تفريغ فارما ١

اسم الموضوع: antianginal drugs

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لجان الدُّفعات

Antianginal Drugs

الذبحة الصدرية

"**Angina pectoris** is a characteristic sudden, severe, pressing chest pain radiating to the neck, (lower) jaw, back, and arms" (Left shoulder)

أعراضه كثير تتشابه مع MI أو acute coronary syndrome

not localized → لأنه لو كان localized كانت اعتبرته muscular

Coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to hypoxia

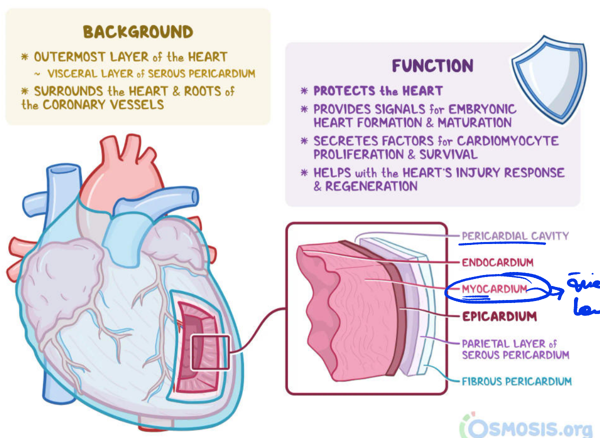
Treatment strategy is based on decreasing the heart demand and improving blood supply to the heart

* سبب الـ angina صار فيه imbalance في الميزان بين :

O_2 supply (المزوّد) —— O_2 demand (المطلوب)

- الطبيعي إنه الـ supply يغطي الـ demand (need)
وإذا زاد الـ demand لازم يزيد الـ supply

* في حالة الـ angina :
supply قليل بالتالي ما يغطي الـ demand normal
or
زاد الـ demand فصار الـ supply normal غير كافي .



العضلة نفسها → مين تغذيها ؟ coronary arteries (الشرايين التاجية)

* preload → كمية الدم الداخلة على القلب
* after load → كمية الدم الخارجة من القلب

← كما زاد الجهد على العضلة وظيفة هاي الشرايين إنها تغذي القلب أكثر .
∴ بالتالي إذا كان في أي تضيق في هاي الشرايين، ما رح يكون في
نقص O_2 supply ← كفاية هاي الخلايا ما وصلها O_2
→ hypoxia or ischemia
(نقص أكسجين) (نقص تروية)

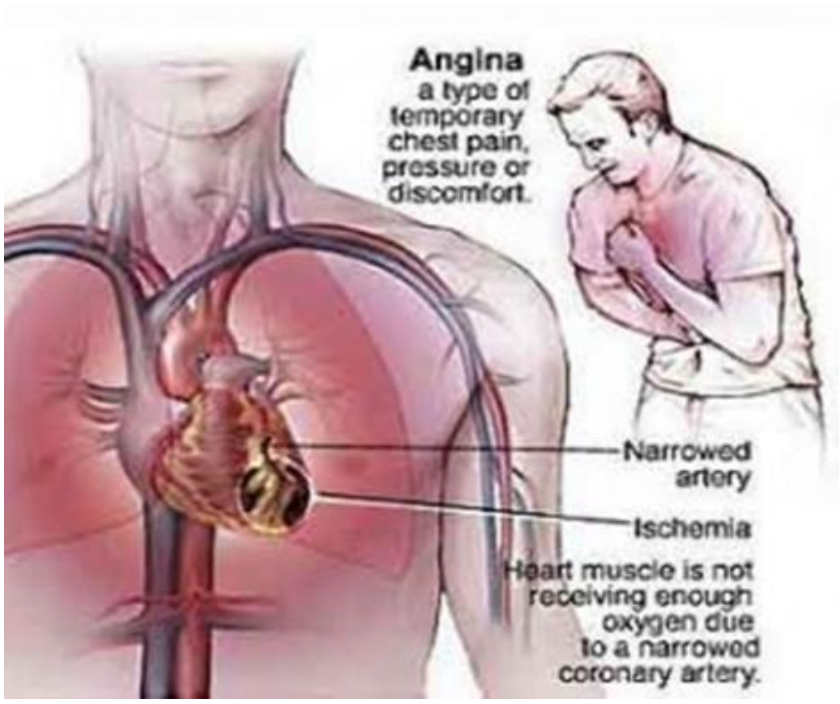
* السبب الرئيسي هو مشكلة في الـ coronary vessels

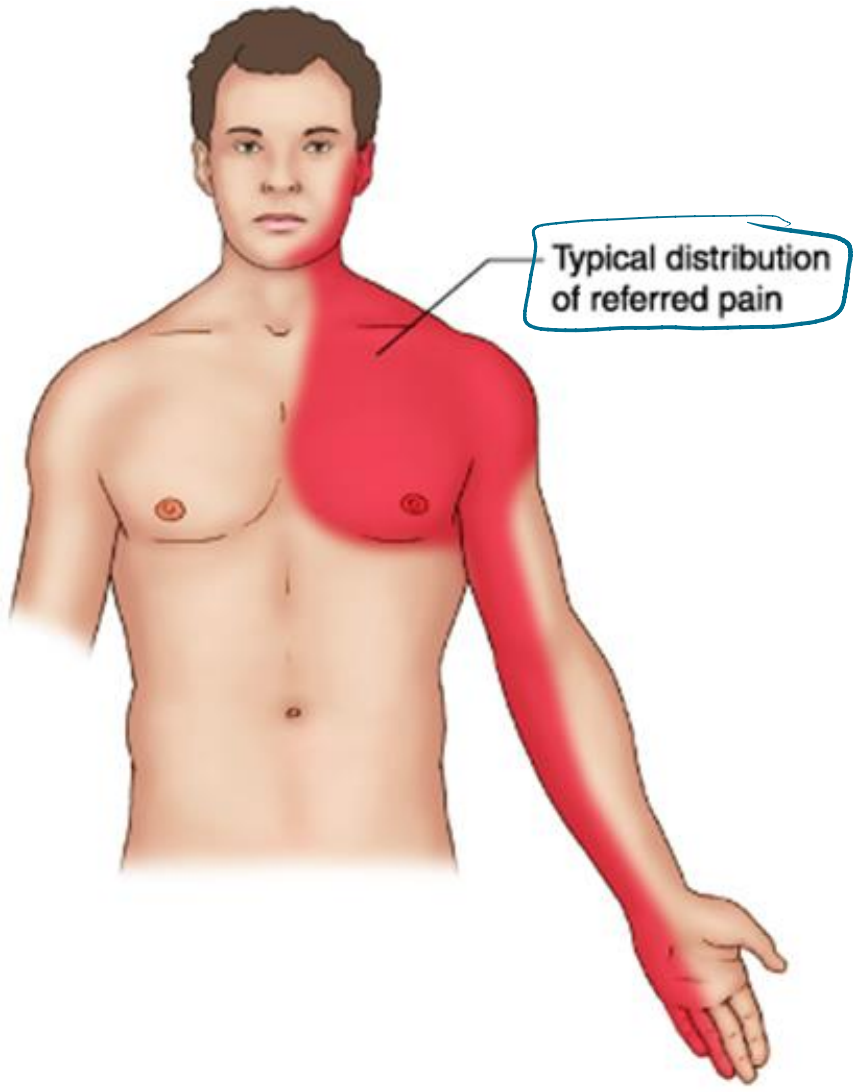
* كيف بدي أعالجها ؟
- بعمل vasodilation ← بقلل preload (vasodilation) (dilation in veins) ← تخف كمية الدم الداخلة على القلب ← ما رح يكون في زيادة O_2
[nitrates : في vasodilators كعلاج بستخدم]
بقلل الـ resistance ← بتقل كمية الدم الخارجة من القلب (afterload) .

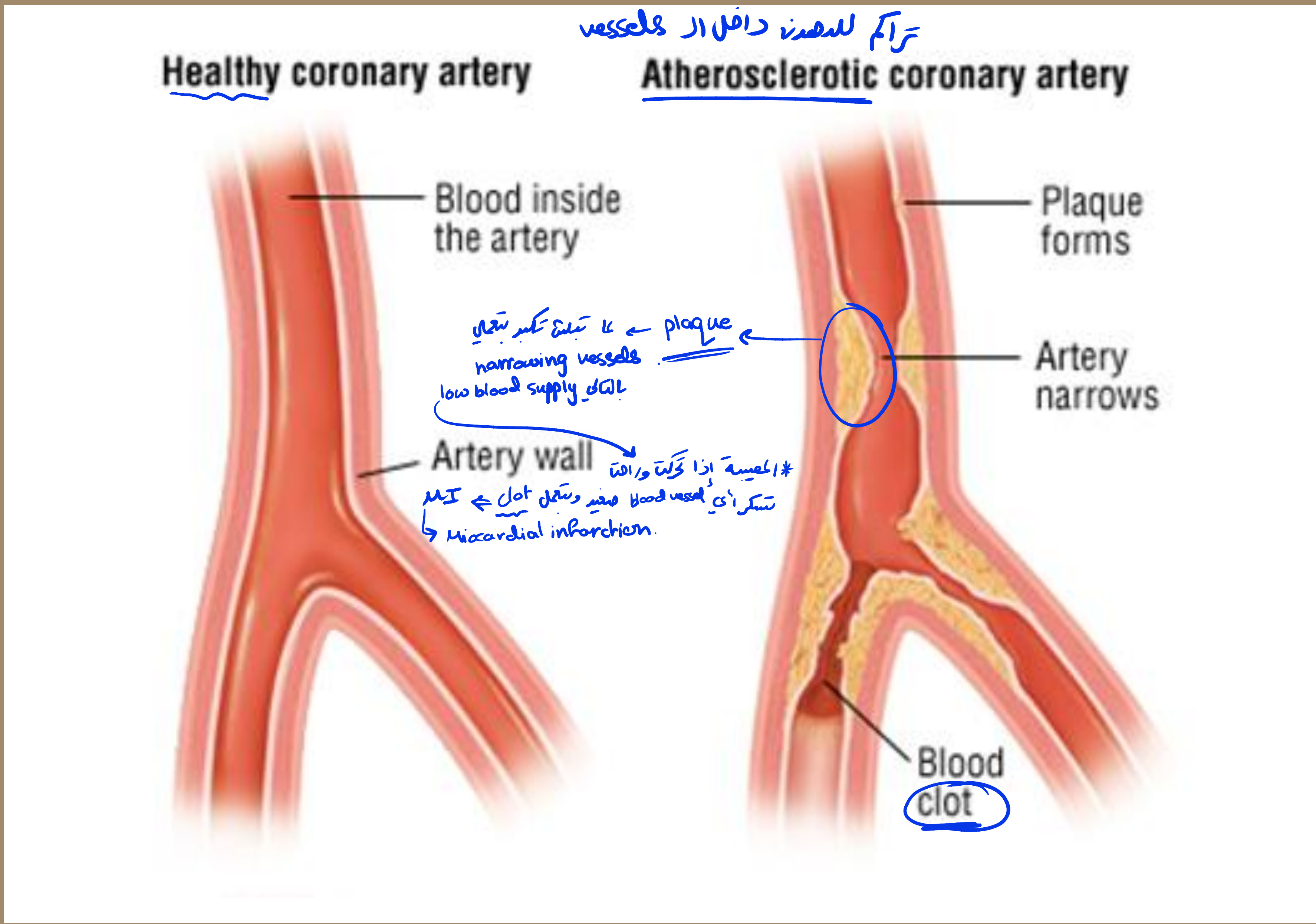
- β-blockers ← ↓ contractility ← ↓ HR
[بس مش أي واحد أعطيه لأنه في β-nonselective بعملي bronchoconstriction لأنه أثر ع β2 (بقلل O_2 supply)]

- calcium channel blockers ← verapamil, deltiazem (nondihydropyridine) / dihydropyridine

* أكثر إشي مهم بعين الاعتبار إنه الـ vasoconstriction بالـ coronary arteries رح يصير ع مستوى الجسم وإنما رح يكون بالـ coronary arteries إلي بتغذي القلب .


Angina
a type of temporary chest pain, pressure or discomfort.
Narrowed artery
Ischemia
Heart muscle is not receiving enough oxygen due to a narrowed coronary artery.


Typical distribution of referred pain


تراكم للدهون داخل ال vessels
Healthy coronary artery
Atherosclerotic coronary artery
Blood inside the artery
Artery wall
Plaque forms
Artery narrows
Blood clot
plaque ← لا تبلش تكبر بتعمل
narrowing vessels.
low blood supply بالتالي
*المصيبة إذا تحركت والتا تسكر أي blood vessel صغير وتعمل clot ⇐ MI
↳ Miocardial infarction.

TYPES OF ANGINA

تقسيم
بناءً على متى تبقيس
بناءً على المسبب

stable, unstable → caused by atherosclerosis in blood vessels
prinzmetal → vaso constriction only (vasospasm)

لما الشخص مثلاً يلبس يلعب رياضة

1. Effort-induced angina, classic or stable angina

الاعصار عنده إنه زاد O_2 demand وبس.
علاجه لتخفيف O_2 demand
باستخدام vasodilators أو CCB أو بعطيه B-blockers

2. Prinzmetal, variant, vasospastic angina

الحل vasodilators / ما بستخدم B-blockers لأنه الوضع أصلاً ما في دفق بالقلب.

at rest
أخطرهم لأنه ممكن تقيس وإنت نايم

3. Unstable angina or acute coronary syndrome

الحل: بتقلل O_2 demand وبزيد O_2 supply
وحدة من أجزاءها MI

بكل أنواع الـ angina لازم نستخدم معاهم الـ statins
statins → antihyperlipidemic agents
أدوية الدهنيات ← عشان أخفف من atherosclerosis

- 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.

Unstable angina management

- Risk assessment:
  - High risk patient (revascularisation)
  - Low risk (non-invasive management)
- Aspirin and clopidogrel together
- Glycoprotein IIb/IIIa inhibitors (Eptifibatide)
- Parntral anticoagulants (low-molecular weight heparin, Fondaprinux)

Antianginal

I. **NITRATES**

II. **β-ADRENERGIC BLOCKERS**

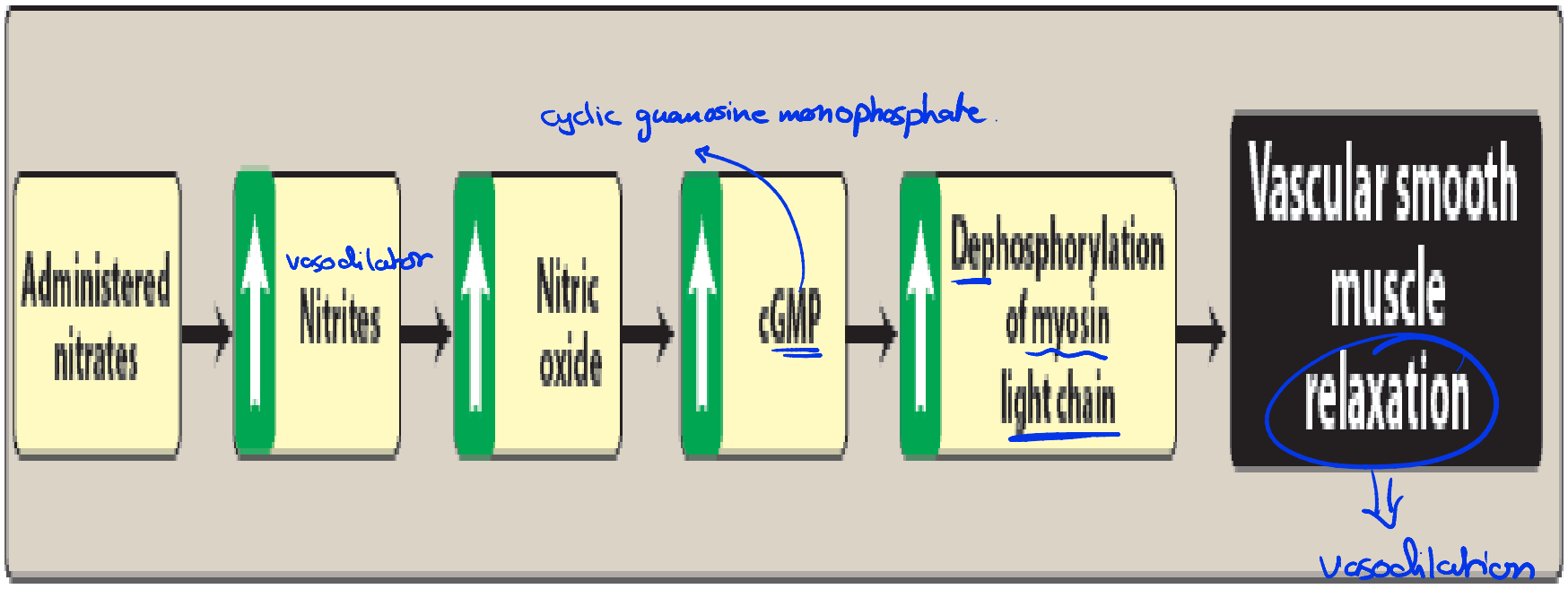
III. **CALCIUM-CHANNEL BLOCKERS**

IV. **SODIUM-CHANNEL BLOCKER**

NITRATES

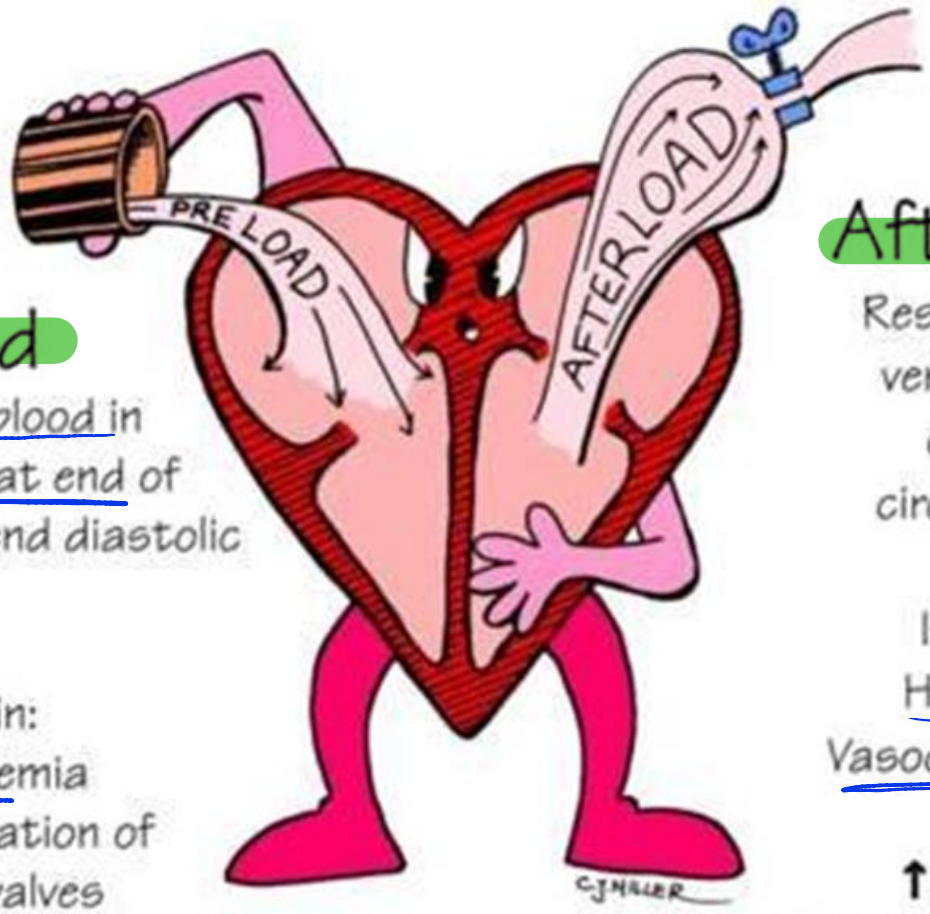
- ***Isosorbide dinitrate*** *and* ***isosorbide mononitrate*** *are solids at* room temperature, ***nitroglycerin*** *is only moderately volatile, and* ***amyl nitrite*** is extremely volatile.
- Cause a rapid reduction in myocardial oxygen demand and symptom relief (life saving)
- Nitrates inhibit coronary vasoconstriction or spasm, increasing perfusion of the myocardium and, thus, relieving vasospastic angina.
- In addition, nitrates relax the veins (venodilation), decreasing preload and myocardial oxygen consumption

MOA of Nitrates



Nitrates Improve blood supply and reduce Oxygen demand

PRELOAD AND AFTERLOAD



Preload

Volume of blood in ventricles at end of diastole (end diastolic pressure)

Increased in:

- Hypervolemia
- Regurgitation of cardiac valves
- Heart Failure

Afterload

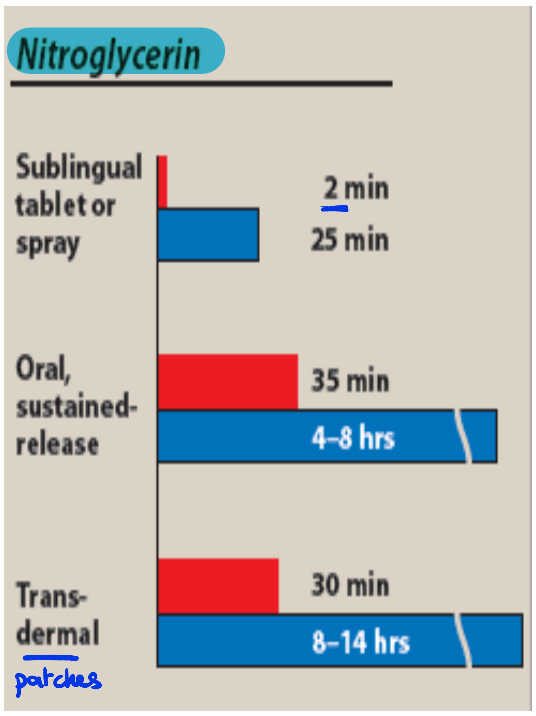
Resistance left ventricle must overcome to circulate blood

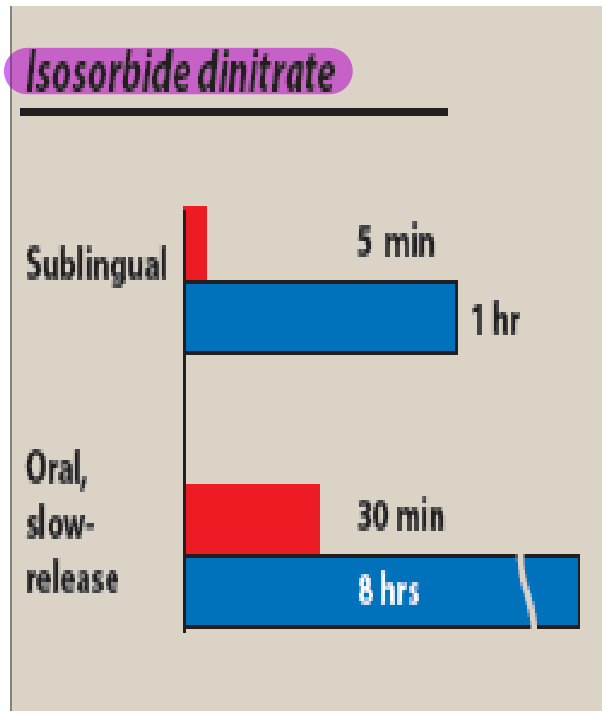
Increased in:

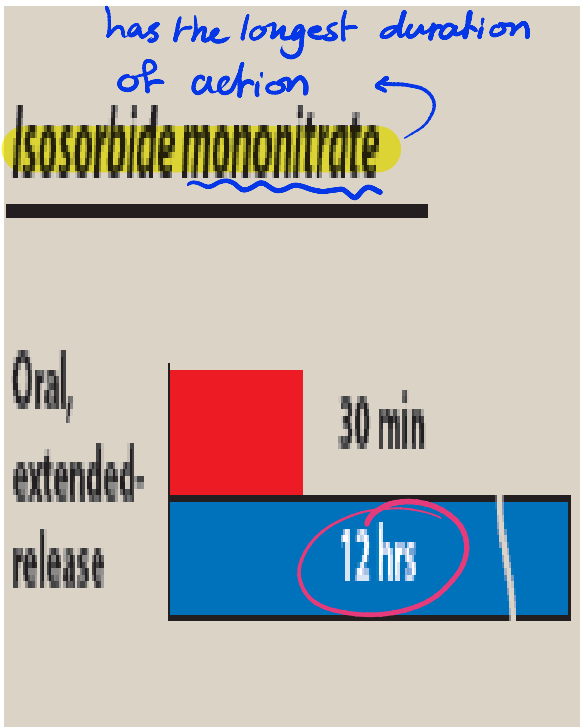
- Hypertension
- Vasoconstriction

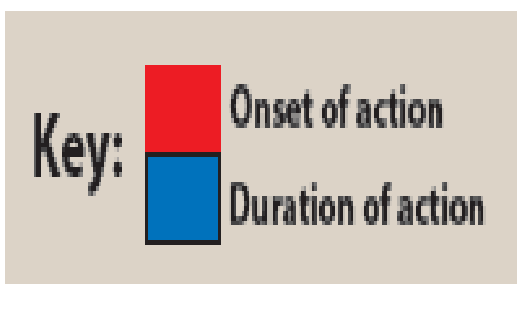
↑ Afterload = ↑ Cardiac workload

Differ in their Kinetics









Monday disease, also known as **Monday morning syndrome**, refers to the recurrence of symptoms in workers after returning to work following a break, typically over the weekend. This condition is often associated with industrial workers who are exposed to certain chemicals or dusts.

One classic example is the recurrence of severe headaches in workers exposed to **nitroglycerin**. These workers might experience headaches when they return to work on Monday after a weekend away from exposure.

Adverse effects

- Headache is the most frequent*
- Postural hypotension at high doses
- Reflex tachycardia
- C/I with sildenafil
  - Tolerance occur to nitrates, so " nitrates free periods" are important

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

β-ADRENERGIC BLOCKERS

- The β-adrenergic–blocking agents decrease the oxygen demands of the myocardium by lowering both the rate and the force of contraction of the heart

- Due to their cardioselectivity, *metoprolol and atenolol,* are preferred

CALCIUM-CHANNEL BLOCKERS

- Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces
- The calcium-channel blockers protect the tissue by inhibiting the entrance of calcium into **cardiac** and smooth muscle cells of the **coronary and systemic arterial beds.**

➢ **Verapamil** ⟶ **Myocardium**

➢ **Nifedipine** ⟶ **Peripheral** → dihydropyridine

➢ **Diltiazem** ⟶ **Intermediate**

Nifedipine

- ✓ Dihydropyridine derivative
- ✓ An arteriolar vasodilator
- ✓ ER oral tablets
- ✓ Potent vasodilator, beneficial in angina
- ✓ Cause: headache,flushing, peripheral edema
- ✓ Reflex tachycardia

"*Avoided in coronary artery disease because of evidence of an increase in mortality after an MI and an increase in acute MI in hypertensive patients*".

Verapamil → treat arrhythmia

- Diphenylalkylamine
- Slows cardiac atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand.
- *Verapamil causes greater* negative inotropic effects than *nifedipine, but it is a weaker vasodilator.*

Verapamil

- Contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities.
- Causes constipation
- *Verapamil* increases *digoxin levels.*

Diltiazem: Dual Mechanism

- Similar to verapamil effects but less effective in decreasing HR
- But also it decreases BP
- Useful in HTN with mild angina
- Extensive metabolism

DRUGS COMMONLY USED IN TREATING ANGINA

CONCOMITANT DISEASE			
NONE	Long-acting nitrate	β-Blockers	Ca^{2+} channel blockers
RECENT MYOCARDIAL INFARCTION	Long-acting nitrate	β-Blockers	
ASTHMA, COPD	Long-acting nitrate		Ca^{2+} channel blockers
HYPERTENSION	Long-acting nitrate	β-Blockers	Ca^{2+} channel blockers
DIABETES	Long-acting nitrate		Ca^{2+} channel blockers
CHRONIC RENAL DISEASE	Long-acting nitrate	β-Blockers	Ca^{2+} channel blockers

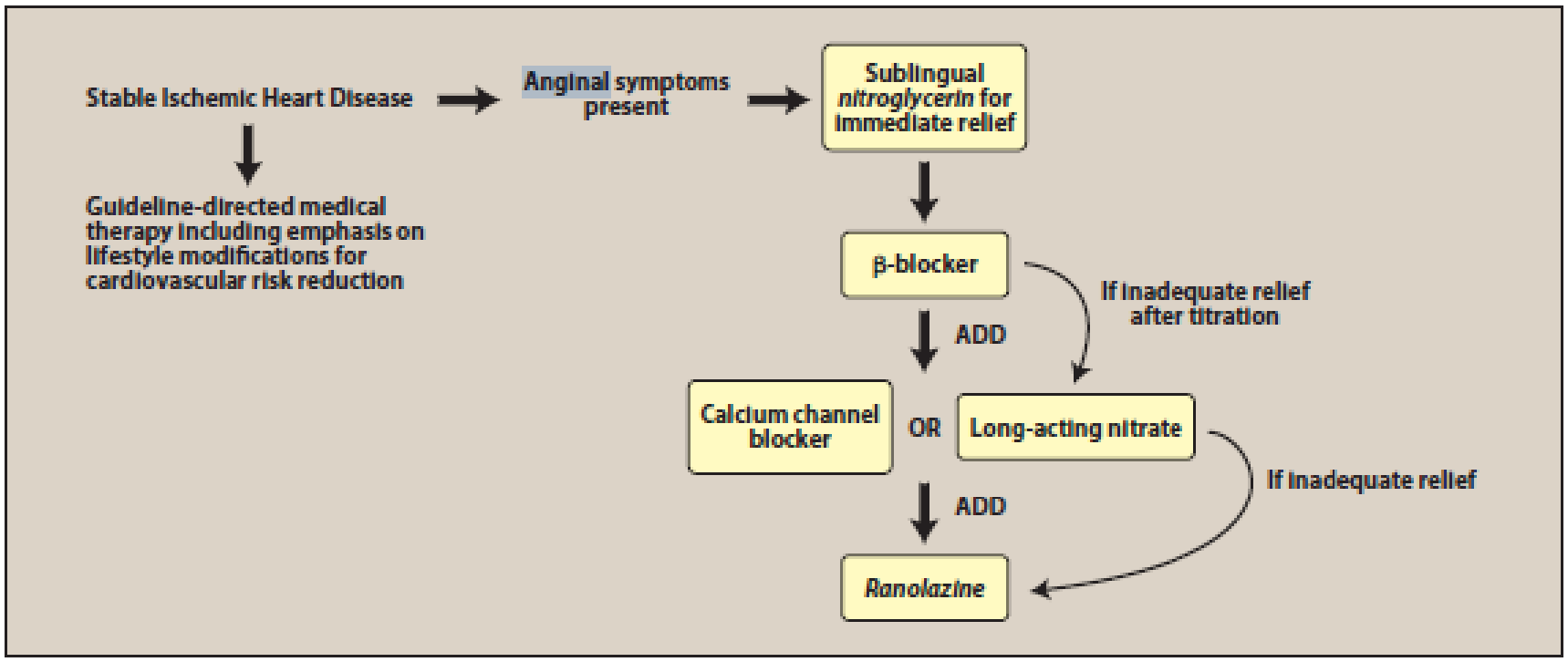
KEY:

- Drug class — Commonly used drugs
- Drug class — Less effective drugs

SODIUM-CHANNEL BLOCKER
Ranolazine

- **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.


Stable Ischemic Heart Disease
Anginal symptoms present
Sublingual nitroglycerin for immediate relief
Guideline-directed medical therapy including emphasis on lifestyle modifications for cardiovascular risk reduction
β-blocker
If inadequate relief after titration
ADD
Calcium channel blocker
OR
Long-acting nitrate
If inadequate relief
ADD
Ranolazine