

# CARDIOVASCULAR SYSTEM

SUBJECT : \_\_\_\_\_

LEC NO. : 5

DONE BY : Tabark Aldaboubi, Raneem Azzam

وَقُلْ رَبِّ زِدْنِي عِلْمًا



SCAN ME!

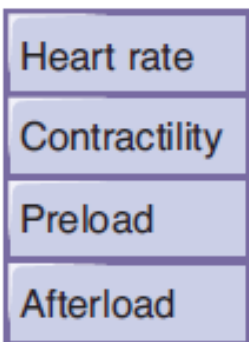
# CVS- Pharmacology 5

# Antianginal drugs 2

Faculty of Medicine  
The Hashemite University  
Arwa Al Anber (MD, PhD)  
Office: 1018

Agents decreasing O<sub>2</sub> demand

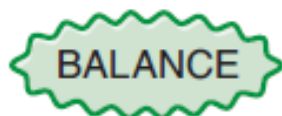
β Adrenergic antagonists  
Some Ca<sup>2+</sup> entry blockers



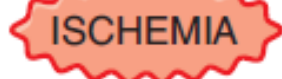
Organic nitrates  
Ca<sup>2+</sup> entry blockers



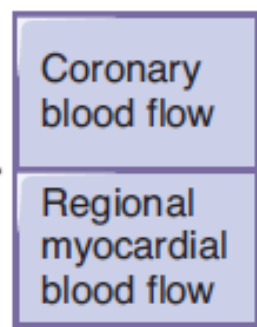
O<sub>2</sub> Demand



O<sub>2</sub> Supply



Agents increasing O<sub>2</sub> Supply



Vasodilators  
(esp. Ca<sup>2+</sup> entry blockers)

Also statins,  
anti-thrombotics



# Organic Nitrates

بدنا نعرف كيف اكتشفوا الدواء، كان في مصانع بتستخدم مادة الدينامايت وهاد بنتج مادة ال **nitroglycerin**، فلاحظو انو العمال في هاي المصانع الي يكون عندهم صداع خلال دوامهم يخف ووقت العطلة يرجع الوجع، ولاحظو انو المرضى الي عندهم **chest pain** خلال الاسبوع في فترة الدوام بخف و وقت العطلة يرجع (\*ملاحظة هذول الي عندهم **chest pains** وصداع يكونوا مرضى ضغط او **angina**، فكل الاعراض بتتحسن عندهم وقت الدوام عشان بتعرضوا لهالمادة)، بعد هاي الملاحظات عرفو عن تأثير ال **nitrate** وكيف الو دور على مرضى ال **angina**



# After 130 years, the molecular mechanism of action of nitroglycerin is revealed

Louis J. Ignarro\*

Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, CA 90095

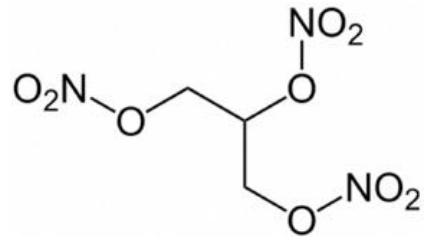
**N**itroglycerin, which was originally synthesized by Ascanio Sobrero, was used by Alfred Nobel to manufacture dynamite. It was in Nobel's dynamite factories in the late 1860s that the antianginal effect of nitroglycerin was discovered. Two interesting observations were made. First, factory workers on Monday mornings often complained of headaches that disappeared over the weekends. Second, factory workers suffering from angina pectoris or heart failure often experienced relief from chest pain during the work week, but which recurred on weekends. Both effects were attributed to the vasodilator action of nitroglycerin, which quickly became apparent to the physicians and physiologists in local communities.

to occur and that repeated administration of nitroglycerin caused sulfhydryl depletion (via oxidation) and consequent tolerance to further vasodilation (7–9). Subsequent studies addressing the activation of cytosolic guanylate cyclase by organic nitrate esters (nitroglycerin), organic nitrite esters (isoamyl nitrite), and nitroso compounds revealed that a chemical reaction occurred between the nitro compound and a thiol to generate an intermediate *S*-nitrosothiol, which then decomposed with the liberation of NO (3). Tolerance to nitroglycerin was explained simply by thiol utilization and depletion in the presence of excess nitroglycerin, thereby resulting in deficient production of *S*-nitrosothiol and NO. This working

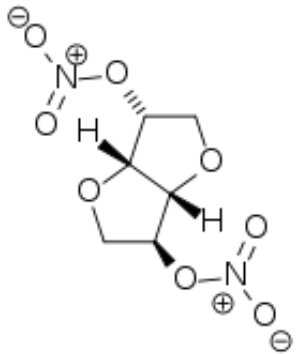
of mitochondrial aldehyde dehydrogenase, which specifically generates 1,2-glyceryl dinitrate from nitroglycerin, in the bioactivation of nitroglycerin to elicit vasorelaxation and in the development of tolerance to nitroglycerin.

Chen *et al.* (6) used several ingenious approaches to elucidate the enzymatic mechanism of bioactivation of nitroglycerin: a source of large numbers of cells so that the lack of starting material would not be a limiting factor. By using mouse macrophages grown in cell culture, physiologically relevant, relatively low concentrations of nitroglycerin (0.1  $\mu\text{M}$ ) were shown to generate 1,2-glyceryl dinitrate through the catalytic action of an enzyme that was virtually identical to mouse mi-

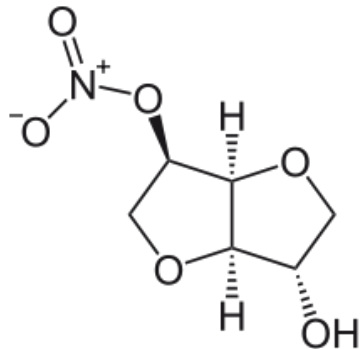
# Organic Nitrates



Nitroglycerin



Isosorbide dinitrate



Isosorbide mononitrate

-**Nitric oxide (NO)** is produced by vascular endothelial cells and other cells of the body. *تأثيرها على الجسم*

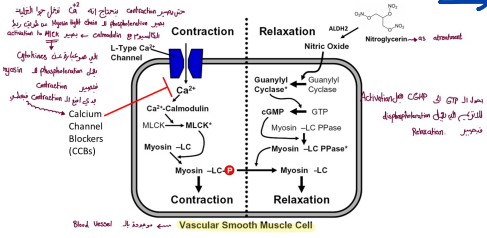
Endothelial-derived **NO** relaxes vascular smooth muscle cells (resulting in vasodilation).

هذول الثلاث نستخدمهم للعلاج ، ، بس بدنا نعرف انو في منهم بحاجة ل enzyme activation وهو ALDH2 ، وفي منهم لا بصيرو spontaneously

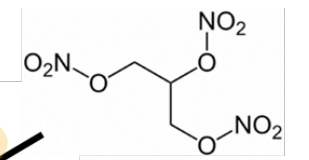
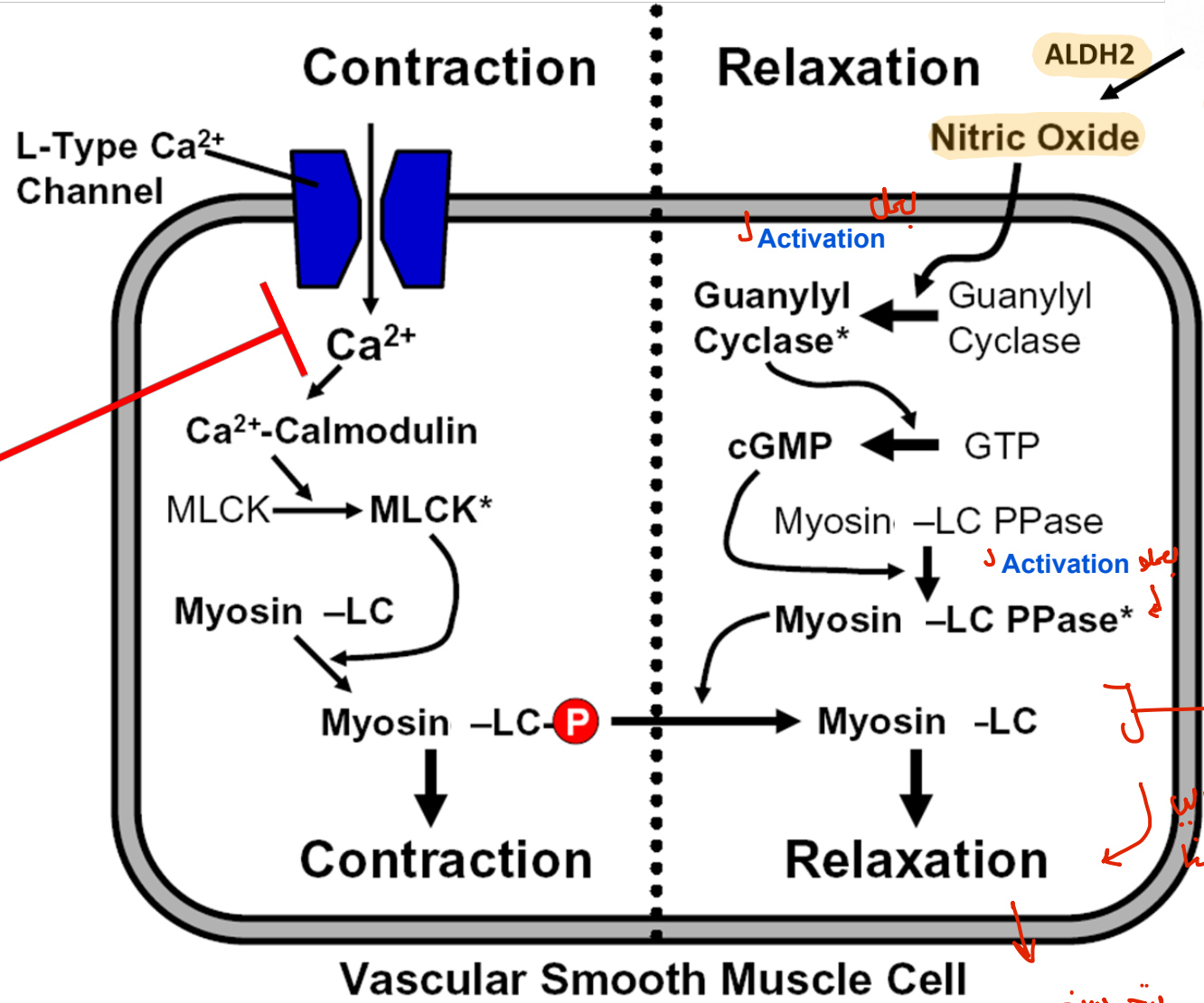
-Organic nitrates **mimic** the actions of **endogenous NO**. Some of these drugs (e.g. **sodium nitroprusside**) release NO **spontaneously**, whereas others liberate NO through an **enzymatic process** (e.g. **nitroglycerin, isosorbide dinitrate, isosorbide mononitrate**). The enzyme was recently identified as **aldehyde dehydrogenase type 2 (ALDH2)**.

حتى يحول ل'  
active NO

Drugs for Chronic Stable Angina



في المحاضرة  
الما قبل



Nitroglycerin

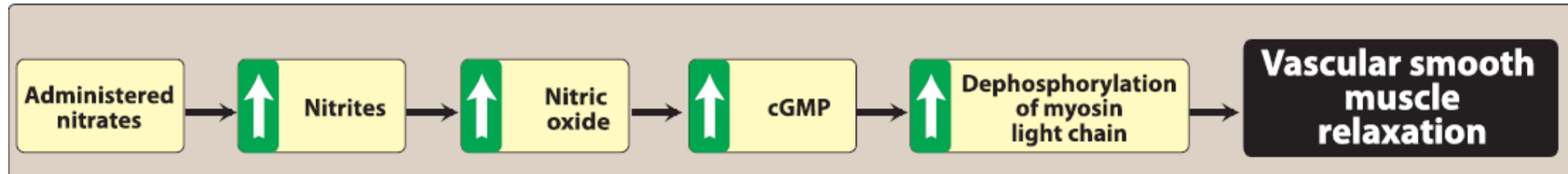
Calcium Channel Blockers (CCBs)

دخيلة بيشيل  
P  
بالتالي  
بصحننا

تحسن  
blood flow

ملخص

# Organic Nitrates



The released NO acts directly on vascular smooth muscle cells to cause muscle relaxation and vasodilation.



# Ventricular Wall Tension Is A Major Determinant of Oxygen Demand

كيف رح يشتغل على القلب والجسم بالزبط؟؟

بشكل رئيسي يشتغل على الvenous ومنه رح يقل ال preload لانو كمية الدم الي رح توصل للقلب رح تقل لانها رح تضل بالوريد

-Nitrates such as Nitroglycerin dilate venous capacitance vessels, reducing preload. With more blood on the venous side, afterload is also reduced.

\* كمية الدم عنا بالجسم ثابتة، يعني اذا فيه ٥ لتر، فاذا صار عندي vein dilation رح تزيد الكمية بالوريد وكمية اقل في الشرايين ف الضغط الي بالشرايين رح يقل، فهو mainly بقتل ال preload وشوي ال afterload

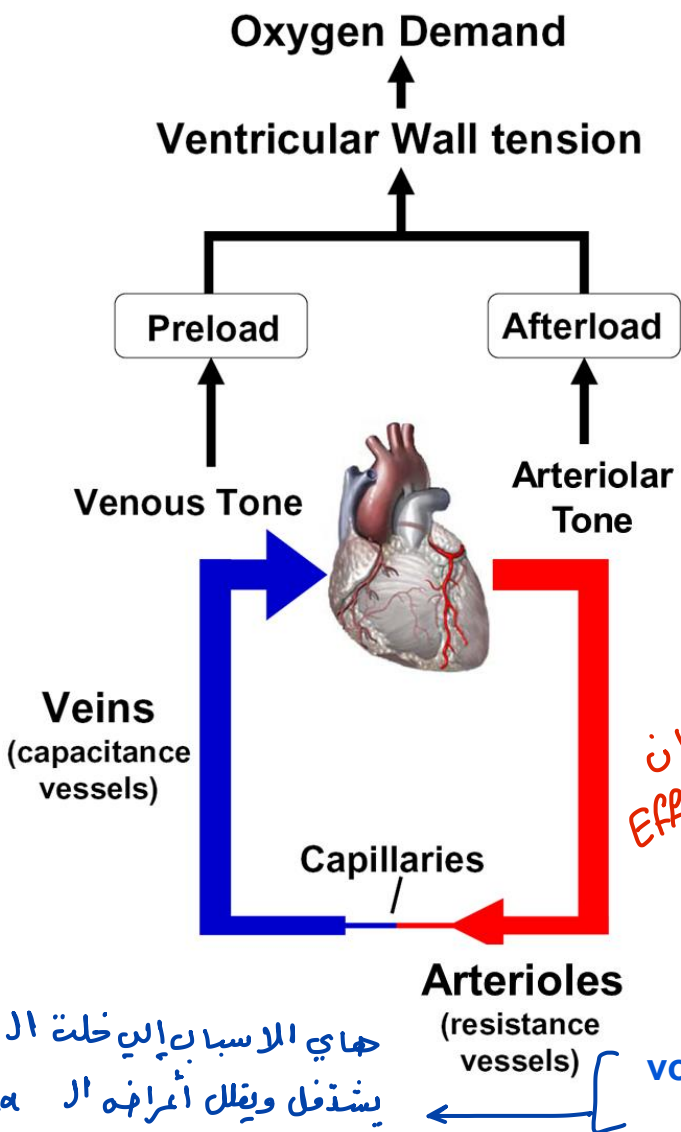
-Nitroglycerin also dilates arterioles, but to a lesser extent.

-The net effect is a reduction in ventricular wall tension and oxygen demand.

كان Effect +

Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart.

حاي النتجة المشالفة



حاي الاسباب الي خلت ال Nitrat يشدقل ويقلل اعرافه ال angina

\*ملخص: اول شي صار عنا vasodilator ف صار عنا more blood in venous system، فقلل عنا ال preload وبقتل ال volume of blood الي راجع للقلب، ولما قل ال preload صار عنا less wall tension فقلل ال o2 demand. النقطة الثانية لما صار عنا vein dilator، صار rest blood in arteries بالتالي قل ال afterload ومنه برضو قل ال o2 demand

## Nitroglycerin

-Explosive in pure liquid form. ↗

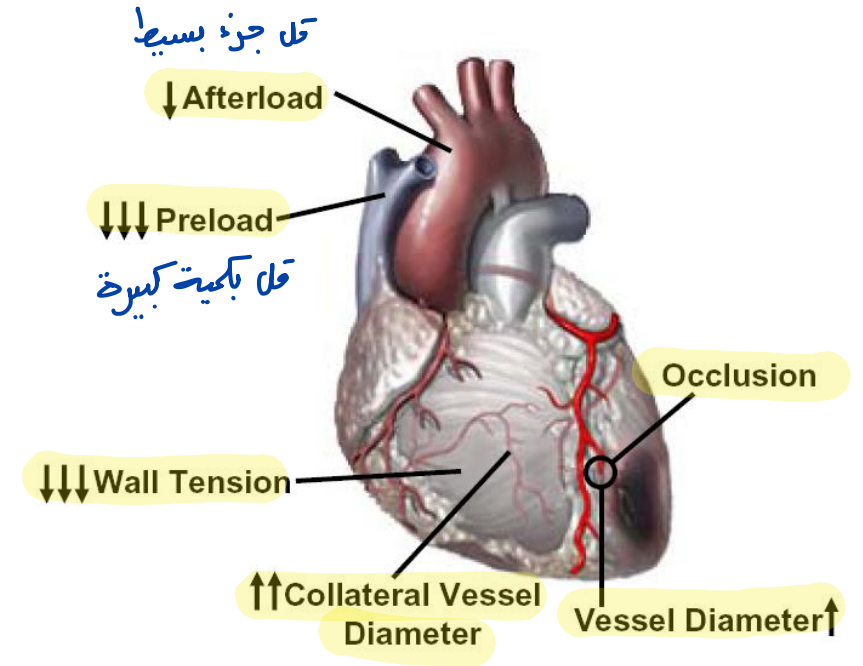
فشان هيك  
فابنوطن غير

-Administered **sublingually** as tablets or sprays. Also available as a transdermal patch. Nitroglycerin readily **crosses lipid bilayers**;

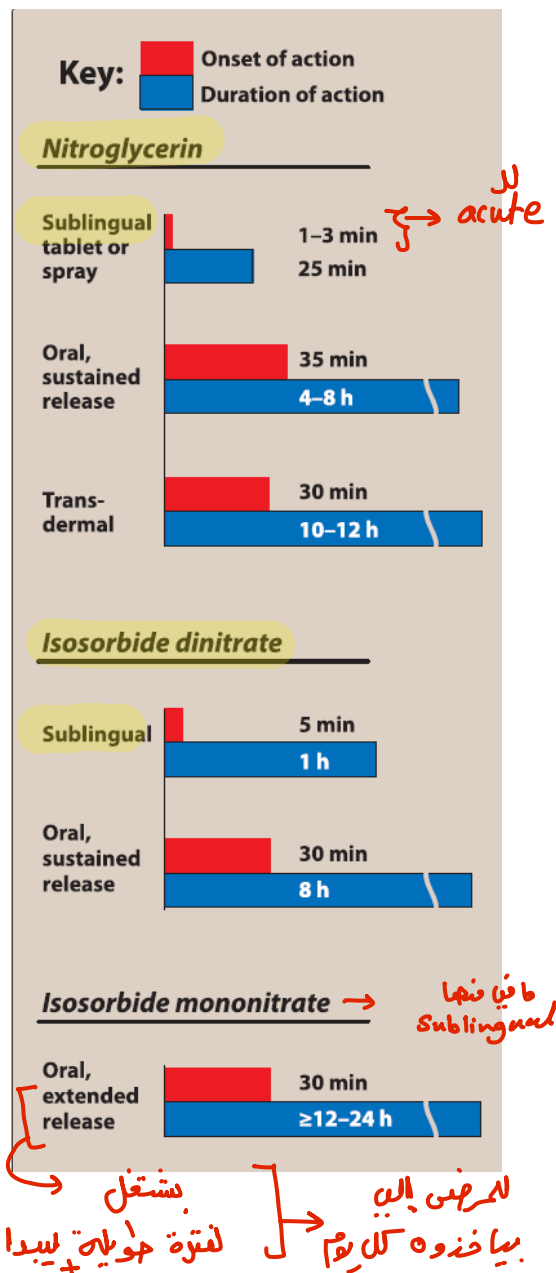
من الحضاية  
العنية فيه

-The sublingual route avoids the first-pass effect, so the therapeutic blood level can be achieved rapidly.

-Effective at relieving **stable, unstable and variant angina**.



# Organic Nitrates



- Nitroglycerin is available in tablet or spray formulation, It is the drug of choice **for prompt relief of an angina attack precipitated by exercise or emotional stress.**

- All patients should have **nitroglycerin on hand to treat acute angina attacks.**

- Significant first-pass metabolism of nitroglycerin occurs in the liver. Therefore, it is commonly administered via the sublingual or transdermal route (patch or ointment).

*لأنه في البداية نفضيه حينه*  
*لأنه يشتغل أسرع*

# Organic Nitrates

تعدن تادي ل

- Tolerance develops rapidly as the blood vessels become desensitized to vasodilation

حتى ما يصير عنا Tolerance

- Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug. The nitrate-free interval of 10 to 12 hours is usually taken at night when myocardial oxygen demand is decreased.

يعني يعطي نايتريت المريض ل ١٢ ساعة وبعدها وبعدها عشان المفعول يروح منعطيه free nitrates

- Nitroglycerin patches are worn for 12 hours and then removed for 12 hours to provide the nitrate-free interval.

بعدها بشيلها  
12 ساعة

# Side Effects of Nitroglycerin

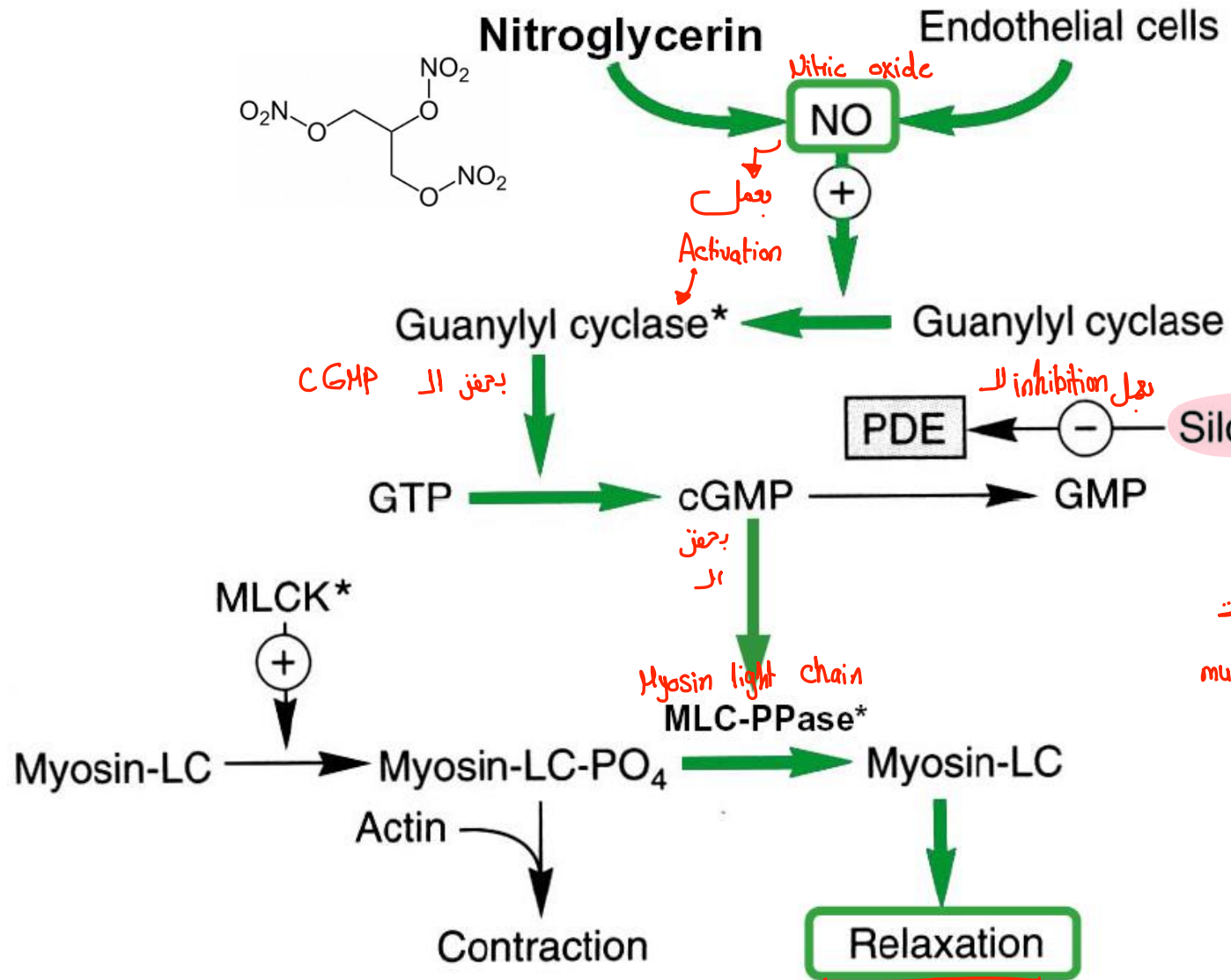
Adverse effects are related to the therapeutic effects of the drug:

- Postural hypotension اسوء سايد ايفكت تخلي المرضى يوقفو الدوا مرات
- Reflex tachycardia بتعمل HT بتدخل الجسم بحالة شوك بدو يتصدالها ويرفعه ف يصير عنا كونتراكت
- Headache (most prominent side effect)

**Drug interactions:** Phosphodiesterase type 5 inhibitors such as *sildenafil* (Viagra) potentiate the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.

✦ ما يصير نفعناهم مع بعض ✦

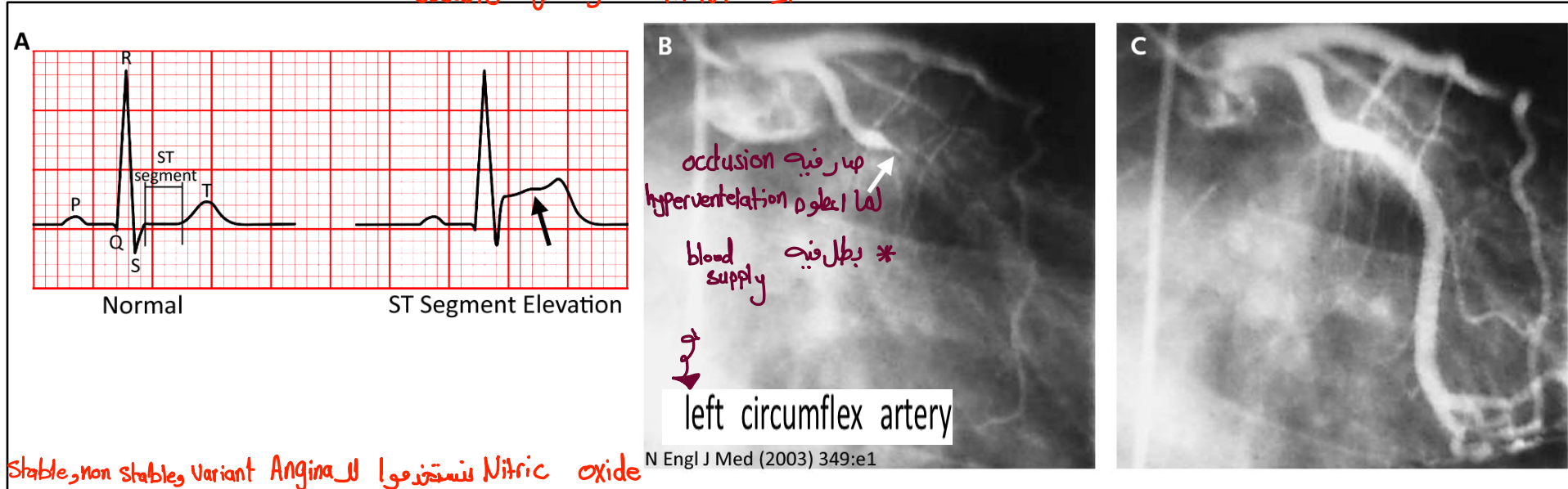
# Coadministration of Nitroglycerin and Sildenafil Is Contraindicated



PDE مخفیقتا = یحول cGMP → GMP  
 بس یمیر لووا inhibition وکانت NO وعتیت  
 much activation to MLC-P بسیر more cGMP  
 بسیر more Relaxation

# Coronary Artery Spasm (Variant Angina)

بتميز عند اي مريض عنده (Coronary Spasm) ممكن يكون Familiar عند ال Japanese مافى ال Family history ، في شظايت بتخلبي ال attack اكثر مثل cocaine



- A 39-year-old man with a history of smoking, alcohol abuse, and cocaine use (but no other medical problems) presented to the emergency department with frequent episodes of chest pain, shortness of breath, and sweating while at rest.
- During an episode of angina, transient **ST-segment elevation** was observed (Panel A).
- Subsequent cardiac catheterization revealed hyperventilation-induced total occlusion of the proximal left circumflex artery (visible on angiography, Panel B) that resolved with the administration of intracoronary nitroglycerine and diltiazem (Panel C).
- The diagnosis of variant angina (coronary artery spasm) was made.
- The patient's symptoms have been controlled with oral nitrates and calcium-channel blockers during a follow-up of two years. Modified from: N Engl J Med (2003) 349:e1 (DOI: 10.1056/ENEJMicm020631)

دليل على ال Ischemia

الاسباب ال Coronary Artery Spasm

To diagnose these patient



↳ (NO)

↳ Calcium channel blocker

علاج

اخر ال Side effect تااعها انما بتعمل reflex Tachycardia لهيك  
 ما بنعطر لهاله .

# Effects of nitrates alone and with Beta blockers or calcium channel blockers in angina pectoris

more symptome اذا انعطت لهاله  
 بتعمل

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers alone	Combined Nitrates with Beta Blockers or Calcium Channel Blockers Combination
Heart rate	Reflex <sup>1</sup> increase	Decrease	<u>Decrease</u>
Arterial pressure	<u>Decrease</u>	Decrease	Decrease Nitret -
End-diastolic volume	Decrease	Increase	None or decrease butter effect
Contractility	Reflex <sup>1</sup> increase	Decrease	None contractility ال باأش على ال
Ejection time	Decrease <sup>1</sup> ↑↑ HR ال كونه	Increase	None

كونه هذول بزبوا  
 باستخرام هالهوا  
 فما بوطيه المرصن  
 ال Angina لهيك  
 بوطيه مع دوا ثاني

لقلب المرصن بكونوا اصل ال hypertension لهيك فينج بين لطيدهم سوا كونه بقلل  
 بين اذا ما كان hypertension فاكسنة بيشتر على ال Calcium blocker or β-blocker



# Sodium Channel blocker: Ranolazine



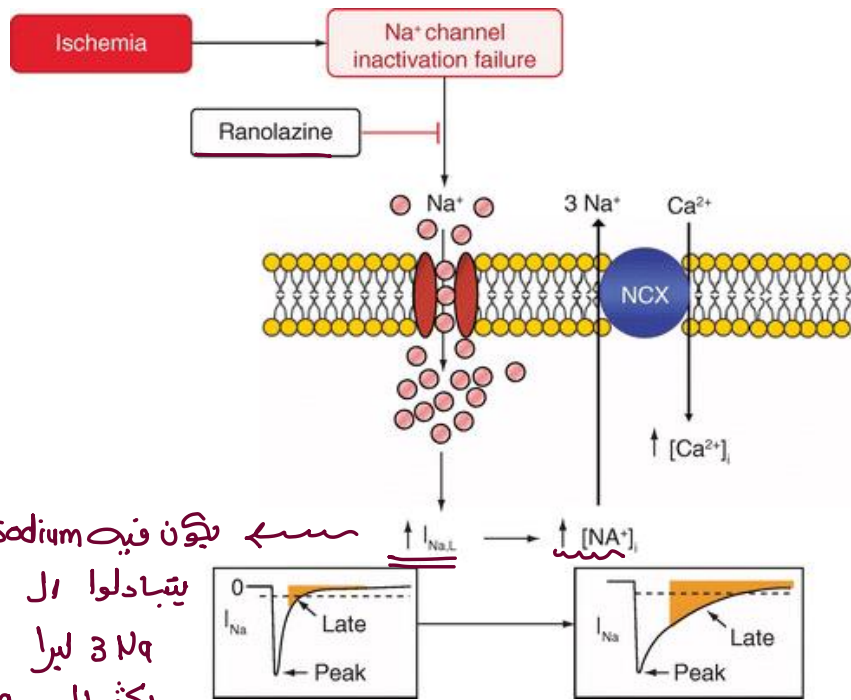
## من وصايا النبي ﷺ

أنه قال: "أحرص على ما ينفعك، واستعن بالله ولا تعجز، وإن أصابك شيء فلا تقل: لو أني فعلت كان كذا وكذا، ولكن قل: قدر الله وما شاء فعل، فإن لو تفتح عمل الشيطان." رواه مسلم.

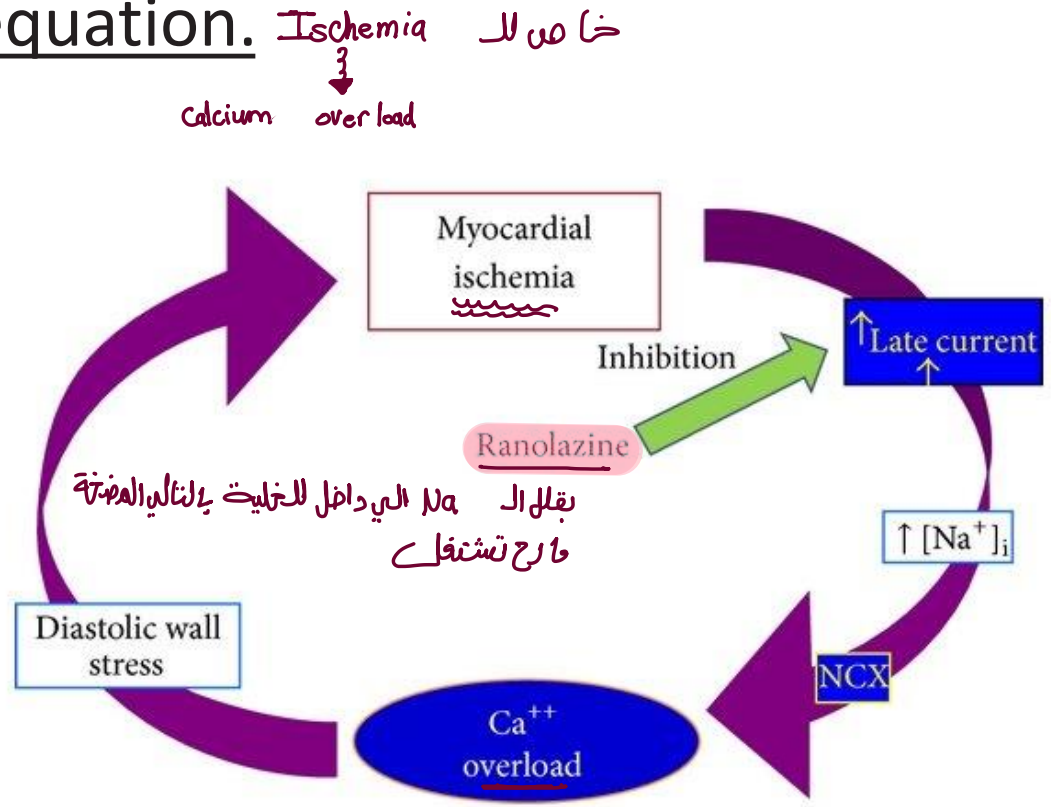
بالعادة بتلزم هالدوا للاخر (اذا العريض اعطيتوا كل الادوية الي قبل وفيل Symptom بعضيه اياه)

# Sodium Channel blocker: Ranolazine

- Ranolazine inhibits the late phase of the sodium current improving the oxygen supply and demand equation. خاصه لـ Ischemia



يكون فيه more sodium بصير  
يتبادلوا ال Ca و Na  
3 Na ليبر و صدة Ca لجوا  
بكثر ال Ca  
فبصير Ca overload



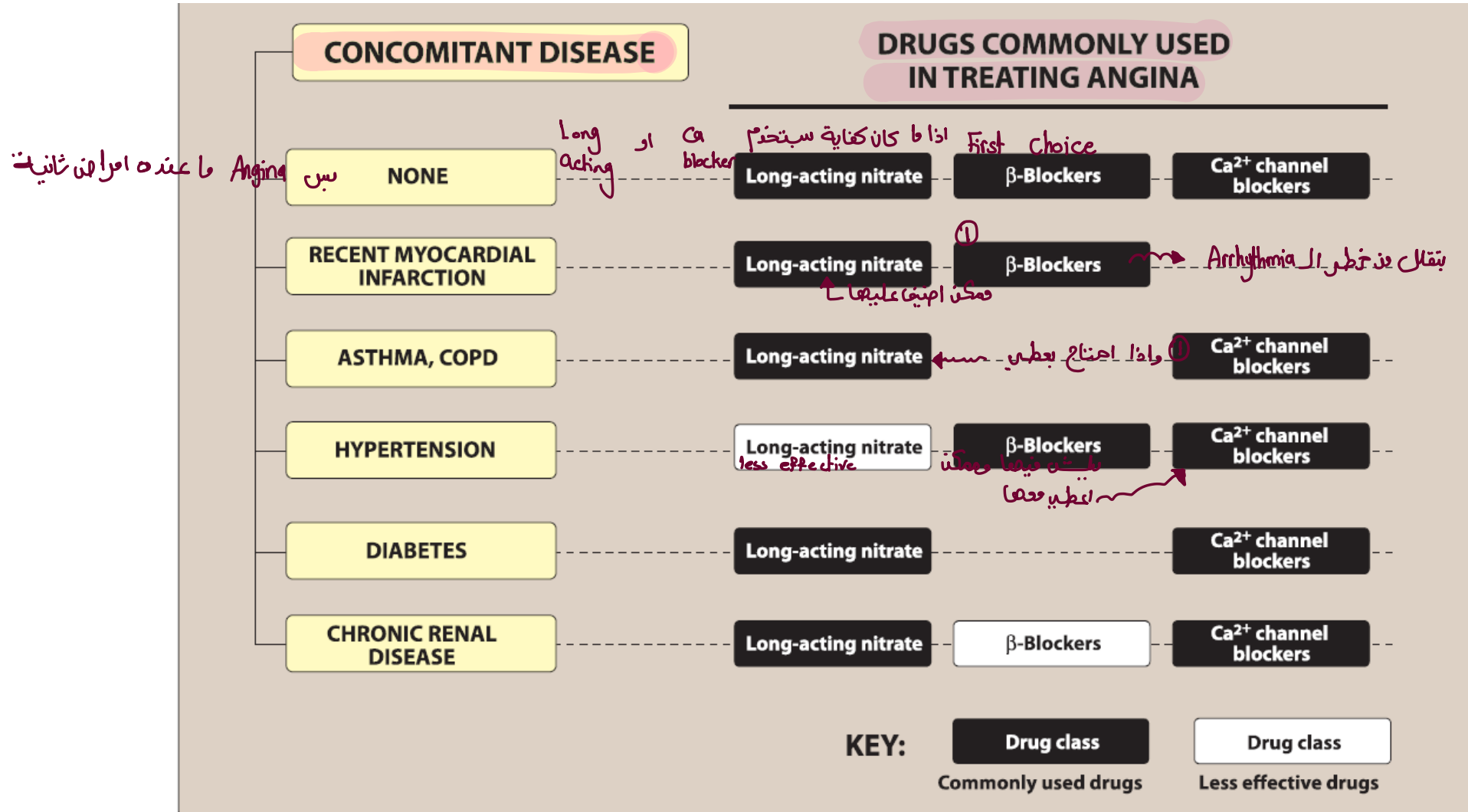
بقلال Na الي داخل للخلية بالتالي العضلة  
مارح تشتغل

# Sodium Channel blocker: Ranolazine

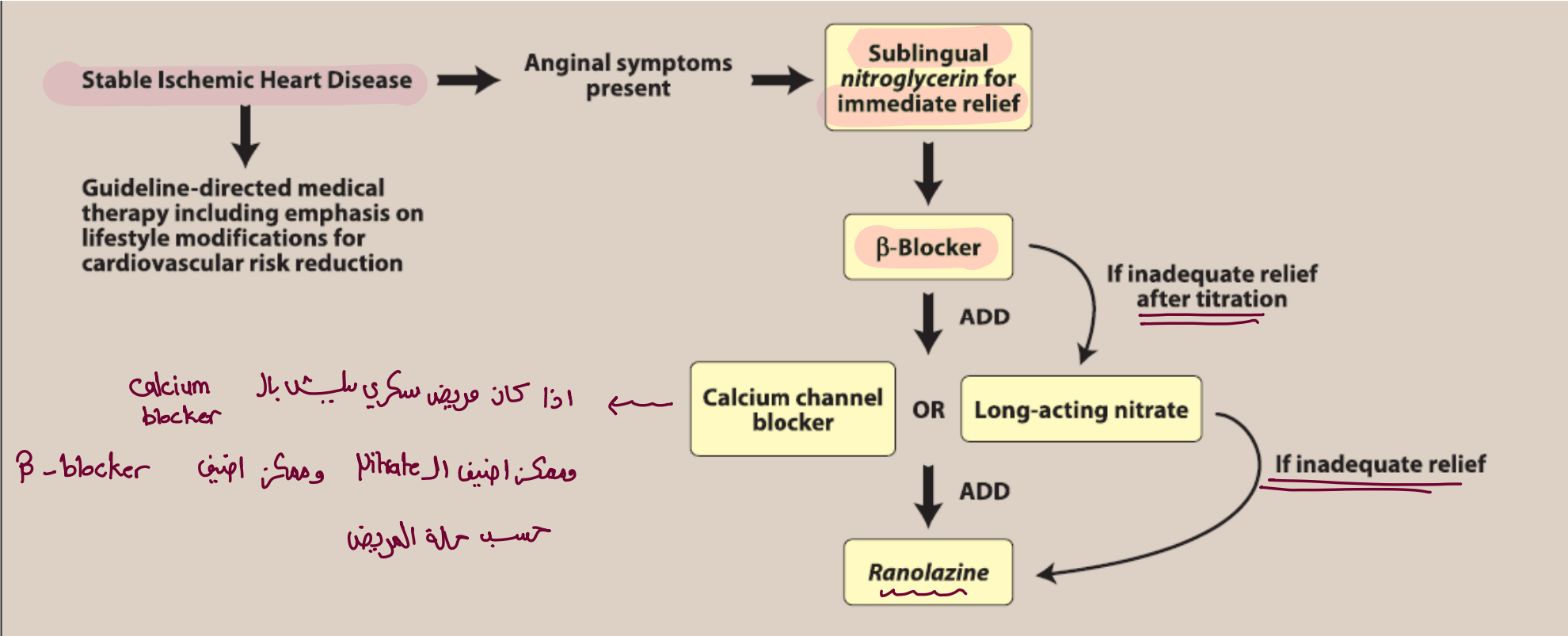
- Inhibition of late Na current **reduces intracellular sodium and calcium overload, thereby improving diastolic function.**
- Ranolazine is most often used in patients who have failed other antianginal therapies.
- The antianginal effects of ranolazine are **considerably less in women than in men.**
- Ranolazine can <sup>Pro Arrhythmia</sup> **prolong the QT interval** and should be avoided with other drugs that cause QT prolongation

Arrhythmia مبروحه Prolong QT مريض عنده  
magnesium sulfate شوالعلاج!!

# Treatment of angina in patients with concomitant diseases



# Treatment algorithm for improving symptoms in patients with stable angina.



# Study Questions



الاجوبة براس السلايد من تحت عشان يضل الجواب مخبي ،، ما تنزلو كثير وتشوفوا السلايد

Which medication should be prescribed to all angina patients to treat an acute attack?

- A. Isosorbide dinitrate
- B. Nitroglycerin patch
- C. Nitroglycerin sublingual tablet or spray
- D. Ranolazine

Which of the following correctly ranks the calcium channel blockers from most active on the myocardium to most peripherally active?

- A. Diltiazem, amlodipine, verapamil
- B. Verapamil, diltiazem, nifedipine
- C. Nifedipine, verapamil, diltiazem
- D. Amlodipine, diltiazem, verapamil



A 76-year-old man with uncontrolled hypertension is experiencing typical angina pain that is relieved with rest and sublingual nitroglycerin. He has a high blood pressure (178/92 mm Hg) and a low heart rate (54 bpm). Which is the most appropriate therapy for his angina at this time?

- A. Ranolazine
- B. Verapamil
- C. Metoprolol
- D. Amlodipine

A 65-year-old male experiences uncontrolled angina attacks that limit his ability to do household chores. He is adherent to a maximized dose of beta-blocker with a low heart rate and low blood pressure. He is unable to tolerate an increase in isosorbide mononitrate due to headache. Which is the most appropriate addition to his antianginal therapy?

- A. Nifedipine
- B. Aspirin
- C. Ranolazine
- D. Verapamil

A 64-year-old man was prescribed atenolol and sublingual nitroglycerin after his recent hospitalization for unstable angina. Which of his current medications should be discontinued?

- A. Sildenafil
- B. Amlodipine
- C. Metformin
- D. Lisinopril

A