Clinical Pharmacology of Angina Pectoris

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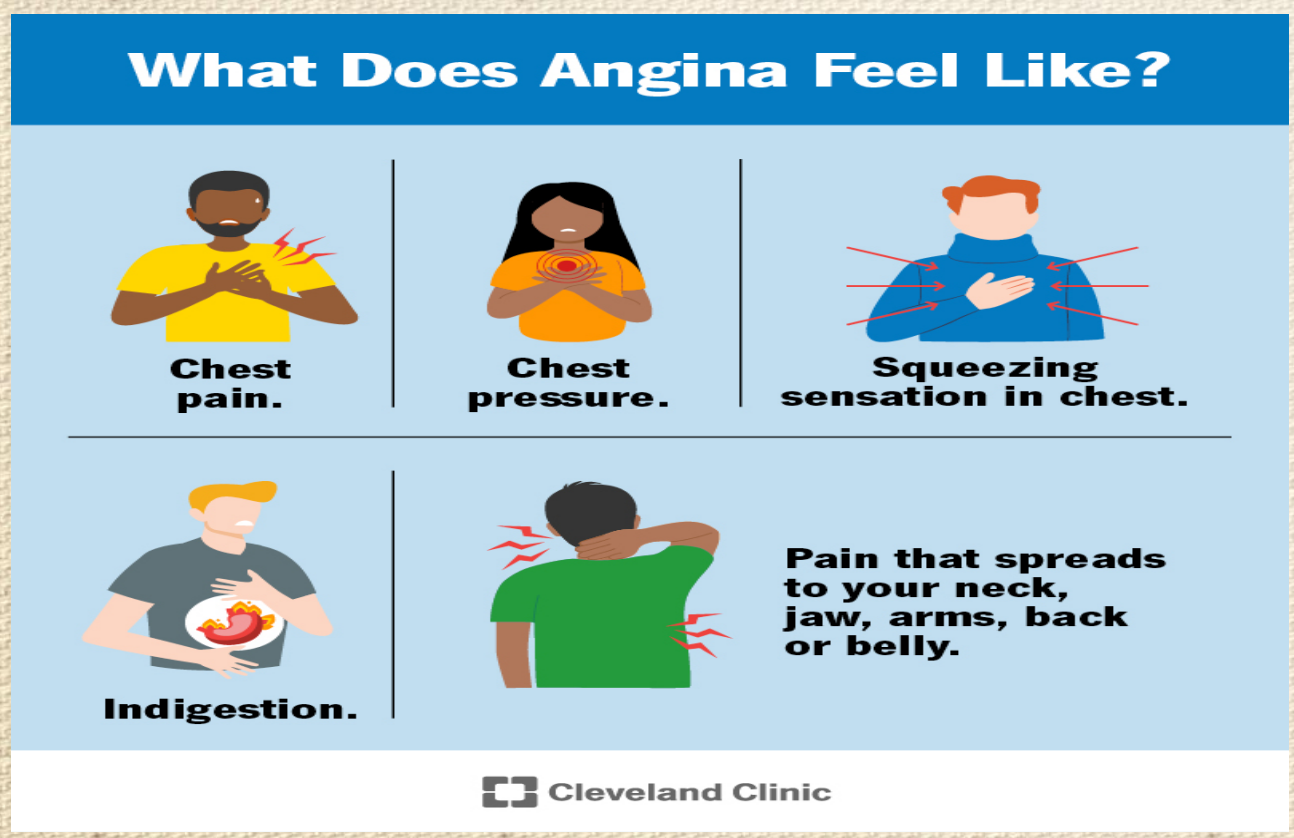
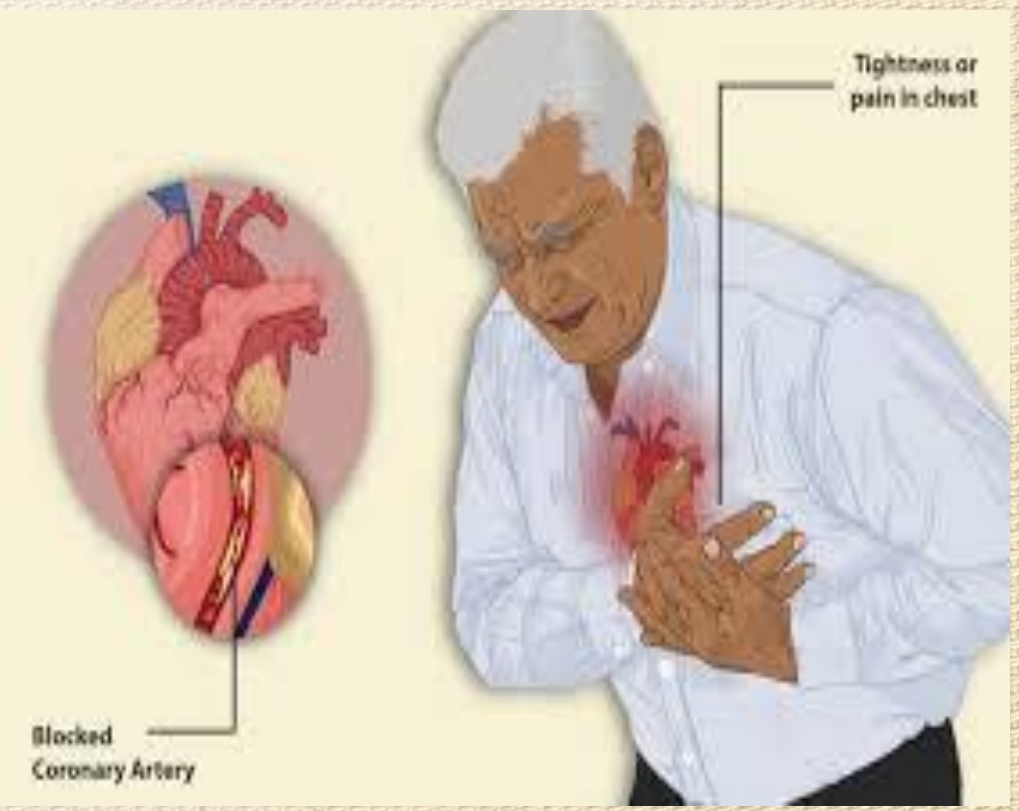
Angina Pectoris

- Chest pain due to transient myocardial ischemia (coronary blood flow≠ o2 demand)
- Due to imbalance between oxygen demand and coronary oxygen supply

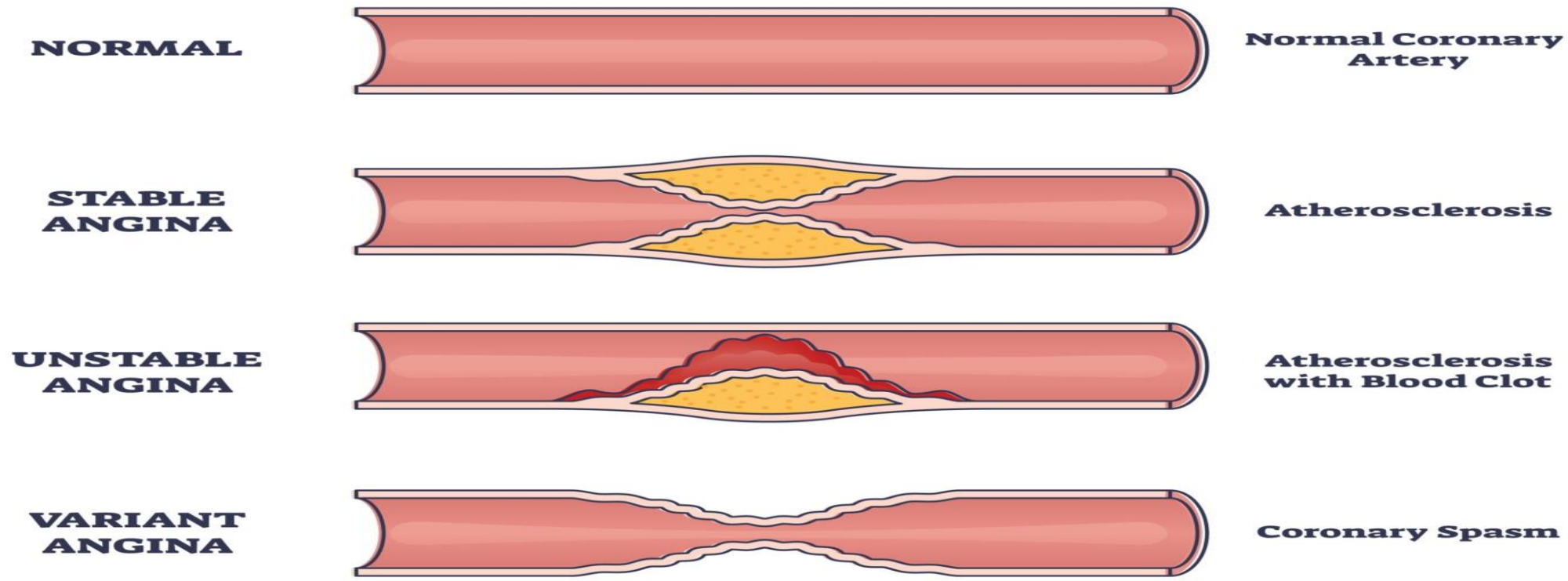




Types of angina pectoris

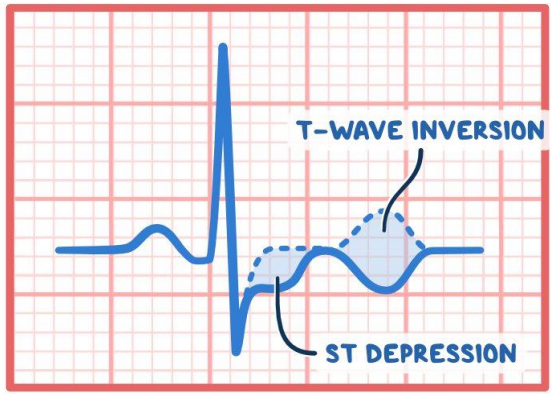
Angina of effort (exertional, stable angina)	**Unstable angina (pre-infarction)**	**Variant (Prinzmetal's) angina**
✓ The most common type ✓ Occurs on exertion ✓ Due to **coronary atherosclerosis** ✓ Treatment by **↓↓cardiac work**	✓ Occur at rest with change in the frequency and duration of chest pain ✓ Due to formation of **non-occlusive thrombi** at the site of a fissured or ulcerated atherosclerotic plaque ✓ Treatment: **Hospitalization+ Coronary VDs+ ↓Cardiac work+ Antiplatelets+ LMW heparin & statins**	✓ Occurs at rest, usually accompanied by arrhythmia ✓ Due to reversible **coronary vasospasm** ✓ Treatment by Coronary VDs

TYPES OF ANGINA



STABLE ANGINA

* OCCURS with SUBENDOCARDIAL ISCHEMIA
  ↳ USUALLY RESULTS when ≥ 70% STENOSIS in ONE of CORONARY ARTERIES



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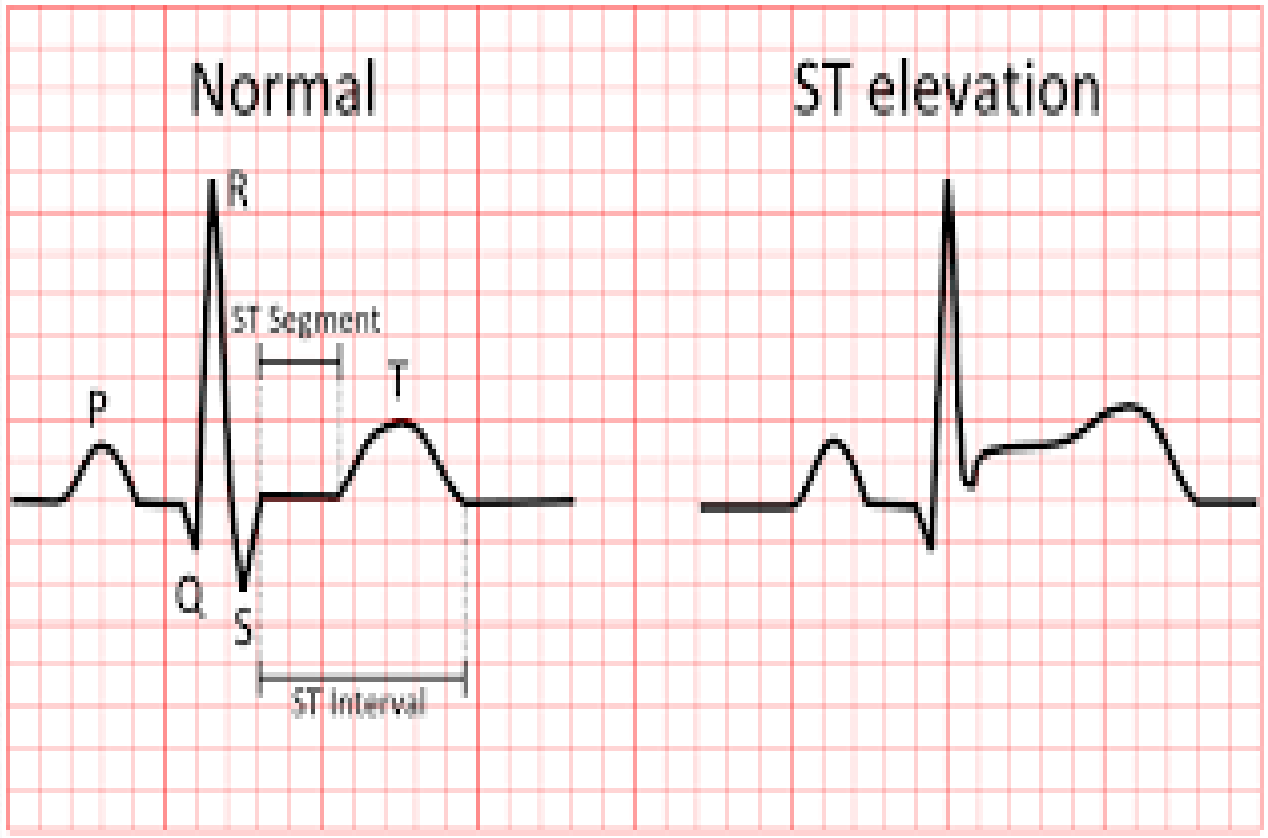


Non-pharmacological treatment

- Diet
- Obesity
- Smoking
- Excises

Drug treatment of angina (3×3)

A- Anti-anginal drugs:

1-Nitrites & nitrates: coronary VD + ↓↓ cardiac work

2-Calcium Channel Blockers (CCBs): coronary VD + ↓↓ cardiac work

3-β-blockers: ↓↓cardiac work

- **Other drugs:**

  1-Trimetazidine

  2-Ranolazine

  3-Ivabradine

B- Adjuvant Drugs:

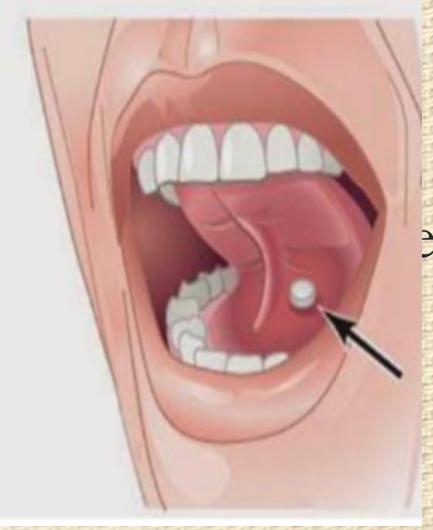
1-Anti-platelet drugs: prevent the conversion of stable angina into unstable angina

2-Statins (even in the absence of hyperlipidemia): ↑ NO release - antioxidant effects- stabilization of atherosclerotic plaques

3-.Treatment of risk & precipitating factors e.g. hypertension, D,M and hyperlipidemia

1- Organic Nitrates

Glyceryl trinitrate (nitroglycerin) isosorbid dinitrate -isosorbid mononitrate

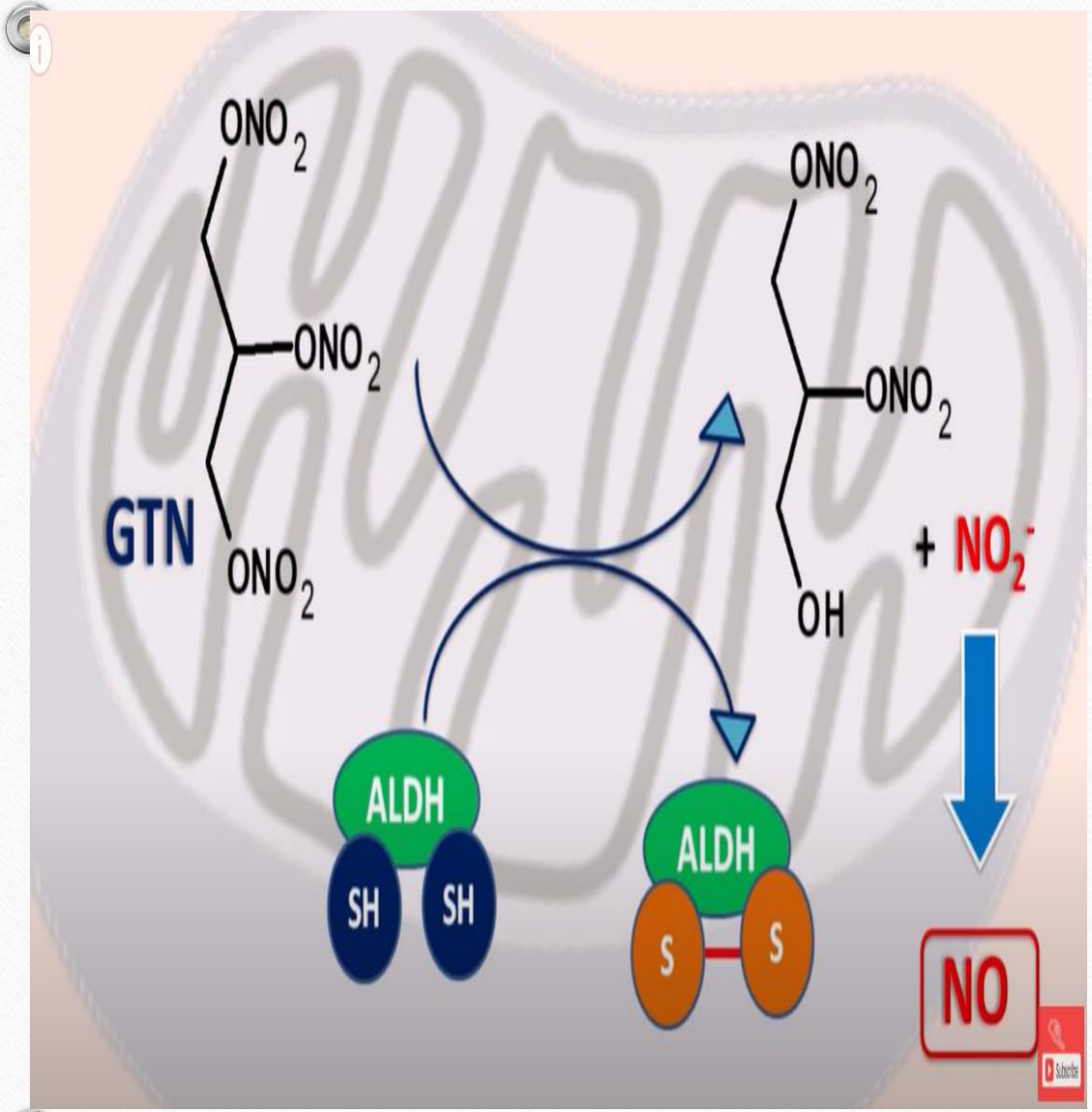


Pharmacokinetics:

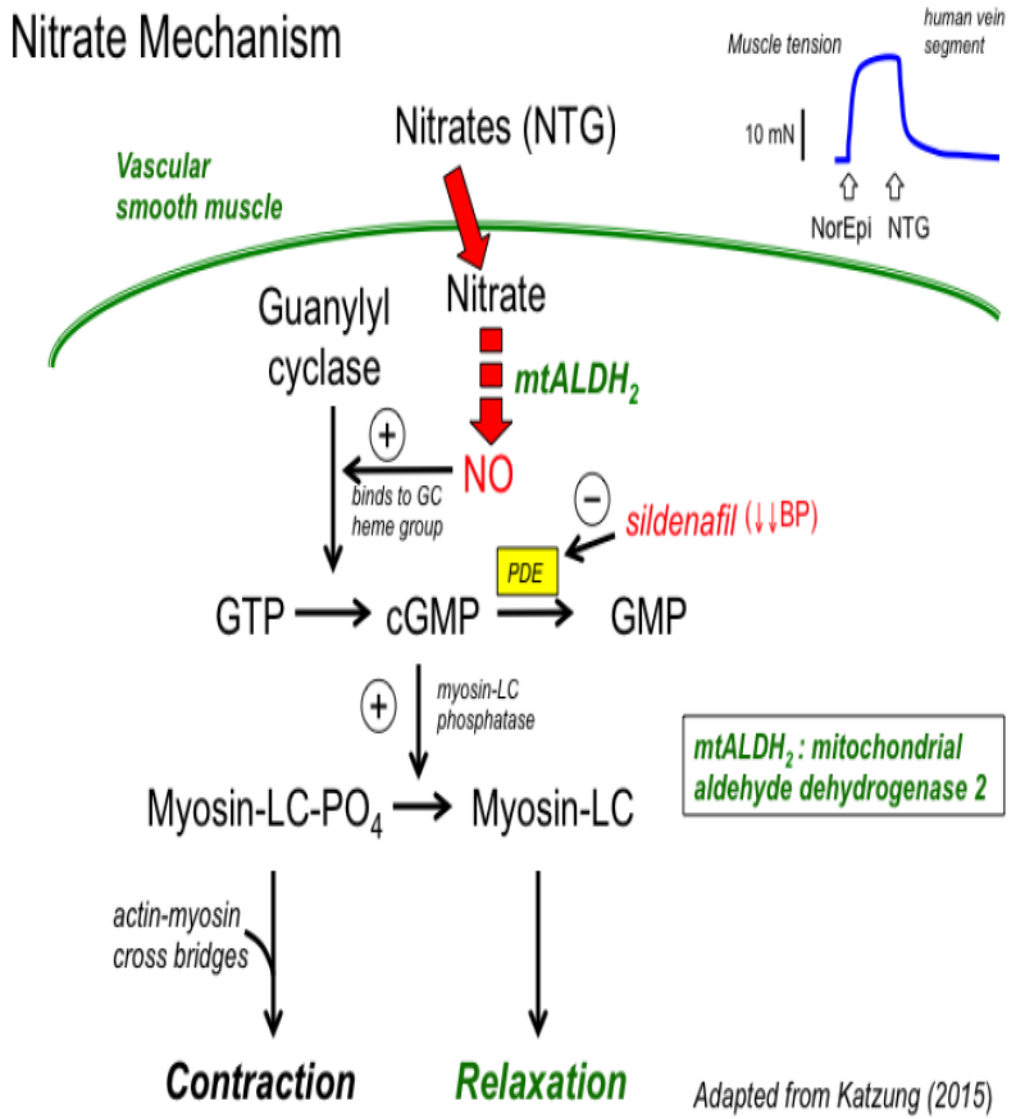
- Extensive **hepatic first-pass metabolism** (90%) → 10% oral bioavailab ed S.L.). Sublingual: Onset: 10-20 min with a duration of 30min. Oral form Transdermal formulations: 24 hours.

Pharmacodynamics:

- In the body, nitrates are denitrated by ALDH (consuming SH group) → release of nitric oxide (NO) that activates soluble guanyl cyclase enzyme (sGC) → ↑↑ cGMP:
  - ✓ Dephosphorylation of myosin light chain → smooth muscle relaxation → VD
  - ✓ ↓↓ Platelet aggregation
  - ✓ Increase PGI2



Nitrate Mechanism



Pharmacological actions

- **Blood vessels:** VD (especially of the veins):
  - ✓ Venodilation → ↓↓ VR → ↓↓ EDV → ↓↓ **preload**
  - ✓ Some arterial dilatation → ↓↓ TPR → ↓↓ **afterload**
- **Other Blood vessels:**
  - ✓ Retinal VD → ↑↑ IOP
  - ✓ Cutaneous VD → flush of face & chest
  - ✓ Pulmonary VD & ↓↓ VR →↓↓ pulmonary pressure
  - ✓ Meningeal VD → headache

- **Heart:**

✓ ↓↓ cardiac work (↓↓ preload > ↓↓ afterload) → ↓↓ O_2 consumption

✓ Venodilator → ↓↓ preload → ↓↓ contractility → ↓↓ pressure on sub-endocardial coronaries.

✓ Some arteriodilator → ↓↓ TPR → ↓↓ afterload

✓ Hypotension → **reflex sympathetic activation** → ↑↑ contractility & tachycardia → shorten diastolic coronary perfusion time .

Therapeutic uses

- **All types of angina pectoris:**
  - **Mechanism:**
    - **Angina of effort:** ↓↓ cardiac work & ↓↓ O_2 consumption
    - **Variant angina:** coronary VD
    - **Unstable angina:** ↓↓ cardiac work & ↓↓ O_2 consumption + coronary VD
- **Congestive heart failure:** ↓↓ preload and relieve pulmonary congestion
- **Cyanide poisoning:** due to the affinity of cyanide to iron in met HB , not cytochrome oxidase.

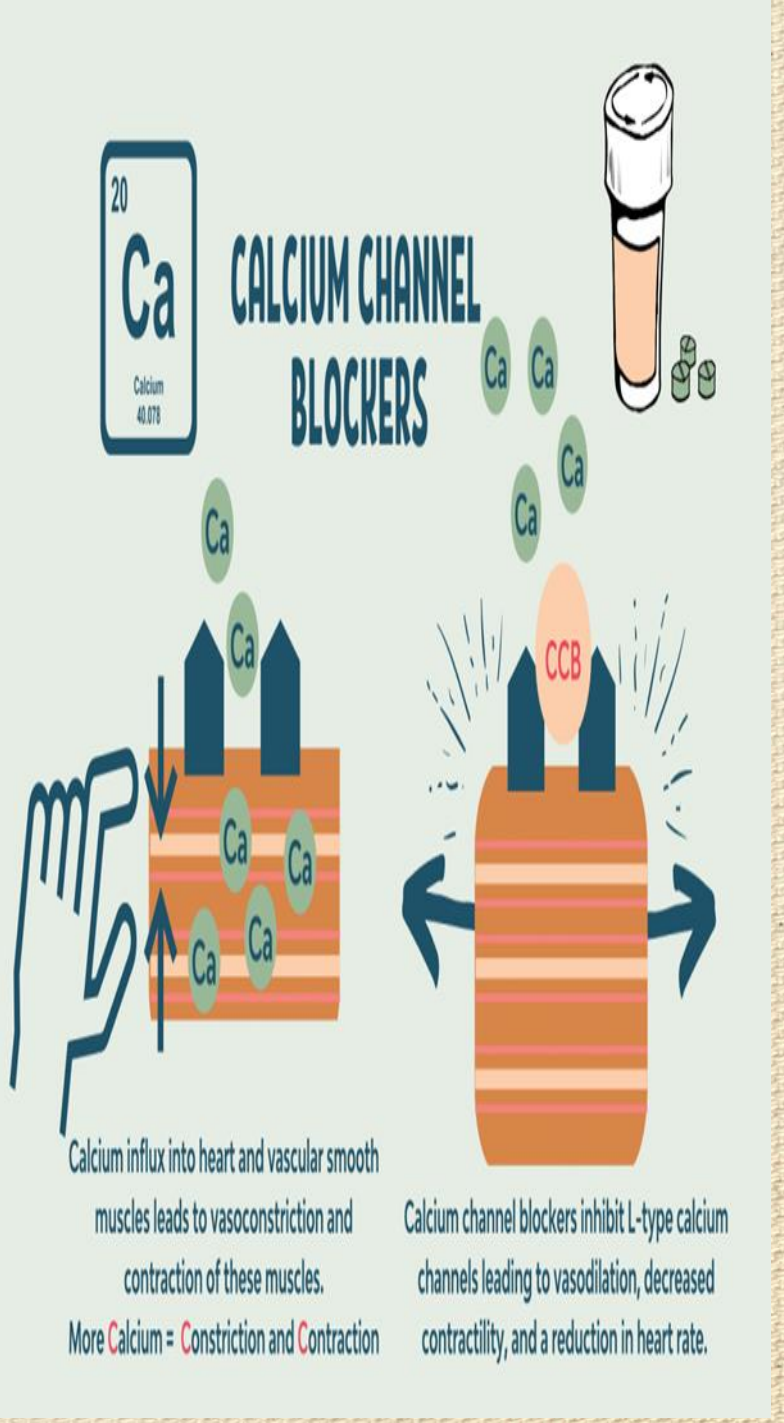
Adverse Effects

- Headache, flush & ↑↑ IOP
- Postural hypotension & syncope (sit while taking rapidly-acting nitrate)
- **Hypotension** → reflex tachycardia (**prevented by adding β-blocker or verapamil**)
- **Tolerance** & **cross-tolerance** between nitrites & nitrates
  - ✓ Due to the depletion of the SH group required for denitration & Activation
  - ✓ Avoid by daily 8-12 hrs **nitrate-free period** or alternate with another anti-anginal drug every 2 weeks. When (interval in night or afternoon).
- Hypersensitivity reactions
- Met-Hb (in high doses)
- Not with phosphodiesterase inhibitors (sildenafil)due to fatal hypotension and tachycardia

2- Calcium Channel Blockers (CCBs)

- **Dihydropyridines (DHPs):** VD > cardiac depression:
  - ✓ **Long-acting:** amlodipine
  - ✓ **Intermediate-acting:** nifedipine, felodipine
  - ✓ **Short-acting:** isradipine & nimodipine
- **Non-DHPs:** verapamil & diltiazem: cardiac depression > VD

- **Mechanism of Action:**
  - Block **Voltage-dependent L-type** calcium channels present in heart, blood vessels and smooth muscles
  - They ↓↓ Ca^{2+} influx into:
    - ✓ Cardiac muscle → cardiac inhibition (especially verapamil & diltiazem)
    - ✓ Blood vessels → arteriolar VD (especially DHPs)
    - ✓ Smooth muscles → relaxation [biliary, intestinal and bronchial]



- **Pharmacological actions:**

A) Verapamil & diltiazem (↓ Heart > VD):

- ✓ Negative chronotropic effect
- ✓ Negative inotropic effect (**contraindicated in heart failure**)
- ✓ Negative dromotropic effect (**contraindicated in heart block**)
- ✓ NOT combined with β-blockers or digitalis. (Why?)
- ✓ Automaticity →↓ Ectopic Focus Formation → Class IV Anti-Arrhythmic

- **Pharmacological actions:**

B) Nifedipine & amlodipine:

- ✓ VD > cardiac depression: arteries > veins: ↓↓ TPR → ↓↓ afterload and ↓cardiac work
- ✓ Weak venodilator → ↓↓ VR → ↓↓ preload → ↓↓ O_2 consumption
- ✓ Hypotension → **reflex sympathetic activation** → tachycardia → short diastolic filling time **(minimal with amlodipine)**

Therapeutic uses of CCBs:

1- All Types of angina (↓↓ cardiac work & coronary VD):

- **Mechanism of CCBs in angina:**
  - ✓ Coronary VD → treat **variant Angina.**
  - ✓ ↓↓ Cardiac work & ↓↓ O_2 consumption → treat **effort angina**
  - ✓ Powerful arteriolar dilator → ↓↓ TPR → ↓↓ afterload
  - ✓ Mild venodilator → mild ↓↓ VR → mild ↓↓ preload
  - ✓ Negative inotropic effect (non-DHPs)
  - ✓ ↓↓ platelet aggregation

Therapeutic uses of CCBs:

2- Cardiac arrhythmia (verapamil)

3- Hypertrophic obstructive cardiomyopathy with subaortic stenosis: verapamil & diltiazem

4- Hypertension (especially DHPs)

5- Peripheral vascular disease (DHPs)

6- Cerebral spasm due to subarachnoid hemorrhage (nimodipine)

7- Migraine headache prophylaxis*:* (nimodipine & verapamil)

Adverse effects of CCBs:

- Headache & flushing
- **Heart**: (verapamil & diltiazem)
  - ✓ Negative inotropic → heart failure
  - ✓ Negative chronotropic → bradycardia
  - ✓ Negative dromotropic → heart block
- Hypotension
- Constipation (especially with verapamil)
- **Liver impairment** (with ***verapamil***, so it is not used for more than 1 year)
- **Ankle edema** (due to ↓ capillary permeability- treated or avoided by elastic stocks)

NOT combined with β. Blockers

β-blockers

- **All β-blockers are effective in angina pectoris(NOT variant)**
- **Desirable Effects** → ↓↓ cardiac work & ↓↓ O_2 consumption:

a. ↓↓ HR :

✓ ↑↑ Diastolic coronary perfusion time

✓ Prevent tachycardia induced by nitrates & nifedipine

b. ↓↓ Contractility & end-systolic & end-diastolic pressures → relieve compression of the sub-endocardial coronaries

- **Undesirable Effects**

  a. Bradycardia, heart block or heart failure in susceptible patients

  b. Prolonged use increases the incidence of type-2 diabetes mellitus by 50%.

  c. sudden stop leading to rebound angina, arrhythmia, infarction

- **Useful in prophylaxis of angina pectoris:**
  - Useful in stable & unstable angina (better use cardio-selective β-blockers)
  - Non-selective β-blockers are **contraindicated** in **variant angina** (β_2 receptor block → unmasking of α-induced VC → coronary spasm)

- **Beta-blocker: can be combined with nitrates & nifedipine:**
- **Nitrate & nifedipine → ↑↑ HR + ↓↓ diastolic filling + ↓↓ EDV + ↓↓ ejection time**
- **B-blockers→ ↓↓ HR + ↑↑ diastolic filling + ↑↑ EDV + ↑↑ ejection time**

Choice of Treatment

Patient	Useful drugs	Drugs contraindicated
Variant angina	Nitrates & CCB	β-blockers
Angina + B.A, P.V.D or D.M.	Nitrates & CCB	β-blockers
Angina + Heart block	Nitrates & Nifedipine	β-blockers & Verapamil
Angina + H.F.	Nitrates & Nifedipine some β-blockers in small doses	β-blockers in large doses & verapamil.

Other anti-anginal drugs:

- **Trimetazidine:**
  - ✓ Anti-Ischemic & Cytoprotective
  - ✓ Improves cell respiration → ↓↓ lactate production → ↓↓ intracellular acidosis
  - ✓ ↓↓ Intracellular Ca^{+2} overload
  - ✓ ↓↓ Free radical production

- **Ranolazine:**
  - ✓ Prevents abnormal sustained opening of the late Na^+ channels (due to deficiency of ATP)
  - ✓ Ranolazine increases ATP synthesis
  - ✓ Does not affect heart rate or blood pressure
  - ✓ Adverse effects: constipation, nausea, dizziness, headache

Ivabradine

Mechanism of action:

- **Ivabradine** inhibits the cardiac pacemaker *If* current that controls the spontaneous diastolic depolarization in SAN and regulates heart rate.

Pharmacological actions:

- Ivabradine produces dose-dependent reduction in heart rate.

Therapeutic Use:

- **Stable angina pectoris** in adults with normal sinus rhythm.

Adverse Effects:

- **Bradycardia**
- **Luminous phenomena (phosphenes):**
  - ✓ Transient enhanced brightness in a limited area of the visual field
  - ✓ Due to inhibition of the retinal current "I_h" which closely resembles cardiac I_f.

Contraindications:

- Resting heart rate below 60 bpm prior to treatment, sick sinus syndrome, sino-atrial block, and 3rd degree AV block
- Unstable angina, acute MI, cardiogenic shock, acute heart failure & severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency

Anti-platelet drugs

- **Aspirin** in SD (75-150 mg) → ↓↓ platelet TXA_2
- **ADP receptors blockers:** ticlopidine & clopidogrel
- **GP IIb/IIIa receptors blockers:** abciximab & tirofiban

Myocardial revascularization by coronary artery bypass grafting (CABG) OR percutaneous transluminal coronary angioplasty (PTCA) in severe angina to increase coronary blood flow

Drug Group	Decrease Cardiac Work			Coronary VD
	Arterial VD (↓After load)	Venodilation (↓Preload)	↓ Heart (-ve inotropic & -ve chronotropic)	
1- Nitrities & Nitrates		+++		+++
2- C.C.B.	+++		+++ (Verapamil)	+++
3- β-Blockers			+++	

Anti-anginal drug combinations

Favorable Anti-Anginal Combinations:

1. **Nitrate or Nifedipine** →↑ HR + ↓Diastolic filling + ↓Ejection time.

   β Blockers →↓ HR +↑ Diastolic filling + ↑ EDV + ↑Ejection time.
2. **Nitrates** →↑HR + ↓ Diastolic time

   Verapamil → ↓HR +↑ Diastolic time.

Unfavorable Anti-Anginal Combinations:

1. **Nitrate + Nifedipine** → Severe Hypotension & Tachycardia.
2. **β-Blockers + Verapamil** → Severe Cardiac Inhibition
3. Do NOT use 2 drugs of the same class in the same line of treatment.

Management of angina

1. Acute Attacks (Present Pain) & Immediate Prophylaxis:

Rapidly acting Nitrates:

a. ***Nitroglycerine*** **S.L. 0.5 mg or Buccal Spray 0.4 mg.**

b. ***Isosorbid dinitrate*** **S.L. 5 mg or Buccal Spray 1.25 mg.**

N.B.

- **In Acute Attack (pain): Repeat the drug every 5 min. Till disappearance of pain or a maximum of 3 doses; otherwise, Acute Myocardial Infarction.**
- **In Immediate Prophylaxis: Drugs are taken 5 minutes before exertion.**

2. Long Term Prophylaxis

a. **Long Acting Nitrates**: Oral S.R., Trans-dermal patch or Ointment.

- **And/Or**

b. **Calcium channel blockers:**

- Verapamil: 80-160 mg t.d.s.
- Ditiazem: 60 mg t.d.s.
- Nifedipine: 10 → 20 mg t.d.s.

- **And/Or**

c. **β-blockers:**

- Atenolol: 50-100 mg once daily.
- Meteprolol: 50-100 mg twice daily.
- Propranolol: 80-320 mg/day in Divided doses.

MANAGEMENT OF MYOCARDIAL INFARCTION

- Death of an area of the myocardium due to prolonged ischemia, more than 15 minutes, induced by coronary Thrombosis.
- The patient must be hospitalized.

A. Before and During Transfer: (Initial) treatments:

1. Cardio-pulmonary- resuscitation (C.P.R.) if cardiac arrest.
2. Oxygen.
3. Nitroglycerin sublingually or buccal spray up to 3 doses with 5-minute intervals.
4. Aspirin 150-300 mg chewed + clopidogrel 300 mg oral
5. Morphine sulfate 2.5 - 5 mg IV.+ metoclopramide 10 mg I.V. Why? (For-severe pain and / or pulmonary edema.)
6. Furosemide, (20 mg/5 min IV) if acute pulmonary edema with normal B.P.
7. Saline by rapid IV infusion if B.P. is rapidly declining and lungs are free.

B. At the Intensive (Cardiac) Care Unit (ICU & CCU):

1. **Thrombolytic (Fibrinolytic) therapy** within the first 6 hours to dissolve the thrombus:

    a. Recombinant Tissue Plasminogen Activator (rTPA = Alteplase):

    b.Streptokinase

2- Heparin to prevent extension or recurrence of the thrombus.

3. **Nitrates:** nitroglycerine I.V.infusion (10-20μg/min) → Veno-dilator → ↓venous return → ↓ Preload & lung congestion.
4. **Positive inotropic drugs** e.g dopamine or dobutamine if there is cardiogenic shock.
5. **Opiates** e.g. IV morphine + **Anti-emetic** e.g. metoclopramide) 10mg I.V.
    3. Relieve the pain.
    4. Reduce anexiety.
    5. Reduce pre- & after-loads: veno-dilator, ↓ sympathetic & histamine release.
    6. Reduce excess tachypnea induced by pulmonary edema with acute HF.
6. **Oxygen** when indicated.
7. **β-Blockers**, from the 1st day: ↓ cardiac work → cardio-protective →↓ re-infarction.

c. ***Post-MI Drug Therapy:***

1. Aspirin 75 - 150 mg/day orally.
2. Clopidogrel, 75 mg/day for 9 -12 months.
3. β-blocker to maintain heart rate < 60 beats/min e.g. Metoprolol 50 mg twice daily.
4. ACE inhibitors, e.g., Ramipril 2.5 mg twice daily. If not tolerated, use ARBs, e.g., valsartan 20 mg twice daily.
5. Long-term anticoagulants with warfarin may increase the risk of bleeding.
6. Statins, e.g., Simvastatin 20 - 80 mg/day.
7. Aldosterone antagonists, e.g.,. Spironolactone or Eplerenone 25 mg/day in patients with clinical evidence of heart failure.

THANK YOU