Drugs used in the treatment of Angina Pectoris

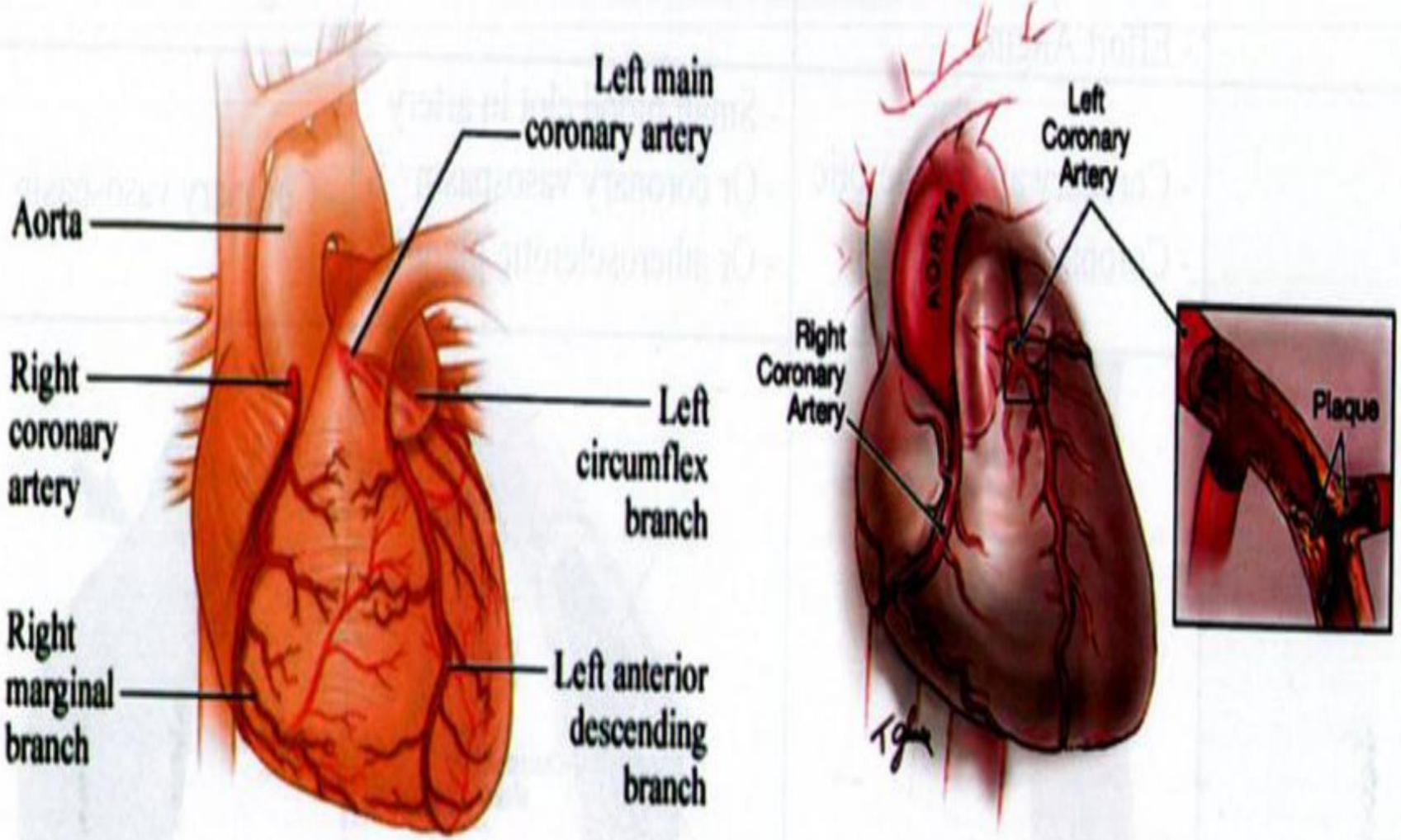
Coronary Heart Disease (CHD)

Coronary Heart Disease (CHD) or **Coronary Artery Disease** (CAD): also known as **Ischemic heart disease** (IHD), **atherosclerotic heart disease**.

Atherosclerotic and cardiovascular disease; is a group of heart diseases that includes: **stable angina, unstable angina, myocardial infarction, and sudden coronary death**.

Ischemic heart disease (IHD); is the most common cardiovascular disease in developed countries and **angina pectoris** is the most common condition involving tissue ischemia.

Coronary Arteries



The heart regulates the amount of vasodilation or vasoconstriction of the coronary arteries based upon the oxygen requirements of the heart (**oxygen demand**).

Failure of oxygen delivery caused by a decrease in blood flow in front of increased oxygen demand of the heart results in tissue ischemia, a condition of oxygen deficiency.

Brief ischemia is associated with intense chest pain, known as **angina**.

Severe ischemia can cause the heart muscle to die from hypoxia, such as during a **myocardial infarction**.

Angina Pectoris

Angina, the term derives from the Latin **angere "to strangle"** and **pectus** "**chest**", and can therefore be translated as **" a strangling feeling in the chest",** commonly known as **angina**.

Definition; Chest pain caused by transient myocardial ischemia due to an imbalance between myocardial oxygen supply and oxygen demand.

Angina is not a disease. It is a symptom of an underlying heart problem and is usually a symptom of **coronary heart disease** (CHD).

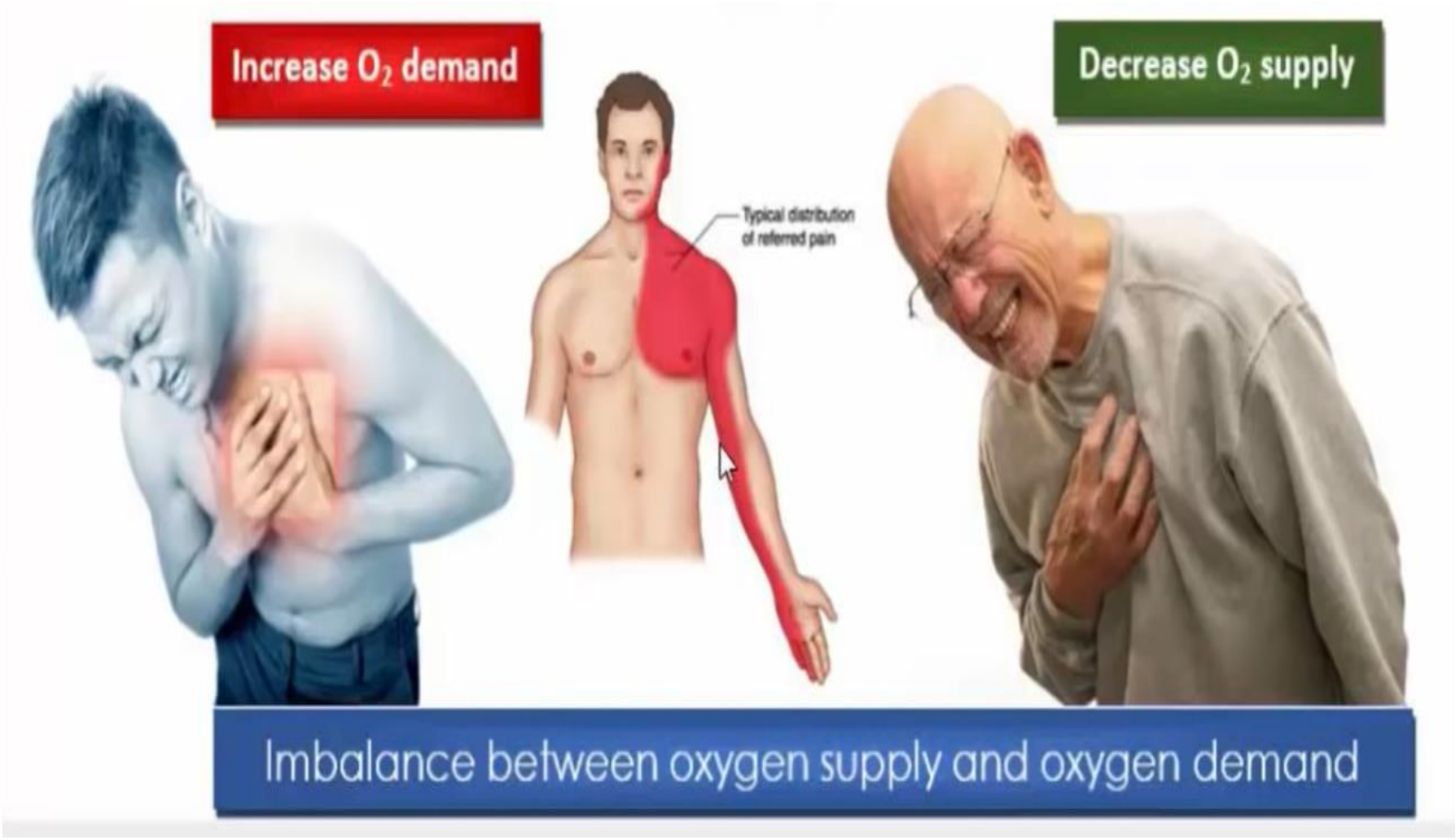
Angina pectoris

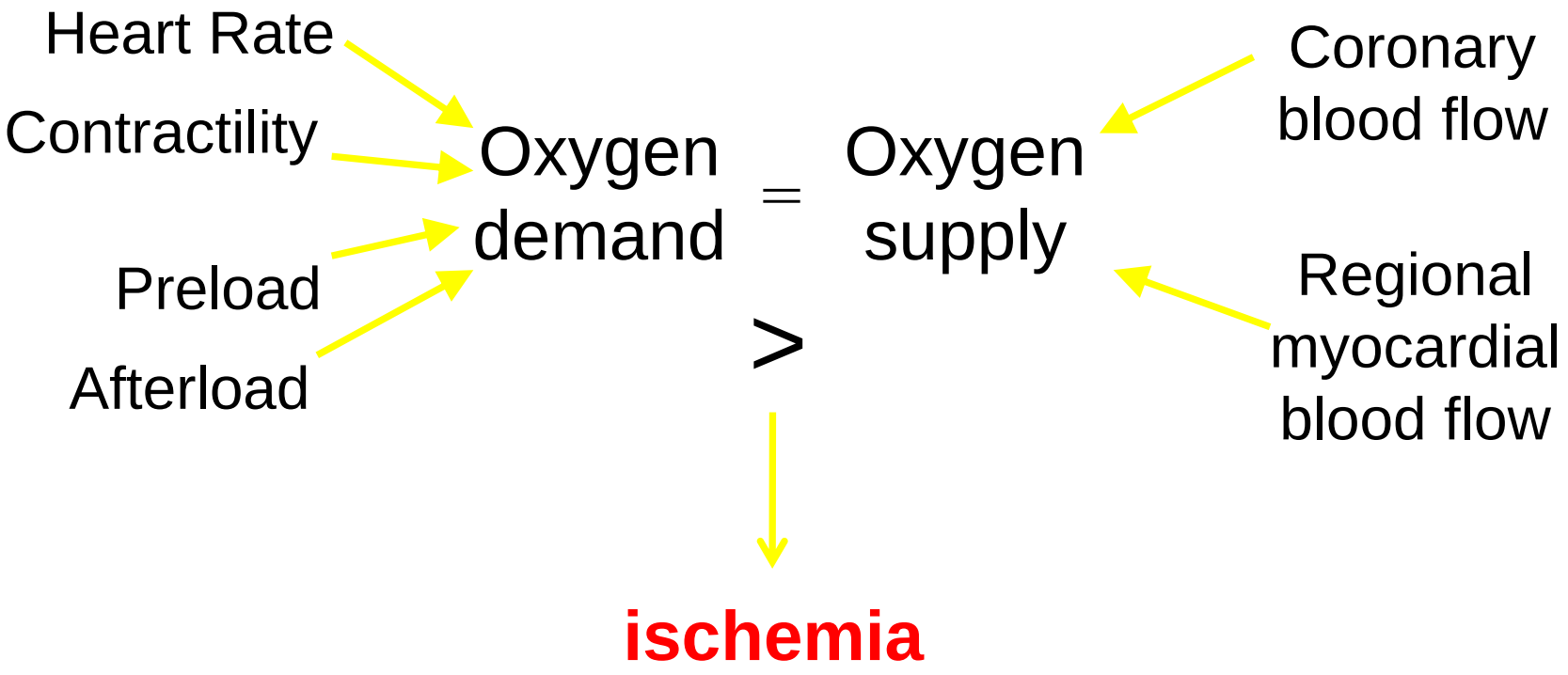
Angina pectoris refers to **sudden**, **severe**, **pressing chest pain radiating** to the neck, jaw, back, and arms caused by **cardiac ischemia**

Other symptoms: Nausea, fatigue, shortness of breath, sweating and dizziness

Occurs due to an **imbalance** in the **myocardial oxygen supply-demand** relationship caused by:

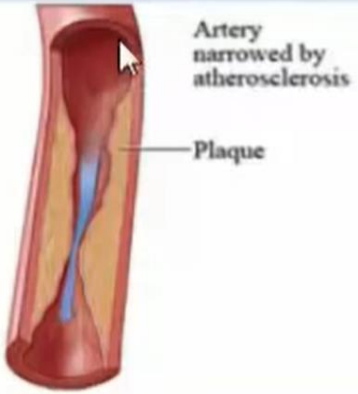
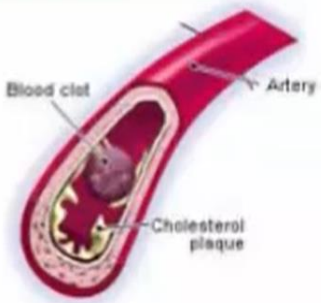
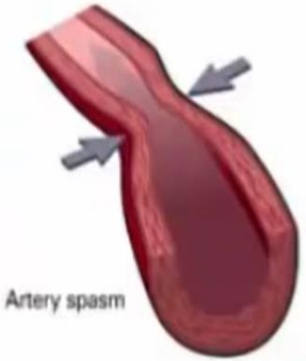
- ✓ An **increase** in myocardial oxygen **demand** (determined by **heart rate**, ventricular **contractility**, and ventricular wall tension)
- ✓ A **decrease** in myocardial oxygen **supply** (primarily determined by coronary **blood flow**)
- ✓ **Both**


Increase O_2 demand
Typical distribution of referred pain
Decrease O_2 supply
Imbalance between oxygen supply and oxygen demand


Heart Rate
Contractility
Preload
Afterload
Oxygen demand
=
>
Oxygen supply
Coronary blood flow
Regional myocardial blood flow
ischemia

Angina Risk Factors

- Coronary heart disease
- Family history of heart disease
- Unhealthy cholesterol levels
- Unhealthy diet (high fat and high salt)
- Smoking
- Diabetes
- Inactivity
- High blood pressure
- Overweight or obesity
- Stressful lifestyle
- Menopause
- Age (Men>45 years- Women >55 years)

	Stable Angina	Unstable Angina	Variant Angina
Other Names	- Classical Angina. - Typical Angina. - Exertional or Effort Angina.	- Crescendo Angina. - Pre-infarction Angina. - Acute Coronary Syndrome.	- Vasospastic Angina. - Prinzmetal's Angina. - Angina Inversa.
Causes	- Narrowing of coronary arteries due to atherosclerosis. 	- Narrowing of coronary arteries due to atherosclerosis, transient formation of a blood clot within a coronary artery, result, total or near-total blockage. 	- Results from coronary vasospasm, which temporarily reduces coronary blood flow. 
Distribution	- Most common type.	- Common.	- Rare (2% of angina cases).
Occurs	- Physical exertion. - Emotions. - Exposure to cold weather. - Heavy meals.	- At rest or minimal exertion.	- At rest between midnight (12:00) and early morning (8:00). - Cold weather and stress can cause spasm.
Attack	- Usually lasts a short time (5 minutes or less).	- More severe and lasts longer, maybe as long as 30 minutes.	- Lasts from 5-30 minutes.
Relief	- Decreases at rest. - Relieved by nitroglycerin.	- Not relieved by rest. - Not relieved by nitroglycerin. - Treated as an emergency.	- Relieved by nitroglycerin.

Types of angina

1. Atherosclerotic or typical angina

- The **most common** form of angina
- Caused by the **reduction of coronary blood flow** produced by **coronary atherosclerosis**
- Symptoms of angina occurs when myocardial oxygen demand increases, as with physical activity, emotional excitement, or any other cause of increased cardiac workload

2. Unstable angina or acute coronary syndrome

- It lies between stable angina on the one hand and myocardial infarction on the other
- Characterized by **pain with increased frequency** that occurs with less and less exertion, culminating in **pain at rest**
- Cause: **abrupt** **reduction in blood flow**, as might result from **coronary thrombosis** or **rupture of an atherosclerotic** plaque, with consequent platelet adhesion and aggregation
- Requires **hospital admission** and more aggressive therapy to **prevent death and progression to MI**

3. Vasospastic or variant angina:

- Occurs at **rest**, even **during sleeping** and is due to **vasospasm** of large epicardial coronary vessels or one of their major branches
- Symptoms are caused by **decreased blood flow to the heart muscles**

Therapeutic objectives

The major therapeutic goals are aimed at:

- ✓ Slow the progression of the disease;Terminating or preventing an acute attack and reduce the possibility of future events, especially myocardial infarction (MI) and future death.
- ✓ Relieve the symptoms; Increasing the patient's exercise capacity

Can be achieved by:

- ✓ **Reducing** overall myocardial **oxygen demand (β- Adrenergic receptor antagonist)**
- ✓ **Increasing oxygen supply** to ischemic areas (Nitrates and Ca channel blockers)
- ✓ Lifestyle modification
- ✓ Treat coronary artery disease (Decrease bad cholesterol level (LDL) and surgical procedures e.g., angioplasty)

Therapeutic objectives

- **Reducing myocardial O_2 demand** can be achieved by decreasing heart rate/ myocardial contractility, reducing preload/cardiac filling, reducing afterload/ arterial pressure, & by shifting myocardial metabolism to substrates that require less oxygen per unit of adenosine triphosphate (ATP) produced
- **Increasing O_2 supply** can be achieved by dilating the coronary vasculature

Therapeutic objectives

- Drugs used in **typical angina** function principally by **reducing myocardial O2 demand** by decreasing heart rate, myocardial contractility, and/or ventricular wall stress
- The principal therapeutic aim in **variant angina** is to **prevent coronary vasospasm** by **nitrate** or **calcium channel-blocking vasodilators**

Therapeutic objectives

- In **unstable angina, vigorous measures** are taken to achieve **both—increase oxygen delivery and decrease oxygen demand**
- strategies include the use of **antiplatelet agents and heparin** to reduce intracoronary thrombosis, often accompanied by efforts to restore flow by mechanical means, including percutaneous coronary interventions using **coronary stents**, or (less commonly) **emergency coronary bypass surgery**

Classification of treatments

Lifestyle modifications

Stop smoking

Reduce weight

Treat hypertension

Treat hypercholesterolemia and diabetes

Drug treatment

Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina

Antiplatelet therapy and lipid-lowering therapy are needed to prevent clot formation and decrease atherosclerosis plaque formation

Antianginal drugs, such as, nitrates, calcium channel blockers (CCBs), -blocking drugs, and others new anti-anginal drugs….)

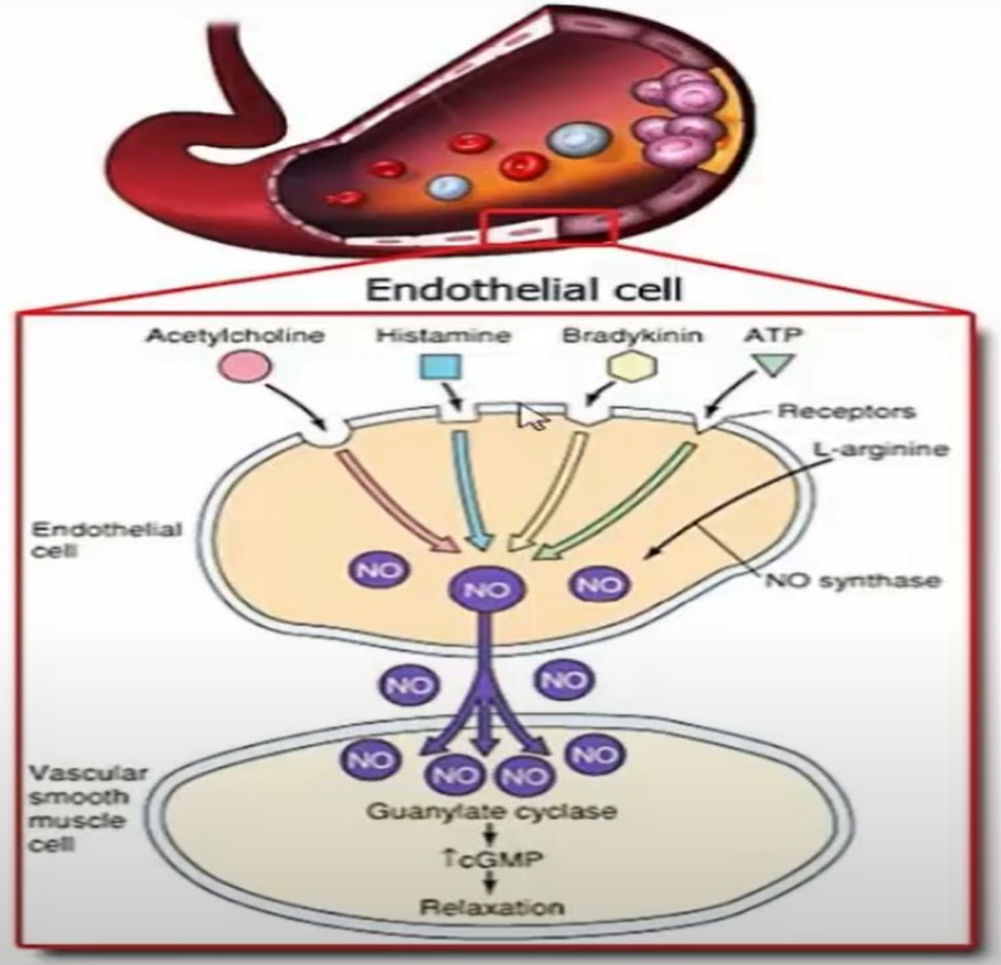
Coronary artery revascularization

Organic Nitrates

<u>Agents:</u> Nitroglycerine (NotromAck®), Isosorbide Mononitrate (Effox®), Isosorbide Dinitrate (Isordil®), and Amyl Nitrate

Nitroglycerin (Glyceryl Trinitrate; GTN) is the prototype of these groups.

- ***Normally***;
  - ***Endogenous*** **nitric oxide (NO)** is primarily produced by vascular endothelial cells, which cause relaxation of vascular smooth muscle.
  - **NO** ☞ act by ***stimulation*** of **guanylate cyclase**, lead to ***increase*** **cyclic guanosine monophosphate (cGMP)**, which subsequently ***cause*** **vascular smooth muscle relaxation** through several possible mechanisms; ***decrease*** **Ca^{2+} influx** and **K^+ channels** ***activation***, (hyperpolarization).



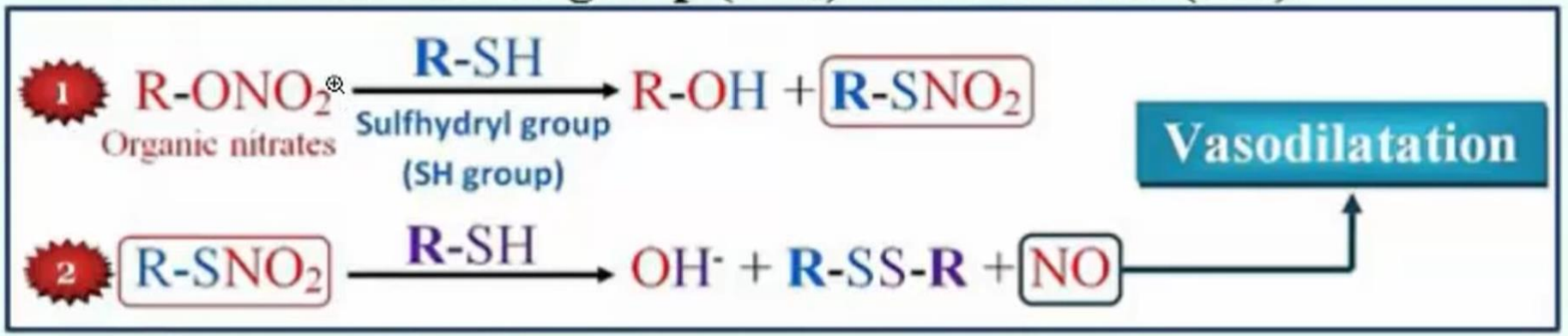
Organic Nitrates

Nitrates are available as oral tablets, transdermal patches, sublingual tablets, and intravenous infusion

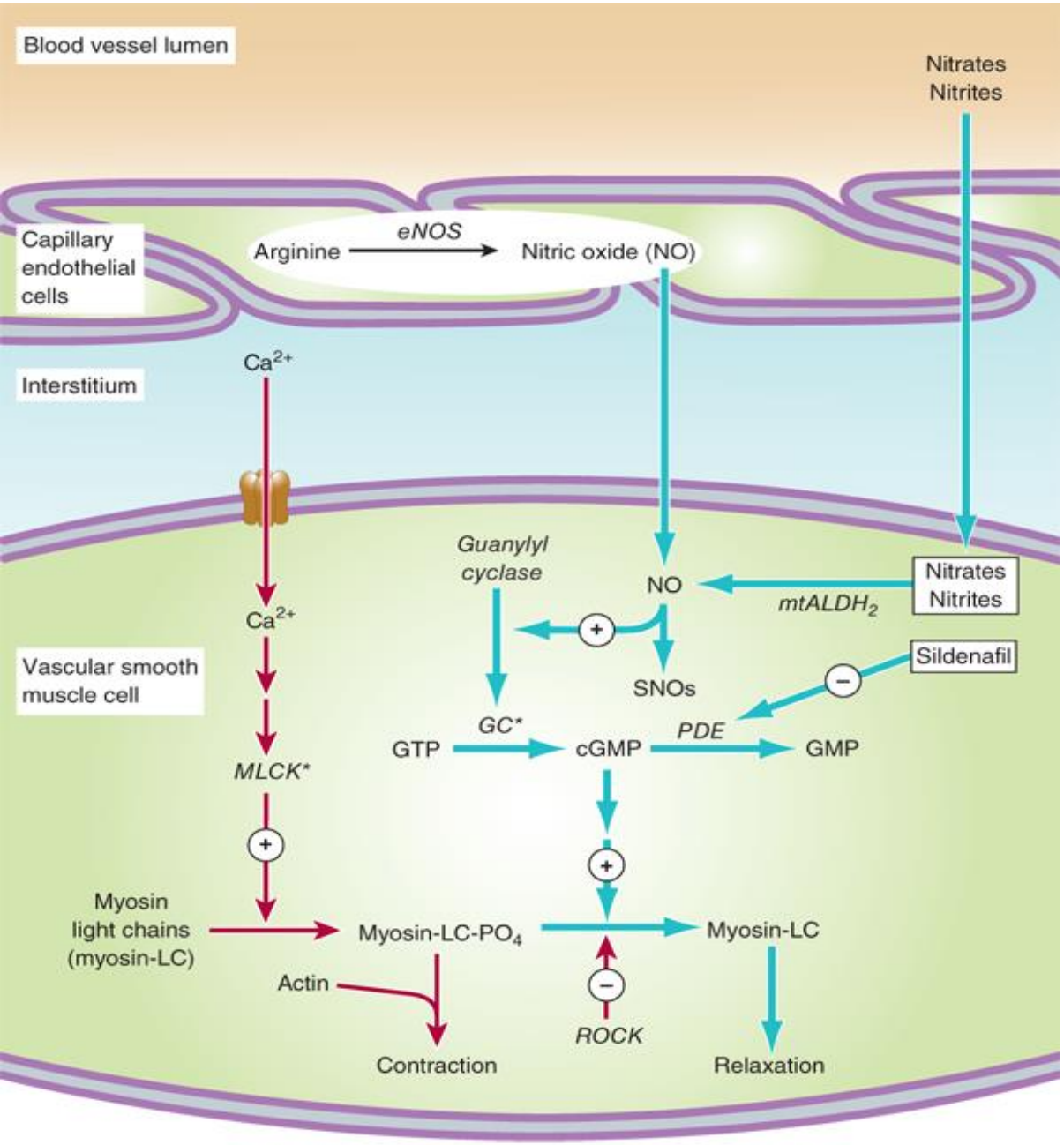
Nitrates exert their effect by **intracellular conversion to nitric oxide (NO)**

NO activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate **(cGMP),** which leads **smooth muscle relaxation by dephosphorylation of myosin light chain phosphate**

- ***Organic Nitrates***;
  - **Organic nitrates** are drugs that ***not directly*** **release** or **synthesis** of endogenous NO within tissues.
  - **Nitrate group** (NO_2) in organic nitrate ***interact*** with **enzymes** (nitric oxide synthase) and intracellular **sulfhydryl group** (R-SH) (**SH group**) that ***reduce*** the **nitrate group** (NO_2) ***to*** **nitric oxide** (**NO**).



- ❑ Depletion of SH group----→ Lead to nitrate tolerance
- ❑ Sildenafil; is selective inhibitors of Phosphodiesterase type 5 (PDE-5) which is responsible for degradation of cGMP into GMP-→ accumulation of cGMP-→vasodilatation of penis-→ Erection

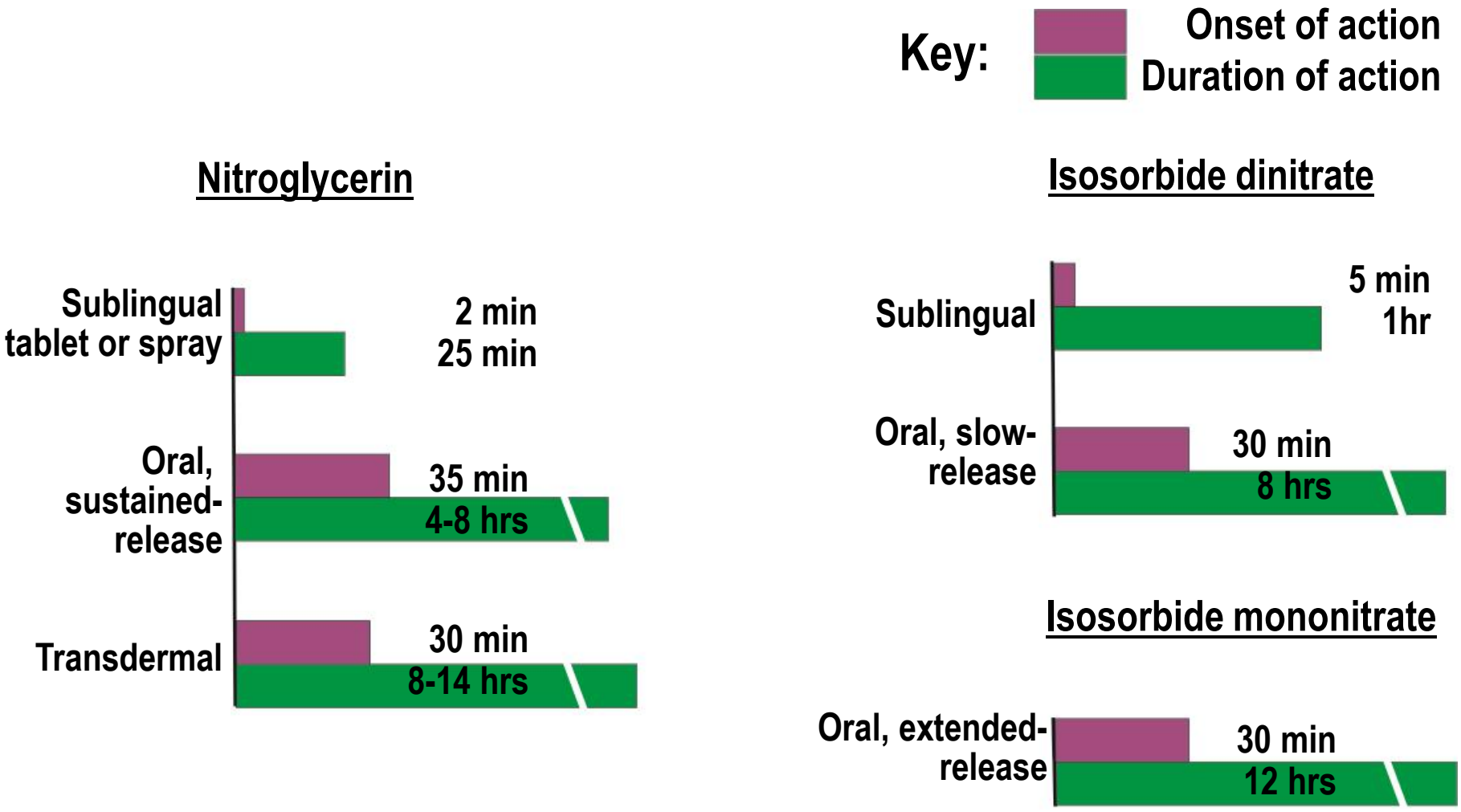


Organic Nitrates/Pharmacokinetic

- The liver contains a high-capacity organic reductase, which sequentially removes nitrate groups from the parent drug, and ultimately inactivate the drug, ***so*** hepatic first-pass metabolism is high and oral bioavailability is very low for the traditional organic nitrates, nitroglycerin (GTN) and isosorbide dinitrate (ISDN).
- Sublingual administration, which avoids the first-pass effect, is therefore preferred for administration of GTN and ISDN.
- ***Pharmacokinetics properties***:

	GTN	ISDN	ISMN
Oral Bioavailability	Less than 1%	About 22%	Nearly 100%
Protein Binding	Moderate	Very low	Very low
Biotransformation	Hepatic (very rapid and nearly complete) and in blood (enzymatically)		
Half-life	Sublingual: 3 min.	Sublingual: 1 hour	Oral: 5 hours
Onset of action	Sublingual: 1-3 min.	Sublingual: 2-5 min.	Oral: 1 hour
Duration of action	Sublingual: 30-60 min. SR formula: 8 to 12 h.	Sublingual: 1-2 h. Oral tablets: 4-6 h.	Oral: 12 hours
Elimination	Renal (after nearly total metabolism)		

Time to peak effect and duration of action for some common organic nitrate preparations



Organic Nitrates/Pharmacokinetic

- **Nitroglyerine:**
  - Rapid onset of action (2-5 mins)
  - Maximal effect observed at 3 to 10 minutes
  - Short half-life (1-3 mins)
  - Significant first-pass metabolism (F < 10-20%)
  - Commonly administered either **sublingually, IV or via a transdermal patch**
- **Isosorbide mononitrate** owes its **improved bioavailability and long duration of action** to its stability against hepatic breakdown
- Oral **isosorbide dinitrate** undergoes **denitration** to **two mononitrates**, both of which possess antianginal activity

Organic Nitrates/Pharmacokinetic

Amyl nitrite and related nitrites: are **highly volatile liquids**. Amyl nitrite is available in **fragile glass ampules packaged in a protective cloth covering**. The ampule can be **crushed** with the fingers, resulting in rapid release of **vapors inhalable through the cloth covering**.

The inhalation route provides **very rapid absorption** and, like the sublingual route, avoids the hepatic first-pass effect. Because of its **unpleasant odor** and **short duration of action**, amyl nitrite is now obsolete for angina

Pharmaceutical preparation
Nitroglycerin

- **Sublingual nitroglycerin:** is the **most frequently used agent for the immediate treatment of angina** b/c of its rapid onset of action (1–3 minutes). Because its duration of action is short (not exceeding 20–30 minutes), it **is not suitable for maintenance therapy (Short acting/Acute attacks)**

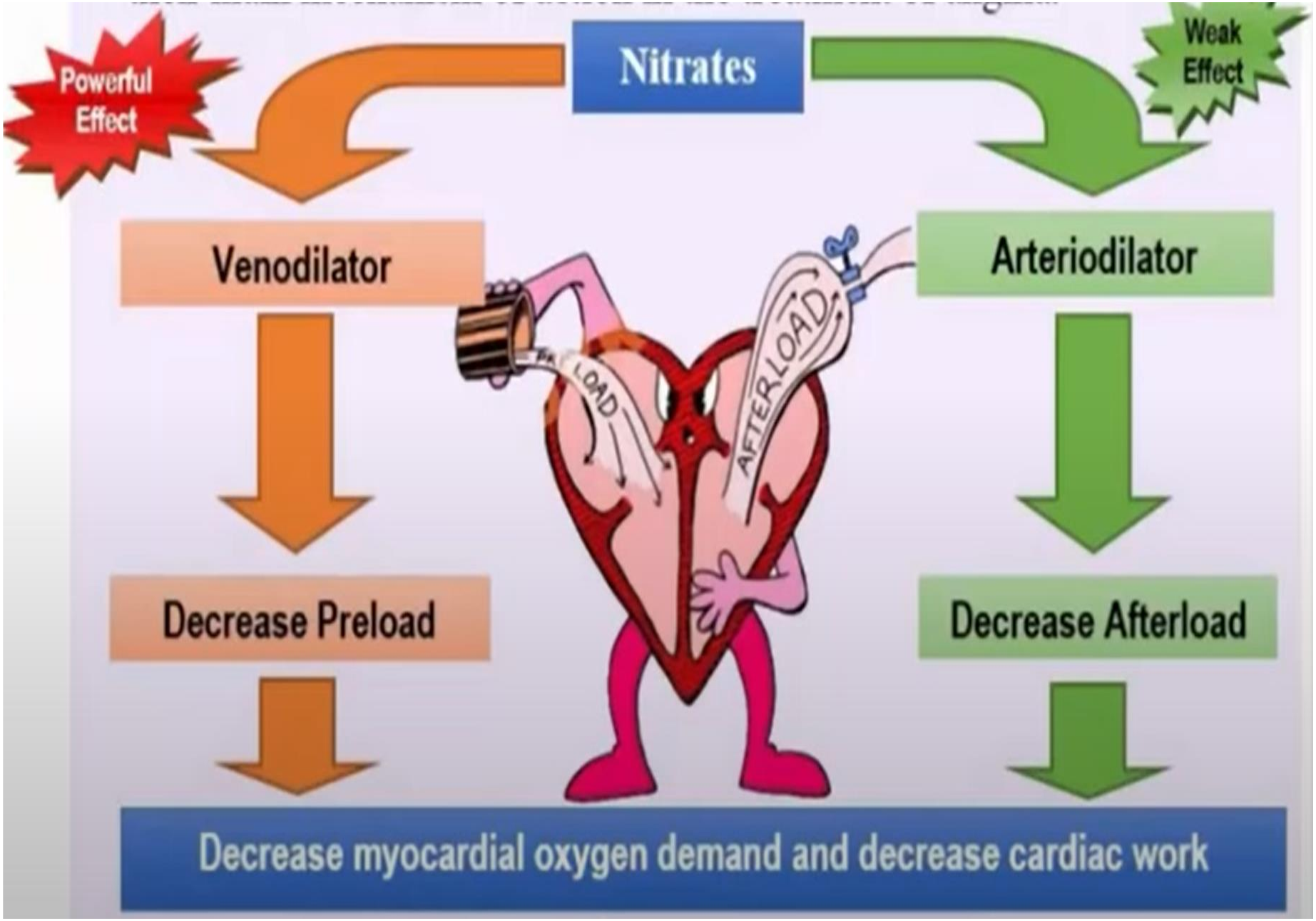
- **IV nitroglycerine:** has a rapid onset of action of intravenous nitroglycerin (minutes), but its hemodynamic effects are quickly reversed when the infusion is stopped. Clinical application of intravenous nitroglycerin is therefore **restricted to the treatment of severe, recurrent rest angina (Short acting/Acute attacks)**

- **Slowly absorbed preparations of nitroglycerin**: such as buccal form, oral preparations, and several transdermal forms have been shown to provide blood concentrations **for long periods** but, this leads to the development of **tolerance (Long acting/ Angina prophlaxis)**

Pharmacological action

Nitrovasodilators relaxes all types of smooth muscle and **promote vascular smooth muscle relaxation. It has no direct effect on cardiac or skeletal muscle.**

Nitrated cause dilation of veins predominates over that of arterioles. This result in **marked relaxation** of veins with increased venous capacitance, decreased venous return to the heart (reduce preload), and reduces the work of the heart (decreases myocardial oxygen consumption)……This is believed to be their main mechanism of action in the treatment of angina


Powerful Effect
Nitrates
Weak Effect
Venodilator
Arteriodilator
AFTERLOAD
Decrease Preload
Decrease Afterload
Decrease myocardial oxygen demand and decrease cardiac work

Pharmacological action

- ***Powerful*** **venous dilation** and ***increase*** venous capacitance ☞ ***decrease*** **ventricular preload**.
- ***Weak*** **arterial dilation** ☞ ***decrease*** **afterload** (minimal effect).
- ***Reduction in preload and afterload lead to***;
  - Decrease myocardial oxygen demand.
  - Decrease cardiac work (decrease CO).
- **Effects on coronary blood flow**;
  - Organic nitrates can relax vasospastic coronary arteries.
  - They have little or no effect on total coronary blood flow in patients with typical angina due to atherosclerosis.
- **Other actions (minimal effect)**;
  - Inhibit platelet aggregation (due to increase cGMP level).
  - Spasmolytic effect (smooth muscle relaxation).
  - Nitrite ion react with hemoglobin to produce methemoglobin.

Because **methemoglobin has a very low affinity for oxygen**, large doses of nitrites can result in **pseudocyanosis, tissue hypoxia, and death**

The plasma level of nitrite resulting from even large doses of organic and inorganic nitrates is too low to cause significant methemoglobinemia in adults

Vasodilation related Adverse effects

- ❑ Orthostatic hypotension (dizziness and syncope)
- ❑ Tachycardia
- ❑ Throbbing headache (Cerebral vasodilation)
- ❑ Reflux tachycardia
- ❑ Facial flushing
- ❑ Nitrate edema (Pulmonary edema)

--→Due to vasodilation which increase permeability of blood vessels

-→ Due to increase Angiotensin II which increases aldosterone hormone (Na and water retention)

Sildenafil potentiates the action of the nitrates. To preclude the **dangerous hypotension** and inadequate perfusion of critical organs that may occur, **this combination is contraindicated**

Nitrate tolerance

- **Repeated** and **frequent** exposure to organic nitrates is accompanied by the development of **tissue tolerance**: the blood vessels become **desensitized to the vasodilating action of nitrates**

- The magnitude of tolerance is a function of **dosage and frequency of use**

Nitrate Tolerance Hpothesis

Depletion of SH group

Excessive generation of free radicals

Dysfunction of endothelial nitric oxide synthase (NOS)

Decrease sensitivity of guanylate cyclase

Activation of renin-angiotensin-aldosterone axis

Avoid of tolerance

☞ **Avoid Nitrate Tolerance**;

1: Nitrate holiday ("nitrate free period" or NFP) of at least 10 hours and preferably up to 14 hours is recommended to avoid tolerance;

- ***For example;***
  - Regular-release isosorbide dinitrate, which is administered 3-4 times daily, may be scheduled at 7:00 AM, Noon, and 5:00 PM.
  - Isosorbide-5-mononitrate and sustained release preparations of nitroglycerin or isosorbide dinitrate may be given twice daily at 8:00 AM and 3:00 PM, allowing a 10-12 hour nitrate holiday.
  - Removal of nitroglycerin ointment paper and residual ointment at bedtime.
  - A nitroglycerin transdermal patch placed at 8:00 AM may be removed at bedtime.

2: Sulfhydryl group donors like **N-acetylcysteine (NAC)** and **L-methionine** have been shown to potentially reduce nitrate tolerance, but they may potentiate the effects of nitrates.

3: Oral **vitamin C**, **vitamin E** (antioxidants) and **folic acid** may be effective in ameliorating nitrate tolerance.

4: Carvedilol (antioxidant properties) and **Nebivolol** (antioxidant properties and NO-mediated vasodilatory effects) may reduce nitrate tolerance associated with continuous nitrate therapy.

- ***Recent study***;
  - ACEIs and ARBs may be effective in nitrate tolerance.
  - Animal studies have demonstrated that statins may be able to prevent nitrate tolerance.

Monday Syndrom

** **Monday Syndrome** or **Monday Morning Sickness**

- Workers in nitroglycerin manufacturing, who are experiencing to regular nitroglycerin exposure in the workplace, leading to the development of tolerance for the vasodilating effects.
- Over the weekend, the workers lose the tolerance and, when they are re-exposed on Monday, the drastic vasodilation produces a fast heart rate, dizziness, and a headache "Monday morning headache".

Beneficial and deleterious effects of nitrates in treatment of angina

Effect	Result
Potential beneficial effects;	
- Decreased ventricular volume, - Decreased arterial pressure, - Decreased ejection time.	- Decreased myocardial oxygen requirement.
- Vasodilatation of epicardial coronary artery.	- Relief of coronary artery spasm.
- Increased collateral flow.	- Improved perfusion to ischemic myocardium.
- Decreased left ventricular diastolic pressure.	- Improved subendocardial perfusion.
Potential deleterious effects;	
- Reflex tachycardia - Reflex increase in contractility	- Increased myocardial oxygen requirement.
- Decreased diastolic perfusion time due to tachycardia	- Decreases coronary perfusion.

- ***Mechanism of Clinical Effect***;

A) Nitrate Effects in Angina Effort;

- Reduction in oxygen consumption is the major mechanism for the relief of effort angina.

B) Nitrate Effects in Variant Angina;

- Relaxing the smooth muscle of epicardial coronary arteries and relieving coronary artery spasm.

C) Nitrate Effects in Unstable Angina;

- Nitrates are also useful in the treatment of the acute coronary syndrome of unstable angina, but mechanism for their beneficial effects is not clear.

- ***Finally***; Nitrates are effective in stable, unstable, and variant angina.

Beta-blockers

β-blockers are the **Drug of choice** to treat **exercise-induced angina**, but are **ineffective** and **should not be used against vasospastic angina**

- Although they are ***not*** **vasodilators** (with the exception of **Carvedilol** and **Nebivolol**), β-blocking drugs are ***extremely*** **useful in the management of effort angina**.
- The ***beneficial*** **effects** of β-blocking agents are related to their ***hemodynamic effects***;
  - ***Decreased*** **heart rate, blood pressure** and **contractility** ⇨ ***Decrease*** **myocardial oxygen requirements at rest and during exercise**.
  - ***Lower*** **heart rate** is also associated with an ***increase*** in **diastolic perfusion time**, may ⇨ ***Increase*** **coronary perfusion**.

** **β-blockers** ***reduce*** the **risk of death** and **MI** in patients who have had a prior MI and ***also improve*** **mortality** in patients with **hypertension** and **heart failure** with reduced ejection fraction.

- Agents with **intrinsic sympathomimetic activity** (**ISA**) such as **Pindolol** ***should be avoided*** in patients with angina and those who have had a MI.
- **β-blockers** ***should be avoided*** in patients with **severe bradycardia**.
- ***Cardioselective*** **β-blockers** can be **used in patients** with **diabetes, peripheral vascular disease,** and **chronic obstructive pulmonary disease** (**COPD**), as long as they are monitored closely.
- ***Nonselective*** **β-blockers** should be ***avoided*** in patients with **asthma** or **COPD**.
- **The β-blockers must be tapered off gradually** over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.
- **β-blocker** ***not used*** with **non-dihydropyridines Ca^{2+} channel blockers** (**Verapamil** and **Diltiazem**) to avoid heart block.
- **Carvedilol** > **Metoprolol** > **Bisoprolol** are ***only*** **β-blockers** ***may be used*** in **CHF**.

Calcium channel blockers

Binding of the drug results in a marked decrease in transmembrane calcium current.

In smooth muscle which in turn results with a long-lasting relaxation

In the vascular system, **arterioles** appear to be more sensitive than **veins**. Therefore, orthostatic hypotension is not a common adverse effect

In cardiac muscle with a reduction in contractility throughout the heart and decreases in sinus node pacemaker rate and AV node conduction velocity

CCBs are **vasodilators** and effective in both **effort angina** (reduction in myocardial oxygen consumption) and **vasospastic angina** (relaxation of coronary arteries)

Calcium channel blockers

Important differences between the available CCBs arise from the **differences in their relative smooth muscle versus cardiac effects**

1. **Diphenylalkylamines (e.g.Verapamil):** is the least selective and has significant effects on both cardiac and vascular smooth muscle cells

2. **Benzothiazepines (e.g. diltiazem):** it affects both cardiac and vascular smooth muscle cells; however, it has a less pronounced negative inotropic effect on the heart compared to that of verapamil. **1 and 2 called Non- Dihydropyridines**
3. **Dihydropyridines:** nifedipine, amlodipine, felodipine, isradipine ,nicardipine , and nisoldipine. They have a much greater affinity for vascular calcium channels than for calcium channels in the heart

Calcium channel blockers

Organ system effects

All the Ca^{2+} channel blockers approved for clinical use decrease coronary vascular resistance and increase coronary blood flow

The dihydropyridines (e.g. nifedipine) are **more potent** vasodilators and have a greater ratio of vascular smooth muscle effects relative to cardiac effects than do diltiazem and verapamil

The dihydropyridines may cause reflex tachycardia if peripheral vasodilation is marked

The non-dihydropyridines Verapamil and diltiazem reduce cardiac contractility & oxygen requirement in a **dose-dependent fashion**

Mechanisms of clinical effects

Angina of Effort

- The beneficial effect is **decrease in O_2 demand** and **increase in coronary flow**

Variant angina

- The beneficial effect is to relieve and prevent the focal coronary artery spasm involved 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

Adverse effects

- ✓ Excessive inhibition of calcium influx can cause serious *cardiac depression*, including **cardiac arrest**, **bradycardia**, **atrioventricular block**, and **heart failure (rare effects)**
- ✓ Minor toxicities include **flushing, dizziness, nausea, constipation, and peripheral edema**
- ✓ **Constipation** is particularly common with verapamil
- ✓ Patients receiving **β-blocking** drugs are more sensitive to the **cardio-depressant effects of calcium** channel blockers

Newer Antianginal Drugs

Ranolazine (Ranexa®)	
Mechanism of action	- Block sodium-dependent calcium channels → decrease Ca^{2+} influx. - Partial fatty acid oxidation inhibitor.
Uses	- Used in combination with antianginal drugs. - Has no effect on HR (Unlike β-blocker or CCB).
Adverse effects	- Prolonged QT interval → Ventricular arrhythmia.
Trimetazidine (Vastarel®)	
Mechanism of action	- The first cytoprotective anti-ischemic agent. - Increase glucose metabolism. - Improve myocardial glucose utilization. - Decrease fatty acid metabolism (FA oxidation inhibitors). - Decrease O_2 requirement and consumption (Anti-anginal). - Decrease accumulation of lactic acid decrease Angina pain. - Prevent excessive production of free radicals (Antioxidant).
Uses	- Used in combination with antianginal drugs.
Nicorandil (Randil®)	
Mechanism of action	- Vasodilator antianginal agent. - Stimulates guanylate cyclase to increase formation of cGMP → VD. - K^+ATP channel opener → Increase K^+ influx → Hyperpolarization. - This hyperpolarizes the cell, which inactivates voltage-gated calcium channels & reduces intracellular Ca^{2+} (Indirect blocking Ca^{2+} channel).
Uses	- Used in combination with antianginal drugs.
Side effects	- Mouth ulcer, Flushing, and perianal ulcer, palpitation and anal ulcer.

Sodium channel blocker: Ranolazine

Ranolazine is a newer anti-anginal drug, classified as Na channel blocker. It is indicated for the treatment of chronic angina, and may be used alone or in combination with other traditional therapies

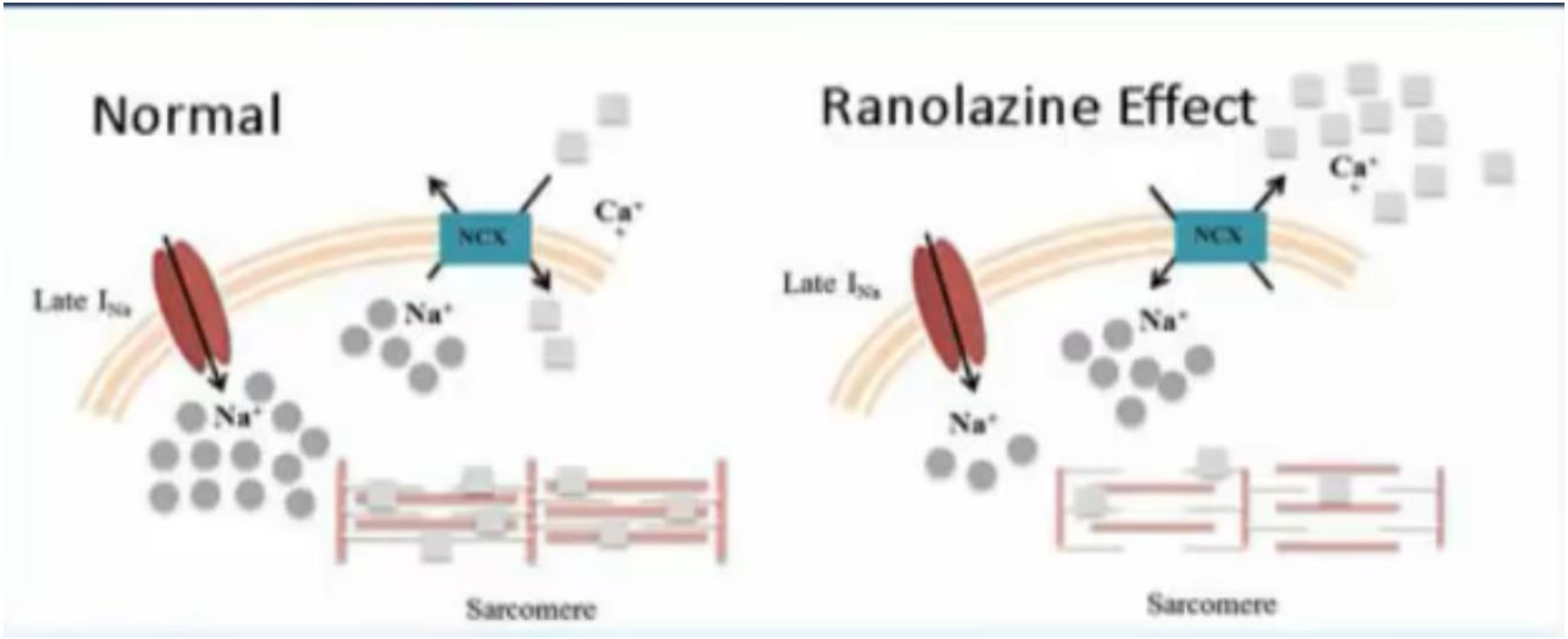
Mechanism of Action:

- It reduces contractility resulting from the blockade of a late sodium current (late I_{Na}) **in myocardial** cells **that facilitates calcium entry via the sodium-calcium exchanger**
- The decrease in intracellular sodium causes and increase in calcium expulsion via the Na-Ca^{+2} exchanger

Adverse Drug Effect:

- The most common ADRs are constipation, nausea, and weakness

Ranolazine: Mechanism of action



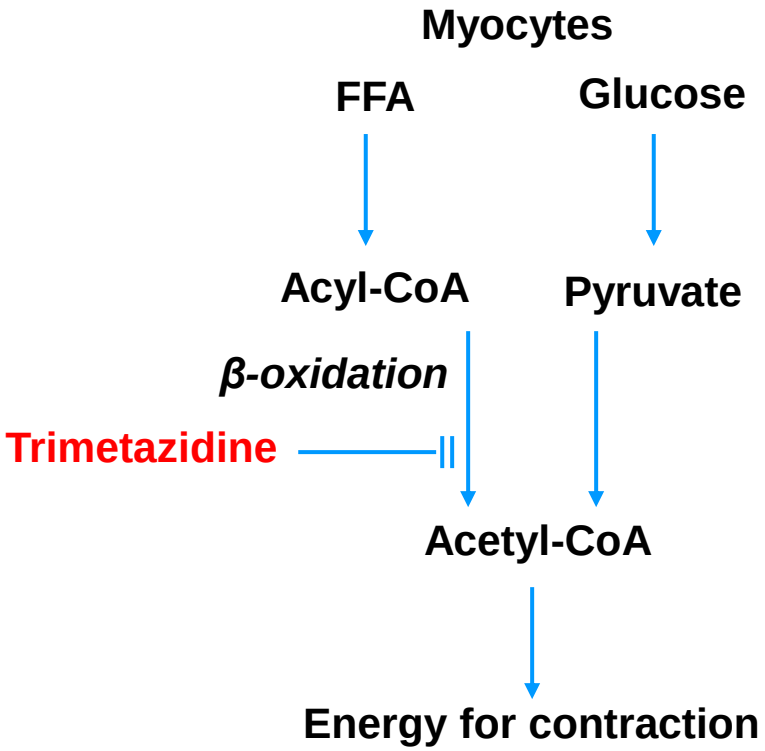
Metabolic modulation (pFOX): Trimetazidine

Trimetazidine: Is a first cytoprotective anti-ischemic agent. Is clinically effective anti-anginal agent that has no negative inotropic or vasodilator properties.

Mechanism of Action:

- Trimetazidine is metabolic modulator that **does not** reduce oxygen demand or increase blood supply
- It act by **shifting** myocardial metabolism to substrates that require less oxygen per unit of ATP produced

Metabolic modulation (pFOX): Trimetazidine



- O_2 requirement of glucose pathway is lower than FFA pathway
- During ischemia, oxidized FFA levels rise, blunting the glucose pathway

Adverse Drug Effect:

- GIT disturbance, dizziness, and headache.
- Trimetazidine use can result in movement disorders such as parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, and restless legs

Contraindications:

Parkinson disease and sever renal impairment (creatinine clearance <30 ml/min.)

pFOX = partial fatty acid oxidation
FFA = free fatty acid

Nicorandil

Nicorandil is a **new organic nitrate** with **vasodilator properties**. It is an anti-anginal drug that has the **dual properties of a nitrate and potassium channel activators.**

Mechanism of Action:

a) **K channel opener:** It opens ATP-sensitive K^+ channels, causing **K efflux**. This hyperpolarizes the cell, which **inactivates voltage-gated calcium** channels and **reduce free intracellular Ca;** thereby causing **dilatation** of peripheral and coronary resistant arterioles

b) **Nitrate:** It contains an **NO_2-moiety**, it stimulates **guanylate cyclase** to increase formation of **cyclic GMP**, decreasing the calcium influx, leads to **smooth muscle vasodilation-→**which dilates systemic veins and epicardial coronary arteries

Most common adverse drug effect:

Headache, dizziness, flushing and reflex tachycardia

Ivabradine

It is indicated for the symptomatic treatment **of chronic stable angina pectoris**

Mechanism of action:

Ivabradine is the **first selective sinus node I_f channel inhibitor**, **slowing the heart rate** and allowing more time for blood to flow to the myocardium, **decreasing the myocardial oxygen demand without effect on inotropic or blood pressure**.

Heart rate is determined by spontaneous electrical pacemaker activity in the sinoatrial (SA) node controlled by the I_f current (I_f channel, f for "funny")

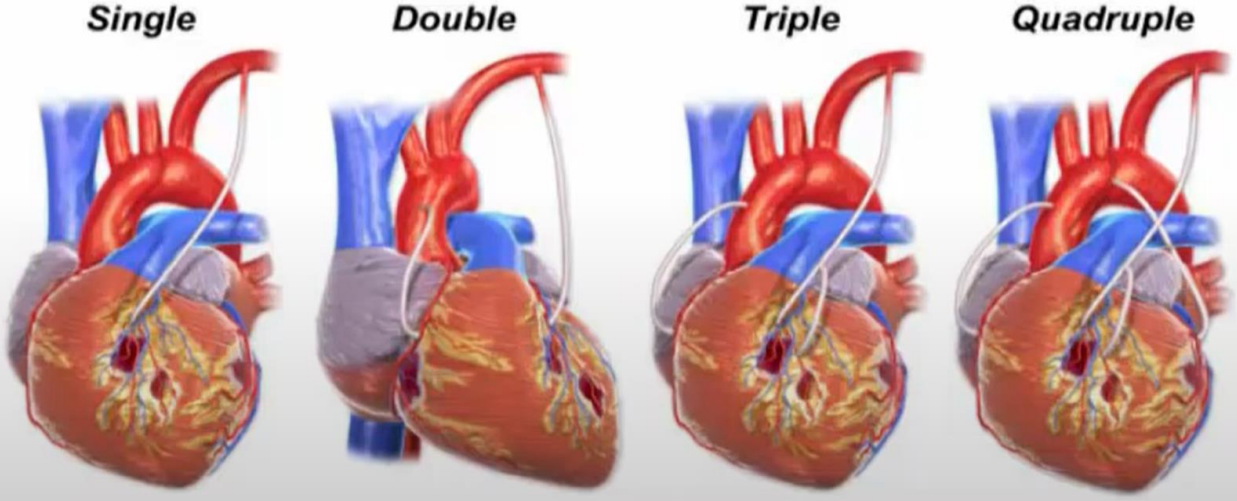
Most common adverse effect:

Luminous phenomena or **phosphenes** (seeing light without light actually entering the eye; visual **"flashing lights"** which are usually only mild to moderate in intensity and transient), dizziness and/or blurred vision.

Coronary artery revascularization

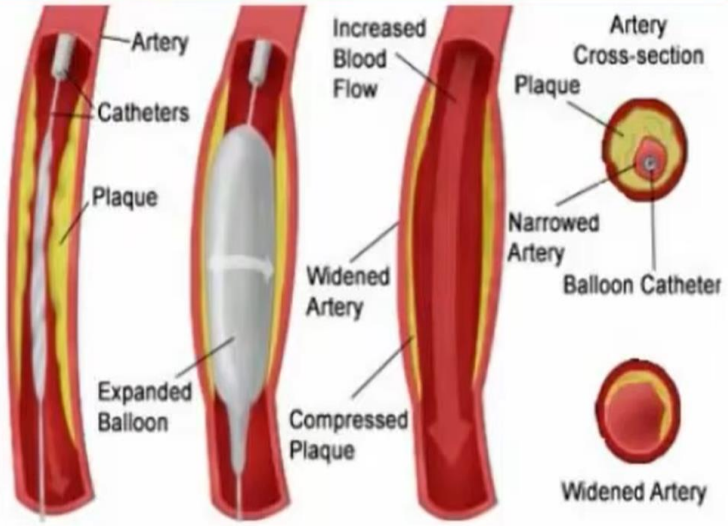
Coronary Artery Bypass Grafting (CABG)

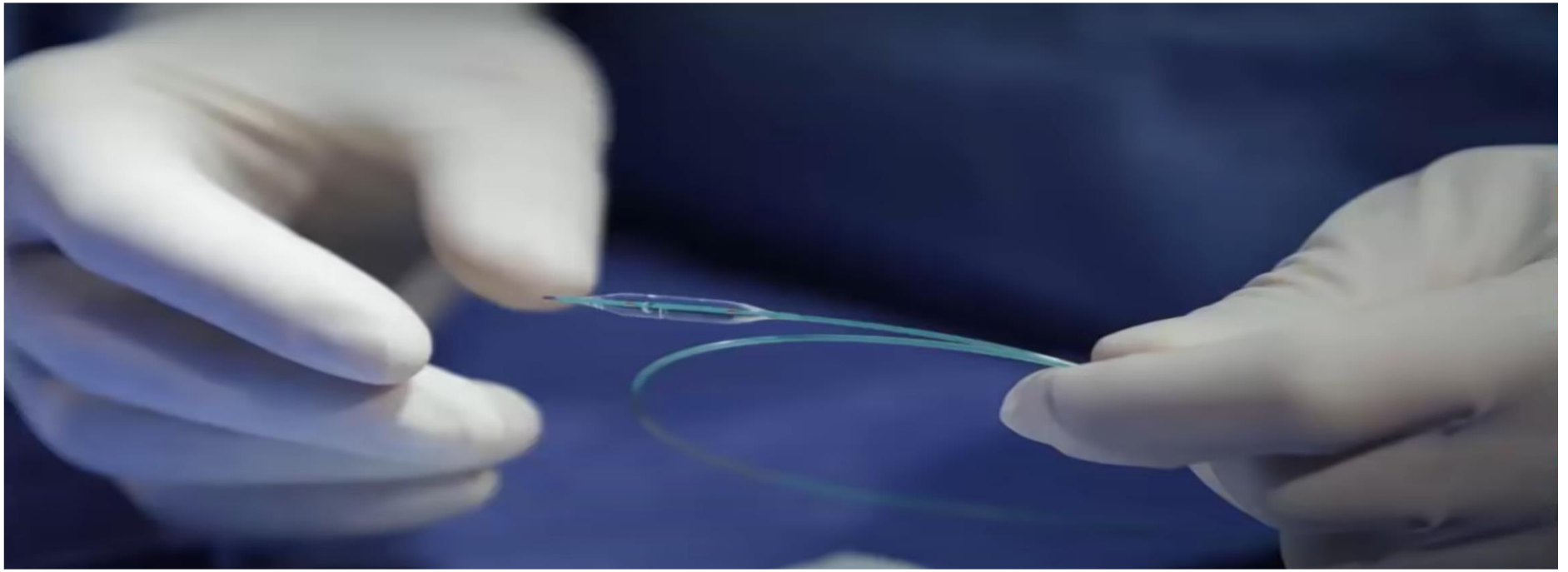
- Bypass typically requires open-chest surgery. The surgical procedure places new blood vessels around existing blockages to restore necessary blood flow to the heart muscle.



Coronary Artery Balloon Angioplasty

- ***It also called*** **Percutaneous coronary intervention (PCI).**
- In the late 1970s, doctors began using balloon angioplasty to treat narrowed coronary arteries.
- During this procedure, a very thin, long, balloon-tipped tube, called a catheter, is inserted into an artery in either the groin or arm and is moved to the site of the blockage with help from an X-ray.
- The balloon at the tip of the catheter is then inflated to compress the blockage and restore blood flow, and then it's deflated to allow the catheter and balloon to be removed.

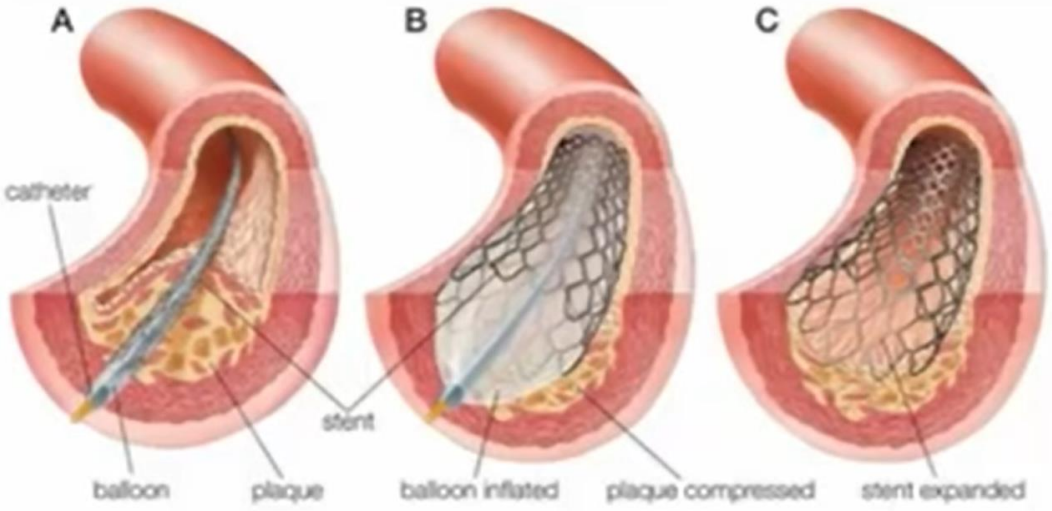




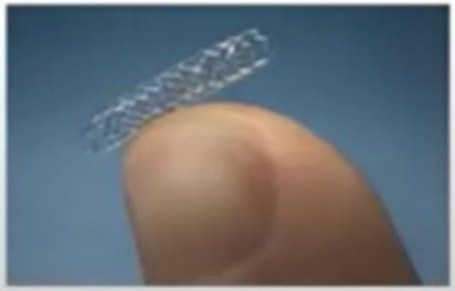
Coronary artery revascularization

Coronary Artery Stents

- A coronary stent is a tube-shaped device placed in the coronary arteries that supply blood to the heart, to keep the arteries open in the treatment of coronary heart disease.
- In 1986, French researchers implanted the first stent into a human coronary artery.
- In 1994, the FDA approved the first heart stent for use in the U.S.
- There are many types of coronary stent (Next page)



- ***Coronary stent types***:
  - **Bare-Metal Stent (BMS)**; Metallic stent without a coating.
  - **Drug-Eluting Stent (DES)**; Stent are coated with an antiproliferative drug, allows drug elution into the coronary wall for weeks after implantation.
  - **Bioresorbable stent**; Developed (2011) by Abbott (**Absorb®**), also called ***Abbott*** **Vascular Bioresorbable Vascular Scaffold (BVS)**, stent dissolves after about two years.



  - **Dual-Therapy Stent**; **COMBO Stent®** is the only dual therapy stent available today, Developed (2013) by OrbusNeich, combines the **Genous technology** (endothelial progenitor cell; EPC) which promotes the accelerated natural healing of the vessel wall ***with*** an **antiproliferative**

Coronary artery revascularization

Transmyocardial Laser Revascularization (TMLR)

- Transmyocardial Laser Revascularization (TMLR) is a type of surgery that uses a laser to make tiny channels through the heart muscle and into the lower-left ventricle.
- After TMLR, when oxygen-rich blood enters the left ventricle, some of that blood can flow through the tiny channels and carry much-needed oxygen to the starving heart muscle.
- During a typical procedure, approximately 10 –50 channels are made in each targeted region of the heart muscle.

Strategy of treatment of angina

- **Lifestyle modification:-**
- **Drug Treatments:-**

A: Stable Angina	
Short-Acting (Acute attacks)	
Nitroglycerin (sublingual, spray) **Isosorbide dinitrate** (sublingual, spray)	
Repeat the dose every 5 min. till disappearance of pain (Maximum 3 doses).	
Long-Acting (Prophylaxis)	
Nitroglycerin (Oral, Ointment or Patches) **Isosorbide dinitrate** (Oral) **Isosorbide mononitrate** (Oral) **Aspirin** (75-100mg/d)	**Statins** (lower lipid level in the blood) **β-blockers** **Calcium Channel Blockers** **Nicorandil**
Coronary artery revascularization	
B: Variant Angina	
Organic Nitrate Or **Calcium Channel Blockers** (No **β-blockers**)	
C: Unstable Angina	
Organic Nitrate - Antiplatelet - Heparin - Statins - Calcium Channel Blockers - β-blockers (without intrinsic sympathomimetic activity (ISA))	