Basic & Clinical Pharmacology

Twelfth Edition

CHAPTER

12

Vasodilators & the Treatment of Angina Pectoris

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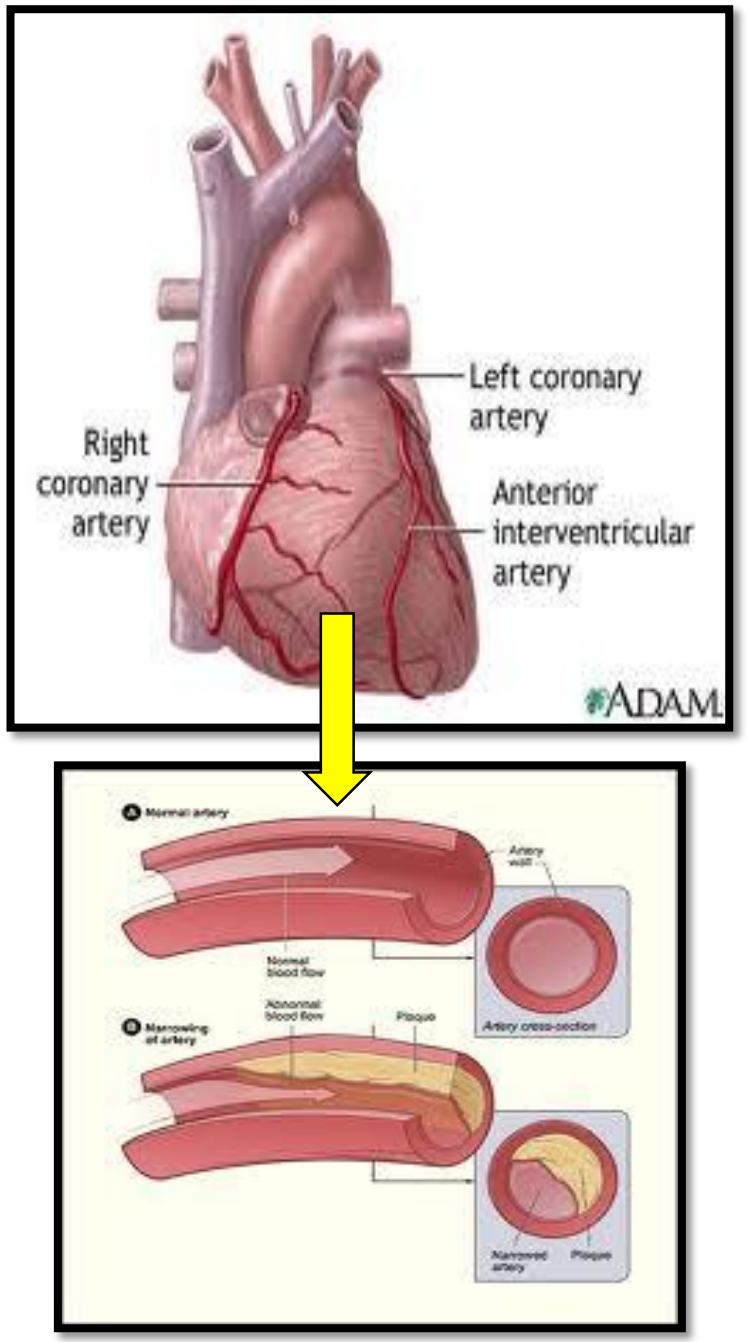
1. Angina pectoris

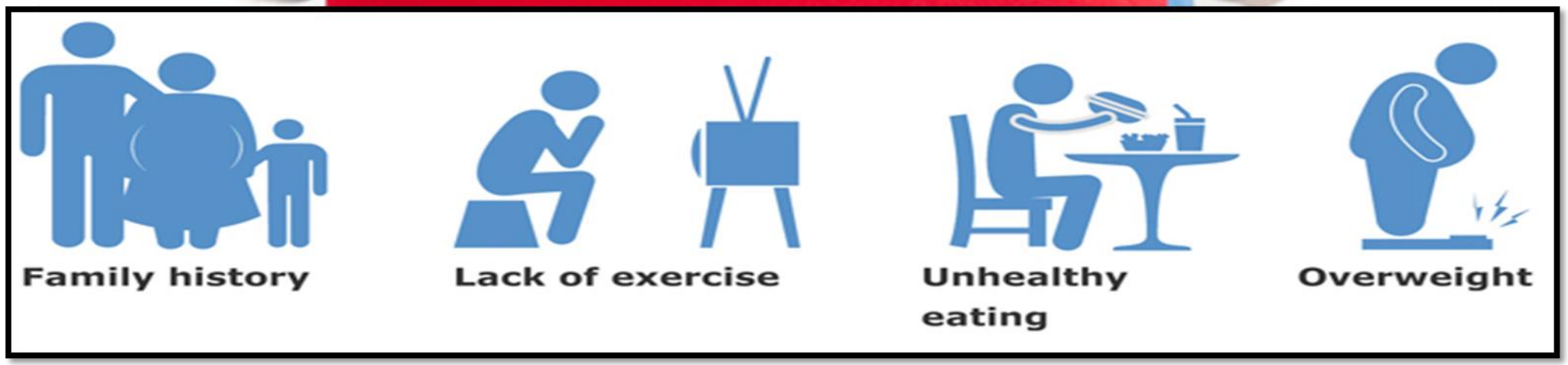
Commonly known as angina, is severe chest pain due to ischemia (a lack of blood, hence a lack of oxygen supply) of the heart muscle, generally due to obstruction or spasm of the coronary arteries (the heart's blood vessels).

- **The imbalance between oxygen delivery and utilization may result during exertion, from a spasm of the vascular smooth muscle, or from obstruction of blood vessels caused by atherosclerotic lesions.**

- **These transient episodes (15 seconds to 15 minutes) of myocardial ischemia do not cause cellular death, such as occurs in myocardial infarction.**

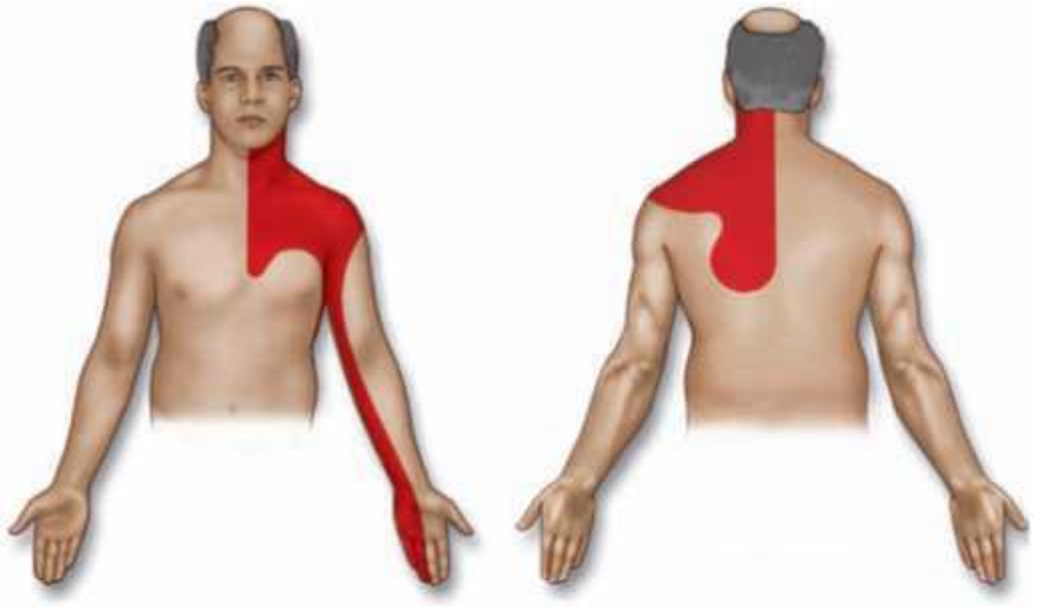



Risk
Factor


Family history
Lack of exercise
Unhealthy eating
Overweight

Types of Angina- A. Stable angina

- **Stable angina is the most common form of angina and, therefore, is called typical angina pectoris. It is characterized by a burning, heavy, or squeezing feeling in the chest.**



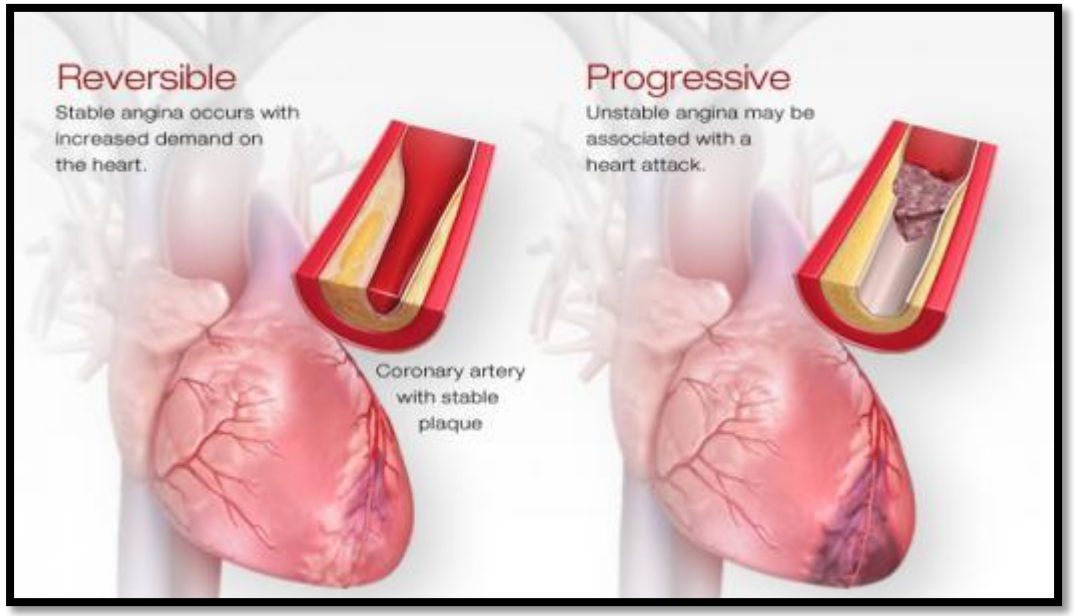
- **It is caused by the reduction of coronary perfusion due to a fixed obstruction produced by coronary atherosclerosis.**

The heart becomes vulnerable to ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload.

Typical angina pectoris is promptly relieved by rest or nitroglycerin (sublingual).

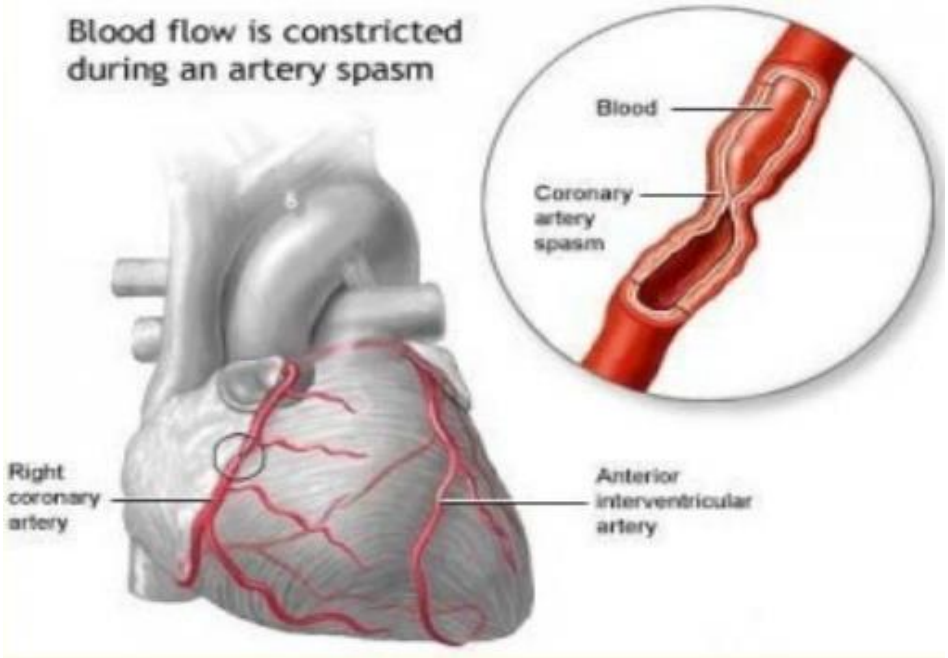
B. Unstable angina

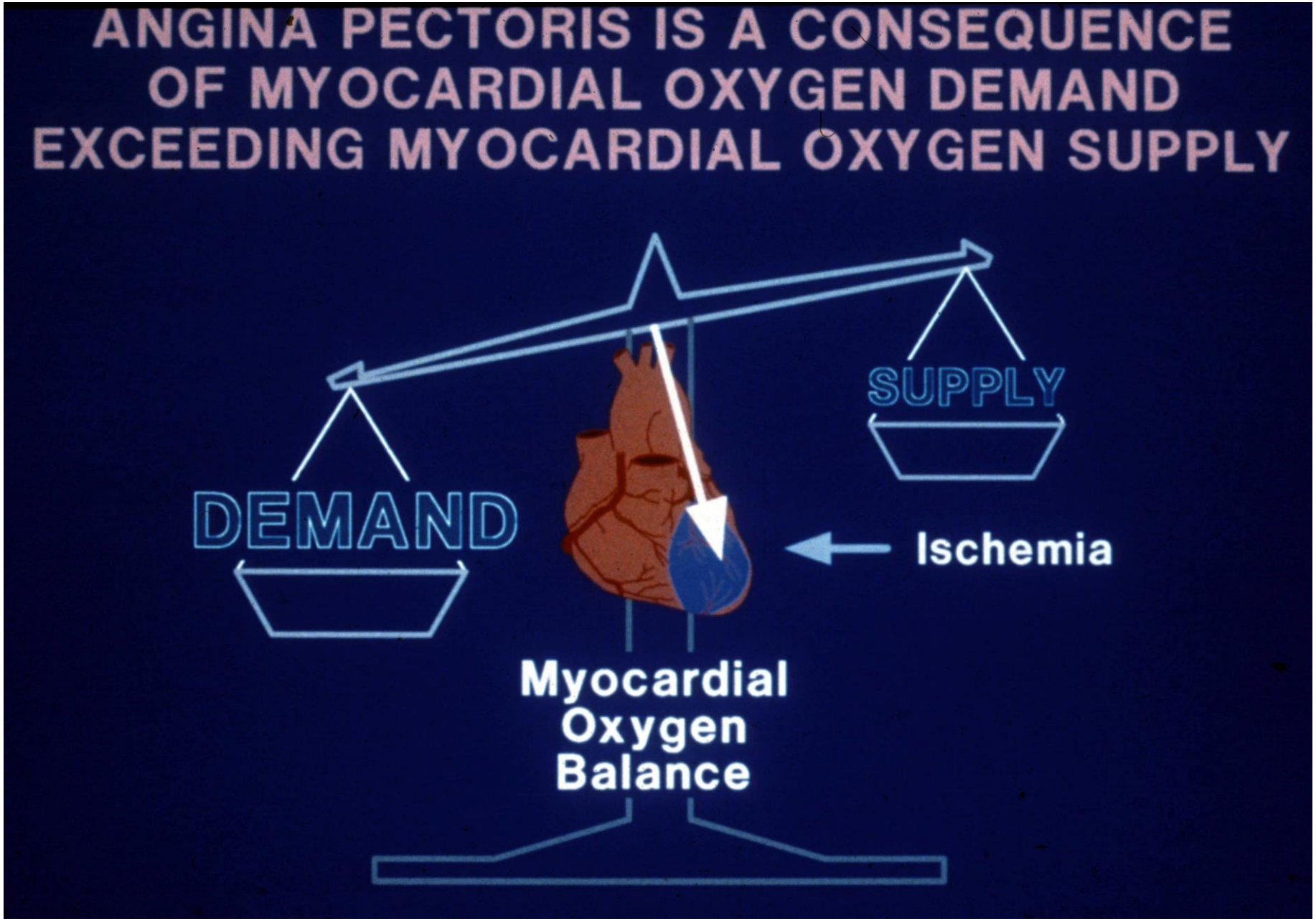
- Unstable angina lies between stable angina and myocardial infarction on the other.
- In unstable angina, **chest pains occur with increased frequency** and are precipitated by progressively less effort.
- The **symptoms are not relieved** by rest or nitroglycerin.
- Unstable angina requires **hospital admission** and more aggressive therapy to prevent death and progression to myocardial infarction.
  - **Antiplatelet**
  - **IV nitrates**



C. Prinzmetal's or variant or vasospastic angina

- **Prinzmetal's angina is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm.**
- **Symptoms are caused by decreased blood flow to the heart muscle due to spasm of the coronary artery.**
- **Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure.**
- **Prinzmetal's angina generally responds immediately to coronary vasodilators, such as nitroglycerin and calcium-channel blockers.**



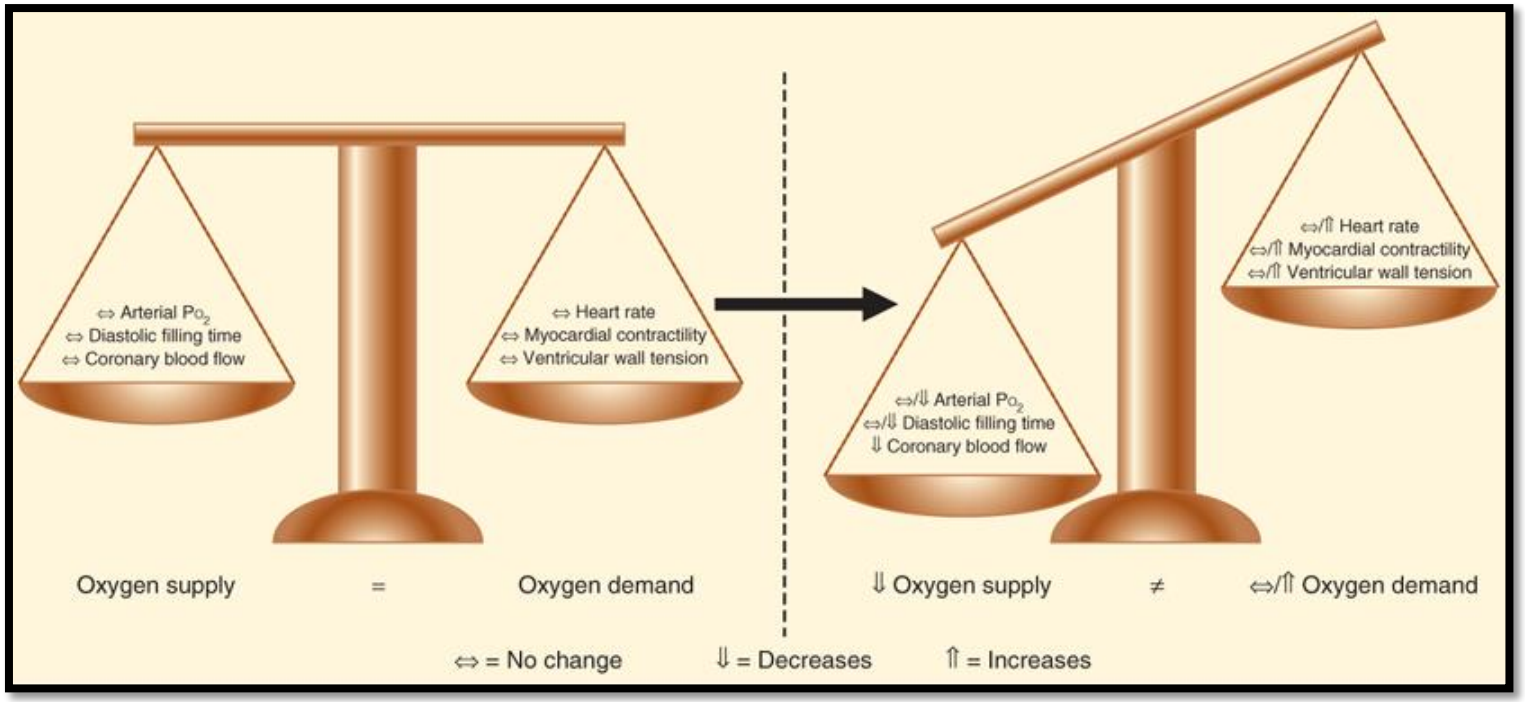

ANGINA PECTORIS IS A CONSEQUENCE
OF MYOCARDIAL OXYGEN DEMAND
EXCEEDING MYOCARDIAL OXYGEN SUPPLY
SUPPLY
DEMAND
Ischemia
Myocardial
Oxygen
Balance

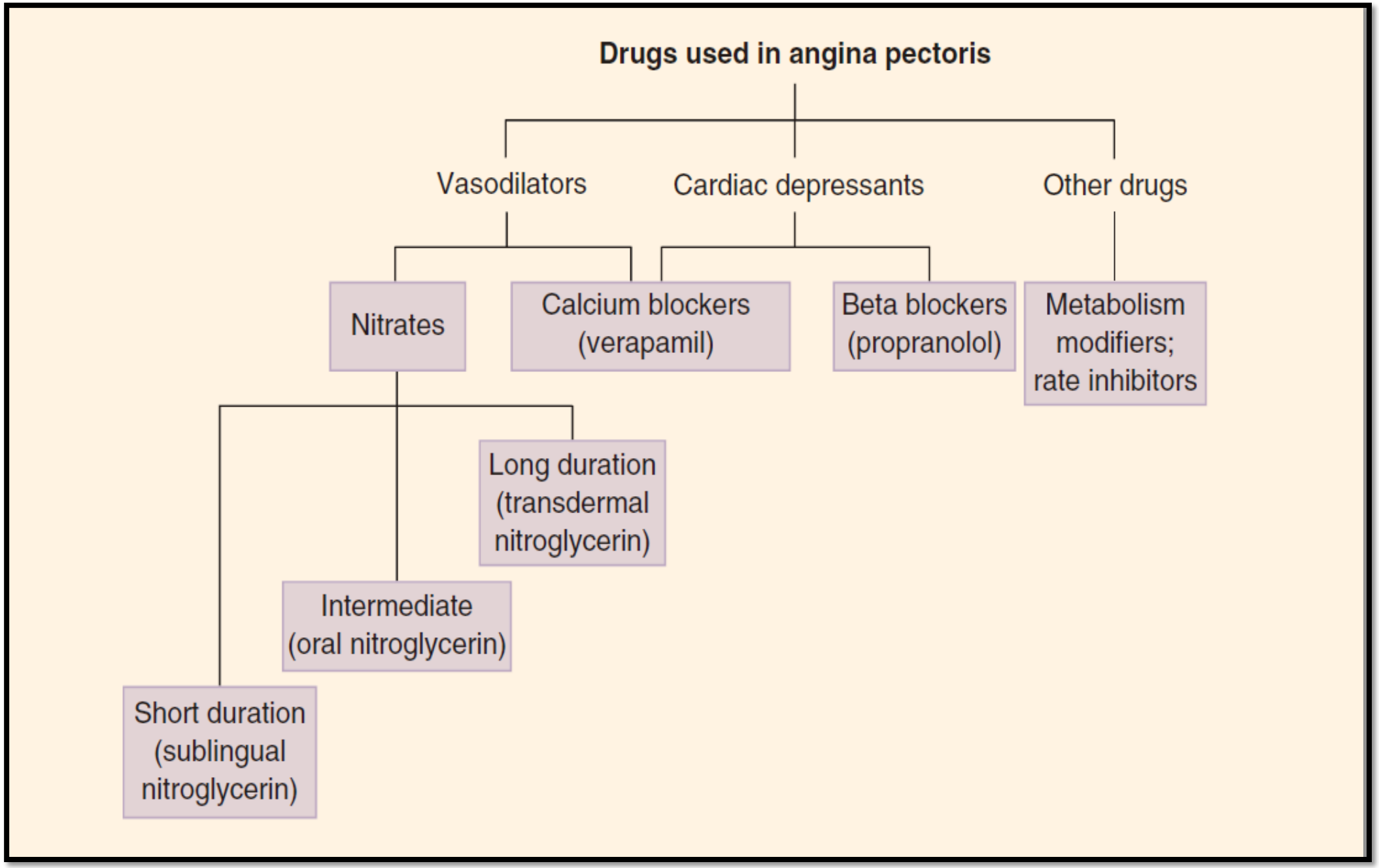
Treatment Plan:

A. Decrease the risk factors

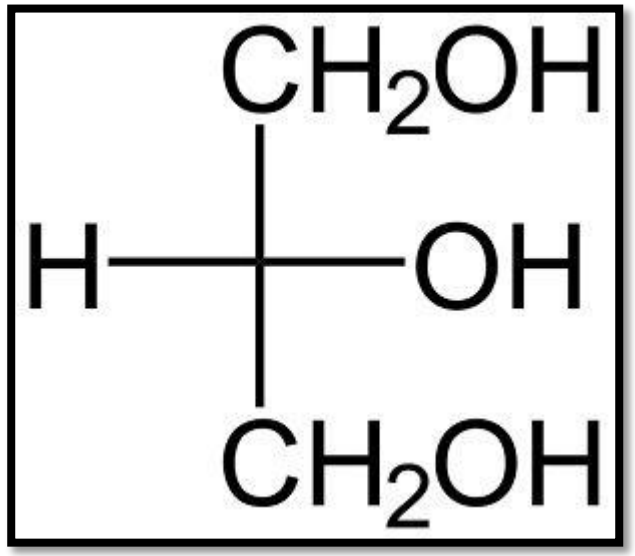
B. Increase oxygen supply

C. Decrease oxygen demand

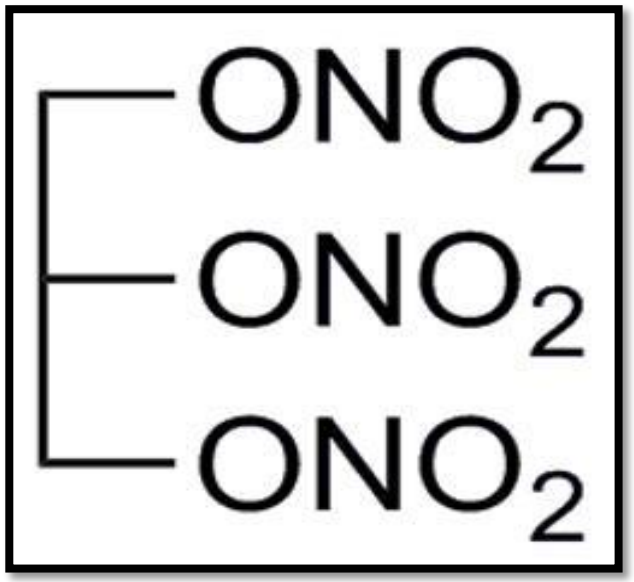



Drugs used in angina pectoris
Vasodilators
Cardiac depressants
Other drugs
Nitrates
Calcium blockers (verapamil)
Beta blockers (propranolol)
Metabolism modifiers; rate inhibitors
Long duration (transdermal nitroglycerin)
Intermediate (oral nitroglycerin)
Short duration (sublingual nitroglycerin)

Nitrates



Glycerin structure

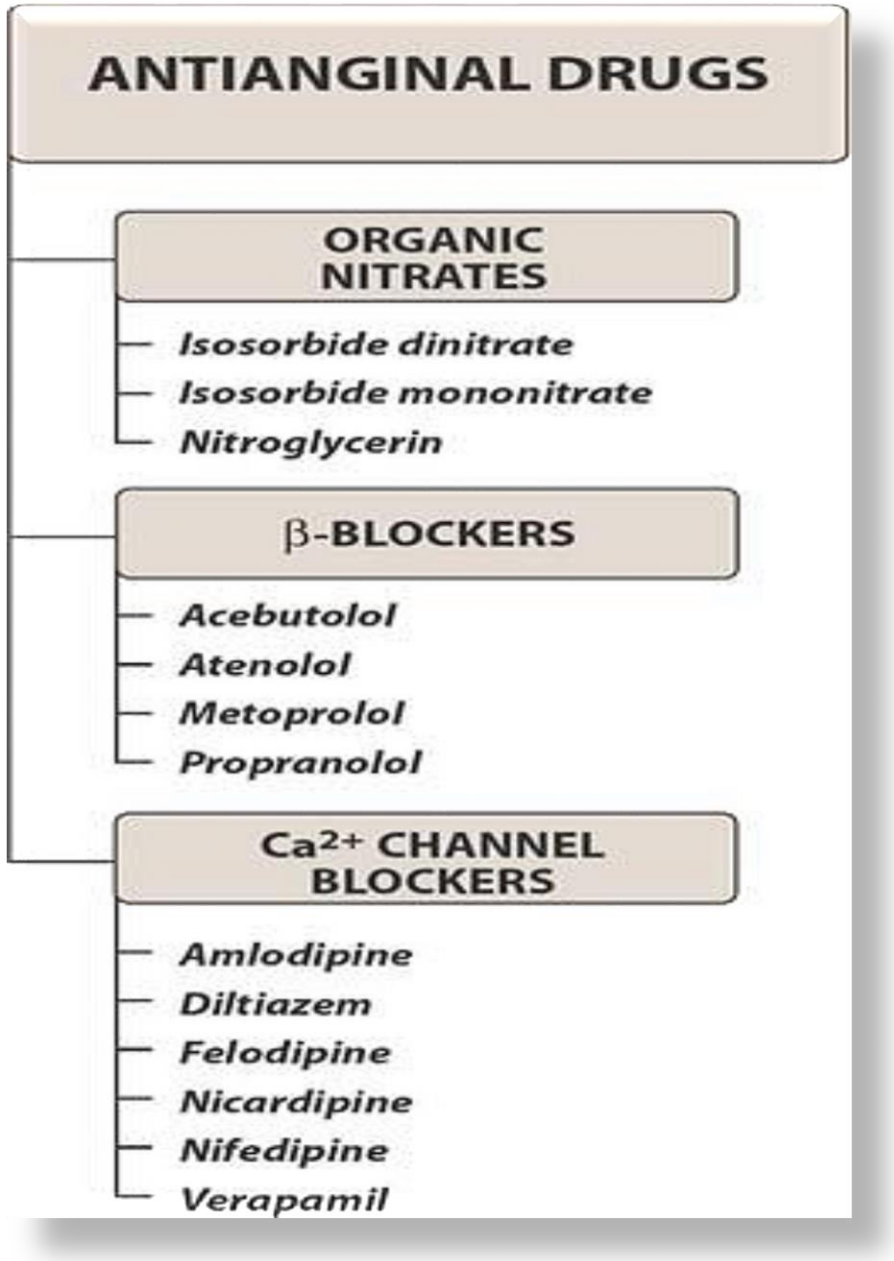


Trinitroglycerin structure

Treatment
Drugs Classification

Three classes of drugs, used either alone or in combination, are effective in treating patients with angina.

These agents lower the oxygen demand of the heart by affecting blood pressure, venous return, heart rate, and contractility.

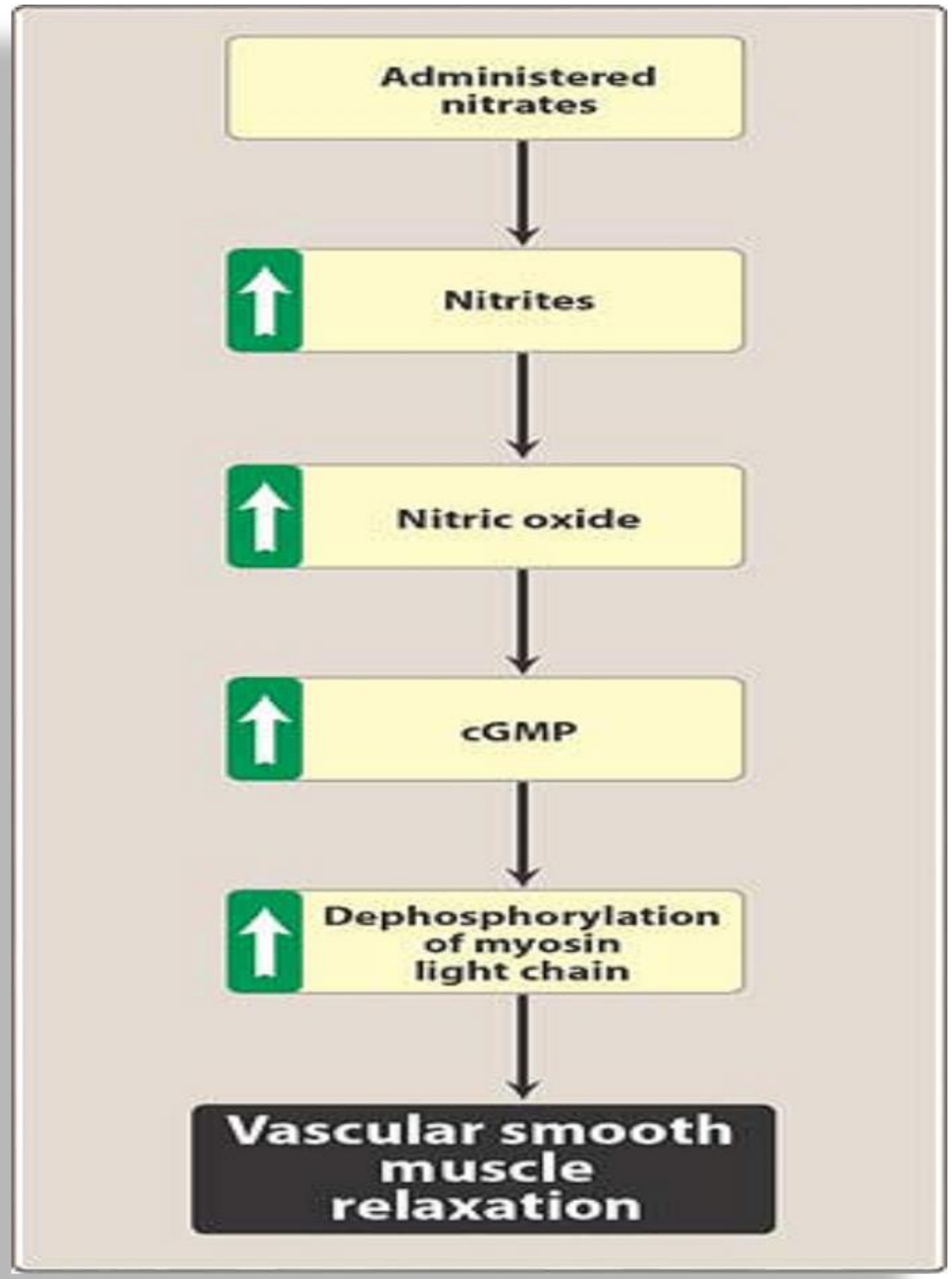


Treatment
1. Organic Nitrates

- Organic nitrates (and nitrites) used in the treatment of angina pectoris are simple nitric and nitrous acid esters of glycerol.
- **These compounds cause a rapid reduction in myocardial oxygen demand, followed by rapid relief of symptoms.**
- They are effective in stable and unstable angina as well as in variant angina pectoris.

Mechanism of action (MOA)

Intracellular conversion to nitrite ions and then to nitric oxide
Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain and then vasorelaxant effect



B. Effects on the cardiovascular system

- All these agents are effective, but they differ in their **onset of action** and **rate of elimination**.

NITRATES AND NITRITES

Classification of nitrates:

1. **Rapidly acting nitrates**
   * used to **terminate acute attack** of angina
   * e.g.- **Nitroglycerin[a]** and **Amyl nitrite**
   * [a]usually administered sublingually
2. **Long acting nitrates**
   * used to **prevent an attack** of angina
   * e.g. -Isosorbide dinitrate and mononitrate
   * administered orally or topically

- For prompt relief of an ongoing attack of angina precipitated by exercise or emotional stress, **sublingual pearl (or spray form) nitroglycerin is the drug of choice.**

ROUTES OF ADMINISTRATION

1. Sublingual route

rational and effective for the treatment of **acute attacks** of angina pectoris.

2. Oral route

to provide convenient and **prolonged prophylaxis** against attacks of angina

3. Intravenous Route

useful in the treatment of **coronary vasospasm** and **acute ischemic syndrome**.

4. Topical route

used to provide gradual absorption of the drug for **prolonged prophylactic** purpose.

ects on the cardiovascular system

- At therapeutic doses, nitroglycerin has two major effects.
- **First**, it causes **dilation** of the **large veins**, resulting in pooling of blood in the veins. This diminishes preload (venous return to the heart) and reduces the work of the heart.

- **Second**, nitroglycerin **dilates** the **coronary vasculature**, providing an increased blood supply to the heart muscle. Nitroglycerin decreases myocardial oxygen consumption because of decreased cardiac work.

Nitrates

Reduced venous return

(Due to dilatation of the veins)

↓

Decrease left ventricular volume

↓

Decrease preload

↓

Decrease workload

↓

Decrease oxygen consumption

Nitrates

Coronary artery dilatation

↓

Decrease coronary bed resistance

(Relieved coronary vasospasm)

↓

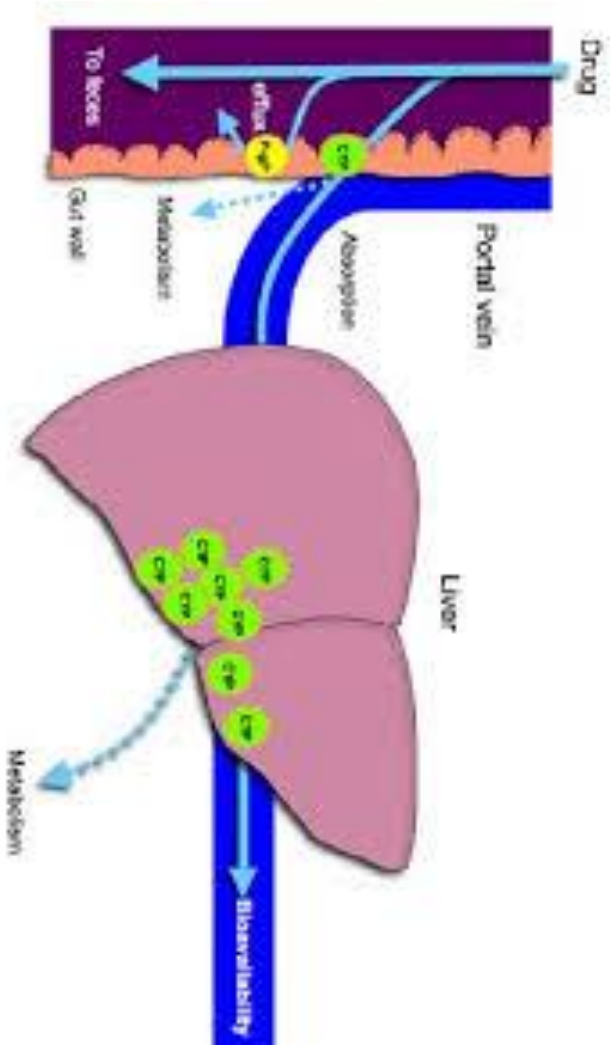
Increase coronary blood flow

↓

Increase oxygen supply

C. Pharmacokinetics

- **Significant first-pass metabolism of nitroglycerin occurs in the liver. Therefore, it is common to take the drug either sublingually or via a transdermal patch, thereby avoiding this route of elimination.**
- **Isosorbide mononitrate owes its improved bioavailability and long duration of action to its stability against hepatic breakdown.**
- **PK is important to choose a drug**



Important points to know

- Keeping in glass container is better
- Affinity to smooth muscle:

  Large veins and coronary vesseles > Large arteries > > > Arteriols
- Effects of nitrates on cardiac output with/without Heart failure?
- Direct effect of NG on heart?
- Are they effective on bronchial, GI, uterus, and other smooth muscles?
- The nitrate effects on platelet function?
- Nitrate application in toxicity?

D. Adverse effects

NITRATES

- Adverse Effects
- Throbbing Headache (Stimulation of pain receptors in cranium with each systole)
- Flushing & Syncope (Arterialdilation)
- Postural Hypotension (Venodilatation)
- Reflex Tachycardia (Sympathetic outflow)

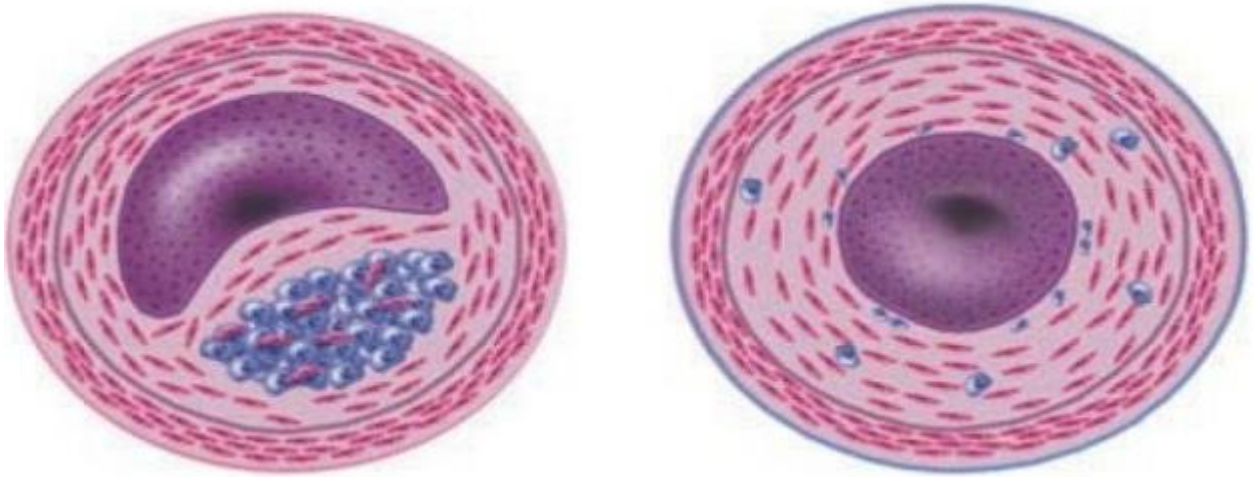
Monday Disease

What is the mechanism of tolerance to nitrates?

Nitrates in clinic

Clinical applications:

- Hypertension emergency
- Angina pectoris
- Cyanide toxicity



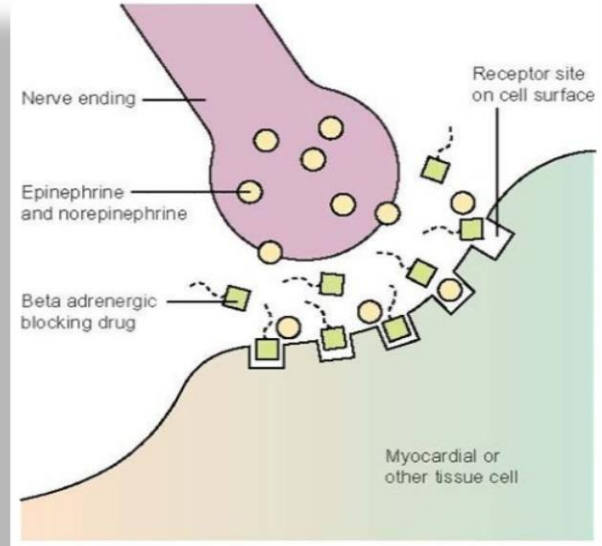
Not permission /need caution:

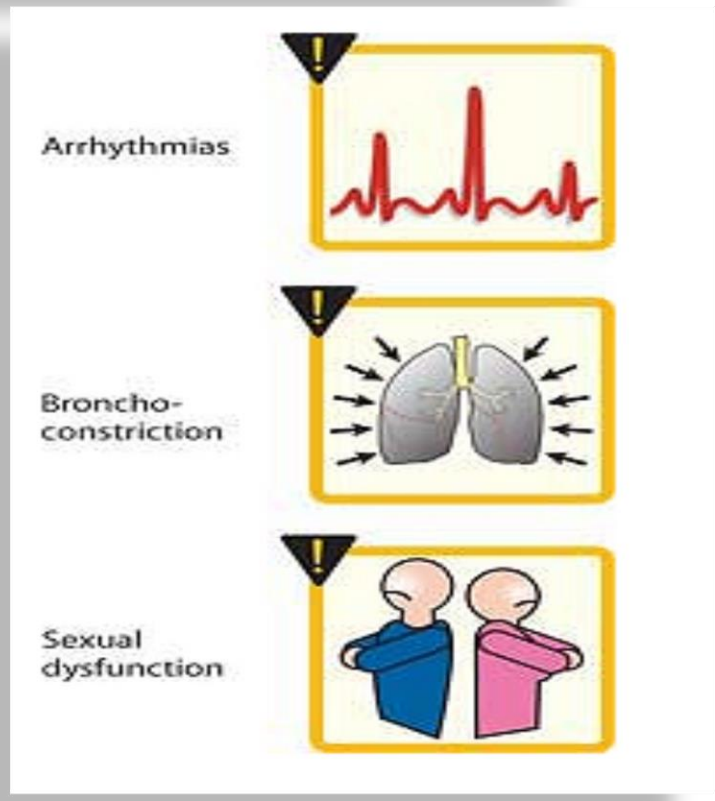
- Increase ICP
- Severe contraindication in patients taking phosphodiesterase 5 inhibitors (sildenafil, tadalafil, vardenafil)- **very dangerous drug interaction**
- External defibrillator in case of transdermal NG patchs

2. 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.
- 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.

- The cardioselective β-blockers, such as *metoprolol* and *atenolol*, are preferred
- Agents with intrinsic sympathomimetic activity (ISA) such as *pindolol* should be avoided in patients with angina and those who have had a MI





2. β-Adrenergic Blockers

- **β-Blockers are more better than Calcium channel blockers in angina**
  - **Prevention of Stable angina**
  - **variant??**

- **Main mechanism: decrease in cardiac workload and increase flow (partial)**
- **β-Blockers are not vasodilator exept: Labetalol, Carvedilol, Nebivolol**
- **In case of diabetes + Angina?**
- **Main negative point of β-Blockers:**
  - ❑ **Increase in empting time**
  - ❑ **Increase in diastolic end volume**

2. β-Adrenergic Blockers

Adverse effects:

Respiratory problems

Conduction problems of the heart

Aggravation of intermittent claudication

Sexual problems

CNS side effects: depression, night mare

B-Blockers

Decrease heart rate & Contractility

Increase duration of diastole

↓

Increase coronary blood flow

↓

Increase oxygen supply

Decrease workload

↓

Decrease O_2 consumption

3. 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.**

- **All calcium-channel blockers are therefore arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance.**

Coronary artery dilatation

↓

Decrease coronary bed resistance

(Relieved coronary vasospasm)

↓

Increase coronary blood flow

↓

Increase oxygen supply

Calcium Channel Blockers

Calcium channel blockers are a recommended treatment option in hypertensive patients with **diabetes or angina**

High doses of short-acting calcium channel blockers should be avoided because of increased risk of myocardial infarction due to **excessive vasodilation** and **marked reflex cardiac stimulation**

Classes of calcium channel blockers

3 chemical classes, each with different PD properties and clinical indications

The different calcium channel blockers differ in their relative effects on vascular and cardiac tissue

1. Diphenylalkylamines: **Verapamil**

Verapamil is the cardioselective calcium channel blocker but has effects on vascular smooth muscle cells It is also used to treat angina and supra-ventricular tachyarrhythmias and to prevent migraine and cluster headaches

Classes of calcium channel blockers

2. Benzothiazepines: Diltiazem

Like verapamil, diltiazem affects both cardiac and vascular smooth muscle cells, but it **has a less pronounced negative inotropic effect on the heart compared to that of *verapamil***. *Diltiazem* has a favorable side effect profile

Classes of calcium channel blockers

3. Dihydropyridines:

- ❑ **Nifedipine**
- ❑ **Amlodipine**
- ❑ **Felodipine**
- ❑ **Isradipine**
- ❑ **Nicardipine**

All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart.

Important points

- Affinity to open or inactive L-type calcium channel
- Other calcium channels are not such sensitive in nerve fibers and secretory tissue
- **Mebefradil, Bepridil, Verapamil**
- **Affinity : vascular SM (arteriols) > vascular SM (veins) > tissues SM**
- **What about Skeletal muscles?? Are they spasmolytic agents?**

- **Non-selective Antiadrenergic activity:**

  Diltiazem > Verapamil > > > Nifedipine

Calcium Channel Blockers: Action

- Calcium enters muscle cells through special ***voltage sensitive calcium channels***. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium.

- Calcium channel antagonists **block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature**. This causes vascular smooth muscle to relax, dilating mainly arterioles.

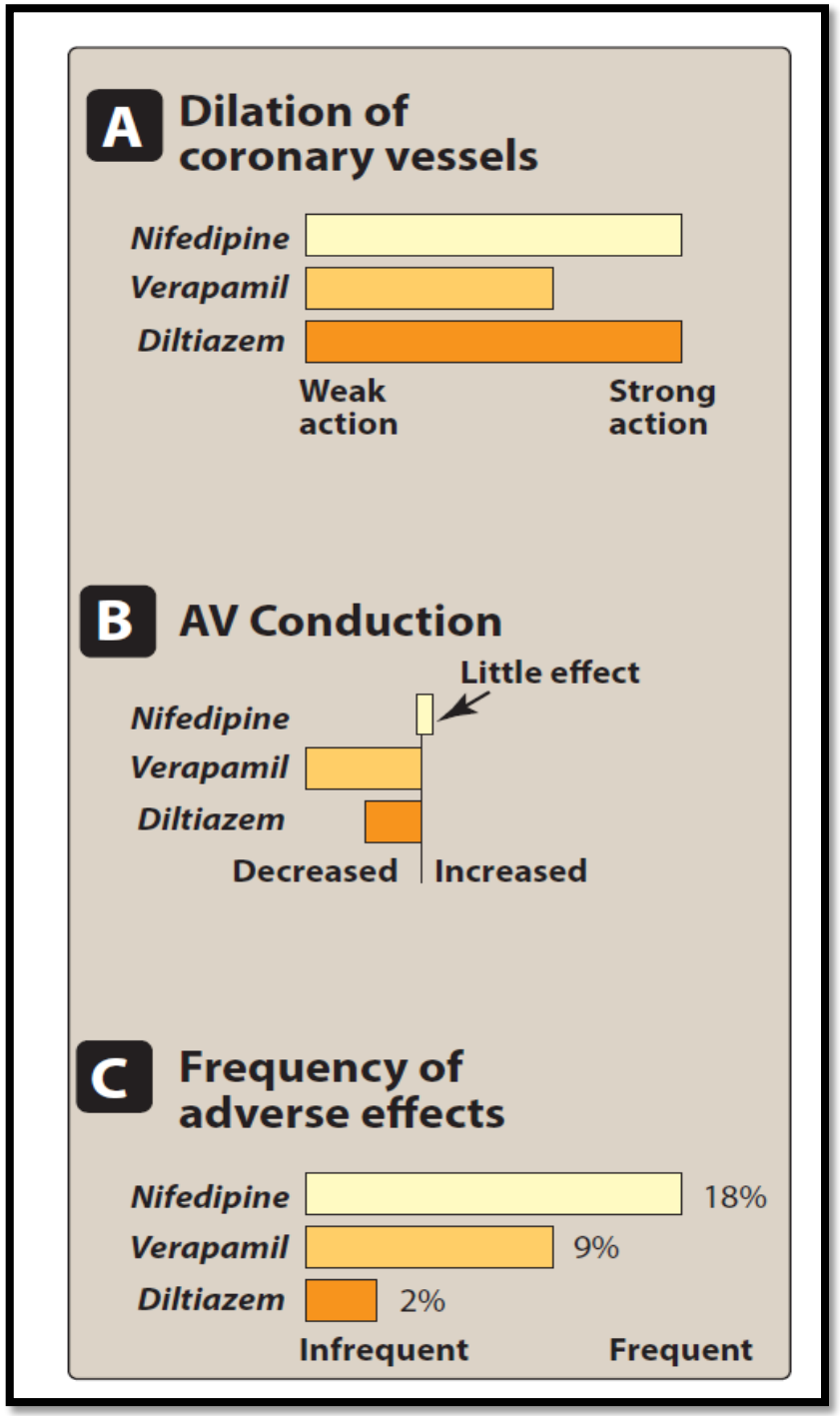
- **Calcium channel blockers do not dilate veins**

Calcium Channel Blockers in clinic:

- Hypertension
- Angina pectoris
- Arrhythmia
- Migraine
- Hypertrophic cardiomyopathy
- Raynaud syndrome
- Preterm labor
- In HF if needed : Amilodipine
- Intravenous/intra-arterial in stroke: Nicardipine (prevention of cerebrovascular spasm)
- **Verapamil is an inhibitor of PGPs**

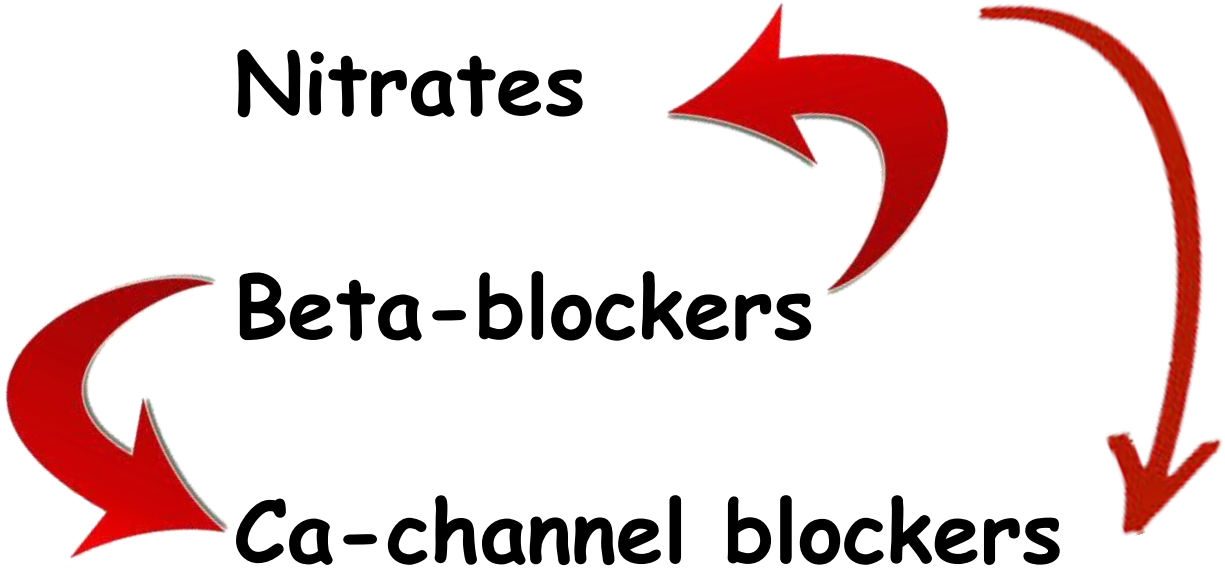
Calcium Channel Blockers Adverse effects

- ❑ Constipation
- ❑ Heart block
- ❑ Hypotension
- ❑ Dizziness
- ❑ Headache
- ❑ Flushing
- ❑ edema



Combination therapy

Combination therapy



New Targets

- **Ranolazine**
- **Trimetazidine**
- **Fasudil**
- **Ivabradine**
- **Alloporinol**
- **Nicorandil**

Intermittent claudication:

. **Antiplatelets / Cilostazol/ Pentoxifylline**