



Artery Academy

Done by Hawazen

اللهم اني اسالك فهم العلماء وبصيرة الانبياء
فرايات ينقذهم من الموت



(Antianginal Drugs)

Pharmacology I
Dr. Heba Khader

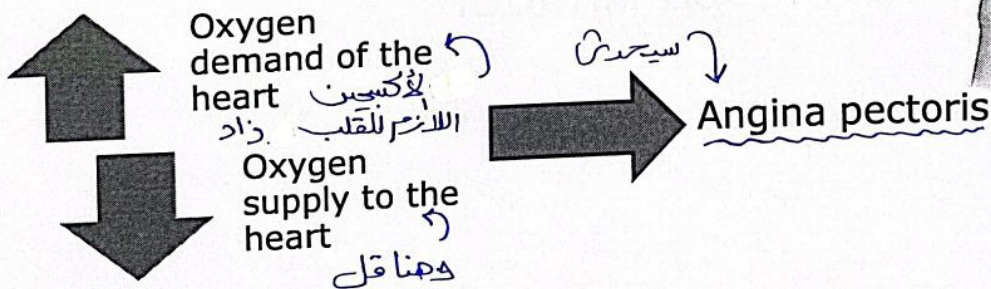
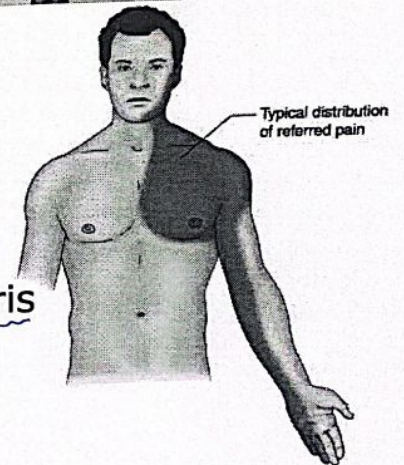
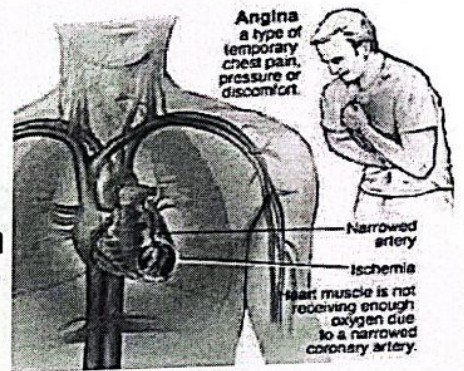
Introduction

← هوعباره عن ألم شديد ومفاجئ على الصدر
يبدأ من الرقبة، والذراع، والظهر، وانتفاخ
بالذراعين (كما موضح بالصورة)

Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms.

- The primary cause of angina pectoris is an imbalance between the oxygen requirement of the heart and the oxygen supplied to it via the coronary vessels.

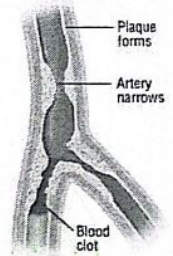
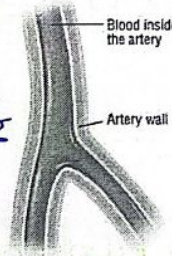
← السبب الرئيسي والأول حدوث هذا الألم حين حاله اختلال لتوازن
في الأكسجين لدى القلب والأوعية (Coronary vessels)



Types of angina

Healthy coronary artery

Atherosclerotic coronary artery



- The most common cause of angina is

وأسباب تراكم
الدهون في جدران
الوعاء
تضيق
بالمهارة

(atheromatous obstruction) of the large coronary vessels (coronary artery disease, CAD).

→ blood flow ينقل عني

- The imbalance between oxygen delivery and utilization may result:

سيؤدي هذا الخلل إلى

1) During exertion → **Effort or Stable (or classic) angina**

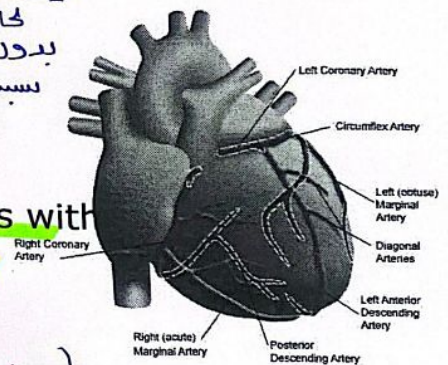
2) From a spasm of the vascular smooth muscle → **vasospastic or variant angina**, (also called **Prinzmetal angina**).
يكون متضيقة
حالة
بدون أي
سبب

3) when episodes of angina occur at rest and when there is an increase in the severity, frequency, and duration of chest pain in patients with previously stable angina → **Unstable angina or acute coronary syndrome.**

المريض كان
Stable angina

(يعني بلك ما يصير عنده Stable angina ما عنده unstable angina)
هناك الخلل كما تظهر فترات ما عنده Damage

Coronary Arteries of the Heart



* Variant → **Coronary vessels** وأغلى توسع
 (Vasodilation) عن طريقه -
 ① Vasodilator
 ② Calcium channel

• The imbalance between oxygen delivery and myocardial oxygen demand can be corrected by:

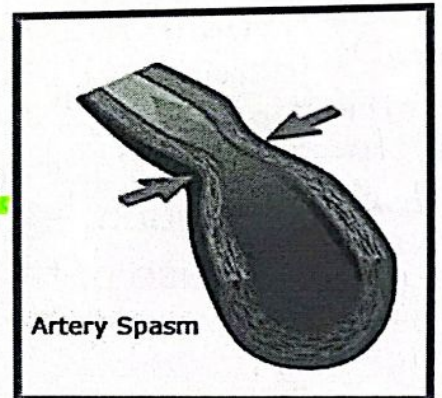
- ✓ - **Decreasing oxygen demand.** ← نقدر نصلح من خلال (نعكسه -)
- ✓ - **Increasing oxygen delivery.**

* ولا بدنا نغل Correction لازم نطلع على نوع Ischemic angina -

* In **effort angina**, oxygen demand can be reduced by decreasing cardiac work.

* In **variant angina**, on the other hand, spasm of coronary vessels can be reversed by nitrate or calcium channel-blocking vasodilators.

* In **unstable angina**, vigorous measures are taken to achieve both—**increase oxygen delivery and decrease oxygen demand.**



في Unstable عن طريق زيادة الأكسجين
 الخارج ويقلل الأكسجين المطلوب (الداخل)

Antianginal Drugs

أي Treatment لنزوفون وظيفته الأساسية هي

- Treatment is based on reduction of myocardial oxygen demand and increase of coronary blood flow to the potentially ischemic myocardium to restore the balance between myocardial oxygen supply and demand.

منع حدوث
Ischemic
عشاه ما يمنع

عندي Antianginal drugs include:

التوازن
منهم

1. Organic nitrates
2. Beta blockers
3. Calcium channel blockers
4. Na^+ channel blockers

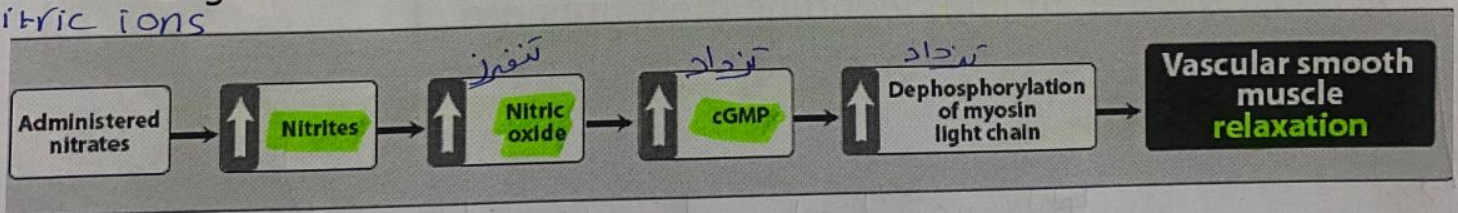
Organic Nitrates

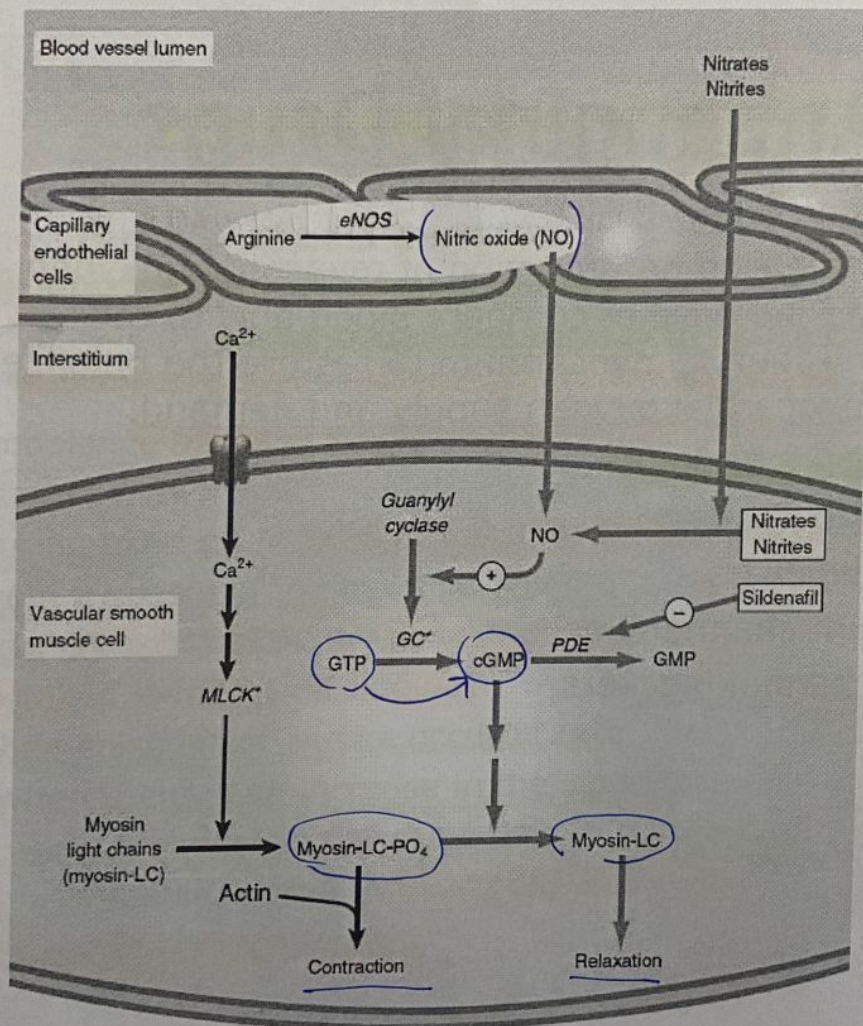
Mechanism of action:

- ① **Nitrates** ^{توقف عندي التشنج} **inhibit coronary vasoconstriction or spasm, increasing perfusion of the myocardium and, thus, relieving angina.** ② ^{تخفف}

- ③ **Organic nitrates** ^{تزداد عندي} are thought to relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which, in turn, activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP). Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation.

Because of this action, nitrates are effective in treating effort angina.

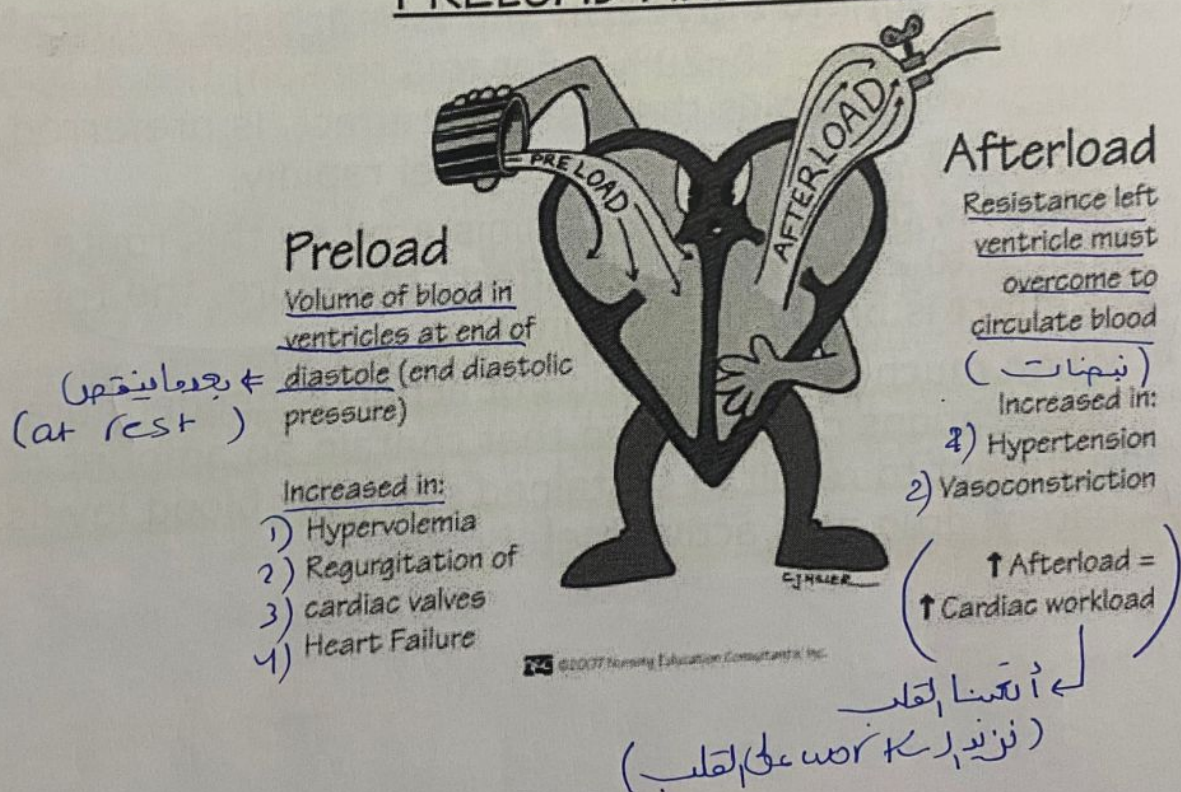




Organic Nitrates

- In addition, nitrates relax the veins (venodilation), by decreasing preload and myocardial oxygen consumption.

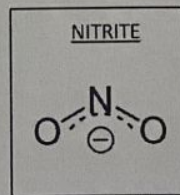
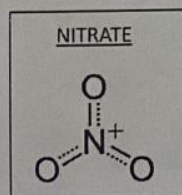
PRELOAD AND AFTERLOAD



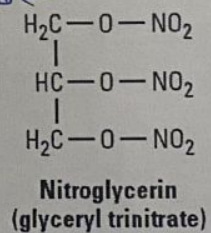
Organic Nitrates

- **Nitroglycerin** may be considered the prototype of the group.
- Other drugs in this group:
 - Isosorbide mononitrate ①
 - Isosorbide dinitrate ②
 - Amyl nitrite (obsolete for angina) ③
- The conventional sublingual tablet form of nitroglycerin may lose potency when stored as a result of volatilization and adsorption to plastic surfaces. Therefore, it should be kept in tightly closed glass containers. Nitroglycerin is not sensitive to light.

القرص تحت اللسان
له لطفه ولا يستعمل تحت اللسان بطريقة
خاطئة من ذلك، لتطهيره بالاحتكاك
على الأسطح البلاستيكية
لذلك يجب حفظها في عبوات زجاجية
مختصة بها.



له حساس للهوى



Organic Nitrates

دقائق شفوية Sublingual Nitrate
(Pharmacokinetics)

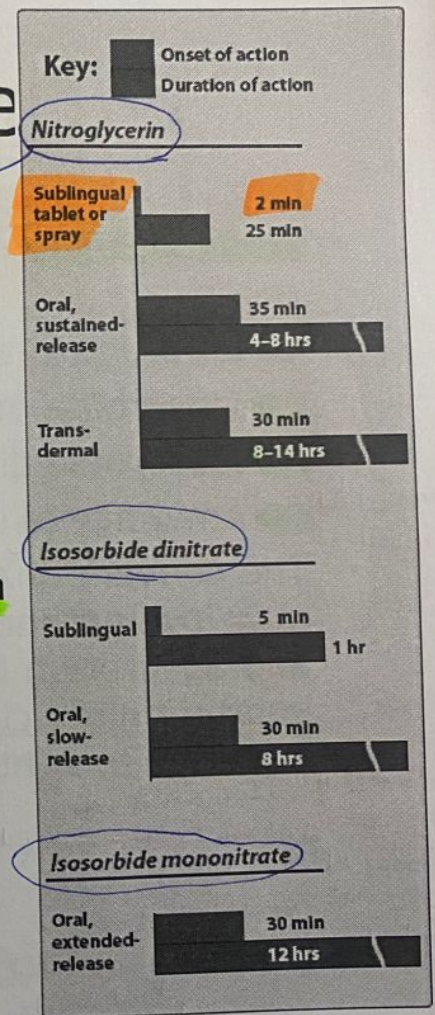
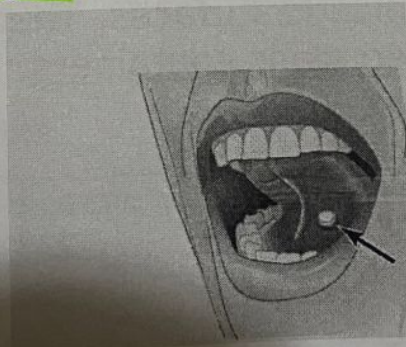
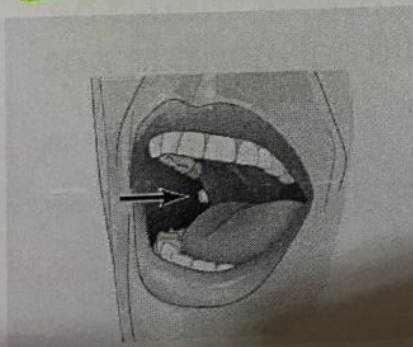
- Significant (first-pass metabolism) occurs in the liver. Therefore, oral bioavailability of the traditional organic nitrates (eg, **nitroglycerin** and **isosorbide dinitrate**) is low (typically < 10–20%). For this reason, the sublingual route, which avoids the first-pass effect, is preferred for achieving a therapeutic blood level rapidly.
- However, the total dose administered by this route must be limited to avoid excessive effect; therefore, the total duration of effect is brief (15–30 minutes).
- When much (longer duration of action is needed), oral preparations can be given that contain an amount of drug sufficient to result in sustained systemic blood levels of the parent drug plus active metabolites.

دقائق شفوية
Limited
عند ما يصير
Excessive
effect

Organic Nitrate

*recomounded in
Attack*

- Other routes of administration available for **nitroglycerin** include **transdermal** and **buccal** absorption from slow-release preparations.
- The 5-mononitrate metabolite of **isosorbide dinitrate** is an active metabolite of the latter drug and is available for **oral** use as **isosorbide mononitrate**. It has a bioavailability of 100%.



Organic Nitrates

- Adverse effects:** (لدرجة عريض ما يقدر) (صداع) (يتصلب) (light)
- The most common one is (headache) (نسبة كبيرة) (30-60% of patients).

- High doses of organic nitrates can also cause postural hypotension, facial flushing, and reflex tachycardia (all are direct extension of therapeutic vasodilation). ⇒ (أذمة زيادة منه) (يؤدي إلى انخفاض ضغط الدم، tachycardia ... facial flushing)

- Tolerance:** (Tachycardia ... facial flushing)
- (Tolerance) to the actions of nitrates develops rapidly (within a few hours of using (long-acting preparations) (oral, transdermal) or continuous intravenous infusions). The blood vessels become desensitized to vasodilation.

- (A nitrate-free period of at least 8 hours between doses) should be observed to reduce or prevent tolerance.

(Tolerance) معناها يعمل على خفض ضغط الدم (يعني ببطيء) (يعني ببطيء) (dose بس ما تخطي) (Effect) (أيضا)

(Monday disease??)

السمة آخر

تيف كل هاي المشكلة ؟

يعني ببطيء
البواقي على 8
المسح على نضج
وبعد على

4
Free

بدون Nitrate

TABLE 12-3 Nitrate and nitrite drugs used in the treatment of angina.

Drug	Dose	Duration of Action
Short-acting		
Nitroglycerin, sublingual	0.15–1.2 mg	10–30 minutes
Isosorbide dinitrate, sublingual	2.5–5 mg	10–60 minutes
Amyl nitrite, inhalant	0.18–0.3 mL	3–5 minutes
Long-acting		
Nitroglycerin, oral sustained-action	6.5–13 mg per 6–8 hours	6–8 hours
Nitroglycerin, 2% ointment, transdermal	1–1.5 inches per 4 hours	3–6 hours
Nitroglycerin, slow-release, buccal	1–2 mg per 4 hours	3–6 hours
Nitroglycerin, slow-release patch, transdermal	10–25 mg per 24 hours (one patch per day)	8–10 hours
Isosorbide dinitrate, sublingual	2.5–10 mg per 2 hours	1.5–2 hours
Isosorbide dinitrate, oral	10–60 mg per 4–6 hours	4–6 hours
Isosorbide dinitrate, chewable oral	5–10 mg per 2–4 hours	2–3 hours
Isosorbide mononitrate, oral	20 mg per 12 hours	6–10 hours

Beta Blockers



لا يعتبر موسع للأوعية

← ليسهم
Mixed

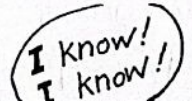
- Although they are **not vasodilators** (with the exception of carvedilol, labetalol and nebivolol), β -blocking drugs are extremely useful in the management of **effort** angina. They suppress the activation of the heart by blocking β_1 receptors, and they reduce the work of the heart by decreasing heart rate, contractility, cardiac output, and blood pressure.

Function of β blockers

- The β -blockers reduce the frequency and severity of angina attacks. β -blockers من Selective
- Cardioselective β -blockers, such as metoprolol and atenolol, are preferred over the nonselective ones.
- Agents with intrinsic sympathomimetic activity (for example, pindolol) are less effective and should be avoided in angina. $\leftarrow$ من Agent يملك risk هي Sympathomimetic activity

(pindolol) Sympathomimetic activity (B-blockers) Effect

Sympathomimetic activity - block وهي يملك activation لا receptor ويملك receptor للكوكتاسيز وعينوا ارتباطه بال receptor



Beta Blockers



- They should be used with caution in patients with asthma, diabetes, and chronic obstructive pulmonary disease.
- It is important not to discontinue β -blocker therapy abruptly. The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, myocardial infarction, and hypertension.
- **Variant** angina caused by spontaneous coronary spasm, either at work or at rest, rather than by increased myocardial oxygen requirement, is controlled by organic nitrates or calcium-channel blockers. β -Blockers are not recommended.

لم في حالة Variant ما يستعملوا بـ β -blocker

شروع لا organic nitrate أو calcium channel blocker

أو كاشين سوا

من الأدوية
يلى ما يقطعها
مرة واحدة
إغا بالتدريج
على طريقه
تقضي
الجهاز
لتجنب
أي أمراض أخرى

Calcium Channel Blockers

Mechanisms of Clinical Effects

- main function
↓ for Calcium Channel blockers
- Calcium channel blockers decrease myocardial contractile force, which reduces myocardial oxygen requirements. ↓
 - Calcium channel block in arterial smooth muscle decreases arterial pressure.
 - Calcium channel-blocking agents also relieve and prevent coronary artery spasm in **variant** angina. Use of these agents has thus emerged as the most effective prophylactic treatment for this form of angina pectoris.

Calcium Channel Blockers

(Pharmacokinetics)

- The calcium channel blockers are orally active agents and are characterized by high first-pass effect, high plasma protein binding, and extensive metabolism. Verapamil and diltiazem are also used by the intravenous route.
- CCBs are metabolized by CYP3A4. Because grapefruit inhibits CYP3A4, it may lead to higher blood levels of CCBs and the potential to increase the drugs' therapeutic and/or toxic effects. *يُصير لهما CYP3A4 بواسطة metabolized*

بعض الاسماء مبداءه بـعـ و انتشار
في الاسواق

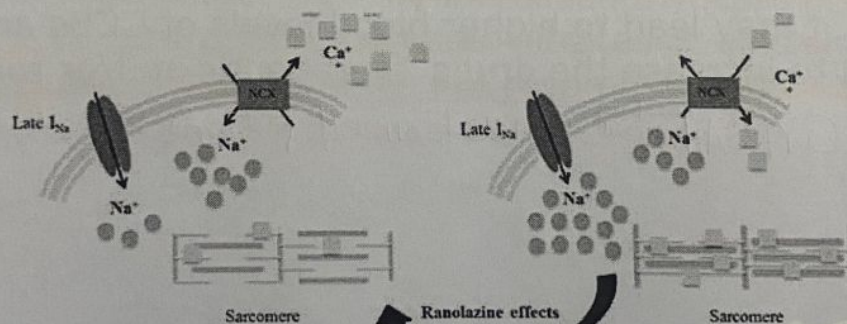
TABLE 12-5 Clinical pharmacology of some calcium channel-blocking drugs.

Drug	Oral Bioavailability (%)	Half-life (hours)	Indication	Dosage
Dihydropyridines				
Amlodipine	65-90	30-50	Angina, hypertension	5-10 mg orally once daily
Felodipine	15-20	11-16	Hypertension, Raynaud's phenomenon	5-10 mg orally once daily
Isradipine	15-25	8	Hypertension	2.5-10 mg orally twice daily
Nicardipine	35	2-4	Angina, hypertension	20-40 mg orally every 8 hours
Nifedipine	45-70	4	Angina, hypertension, Raynaud's phenomenon	3-10 mcg/kg IV; 20-40 mg orally every 8 hours
Nisoldipine	< 10	6-12	Hypertension	20-40 mg orally once daily
Nitrendipine	10-30	5-12	Investigational	20 mg orally once or twice daily
Miscellaneous				
Diltiazem	40-65	3-4	Angina, hypertension, Raynaud's phenomenon	75-150 mcg/kg IV; 30-80 mg orally every 6 hours
Verapamil	20-35	6	Angina, hypertension, arrhythmias, migraine	75-150 mcg/kg IV; 80-160 mg orally every 8 hours

(Sodium Channel Blocker)

مفاتيح

Ranolazine is a new antianginal drug that acts by reducing sodium current that facilitates calcium entry via the sodium-calcium exchanger. The resulting reduction in intracellular calcium concentration reduces cardiac contractility and work.



* لانولازين يمنع الكالسيوم من دخول الخلية
 بالتالي يقلل من قوة انقباض القلب
 وبالتالي يقلل من العمل
 contraction

Sodium Channel Blocker

- **Ranolazine** is indicated for the treatment of chronic angina and may be used alone or in combination with other traditional therapies, but is most often used as an option in angina patients who have failed all other antianginal therapies.
- It is not to be used to treat an acute attack of angina.

ما لنستخدمه لـ acute attack لأنه ما زال response سريع
of angina

Calcium Channel (IV) فقط.

* بالاولادى يستخدموا organic أو Nitret

يعطوا مفعول سريع.