Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 4

ANTIANGINAL DRUGS

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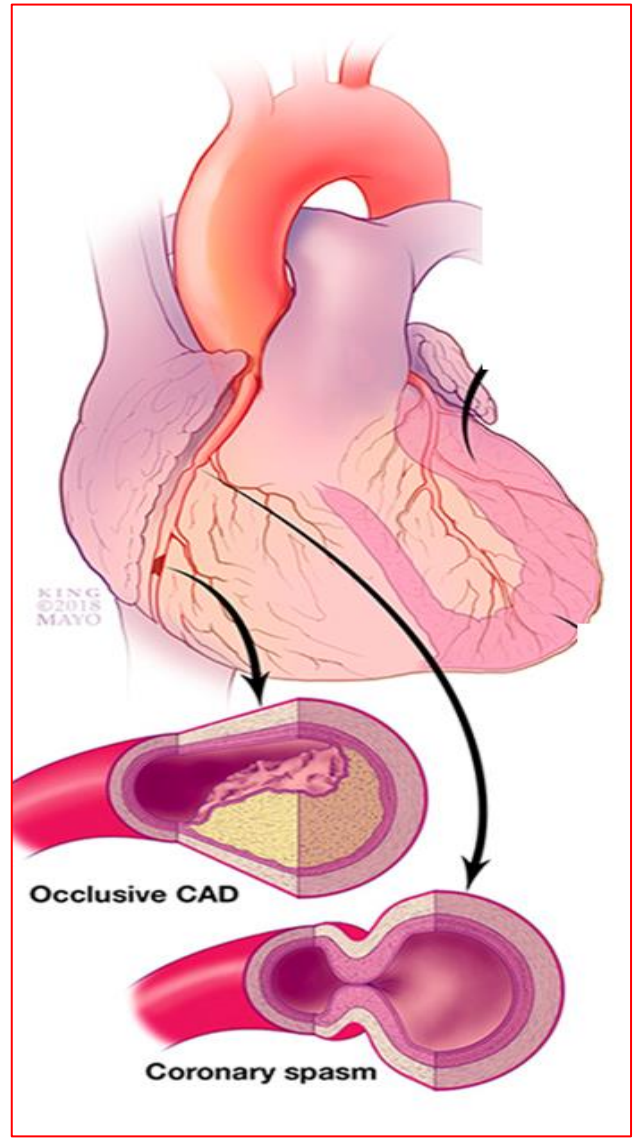
Overview

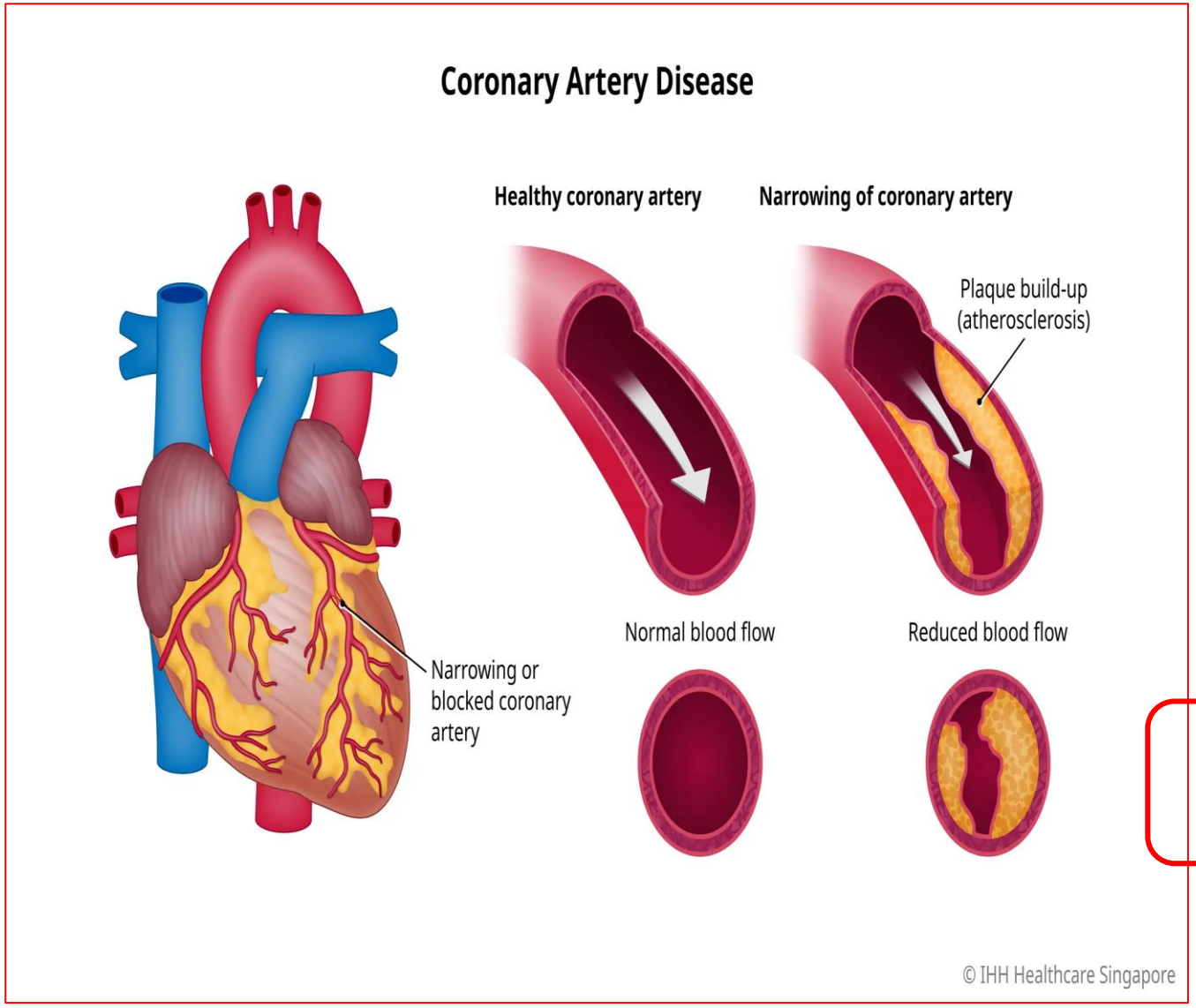
Atherosclerotic disease of the **coronary arteries**, also known as coronary artery disease (**CAD**) or ischemic heart disease (**IHD**), is the most **common** cause of **mortality** worldwide.

Atherosclerotic **lesions** in coronary arteries can **obstruct blood flow**, leading to an **imbalance** in myocardial oxygen **supply** and **demand** that presents as **stable angina** or an **acute coronary syndrome** (MI or unstable angina).

Typical angina pectoris is a characteristic **sudden, severe, crushing chest pain** that may **radiate to the neck, jaw, back, and arms**.



Overview


Coronary Artery Disease
Healthy coronary artery
Narrowing of coronary artery
Plaque build-up (atherosclerosis)
Narrowing or blocked coronary artery
Normal blood flow
Reduced blood flow
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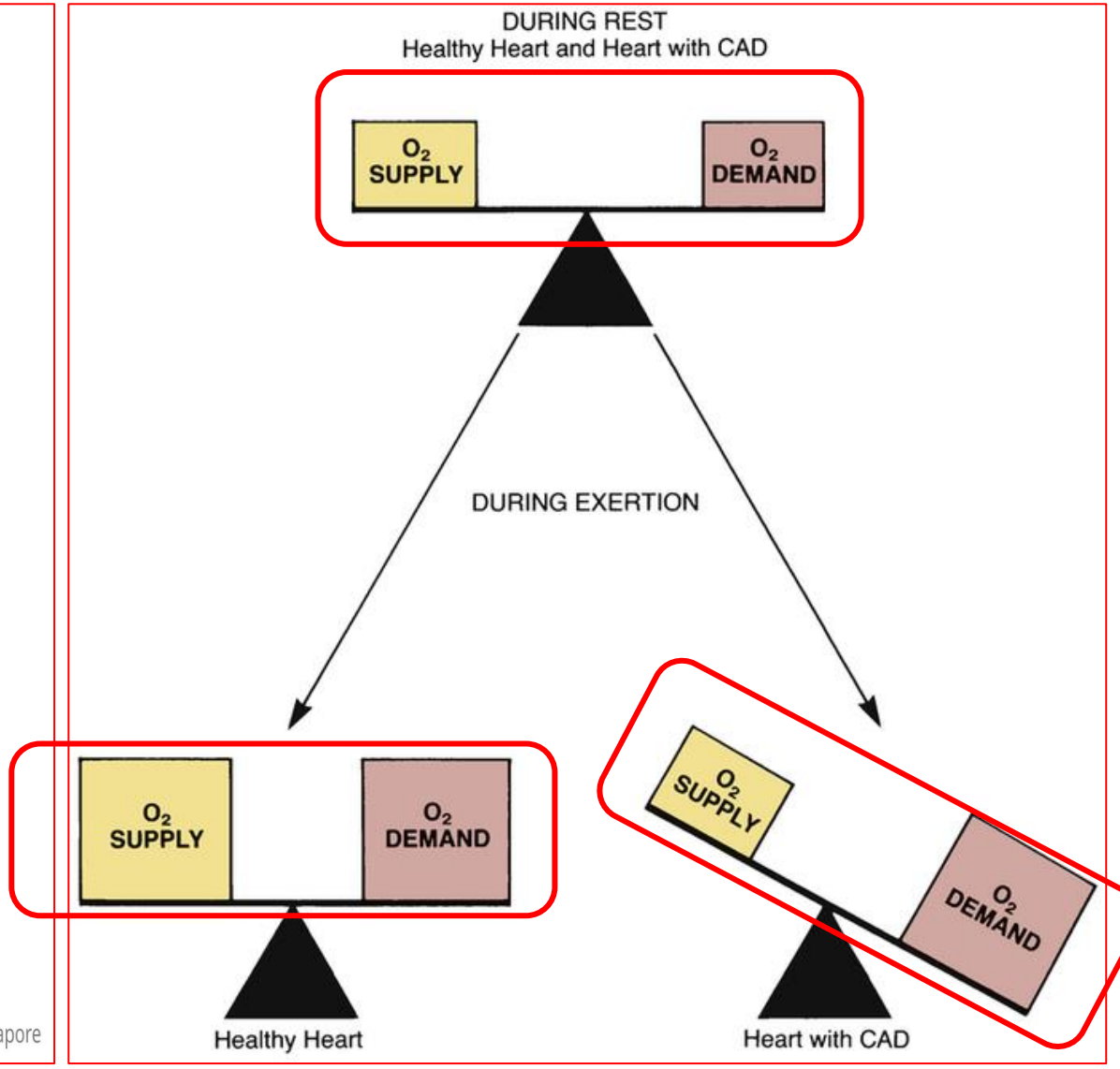
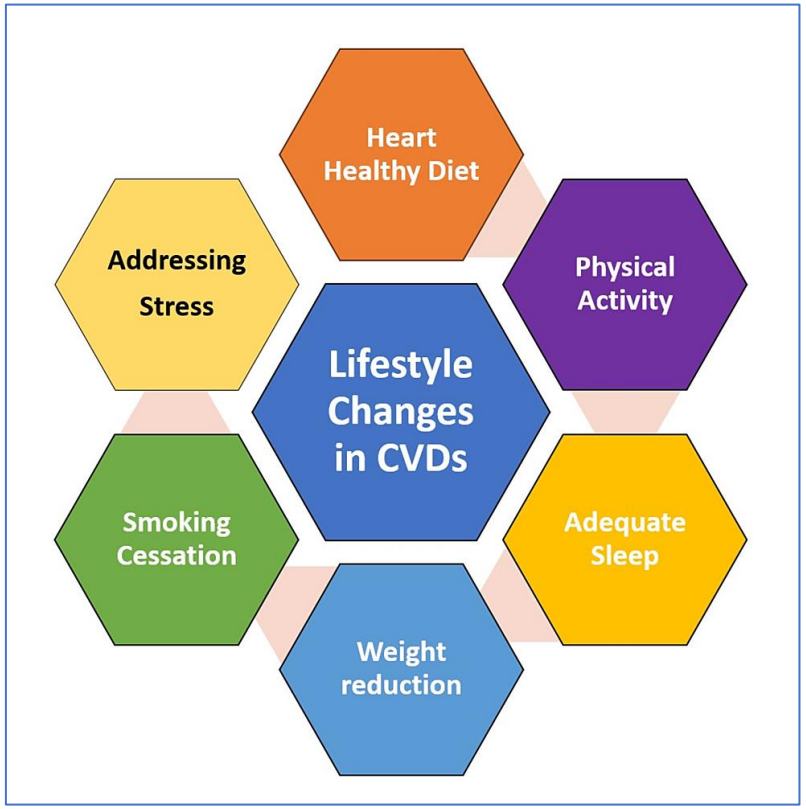

DURING REST
Healthy Heart and Heart with CAD
O2 SUPPLY
O2 DEMAND
DURING EXERTION
O2 SUPPLY
O2 DEMAND
Healthy Heart
O2 SUPPLY
O2 DEMAND
Heart with CAD

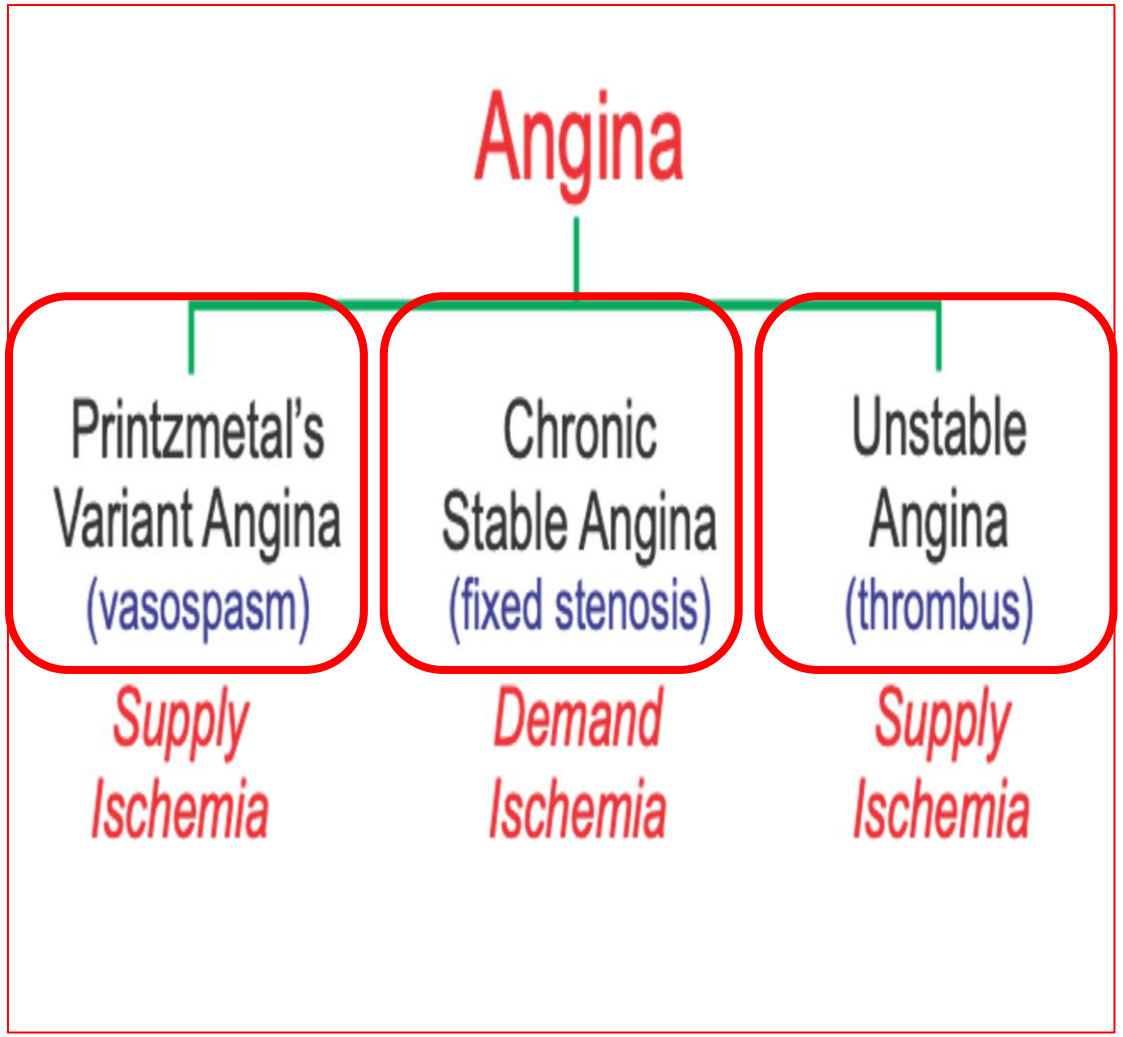
Overview

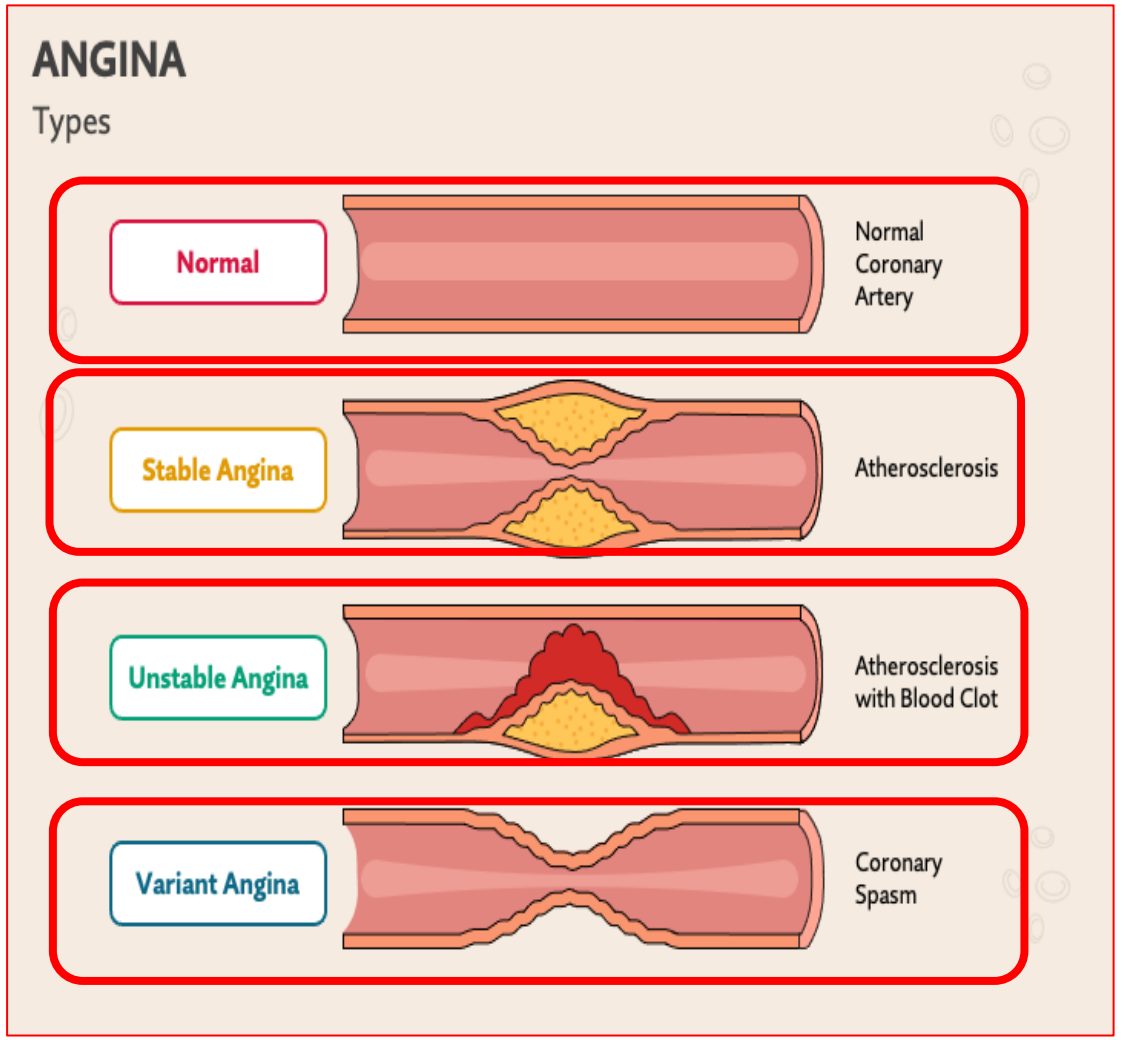
All patients with **IHD and angina should**:

- **Receive** guideline-directed **medical therapy**
- Emphasis on **lifestyle modifications** (smoking cessation, physical activity, weight management)
- Management of **modifiable risk factors** (hypertension, diabetes, dyslipidemia) to **reduce** cardiovascular **morbidity and mortality**.



TYPES OF ANGINA





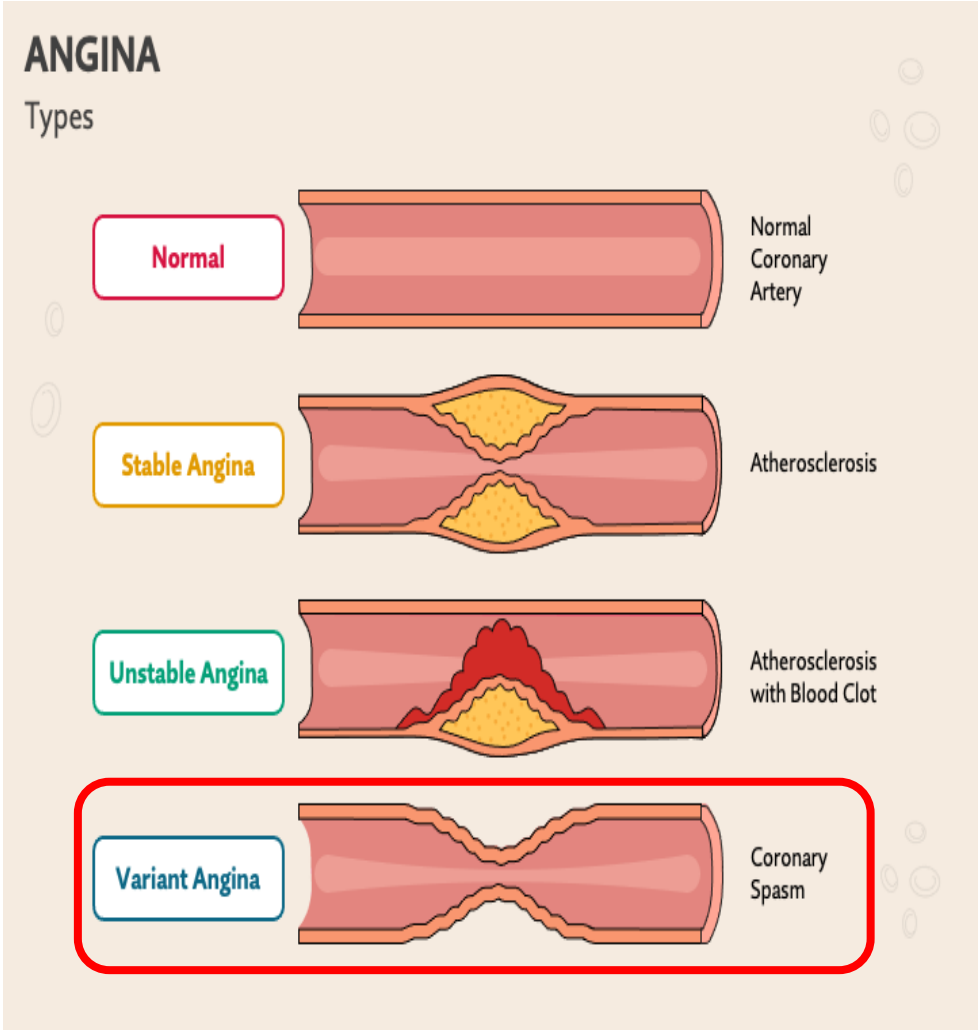
1. Prinzmetal, variant, vasospastic, or rest angina

Prinzmetal angina is an **uncommon** pattern of episodic angina.

It **occurs at rest** and is due to **decreased blood flow** to the heart muscle caused by **spasm of the coronary arteries**.

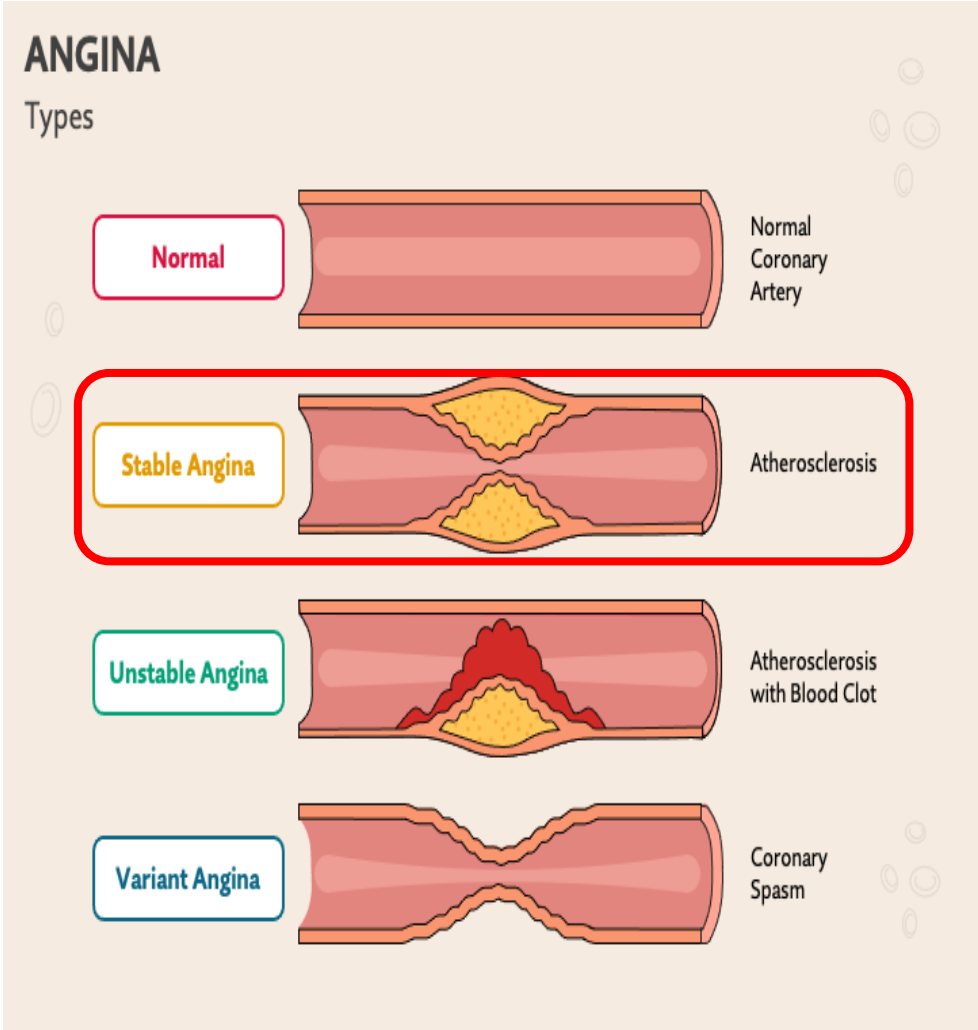
The anginal attacks are **unrelated to physical activity, heart rate, or blood pressure**.

Generally **responds promptly to coronary vasodilators**, such as **nitroglycerin and calcium channel blockers**.



2. Stable angina, effort-induced angina, classic or typical angina

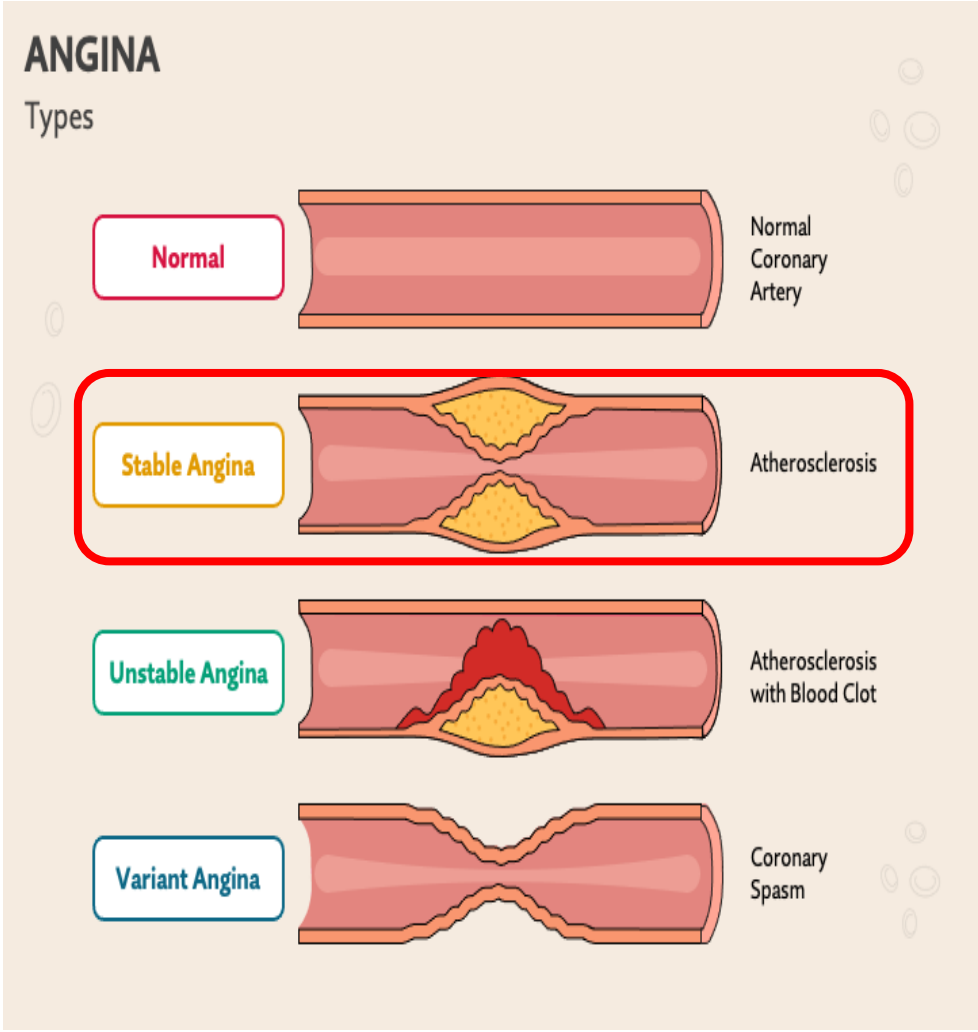
- Classic or typical angina pectoris is the **most common** form of angina.
- It is usually characterized by a **short-lasting burning, heavy, or squeezing feeling in the chest**.
- Classic angina is **caused by** the reduction of coronary perfusion **due to** a fixed obstruction of a coronary artery produced by atherosclerosis.
- **Increased myocardial oxygen demand**, such as that produced by physical activity, emotional stress or excitement, or any other cause of **increased cardiac workload may induce ischemia**.
- Typical angina pectoris is promptly **relieved by rest or nitroglycerin**.



2. Stable angina, effort-induced angina, classic or typical angina

Some ischemic episodes may present "**atypically**"-with extreme fatigue, nausea, or diaphoresis-while **others** may **not be associated** with any symptoms (**silent angina**).

Atypical presentations are **more common** in <u>women, diabetic patients, and the elderly</u>.



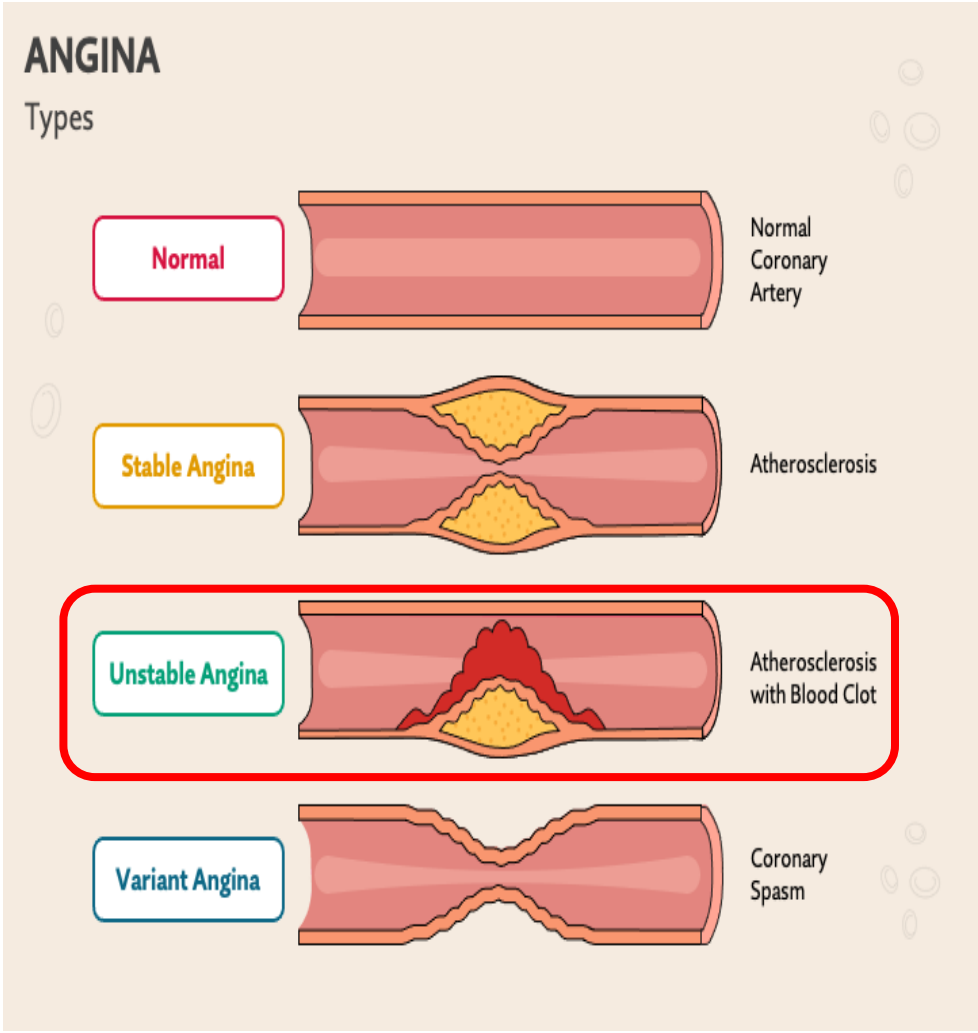
3. Unstable angina

Unstable angina is **chest pain** that occurs with **increased frequency, duration, and intensity** and **can be** precipitated by progressively **less effort**.

Any episode of rest angina **longer than 20 minutes**, or even **sudden development** of **shortness of breath** is suggestive of **unstable angina**.

The symptoms are **not relieved** by rest or nitroglycerin.

Unstable angina is a **form of acute coronary syndrome** and requires **hospital admission** and more **aggressive therapy** to **prevent** progression to **MI and death**.



Acute coronary syndrome

Acute coronary syndrome is an **emergency** that commonly results from **rupture** of an atherosclerotic **plaque** and **partial or complete thrombosis** of a coronary artery.

If the thrombus occludes most of the blood vessel, and, if the occlusion is **untreated**, **necrosis** of the cardiac muscle may ensue.

MI (necrosis) is typified by **increases** in the serum levels of **biomarkers** such as **troponins** and **creatine kinase**.

The acute coronary syndrome may present as **ST-segment elevation MI**, **non-ST-segment elevation MI**, or as **unstable angina**.

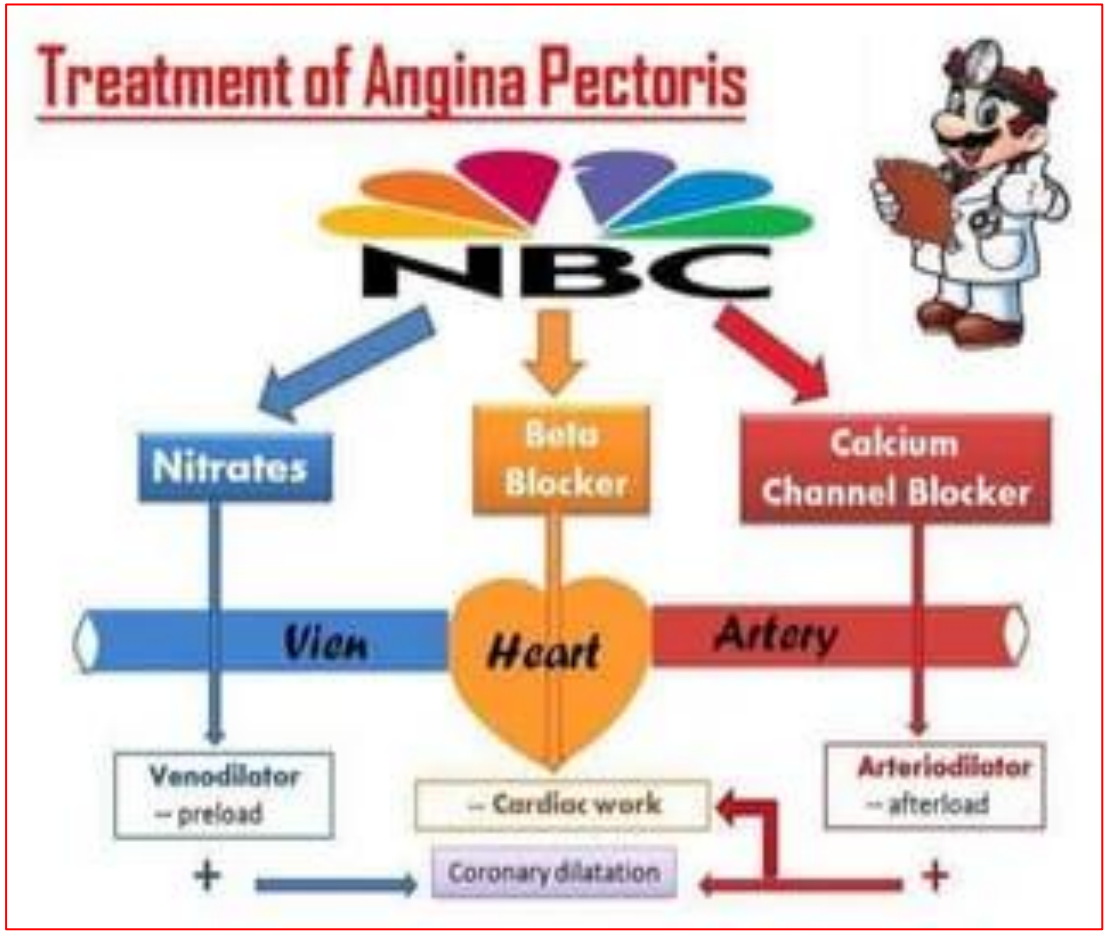
Note: **In unstable angina**, increases in **biomarkers** of myocardial necrosis are **not present**.

TREATMENT STRATEGIES

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

1. **Beta-blockers**
2. **Calcium channel blockers**
3. **Organic nitrates**
4. **Sodium channel-blocking drug** (ranolazine)

- These agents help to **balance** the cardiac oxygen **supply** and **demand** equation by **affecting** blood pressure, venous return, heart rate, and contractility.



1. ORGANIC NITRATES

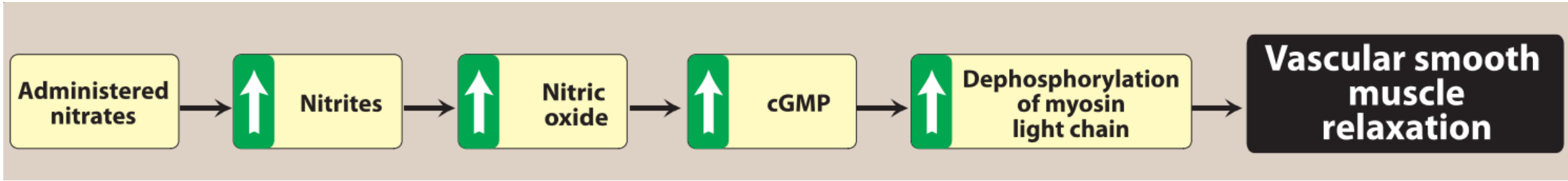
They are **effective** in **stable, unstable,** and **variant angina**.

Organic nitrates **relax the vascular smooth muscle** by their intracellular **conversion** to **nitrite ions** and then to **nitric oxide**, which in turn **activates guanylate cyclase** and **increases** the synthesis of **cGMP**.

Elevated **cGMP** ultimately leads to **dephosphorylation** of the **myosin light chain**, resulting in vascular smooth muscle **relaxation**.

Nitrates such as nitroglycerin cause **dilation of the large veins**, which **reduces preload** (venous return to the heart) and, therefore, **reduces** the **work of the heart**.

Nitrates also **dilate** the **coronary vasculature**, providing an **increased** blood supply to the heart muscle.



1. ORGANIC NITRATES

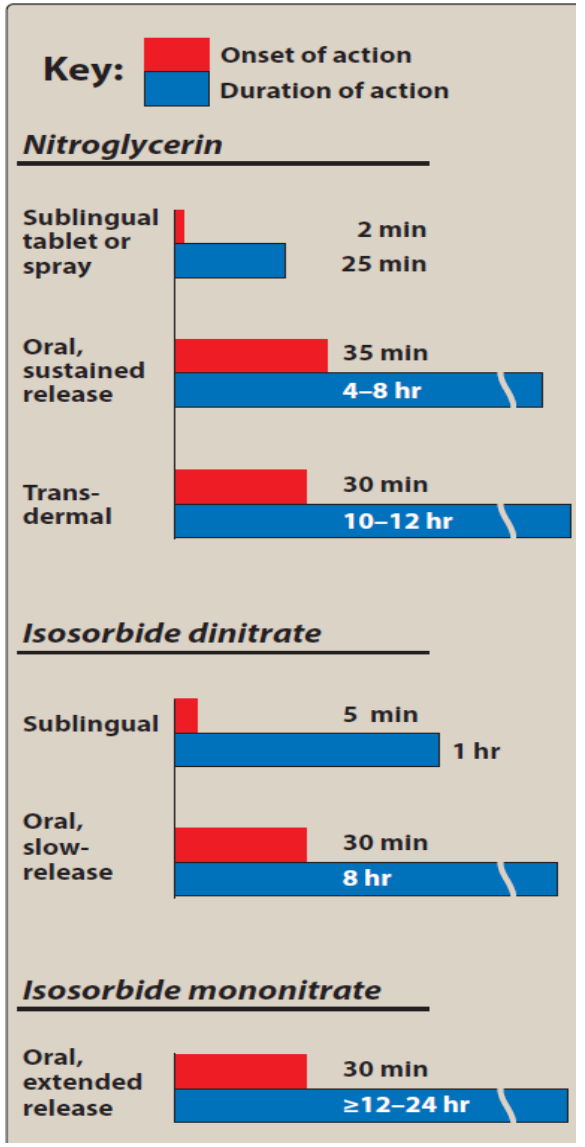
The **onset of action** varies from **1 min. for nitroglycerin** to **30 min. for isosorbide mononitrate**.

Sublingual nitroglycerin, available in **tablet** or **spray** formulation, is the **drug of choice** for **prompt relief** of an angina attack precipitated by exercise or emotional stress.

Significant first-pass metabolism of nitroglycerin occurs in the **liver, Therefore**, it is commonly administered via the **sublingual or transdermal** route.

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.



1. ORGANIC NITRATES

Headache is the most **common** adverse effect of nitrates.

High doses of nitrates can also cause **postural hypotension, facial flushing, and tachycardia.**

Tolerance to the actions of nitrates develops rapidly as the blood vessels become **desensitized** to vasodilation.

Tolerance can be **overcome** by providing a daily **"nitrate-free interval"** to restore sensitivity to the drug.

The **nitrate-free interval** of **10 to 12 hours** is usually taken **at night** when myocardial oxygen demand is decreased.

However, **variant angina** worsens early in the **morning**, perhaps due to circadian catecholamine surges. Therefore, the **nitrate-free interval** in patients with variant angina should occur in the **late afternoon**.

2. Beta-adrenergic blockers

They **decrease** the oxygen **demands** of the myocardium **by blocking beta-1 receptors**, resulting in decreased heart rate, contractility, cardiac output, and blood pressure.

These agents **reduce** myocardial oxygen demand **during exertion and at rest** and can **reduce** both the **frequency** and **severity** of angina attacks.

With the **exception** of **vasospastic angina,** beta-blockers are **recommended** as **initial** antianginal therapy in **all** patients unless **contraindicated**.

Beta blockers **reduce** the risk of **death and MI** in patients who have had a prior MI and also **improve mortality** in patients with HFrEF.

2. Beta-adrenergic blockers

Propranolol is the **prototype** for this class of compounds, but it is **not cardioselective,** Thus, other B-blockers, such as **metoprolol and atenolol**, are **preferred**.

Note: **All** Beta-blockers are **nonselective** at **high doses** and can inhibit Beta2 receptors.

Beta-Blockers should be **avoided** in patients with **severe bradycardia.**

They **can be used** in patients with diabetes, peripheral vascular disease, and chronic obstructive pulmonary disease, as long as they are **monitored closely**.

Nonselective B-blockers should be **avoided** in patients with **asthma**.

3. CALCIUM CHANNEL BLOCKERS

Calcium influx is **increased** in ischemia **because** of the membrane **depolarization** that **hypoxia produces**.

In turn, this **promotes** the activity of several ATP-consuming enzymes, **thereby depleting energy stores** and worsening the ischemia.

Calcium Channel Blockers include:

- **Dihydropyridine** calcium channel blockers
- **NON-Dihydropyridine** calcium channel blockers

A. Dihydropyridine calcium channel blockers

Amlodipine, an oral dihydropyridine, has **minimal effect** on **cardiac conduction** and functions **mainly** as an **arteriolar vasodilator**.

The vasodilatory effect of amlodipine is **useful** in the treatment of **variant angina** caused by spontaneous coronary spasm.

Nifedipine is another agent in this class; it is usually administered as an extended-release oral formulation.

Short-acting dihydropyridines should be **avoided** in **CAD** because of evidence of increased mortality after MI and an increase in acute MI in hypertensive patients.

B. Nondihydropyridine calcium channel blockers

Verapamil slows AV conduction directly and **decreases** heart rate, contractility, blood pressure, and oxygen demand.

Verapamil has **greater negative inotropic** effects than amlodipine, but it is a **weaker vasodilator**.

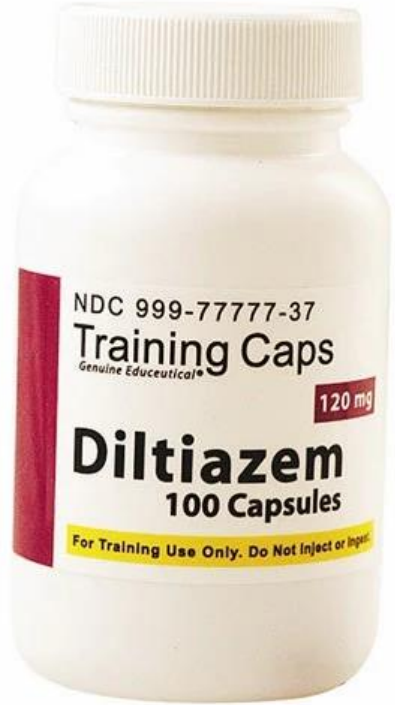
Verapamil is **contraindicated** in patients with preexisting depressed cardiac function or AV conduction abnormalities.

B. Nondihydropyridine calcium channel blockers

Diltiazem also **slows** AV conduction, **decreases** the rate of firing of the sinus node pacemaker, and is also a **coronary artery vasodilator**.

Diltiazem can **relieve coronary artery spasm** and is particularly useful in patients with **variant angina**.

Non-dihydropyridine calcium channel blockers can **worsen heart failure** due to their negative inotropic effect, and their use should be **avoided** in this population.

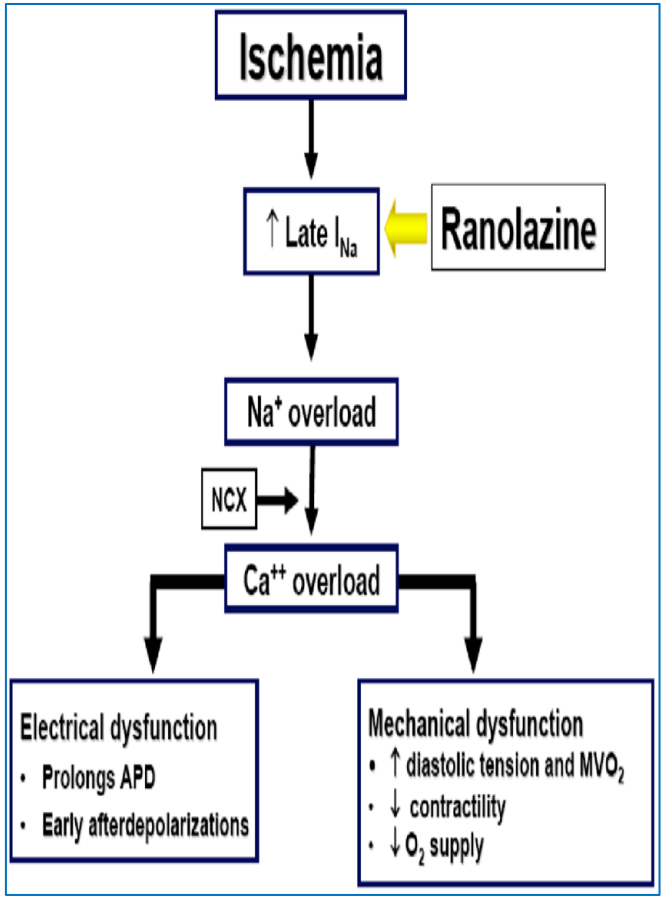


4. SODIUM CHANNEL BLOCKER

Ranolazine inhibits the **late phase of the sodium current.**

Inhibition of late I_{Na} **reduces intracellular sodium and calcium overload**, thereby **improving diastolic function**.

Ranolazine has **antianginal** as well as **antiarrhythmic** properties.

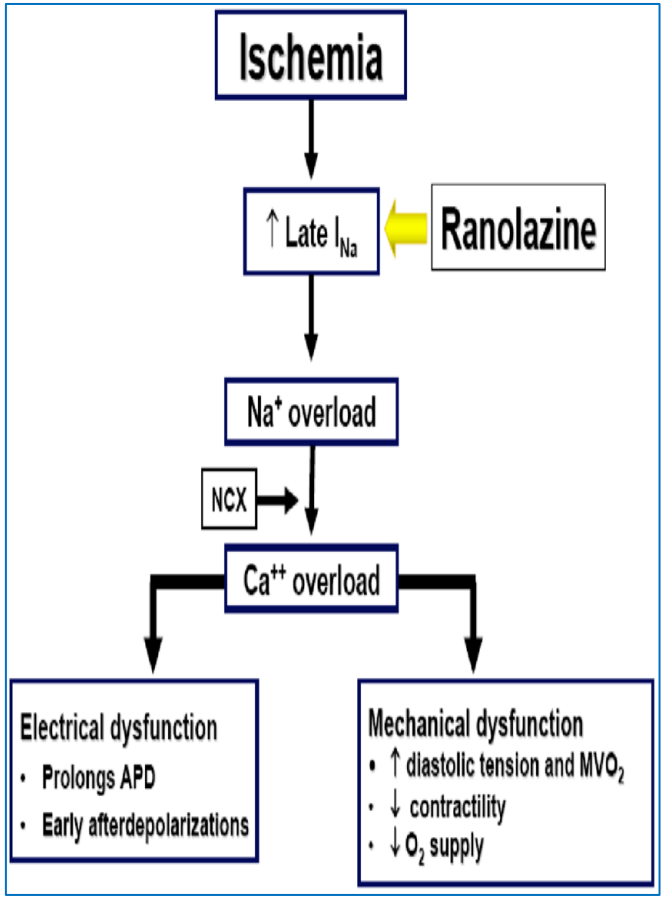


4. SODIUM CHANNEL BLOCKER

It is most often **used** in patients who have **failed other antianginal therapies**.

The **antianginal effects** of ranolazine are considerably **less in women** than in men.

Ranolazine can **prolong the QT** interval and should be **avoided** with other drugs that cause QT prolongation.



Thank You