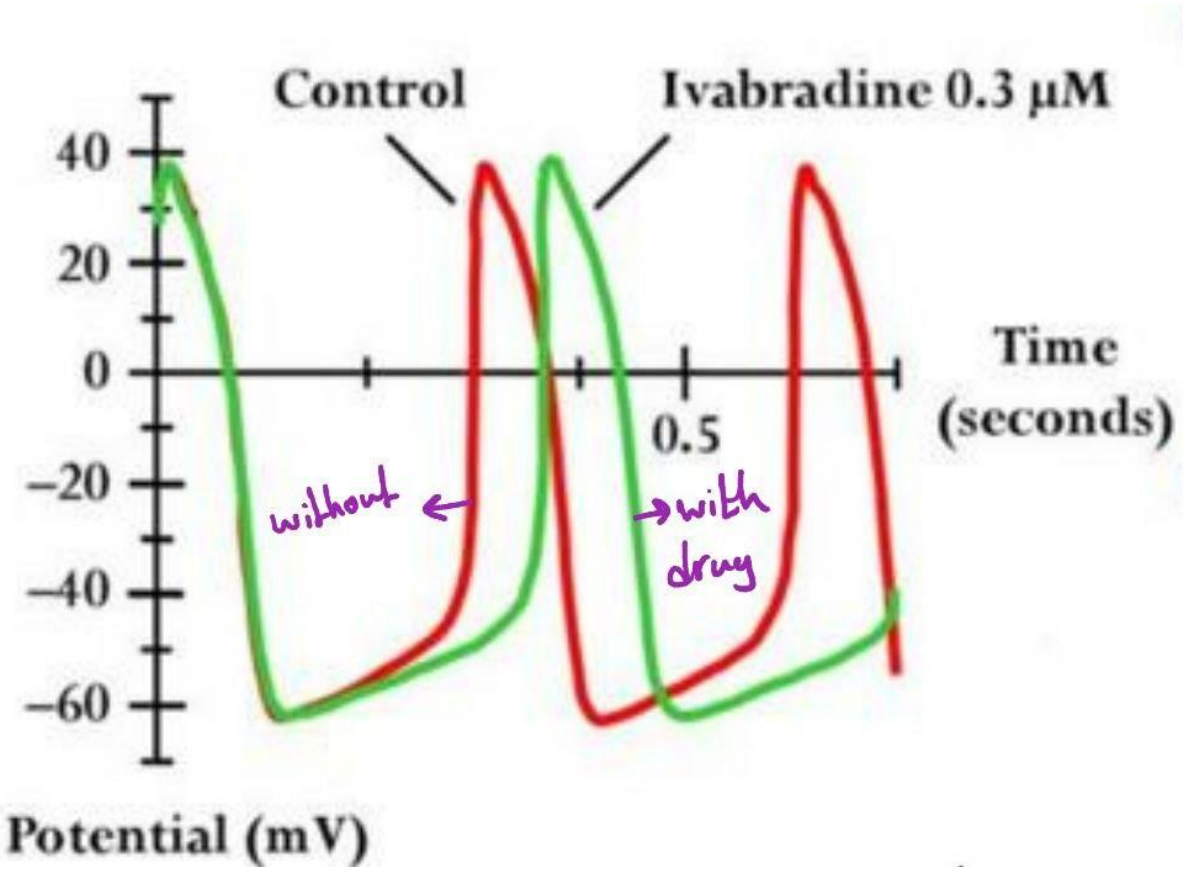
- When we say that ivabradine has a profound effect on the SA node, it means that ivabradine specifically targets the sinoatrial (SA) node, which is the heart's natural pacemaker.

Sinus node inhibition: Ivabradine

Explanation in the next slide



- I_f current is an inward Na+/K+ current that activates pacemaker cells of the SA node
- Ivabradine
  - Selectively blocks I_f in a current-dependent fashion
  - Reduces slope of depolarization, slowing HR



- Look at the graph here. We are reducing the slope of the current, which will slow down the SA node activity.
- We are reducing the oxygen demand, which, generally speaking, will reduce the heart rate, our target in angina.
- However, it is contraindicated to use ivabradine with verapamil and diltiazem (calcium channel inhibitors).

يعني كمختصر، احنا حكينا انه القناة هاي (I_f)بتدخل صوديوم عبين ما اوصل للعتبة وبصير عندي action potential، في حال سكّرت هاي القناة راح يزيد الوقت اللازم عشان اوصل العتبة، بالتالي تقليل نبضات القلب، وهذا هو الي بعمله ال Ivabradine

Ivabradine

- It is used in combination with beta blockers in people with heart failure with LVEF (Left Ventricular Ejection Fraction) lower than 35 percent inadequately controlled by beta blockers alone and whose heart rate exceeds 70 beats per minute.

- However, there is a limitation to that—your patient must have a heart rate of at least 70 beats per minute to avoid the risk of bradycardia.

- In people not sufficiently managed with beta blockers for their heart failure adding ivabradine decreases the risk of hospitalization for heart failure. And this is the other application of Ivabradine.

So, ivabradine is used in angina pectoris and heart failure (HF):

1. In angina, it works by reducing sinus rhythm and SA node activity through blocking the I_f channel. By decreasing the firing frequency of the SA node, it reduces the oxygen demand, thereby alleviating angina symptoms.

2. In heart failure (HF), we aim to reduce the chronotropic activity (heart rate) without affecting the inotropic activity (contractility).

- Left Ventricular Ejection Fraction (LVEF) is a key measurement used to assess the pumping efficiency of the heart, specifically the left ventricle, which is responsible for pumping oxygenated blood to the body.

Adverse effect

More Explanation in the next slide

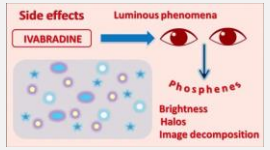
- Overall, 14.5% of patients taking ivabradine experience luminous phenomena (something to do with the eye) , in which the patients described as sensations of enhanced brightness in a fully maintained visual field. This is probably due to blockage of I_h ion channels in the retina, which are very similar to cardiac I_f.

- In a large clinical trial, bradycardia occurred in 2% and 5% of patients taking ivabradine at doses (high doses) of 7.5 and 10 mg respectively (compared to 4.3% in those taking atenolol which is a selctive Beta-blocker). Always remember about the HF which dose you have to use.

- 2.6–4.8% reported headaches. remember, headache is a problem with the nitrates, calcium channel blockers and now again headache will be part of the story

- blurred vision. However, blurred vision is not very common. It occurs in only about 1%-2% of patients.

- luminous phenomena are typically described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency)



- This means that your patient's vision might change, experiencing increased brightness. This effect is related to the I_h ion transporters in the retina, which have a structure similar to the I_f channel. While we previously discussed sodium channels, here we are referring to the potassium I_h ion channel, which is inhibited in the eye. This phenomenon is an example of what we call tissue-selective activity.

- As we mentioned, there is no absolute selectivity. If you bind to inhibit the If current in the SA node for sodium, you may inadvertently produce another activity within the eye.

Smmary of Ivabradine:

- Ivabradine is an I_f inhibitor that reduces SA node firing, leading to a decreased oxygen demand on the heart.
- Side effects:

1. It can affect the retina, but not through the I_f channel—it's through the I_h channel, which results in a phenomenon known as luminous phenomena in about 14.5% of patients. This is reversible and generally not a major concern, as patients typically adapt to it.

2. Blurred vision can occur in some patients.

3. Headache can affect up to 5% of patients (ranging from 2%-5%)

4. Bradycardia can sometimes occur, especially when using 10 mg of the drug, so be sure to monitor your patients for that.

And this is Ivabradine 😁

Let's talk about some concepts to understand Ranolazine: (read them to understand the next slides easily👌)

- Under normal conditions, the entry of sodium during the plateau phase is tightly controlled and brief. However, in certain conditions, the late sodium influx persists longer than normal, contributing to excess sodium within the cell. This leads to an imbalance in the Na+/K+ pump, which normally works to export sodium out of the cell and bring potassium in. This imbalance causes a calcium overload because the Na^+/Ca^{2+} exchanger (which normally pumps calcium out of the cell in exchange for sodium) becomes overwhelmed and unable to export enough calcium. So:

- In a normal person: Sodium influx during the plateau phase of the action potential is brief and controlled, maintaining ion balance and normal heart function, without excessive oxygen demand.
- In angina: Late sodium influx is prolonged, causing calcium overload, increased myocardial contractility, and higher oxygen demand. This leads to wall tension, stiffness, and ischemia, causing chest pain (angina).
- Ranolazine inhibits the late sodium influx, reducing calcium overload, lowering myocardial contractility and wall tension, and decreasing oxygen demand, helping to relieve angina symptoms.

2. Ranolazine

Check next slide plz😊

- It selectively inhibits the late sodium influx in the myocardium, reducing calcium overload, attenuating the ischaemic abnormalities of ventricular repolarisation and the resulting reduced contractility.

- It improves exercise tolerance while reducing the frequency of angina episodes. That is the application because it reduces the demand for oxygen, improves contractility, and reduces diastolic tension within the heart of the patient.

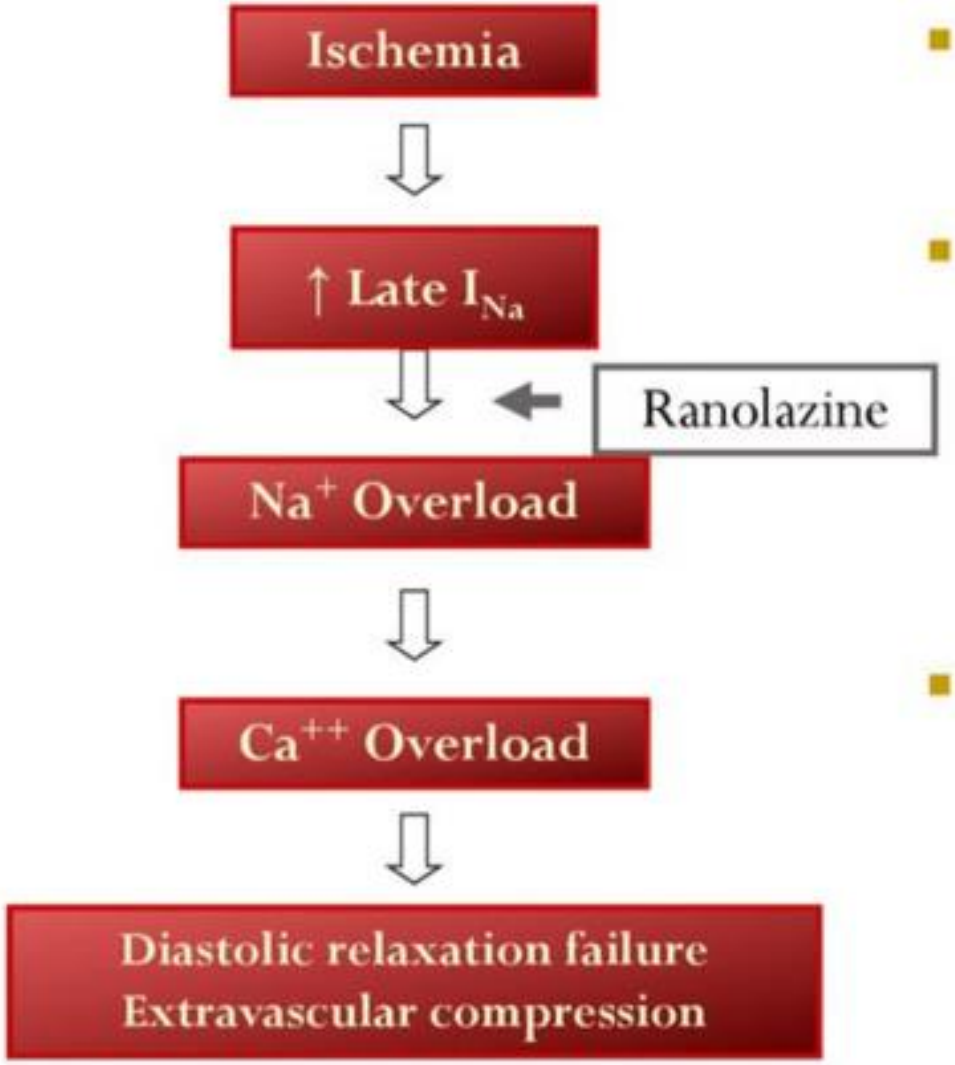
- Can improve myocardial ischaemia without affecting heart rate or blood pressure.

- In the myocardium, there is a late sodium influx that creates tension during diastole. This is particularly important in patients with angina, as it contributes to increased wall tension, vessel tension, and stiffness of the heart wall.

- When sodium enters during the late phase, or diastolic phase, it triggers more calcium influx, leading to calcium overload. This overload is a hallmark of ischemic abnormalities in ventricular repolarization, which reduces contractility and the efficiency of contraction. As a result, the heart experiences an increased oxygen demand, and whenever we talk about oxygen demand, we are referring to angina.

- Ranolazine as we talked inhibits the late sodium influx which will inhibits this calcium overload.

Understanding Angina at the Cellular Level



- **Ischemia impairs cardiomyocyte sodium channel function**
- **Impaired sodium channel function leads to:**
  - Pathologic increased late sodium current
  - Sodium overload
  - Sodium-induced calcium overload
- **Calcium overload causes diastolic relaxation failure** and extravascular compression, which will cause:
  - Increases myocardial oxygen consumption
  - Reduces myocardial blood flow and oxygen supply For the coronary artery to supply the heart, that will:
  - Worsens ischemia and angina

We've written a lot of explanations in this lecture! 😄😭

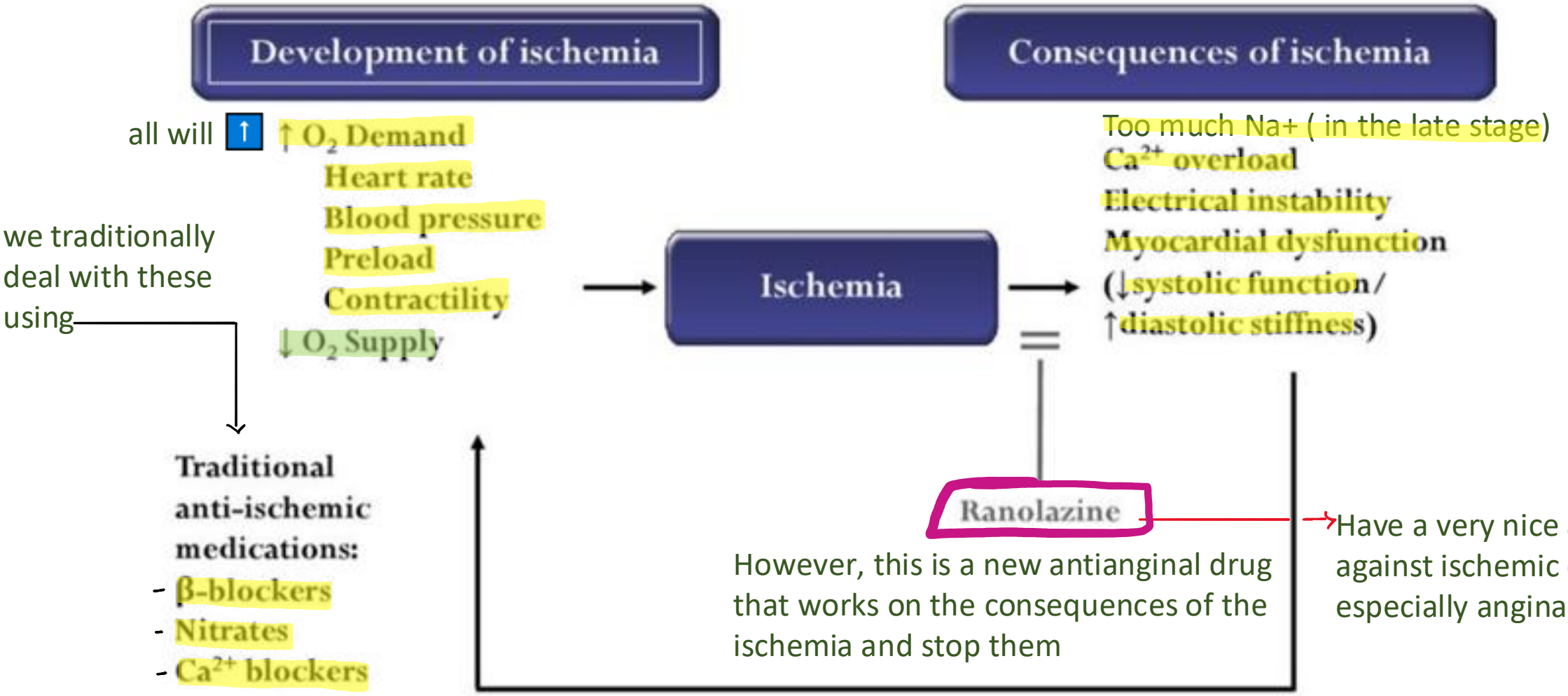
- So simply speaking:
- Ranolazine inhibits late influx of sodium which will inhibit late influx of calcium and reducing all these pathophysiological problems which are:

1. Sodium overload 2. Calcium overload 3. Stiffness of the heart 4. Reducing the myocardium oxygen supply.

- We are now talking in reality about diastolic pressure, diastolic perfusion time, and so on.

- However, we don't have any activity against the contractility of the heart. We are not affecting the contractility; we are not reducing it. Additionally, we are not having any impact on the heart rate (unlike Ivabradine which decreases heart rate).

Myocardial ischemia: Sites of action of anti-ischemic medication



Pharmacologic Classes for Treatment of Angina

Medication Class	Impact on HR	Impact on BP	Physiologic Mechanism
Beta Blockers	↓	↓	**Decrease pump function**
Calc Channel Blockers	↓	↓	**Decrease Pump function + Vaso-dilitation**
Nitrates	↑	↓	**Vaso-dilitation**
Ranolazine	–	–	Reduced Cardiac Stiffness only

Reversed by vasodilators like nitrates (especially on the impact of BP)

Will have –ve impact on chronotropic & tropic activity

Have no effect on chronotropic nor tropic activity

producing more perfusion toward the heart--> bitter diastolic time& less diastolic stiffness

Ranolazine and QT

- Ranolazine slightly increased QT interval in some patients and the FDA label contains a warning for this effect (QT elongation).
- we have QT interval elongation --> you have to watch for all these drugs that produce QT (we will talk more about that during antiarrhythmic drugs).

- The QT prolongation is not much, that come from the effect of ranolazine on the surface electrocardiogram (ECG) is the result of inhibition of (K+ currents) I_{Kr}, which prolongs the ventricular action potential.

- The drug's effect on the QT interval is increased in the setting of liver dysfunction; thus it is contraindicated in persons with mild to severe liver disease. As that will ↑ the level of **ranolazine** ---> the previous unwanted side effect due to ranolazine wii become a problem as we have a problem in the metabolism of ranolazine in this pt with liver disease.

Renolazin will have inhibitory activity toward beta oxidation (in acetyl co A reduction story) red in the image

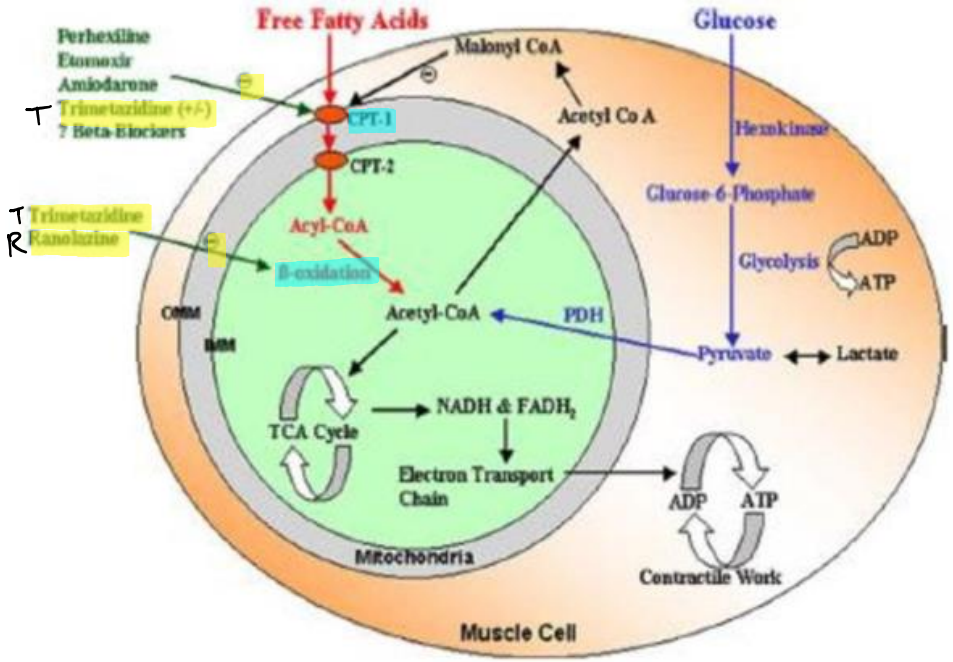
3. Trimetazidine

It has an inhibitory effect on:

1) CPT-1(part of fatty acid utilization toward oxidation)
2) Beta oxidation

- **Inhibition of the reduction of adenosine triphosphate, stimulation of glucose consumption by the myocardium**
- **It has very limited haemodynamic effects, but can cause symptoms of Parkinsonism. Therefore, among its main contraindications is Parkinson's disease.**

- Trimetazidine Have activity of switching - oxidation / ATP(energy) production – from the fatty acid (red) toward glucose (blue)



- In ischemic disease where we have less O2 --> the heart will build its production of ATP on the fatty acid –so--> we will have mostly (about 80% or more of fatty acid utelization to produce activity and we need this ATP to produce contractility. (note: glucose have less demand for O2).

- So, if we switch from fatty acid utilization toward glucose utilization ----->Decrease in O2 demand. That all we could do using **TRIMETAZIDINE**

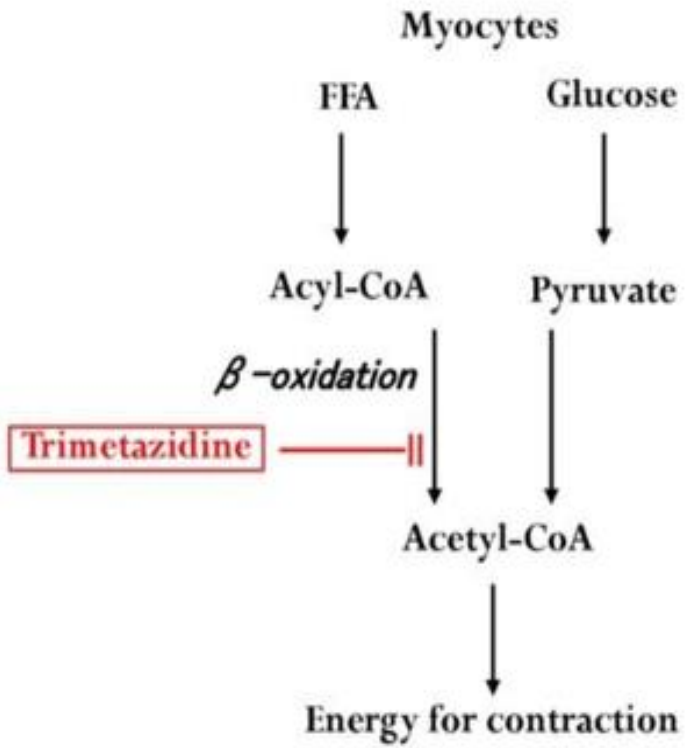
Rinalazine has some of this activity, however,
-its more to do with late influx of Na+ and late overload of Ca+2
-has some activity toward metabolic conditions

Trimetazidine :

- A switcher (stimulate glucose cosumption by myocardiam with no activity homodinamic activity (nothing to do with chronotropic and intropic blood pressure)
- A metabolic drug , has a nice metabolic activity toward metabolism , it's listed within the doping drugs (ضمن الادوية الممنوعة للرياضيين لانها تحسِّن من نشاط القلب) that produce bitter heart activity.

** However, it has a special type of interaction which is to do with the brain:
1) Can cause symptoms of Parkinsons in very rare cases, however, **if your patient has Parkinsons --> its really contraindicated** (because it worsen his Parkinson symptoms)
2) Extrapyramidal SE (next slides)

Metabolic modulation (pFOX): Trimetazidine



- O2 requirement of glucose pathway is lower than FFA pathway
- During ischemia, oxidized FFA levels rise, blunting the glucose pathway

and we want to block this using trimetazidine

pFOX = partial fatty acid oxidation
FFA = free fatty acid

pFOX Trimetazidine is the one that inhibits beta-oxidation here and switches toward glucose --> pyruvate, (rather than free fatty acid) toward Acetyl-coA PATHWAY

Adverse effects

- Parkinsonian may produce little symptoms in patients; However, Parkinson's patients are contraindicated for this durg.
- Extrapyramidal(الاعراض الجانبية فوق الهرمية) rare side effect that happens within less than 1% : symptoms such as tremor, rigidity, akinesia, hypertonia.

  Restless leg syndrome المريض بضل ماسك رجله و هي بترج(القدم الرجاجة)

- Not to prescribe to patients with Parkinson disease(contraindicated), parkinsonian symptoms, tremors, restless leg syndrome.

This drug is special as it hase 2 partes:

1) Part thet will work as a nitrate
2) Other part will Work on the K+ level

4. Nicorandil

It's a nitrate, note the (Dil)

You just need to understand the MOA of this drug generally speaking

Focus on doctor notes here 🔥

- It increases cyclic guanosine monophosphate and facilitates the opening of mitochondrial potassium adenosine triphosphate channels. Generally speaking, it opens the K+ channel

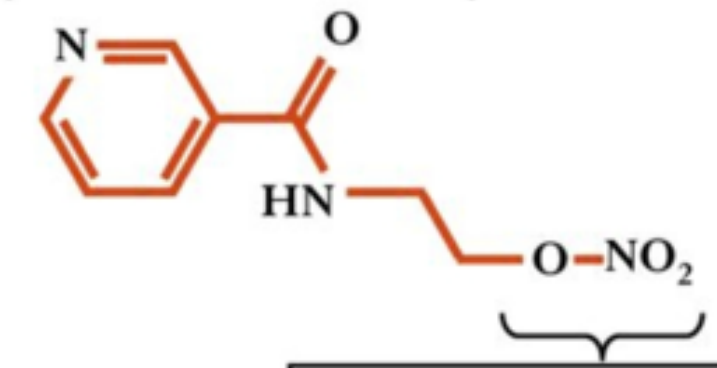
- Nicorandil is considered as a second-line option to treat patients with stable angina when they do not tolerate or cannot use beta-blockers (or calcium channel antagonists such as verapamil and diltiazem) or when they do not respond enough to first-line medications. The use of this drug is limited

- Among the adverse effects are gastrointestinal, skin and mucosal ulcerations (especially if there is concomitant use of acetylsalicylic acid or non-steroidal anti-inflammatory drugs). In this case, the drug should be discontinued permanently.
- If produce GI,skin, and mucosal ulcerations –meaning that --> the drug has a special SE in a special type of population, and this is Nicorandil **(remember this doctor said)** 💡

Preconditioning: Nicorandil

2) K+ opening activity

- Activation of ATP-sensitive K^+ channels
  - Ischemic preconditioning
  - Dilation of coronary resistance arterioles



1) Nitrate part

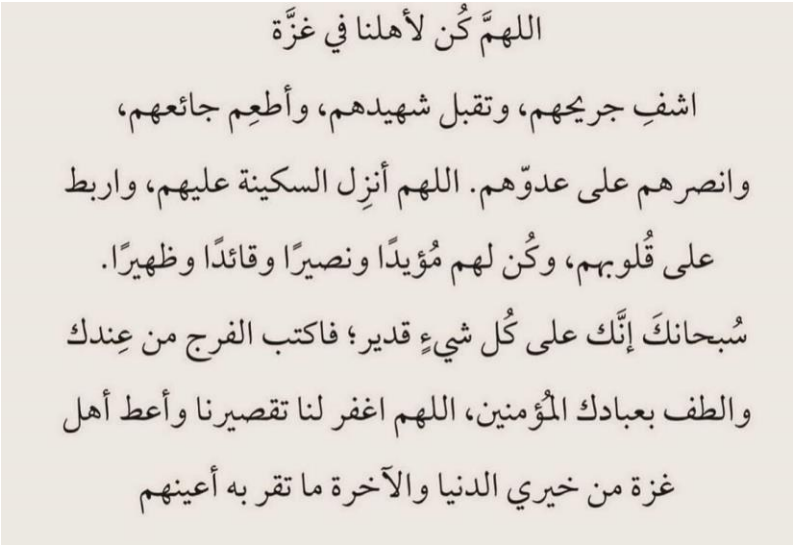
- Nitrate-associated effects
  - Vasodilation of coronary epicardial arteries

So, it's a nitrate-like drug with a positive potassium charge ⚡

IONA Study Group. *Lancet*. 2002;359:1269-75.
Rahman N et al. *AAPS J*. 2004;6:e34.

Additional sources

luminous phenomena paper


اللهمَّ كُن لأهلنا في غزَّة

اشفِ جريحهم، وتقبل شهيدهم، وأطعِم جائعهم،

وانصرهم على عدوّهم. اللهم أنزِل السكينة عليهم، واربط

على قُلوبهم، وكُن لهم مُؤيدًا ونصيرًا وقائدًا وظهيرًا.

سُبحانكَ إنَّك على كُل شيءٍ قدير؛ فاكتب الفرج من عِندك

والطف بعبادك المُؤمنين، اللهم اغفر لنا تقصيرنا وأعط أهل

غزة من خيري الدنيا والآخرة ما تقر به أعينهم

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	23	Increase	decrease
V2→V3	16	, leading to decrease in myocardial contractility, wall tension, and oxygen demand, thereby helping to alleviate angina symptoms.	we just delete it from the last paragraph in this slide

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!