Ischemic heart disease

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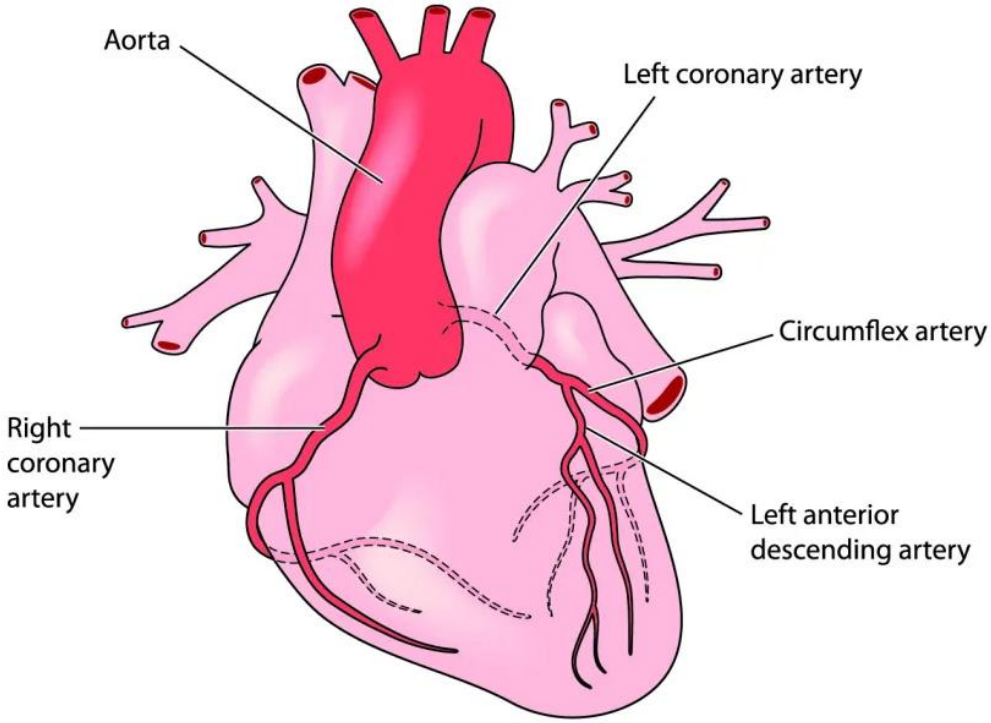


Ischemic heart disease includes:

1) Chronic stable angina
   (Classic; exertional angina).

2) Acute coronary syndromes (ACS).

3) Prinzmetal's angina (Variant angina;

angina of rest; α-mediated angina).

They are caused by varying combinations of **increased myocardial demand** and **decreased myocardial perfusion**

• Angina :

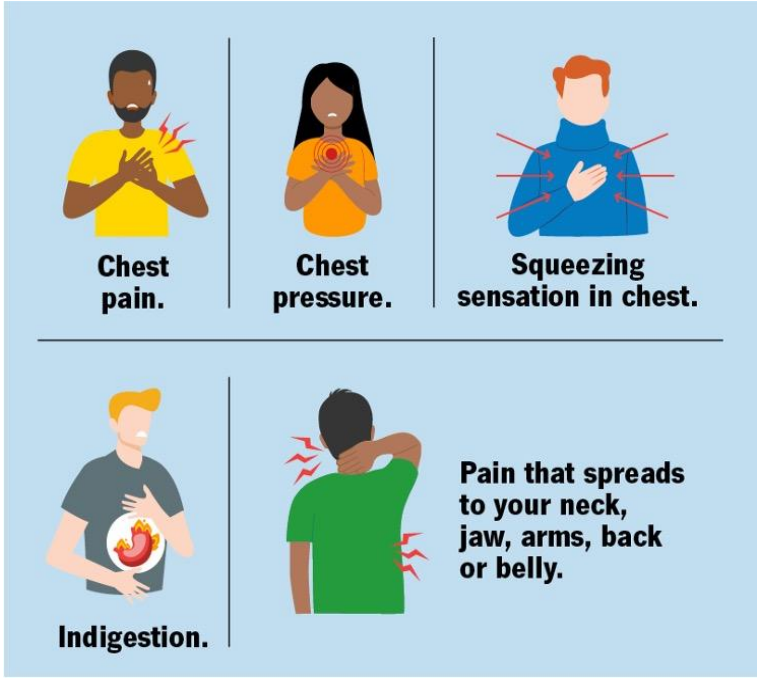
Angina is the cardinal symptom of CAD.

Typically retrosternal chest pain or pressure

- Pain may radiate to the left arm, neck, jaw, epigastric region, or back.
- Pain is not affected by body position or respiration.
- No chest wall tenderness
- May gradually increase in intensity
- May be absent, especially in geriatric and diabetic patients.
- Dyspnea

1 . Chronic stable angina (Classic; exertional angina).

- Its the most common form of angina, therefore, is also called **typical angina**.
- When the pattern of the chest pains and the amount of effort needed to trigger the chest pains do not vary over time, the angina is named "**stable angina**."



- It is due to atheromatous narrowing of the coronary artery.
- Pain is induced by effort and disappears with rest.

- Site and radiation: retrosternal, radiating to the left shoulder and the left arm.
- Duration: usually **< 10-15 min**. If longer than 15 min → suspect ACS.
- Symptoms often subside within minutes with rest or after administration of nitroglycerin
- Common triggers include : Physical exertion, Heavy meals, mental/physical stress or exposure to cold.

2. Acute coronary syndromes (ACS):

A- Unstable angina: It is due to rupture of atheromatous plaque and formation of thrombus. The patient experiences acceleration in the frequency or severity of chest pain, or new-onset angina pain.

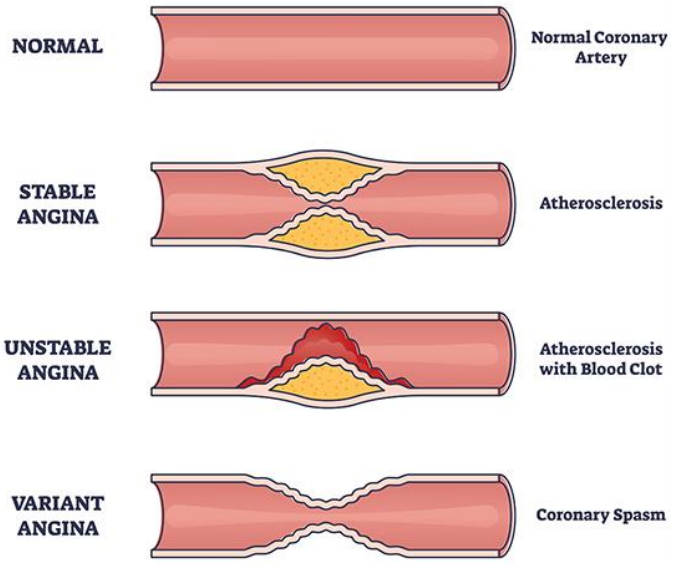
B- Myocardial infarction: An intraluminal thrombus completely occludes the epicardial coronary artery at the site of plaque rupture leading to irreversible coagulative necrosis.

3. Prinzmetal's angina (Variant angina; angina of rest; α-mediated angina):

- Prinzmetal angina is an **uncommon** form of angina that occurs at rest and is due to **coronary artery spasm** causing decreased blood flow to the heart muscle.

May occur due to:

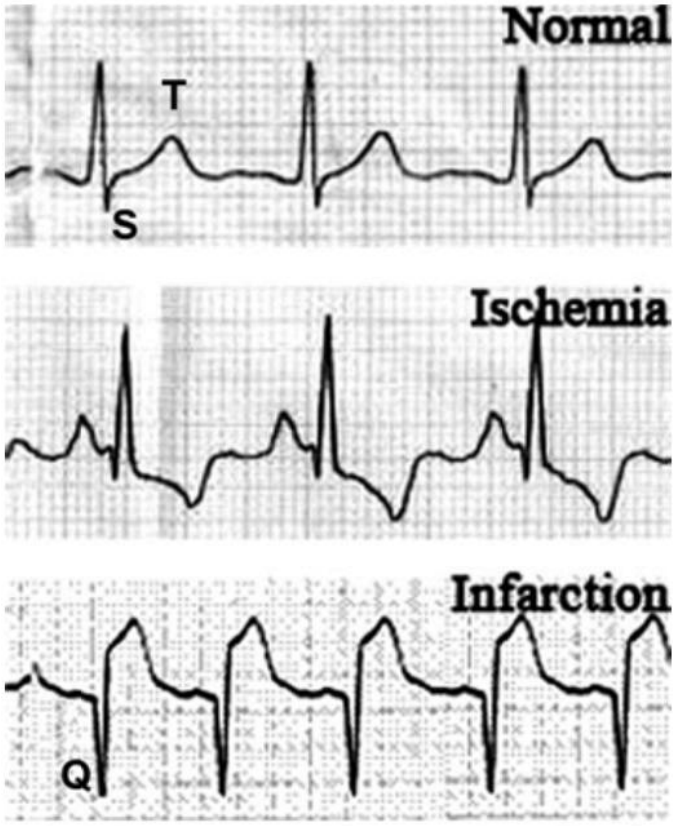
1. Predominant of α-1 on β-2.
2. Inability of Ach to stimulate M3.
3. High level TXA2 which cause VC.



Diagnosis:

1- ECG:

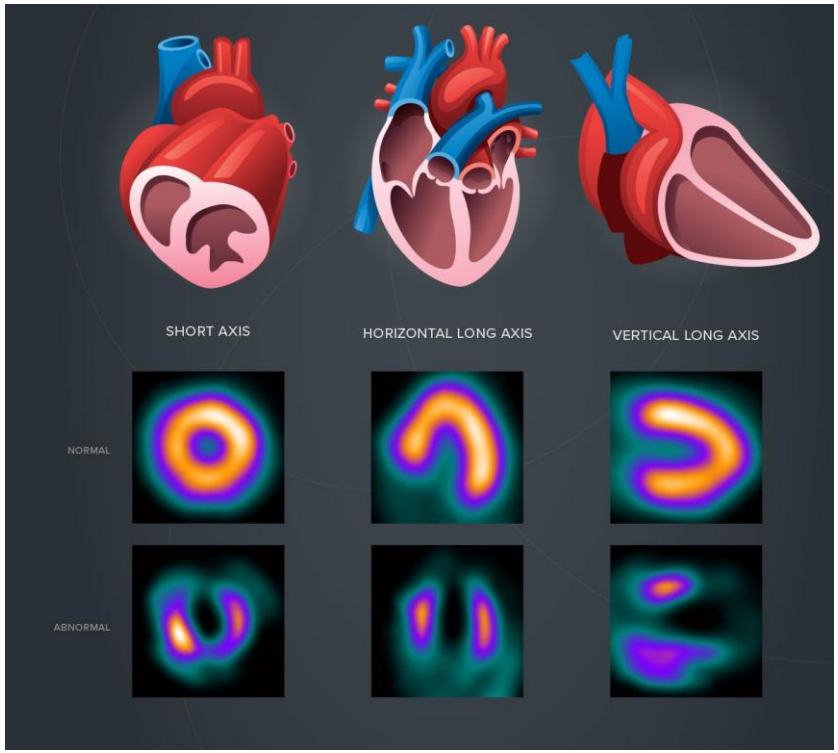
- Resting 12-lead ECG: this is **often normal** and does not exclude ischemic heart disease.
- During attack: there is ST segment depression and T-wave inversion.
- **In myocardial infarction**: ST elevation and late changes deep Q-wave.

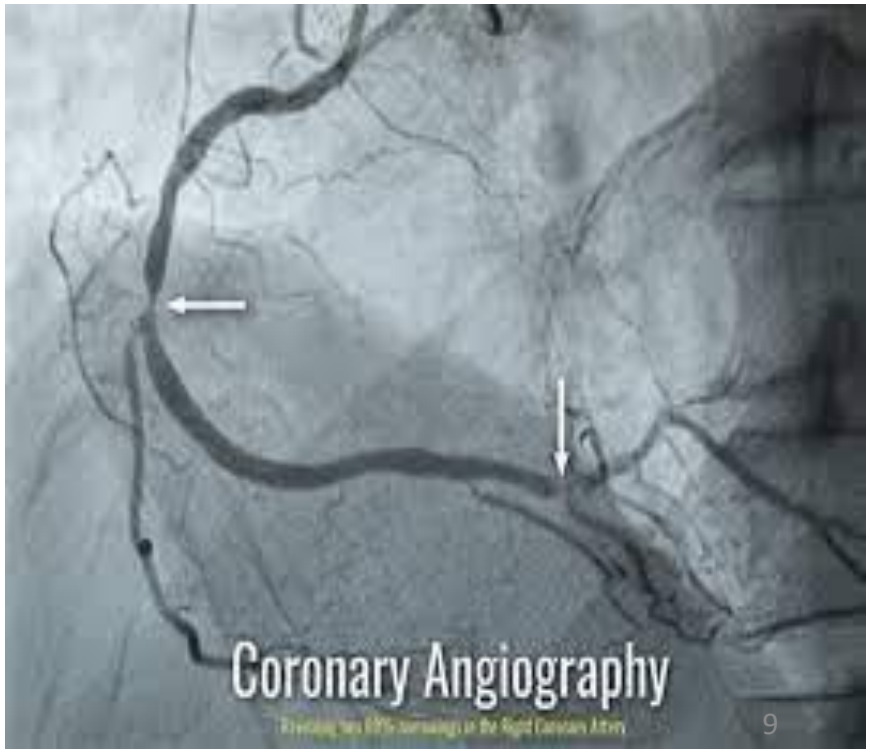


2- Exercise ECG: recording ECG under controlled physical effort to record ischemic changes.

3- Radionuclide myocardial perfusion imaging: decreased myocardial perfusion after stress

4- Coronary angiography.(Gold Standard)





Management of stable angina

i- Non-drug therapy = lifestyle modification

Advice to all patients with angina

- Do not smoke
- Aim for an ideal body weight
- Take regular exercise
- Avoid severe unaccustomed exertion, and vigorous exercise after a heavy meal or in very cold weather
- Take sublingual nitrate before undertaking exertion that may induce angina

Management of stable angina

ii- Pharmacological therapy:

1- Immediate treatment of acute chest pain:

a. Glyceryl trinitrate (GTN): sublingual or spray.

b. Aspirin 300 mg loading dose as soon as possible. It reduces the risk of progression to MI.

c. Refer the patient to hospital if an ACS is suspected.

Management of stable angina

ii- Pharmacological therapy:

Anti-anginal drug therapy

- The goal of anti-anginal therapy is to control symptoms using a regimen that is as simple as possible and does not cause side effects.

1- Nitrates

2- Beta-blockers

3- Calcium channel antagonists

4- Potassium channel activators

d. pFOX inhibitors: trimetazidine

e. Newer antianginal drugs: ranolazine and nicorandil

2- Long-term therapy:

a. Beta-blockers: the first-line agents for chronic stable (exertional) angina.

b. CCBs: the second-line agents for chronic stable angina

c. Long and intermediate acting nitrates.

d. pFOX inhibitors: trimetazidine

e. Newer antianginal drugs: ranolazine and nicorandil

f. Lipid lowering drugs: statins.

g. Antiplatelet drugs: e.g. aspirin, clopidogrel.

iii- Surgical treatment (myocardial revascularization).

Organic nitrates and nitrites:

- Classification:

	Dose	Onset	Duration
Short-acting nitrates:			
Amyl nitrite crushable ampoules	0.3 ml inhalation	1-2 min	5-10 min
Glyceryl trinitrate tablets or spray	0.5 mg SL	1-5 min	10-20 min
Isosorbide dinitrate	5 mg SL	3-5 min	60 min
Glyceryl trinitrate (Tridil®)	5 µg/min i.v.i.		
Intermediate-acting nitrates:			
Isosorbide dinitrate	10 mg oral	15 min	3-6 hrs
	40 mg oral SR	30 min	6-10 hrs
Long-acting nitrates:			
Isosorbide mononitrate	20 mg oral	30 min	6-8 hrs
	60 mg oral SR	30 min	6-10 hrs
Transdermal patches	Nocturnal angina	30 min	12-18 hrs

Pharmacokinetics:

1. **Absorption:** nitrates are **rapidly absorbed** from all sites of administration.
2. **Metabolism:** in the liver:

– If given oral → extensive first-pass metabolism (oral bioavailability <10%)

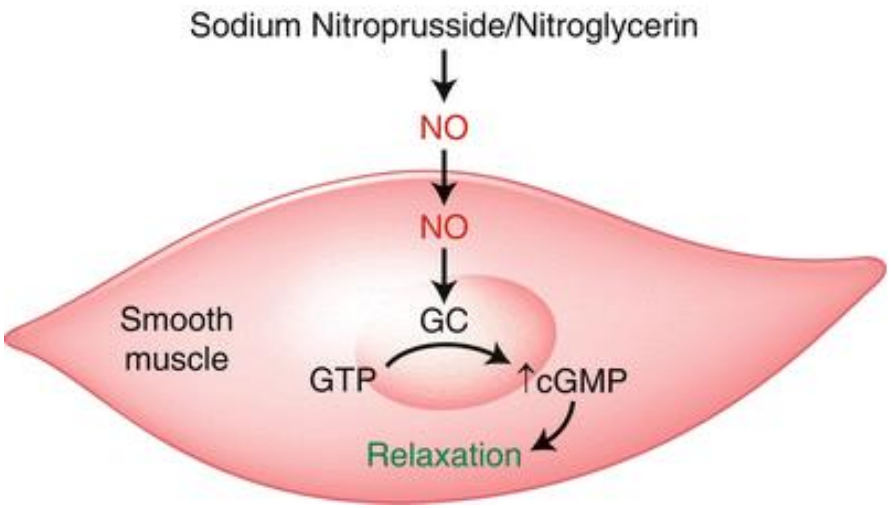
– If given sublingual → no first-pass metabolism → high bioavailability.

– Mononitrate: has no hepatic metabolism → long duration of action.

3. **Excretion:** via the kidney.

Mechanism of action:

1. Nitrates converted by mitochondrial aldehyde dehydrogenase (MALDH) to (NO) which is **identical** to the endothelial derived relaxing factor (EDRF) → ↑ cGMP → VD (more on **veins 90 %** than arteries).
2. They also ↑ formation of vasodilator PGE2 and PGI2.



Pharmacological effects:

1. CVS:

a. Blood vessels:

– VD of the venous (and to lesser extent the arterial side) leading to ↓ preload which leading to ↓ cardiac work.

– VD of coronary arteries leading to increased coronary blood flow.

– VD of arteries in the face and neck leading to flushing of the face (Flushing).

– VD of meningeal vessels leading to throbbing headache.

b. Heart: Reflex tachycardia (in high dose) due to ↓ BP.

2- Smooth muscles: Relaxation of all sm. (bronchial, GIT, uterine, and biliary) due to cGMP activation.

3. Respiratory: Reflex tachypnea due to hypotension **in high doses**.

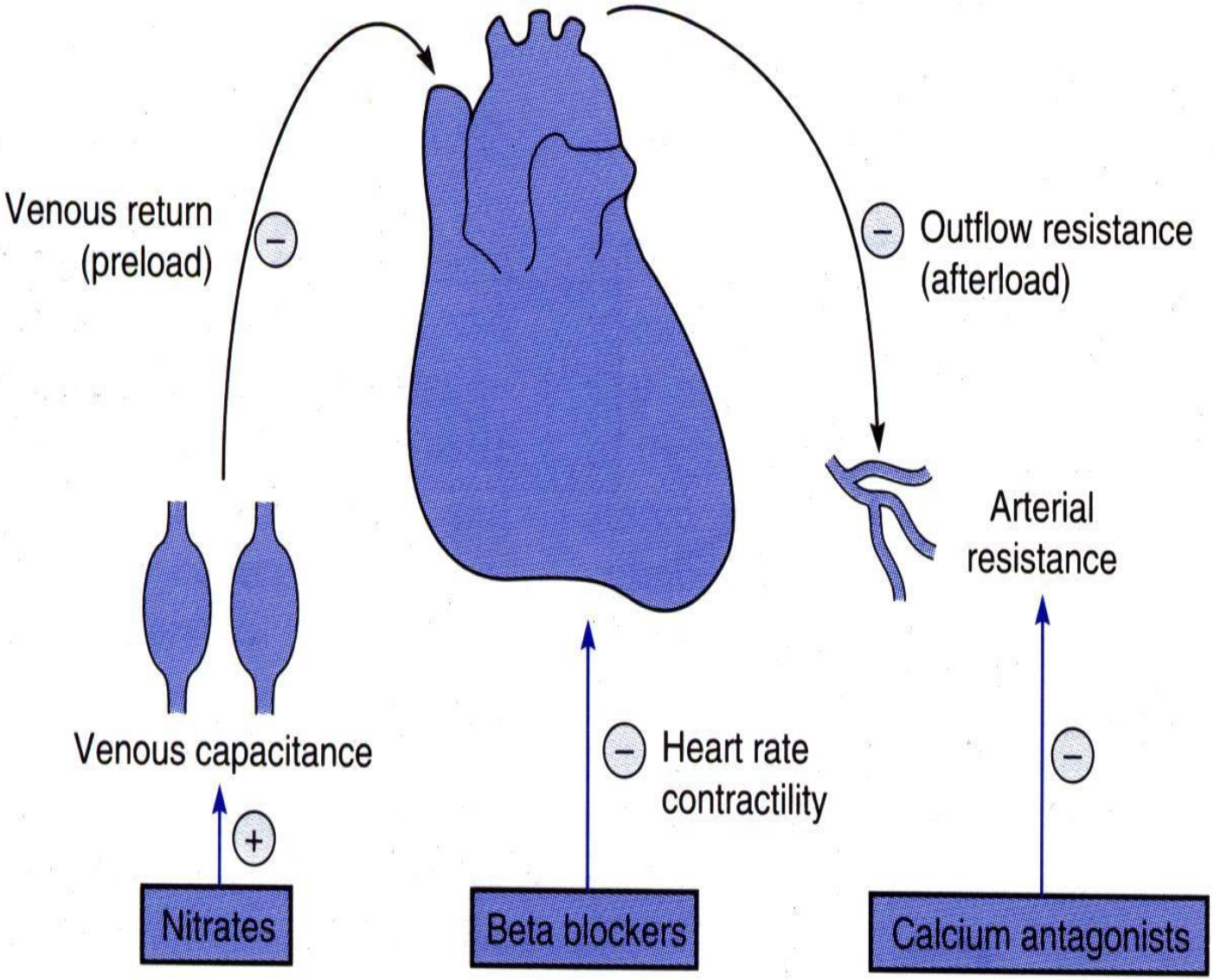
4. Blood: Methemoglobinemia in high doses due to oxidation of Hb into met- Hb.

Management of angina

Relieved/prevented by:

- **Slowing HR**
- **Reducing preload**
- **Reducing afterload - BP**
- **Dilating coronary arteries**
- **Reducing myocardial contractility**

- **Also-**
  - **Correct anemia, tachyarrhythmias**
  - **Modify CV risk factors: Hypertension, DM, smoking cessation, Wt loss, graded exercise**


Venous return
(preload)
Outflow resistance
(afterload)
Arterial
resistance
Venous capacitance
Heart rate
contractility
Nitrates
Beta blockers
Calcium antagonists

Therapeutic uses:

1. **Angina pectoris:** (NO, PGE2 and PGI2 formation) lead to decrease cardiac work & myocardial O2 demand through:

- Venodilatation → ↓ venous return (preload = ↓ end-diastolic pressure).
- Arteriolodilatation → ↓ peripheral resistance (afterload).

2. Enhancement of coronary blood flow (perfusion) through: Coronary VD. and redistribution of blood from large epicardial vessels to ischemic subendocardial vessels.

2. MI: to limit the area of myocardial damage.

3. Acute heart failure: to ↓ preload and afterload.

4. Treatment of cyanide poisoning:

NO oxidate Hb to produce met-Hb, cyanide have higher affinity to bind with oxidized Hb, that will be resulted in cynomet-Hb formation, the later structure detoxed with sodium thiosulfate which convert it to thiocyanate which well **excreted readily by kidney**.

Adverse effects:

1. Hypotension and reflex tachycardia: may aggravate angina (high doses).

2. Throbbing headache: due to VD of meningeal arteries.

3. Flushing of the face.

4. Methemoglobinemia: rare and require high doses.

5. Nitrate tolerance: means diminished response to nitrates with continuous administration which cannot be corrected by increasing the dose. With unclear mechanisms, but 2 theories explain this:

1. continuous administration of nitrates leads to formation of free radicals (ROS) leading to oxidation and inhibition of the enzyme MALDH responsible for bioactivation of nitrites into the vasoactive NO.

2. Prolonged VD by nitrates leads to reflex sympathetic stimulation and activation of RAAS→ VC and salt & water retention.

❖Prevention of nitrate tolerance: make a **daily nitrate-free interval** (10–12 h) to give chance for bioactivating enzymes to regenerate. During this period, give another anti-anginal drug e.g. BBs or CCBs.

Precautions during nitrate therapy:

1. Use the smallest effective dose to avoid hypotension and reflex tachycardia.
2. The patient should **consult his doctor** if anginal pain does not improve after taking **3 SL** tablets of GTN during 15 min (the pain may be due to MI).
3. Nitroglycerine tablets should not be put in direct sunlight (light sensitive) or with cotton (to avoid formation of the explosive nitrocellulose).
4. The expiry date should be checked (active tablets have burning taste).
5. Nitrates should not be used with sildenafil. Why?

Beta-blockers:

1. Its considered first-line in classic angina (note that short acting nitrates are the first line during the acute attack).
2. Treatment objectives include lowering the resting HR to 50-60 beats/min and limiting maximal exercise HR to ~ 100 beats/min or less.
3. There is little evidence to suggest superiority of any particular β-blocker, but β- blockers with intrensic sympathomimetic activity ISA should be avoided because the reduction in HR and O2 consumption would be minimal. E.g. Pindolol.
4. They are contraindicated in Prinzmetal's angina because they block the β2-mediated coronary dilatation leaving the α1 receptors unopposed → ↑ coronary spasm.

Mechanism of β-blockers in exertional angina:

1. They ↓ contractility, HR, and systolic BP → ↓ myocardial work and O2 demand.
2. They ↑ diastolic (coronary) filling time.
3. Cause redistribution of blood from normal to ischemic (subendocardial) regions.
4. Cytoprotective effect: they produce metabolic switch from myocardial fat utilization to CHO utilization (i.e. improves myocardial metabolism).

Why combination of nitrate and BB preferred?

	β-blockers	Nitrates	Combination
– HR	↓	↑ (Reflex)	↓ or no effect
– Contractility	↓	↑ (Reflex)	↓ or no effect
– Diastolic filling time	↑	↓	↑ or no effect
– Blood pressure	↓	↓	↓↓

- Combination of BBs and nitrates ↑ their efficiency & ↓ their side effects (Tolerance).

Calcium channel blockers (CCBs):

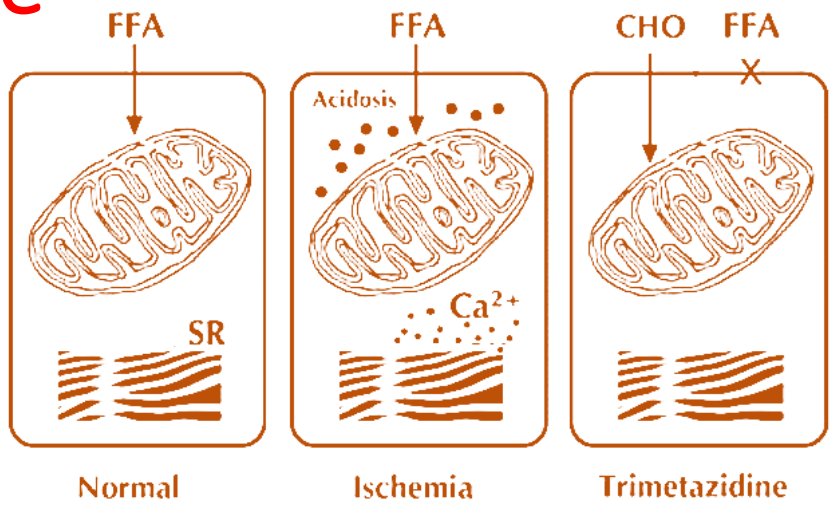
1. They are considered first-line treatment for Prinzmetal's (variant) angina.
2. They are considered second-line alternative after BBs in chronic stable angina in whom BBs are contraindicated (**Asthma**).
3. Short acting dihydropyridines e.g. nifedipine are associated with increased risk of ACS and should be avoided. Long acting dihydropyridines (e.g. amlodipine) and non-dihydropyridines (verapamil and diltiazem) are more preferred.
4. Amlodipine is the CCB of best choice for symptomatic treatment of angina and/or hypertension in patients with chronic heart failure.

Newer options for treatment of chronic angina:

(pFOX inhibitors, k channel openers, ranolazine)

- These drugs alter the balance between myocardial work and O2 supply by novel mechanisms of action.
- Their efficacy in treatment of angina is controversial; however they are approved for treatment of chronic stable angina in combination with βB, CCBs, and nitrates.

pFOX inhibitors (metabolic modifiers): Trimetazidine



- They prevent fatty acid oxidation in the myocardium.

- This "metabolic switch" from fats to CHO utilization requires less O2 consumption.

- By inhibition of fatty acid oxidation, they ↓ intracellular lactic acidosis leading to ↓ intracellular Ca^{2+}. So they prevent cell necrosis and preserve contractile function.

Ranolazine:

- It ↓ intracellular Ca^{2+} indirectly by reducing the late Na+ current that facilitates Ca^{2+} entry into myocardial cells.
- The reduction in intracellular Na+ and Ca^{2+} load reduces cardiac contractility and work.
- *It does not affect HR, blood pressure or coronary blood flow*.

Potassium channel openers: Nicorandil:

– Nicorandil is a new antianginal drug with 2 proposed mechanisms of action:

1. It opens ATP-dependent K+ channels in the vascular wall leading to VD of peripheral and coronary arteries.
2. Nitrate-like activity: **it has a nitrate component** and ↑ cGMP like nitrates but tolerance to its effects is less marked.

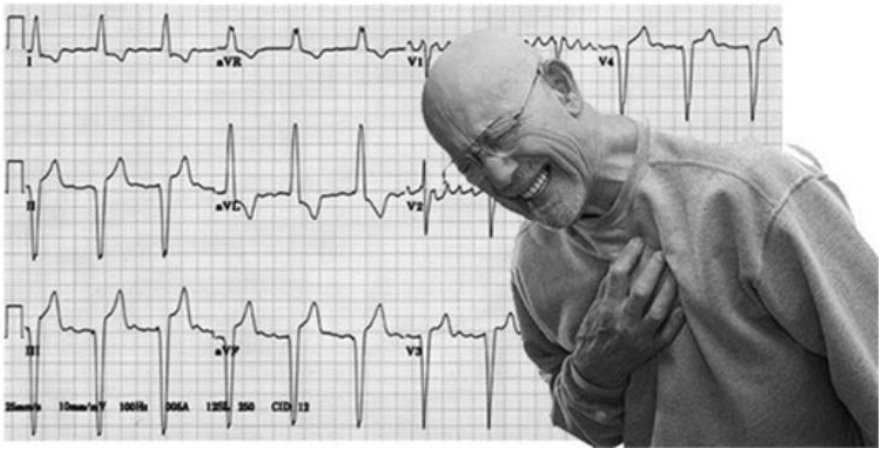
– Like nitrates, it should not be used with sildenafil.

Choice of antianginal drugs in patients with another disease:

Angina with….	Most preferred	Least preferred
Bronchial asthma	Nitrates, CCBs	Beta-blockers
Heart failure	Amlodipine	Beta-blockers, Verapamil
Hypertension	Beta-blockers, CCBs	Nitrates
Diabetes mellitus	Nitrates, Nifedipine	Beta-blockers, Verapamil

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION (AMI):

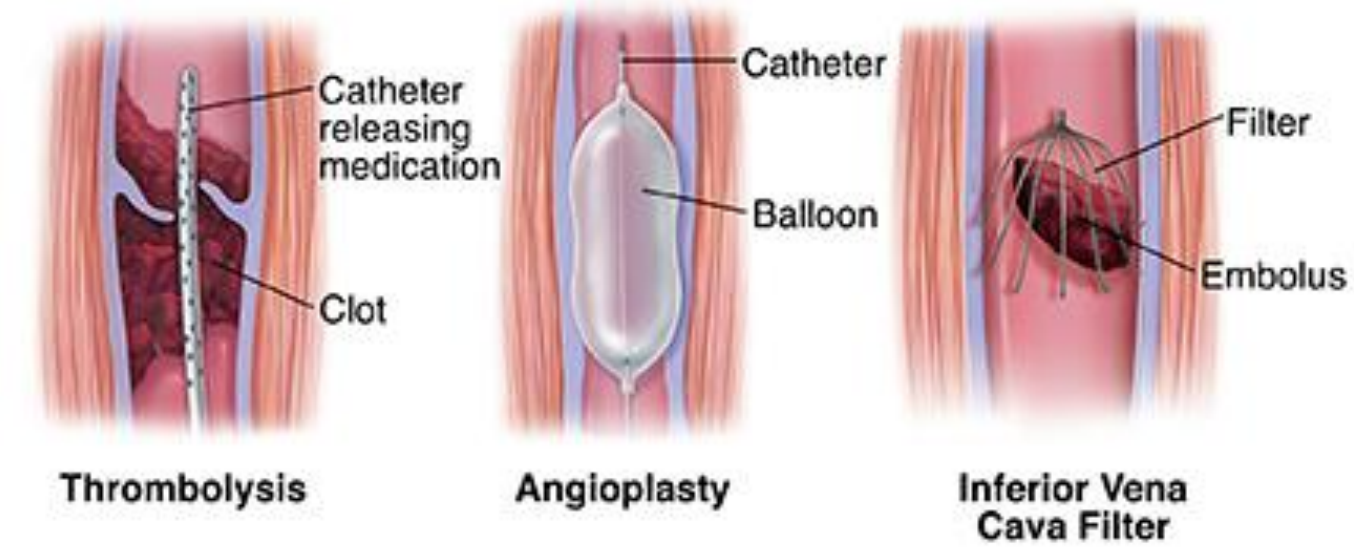
Manifestations: persistent central crushing chest pain + ST segment elevation or depression + pathological Q wave + raised biochemical markers of myocardial cell death (troponin enzyme).



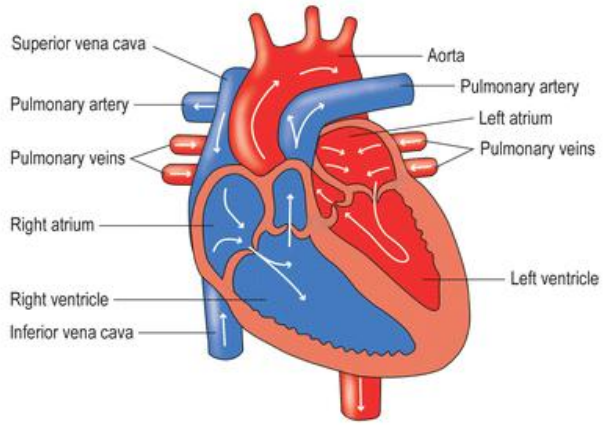
All cases must be hospitalized in a specialized coronary care unit.

Non-pharmacologic therapy:

- Patients presenting within 12 hours of symptom onset, the treatment of choice is percutaneous coronary intervention (PCI, or coronary angioplasty).
- A balloon catheter, guided by x-ray imaging, is introduced into the occluded artery to open it.



Pharmacologic therapy: (MONATSCT)



1. Morphine sulfate (5 mg i.v.):

– To produce analgesia and ↓ stress of the patient → ↓ sympathetic discharge and heart work.

– Morphine causes venodilatation → ↓ venous return and cardiac work.

- In case of inferior MI morphine is contraindicated and must replaced with Meperidine.

2. Oxygen: Recent evidence suggests that routine O2 administration has doubtful significance and did not reduce mortality except in hypoxia.

3. Nitroglycerine and beta-blockers: to limit the infarct size.

4. Anticoagulant drugs: heparin 10,000 IU i.v. then 5000 IU/8h s.c. especially when the patient is obese or if there is history of previous MI.

5.Thrombolytic (fibrinolytic therapy: streptokinase, urokinase, or t-PA as early as possible.

6. Sedatives: Diazepam 5 mg i.v.

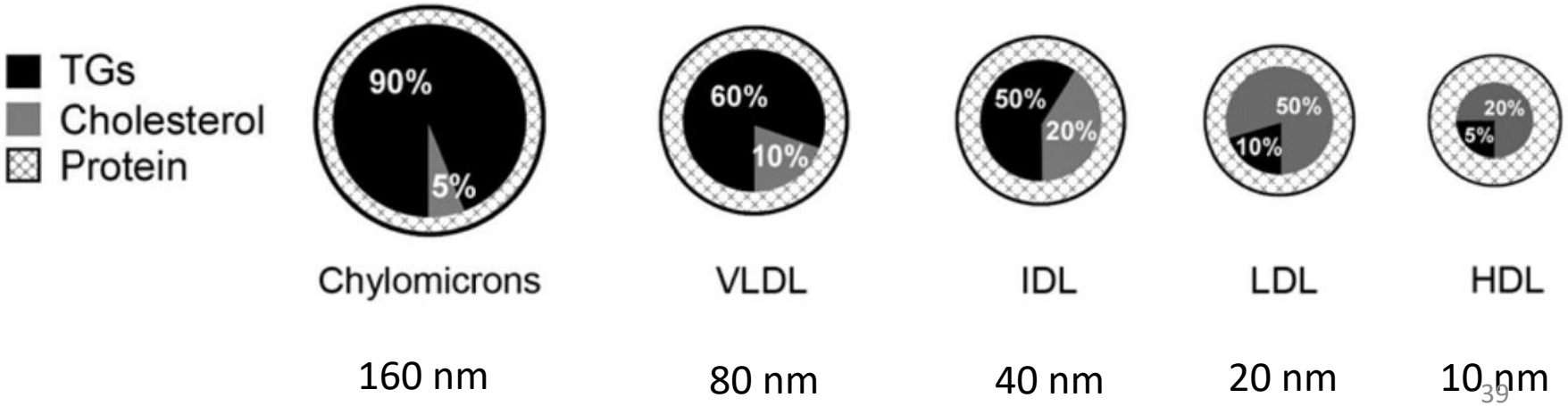
7. Treatment of Complications:

- Cardiogenic shock → dobutamine(hypotention) i.v. (B1 agonist)

- Arrhythmia → lidocaine i.v.

Antihyperlipidemic drugs

- Hyperlipidemia: Elevation of TG or Cholesterol or both.
- Lipoproteins consist of a hydrophobic lipid core (TGs or cholesterol) surrounded by a hydrophilic coat of phospholipids and proteins (apoproteins), which render them miscible in aqueous plasma.
- There are 5 classes of lipoproteins depending on their relative proportion of the core lipids, type of apoprotein, size, and density:



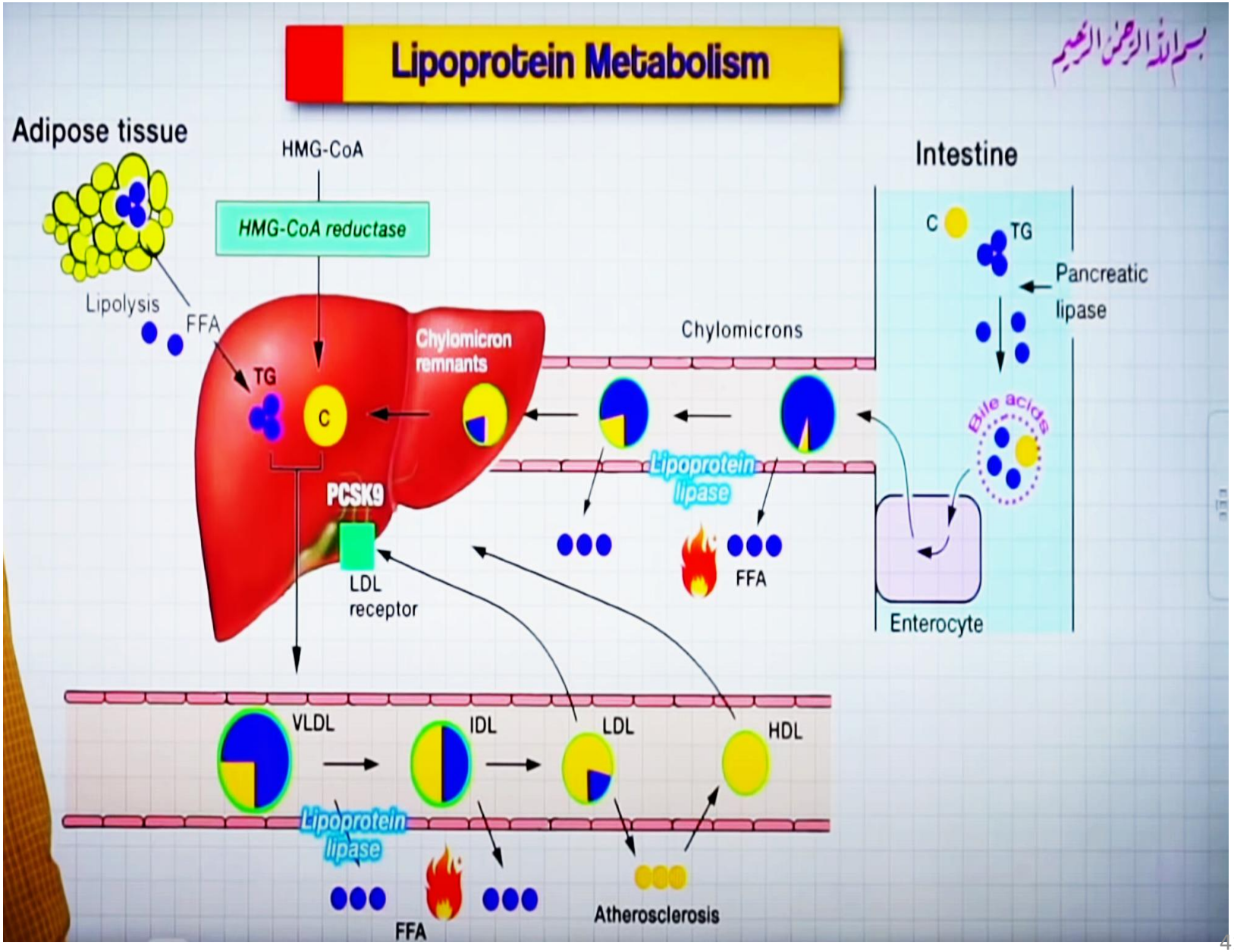
Classification of hyperlipidemia:

1. Primary (familial; hereditary) hyperlipidemia:

Class	Increased lipoprotein	Synonym
Type I	↑ chylomicrons	Familial chylomicronemia
Type IIa	↑ LDL	Familial hypercholesterolemia
IIb	↑ LDL and VLDL	Familial combined hyperlipidemia
Type III	↑ IDL	Familial dysbetalipoproteinemia
Type IV	↑ VLDL	Familial hypertriglyceridemia
Type V	↑ VLDL and chylomicrons	Familial mixed hyperlipedemia

2. Secondary (acquired) hyperlipidemia:

- Hypercholesterolemia: hypothyroidism, nephrotic syndrome, and drugs e.g. thiazide .
- Hypertriglyceridemia: DM, alcohol, gout, chronic renal failure.


Lipoprotein Metabolism
بسم الله الرحمن الرحيم
Adipose tissue
HMG-CoA
HMG-CoA reductase
Intestine
C
TG
Pancreatic lipase
Lipolysis
FFA
TG
C
Chylomicron remnants
Chylomicrons
Bile acids
Lipoprotein lipase
PCSK9
LDL receptor
FFA
Enterocyte
VLDL
IDL
LDL
HDL
Lipoprotein lipase
FFA
Atherosclerosis

LIPID LOWERING DRUGS:

1. Inhibitors of intestinal cholesterol absorption:

– Bile acid binding resins: cholestyramine, colestipol – Ezetimibe

2. Activators of plasma lipoprotein lipase: fibric acid derivatives

3. HMG-CoA reductase inhibitors: statins.

4.Inhibitors of hepatic lipid production: nicotinic acid,

Acipimox.

5. Other drugs: d-thyroxin, neomycin, and probucol

Cholestyramine and colestipol:

Mechanism of action:

They form complexes with bile acids in the intestine and ↓ enterohepatic absorption of bile salts and ↓ absorption of cholesterol.

Therapeutic uses:

1. Hypercholesterolemia (type IIa): Bile acid sequestrants are effective in reducing plasma cholesterol (10%–20%) in patients with some normal LDL receptors.
2. Diarrhea due to bile acid malabsorption.
3. Pruritus due to obstructive jaundice.

Adverse effects:

1. GIT upset (the most common): nausea, vomiting and **steatorrhea** (due to ↓ fat absorption).
2. ↓ absorption of fat-soluble vitamins.
3. ↓ absorption of anionic drugs e.g. digitalis and warfarin.

Ezetimibe:

Mechanism of action:

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption. It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.

Therapeutic uses:

Hypercholesterolemia: Ezetimibe is synergistic with HMG-CoA reductase inhibitors, producing decrease of 25% in LDL cholesterol.

Adverse effects:

Reversible hepatic dysfunction: liver function tests should be done at regular intervals.

Fibric acid derivatives (Fibrates):

(Clofibrate, Fenofibrate, Bezafibrate,

Gemfibrozil)

Mechanism of action:

Fibrates act on nuclear receptors called peroxisome proliferator activated receptors-α (PPAR-α) leading to ↑ synthesis of lipoprotein lipase → ↑ peripheral catabolism of VLDL and chylomicrons (TGs).

Therapeutic uses:

1. Hypertriglyceridemia (types IIb, III, IV and V).
2. Fenofibrate has antidiuretic action in individuals with mild to moderate diabetes insipidus.

Adverse effects:

1. GIT upsets: nausea, vomiting (the most common).
2. Increase formation of cholesterol gallstones.
3. Hepatic dysfunction and elevation of serum transaminases.
4. Fibrates increase the risk of myopathy if used in combination with statins.
5. Skin rash and dermatologic reactions.

HMG-CoA reductase inhibitors (Statins):

(Lovastatin, Pravastatin, Mevastatin, Atorvastatin)

Mechanism of action:

Competitive inhibition of hydroxy-methyl-glutaryl coenzyme-A (HMG-CoA) reductase → ↓ cholesterol synthesis and ↑ hepatic uptake of LDL.

Therapeutic uses:

- Hypercholesterolemia (type II).
- With other drugs for combined hyperlipidemia.

Adverse effects:

H : **Hepatic dysfunction** leading to elevation of serum transaminases. Therapy should be stopped if liver enzymes rise > 3-folds the upper normal value.

M :(Muscle) **Myopathy**, **myositis** and **rhabdomyolysis** in both skeletal and cardiac muscle leading to ↑ of creatine phosphokinase (CPK) enzyme.

G : **GIT upsets**: nausea, vomiting, anorexia (the most common).

Co-A : **Cataract** (lenticular Opacity) in middle-Aged individuals.

Reductase **Renal dysfunction** (especially with lovastatin).

Fibrates, particularly **gemfibrozil**, increase the risk of **myopathy and rhabdomyolysis** when used in combination with statins due to several pharmacokinetic and pharmacodynamic interactions

1. Impaired Statin Metabolism (Pharmacokinetic Interaction)

Gemfibrozil strongly inhibits the enzyme CYP2C8 and **inhibits OATP1B1 transporters** in the liver.

OATP1B1 transporters help statins (especially simvastatin, atorvastatin, and rosuvastatin) enter liver cells for metabolism and clearance.

When OATP1B1 is inhibited, statin levels in the blood **increase significantly**, leading to a **higher risk of myopathy**.

2. Increased Muscle Toxicity (Pharmacodynamic Interaction)

Both statins and fibrates independently have the potential to cause **muscle toxicity** by interfering with muscle energy metabolism.

The combined use leads to **synergistic muscle damage**, increasing the risk of **myopathy and rhabdomyolysis**.

3. Different Risk with Different Fibrates

Gemfibrozil has the highest risk due to its strong effect on statin metabolism.

Fenofibrate has a much lower risk because it has minimal interaction with statin metabolism.

Nicotinic acid (Niacin; vitamin B3):

Mechanism of action:

- Niacin *(but not nicotinamide)* **inhibits lipolysis** in adipose tissue and inhibits fatty acid synthesis by the liver → ↓ hepatic VLDL and LDL synthesis.

Therapeutic uses:

In combination with other drugs for all types of hyperlipidemia (except type I which is mainly treated by diet control).

Adverse effects:

1. **Skin flushing** and burning sensation (the most common). It is harmless effect mediated by PGs and histamine release and can be diminished by taking aspirin 30 minutes before taking nicotinic acid.
2. Gastric irritation (the drug should be avoided in peptic ulcer).
3. Hyperglycemia, hyperuricemia, and reversible increase in serum transaminases.

Key Clinical in cases

Avoid gemfibrozil + statin combinations due to the high risk of myopathy.

Fenofibrate is safer with statins but still requires monitoring.

Monitor for muscle symptoms (weakness, pain, dark urine) in patients on combination therapy.

Coenzyme Q10 (CoQ10), Statins, and Fibrates:

Coenzyme Q10 (CoQ10) is essential for **mitochondrial energy production** and **antioxidant protection** in muscle cells. Both **statins and fibrates** can reduce CoQ10 levels, which may contribute to **muscle-related side effects** such as myopathy and fatigue.

1. Statins and CoQ10 Depletion

Statins inhibit HMG-CoA reductase, the enzyme responsible for cholesterol synthesis.

This also blocks the production of **mevalonate**, a precursor for CoQ10.

As a result, CoQ10 levels **decrease**, leading to impaired muscle function and a higher risk of **myopathy, fatigue, and muscle pain**.

2. Fibrates and CoQ10 Levels

Fibrates lower triglycerides by activating **PPAR-α**, but they may also **reduce CoQ10 levels** by increasing its clearance.

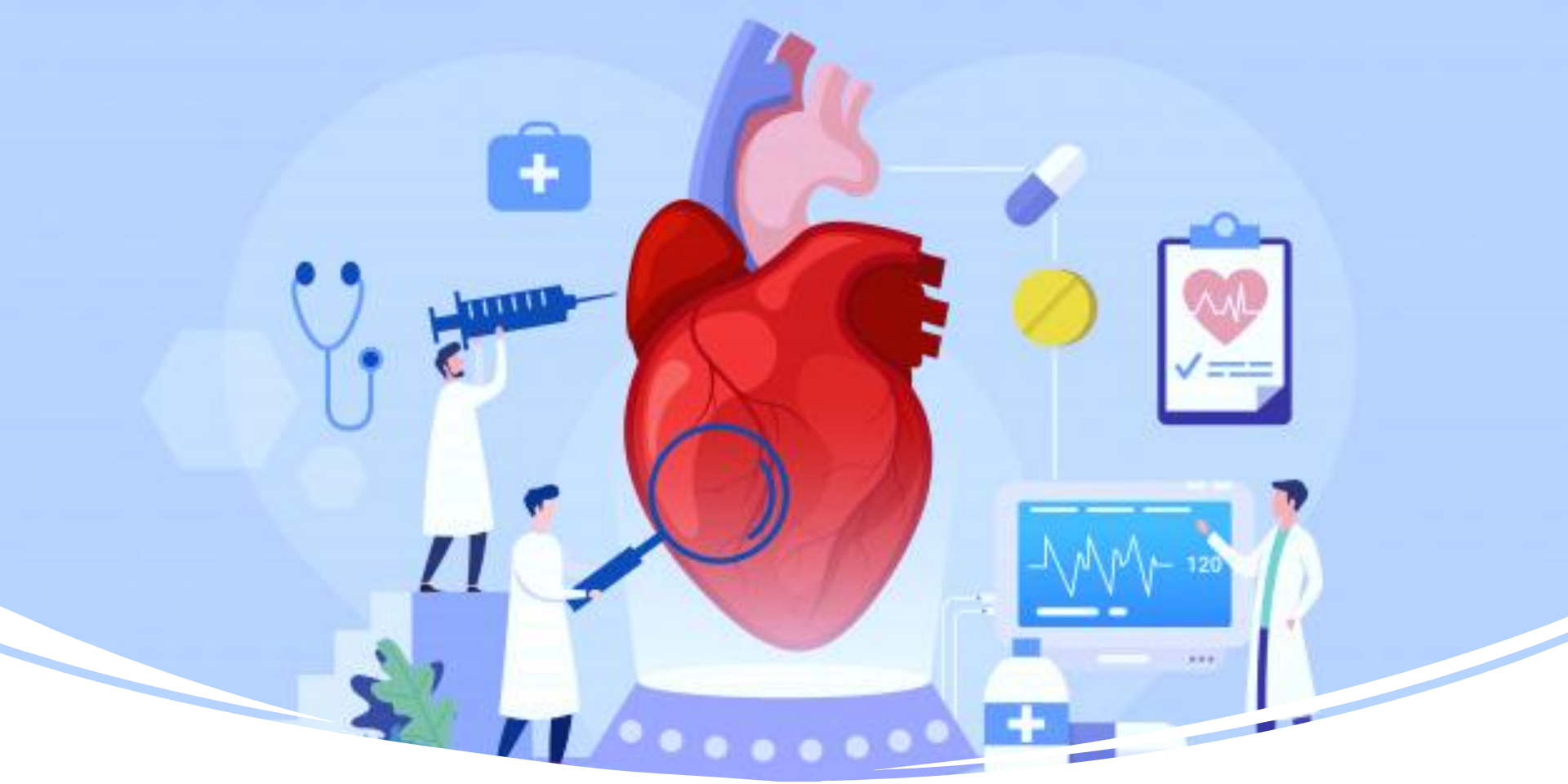
The exact mechanism isn't as well understood as with statins, but fibrates alone can also contribute to **muscle-related side effects**.

Summary

	Effect on LDL	Effect on HDL	Effect on TGs
Bile acid-binding resins	↓↓↓	↑	----
Reductase inhibitors	↓↓↓	↑	↓
Fibrates	↓	↑	↓↓↓
Niacin	↓	↑↑↑	↓↓

Treatment with drug combinations

Hypercholesterolemia	Cholestyramine + Reductase inhibitors
Hypertriglyceridemia	Niacin + Fibrates
Familial combined hyperlipidemia	Cholestyramine + Fibrates. Cholestyramine + Niacin. Statins + Fibrates *(this combination may ↑ risk of myopathy).*



Thank You

- Nitrates (e.g., **nitroglycerin, isosorbide dinitrate**) and **sildenafil** (Viagra) cannot be used together because they both cause **vasodilation** by increasing nitric oxide (NO) levels, which can lead to a **severe and potentially life-threatening drop in blood pressure** (**hypotension**).
- **Mechanism of Action**
- **Nitrates:**
  - Release **nitric oxide (NO)** → activates **guanylate cyclase** → increases **cyclic GMP (cGMP)** → **smooth muscle relaxation** → vasodilation → **lower blood pressure**.
- **Sildenafil (PDE-5 Inhibitor):**
  - Inhibits **phosphodiesterase-5 (PDE-5)**,

  which normally breaks down **cGMP**.
  - Leads to **increased cGMP levels**, enhancing vasodilation.