

Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 6

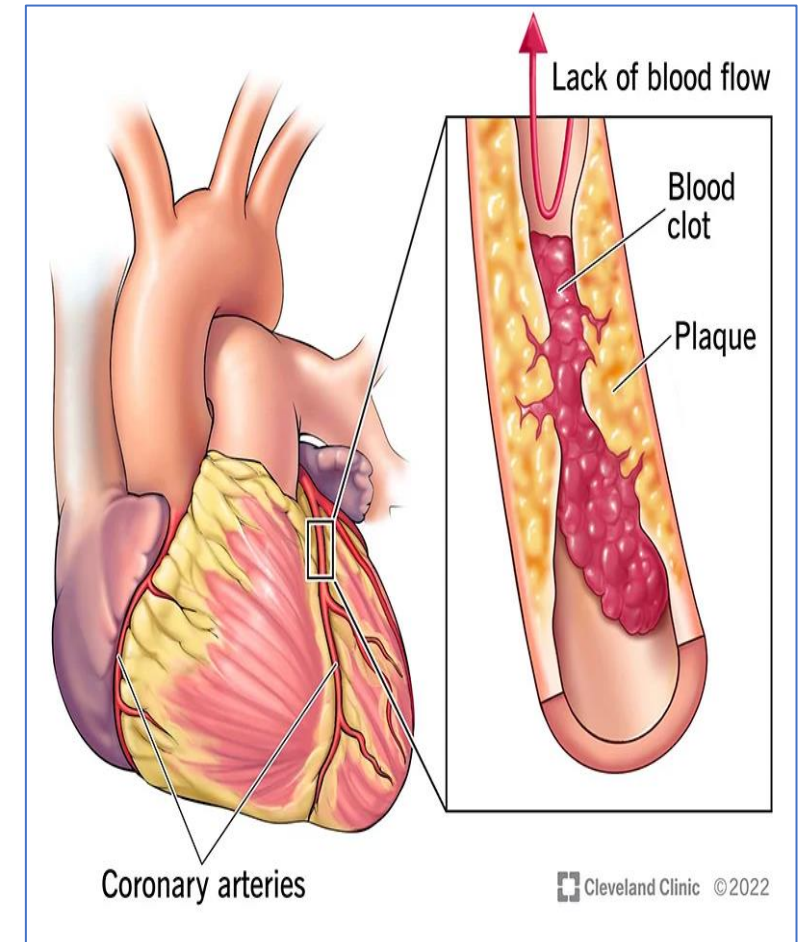


ANTIANGINAL DRUGS

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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** (myocardial infarction [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**.

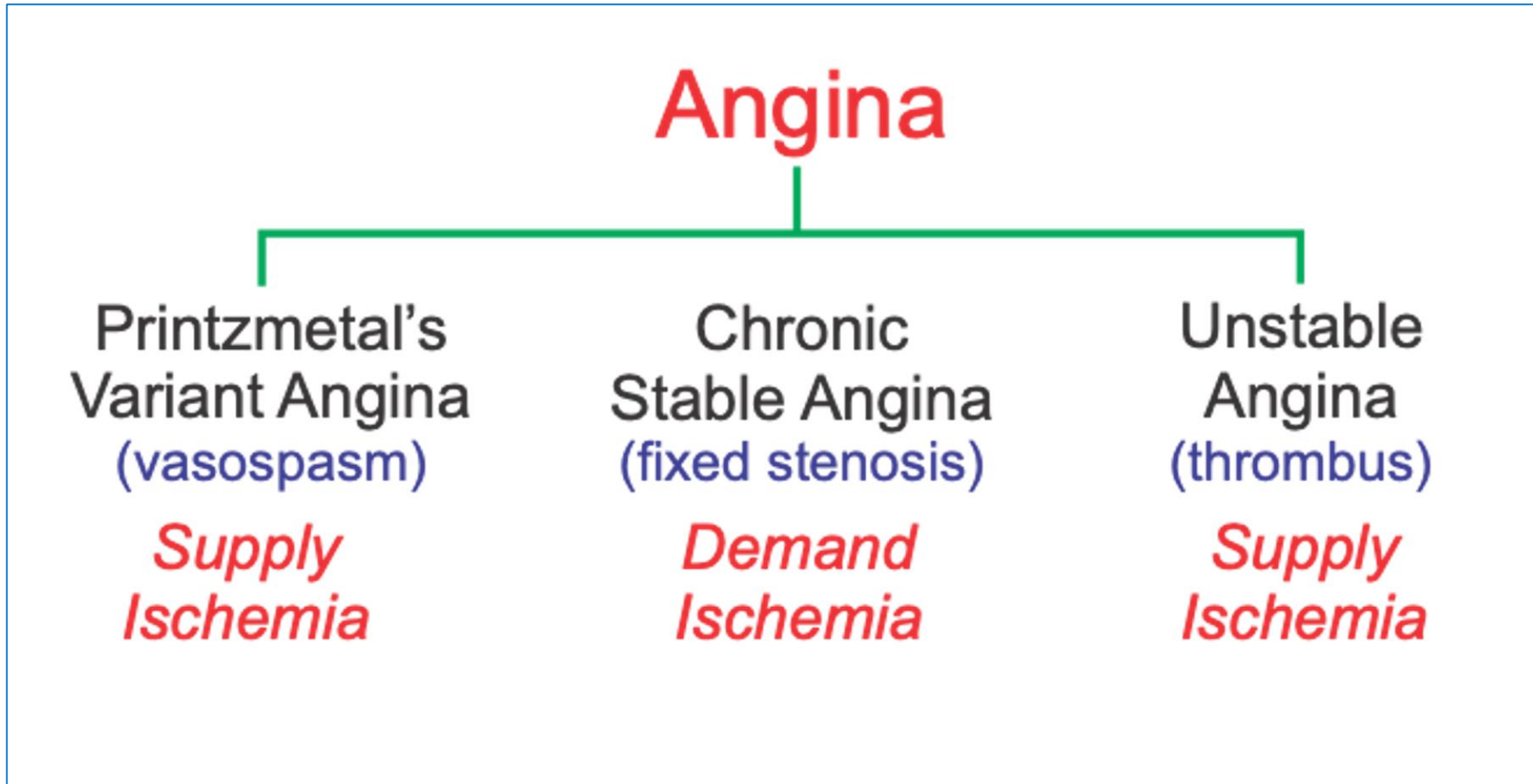


Overview

- All patients with IHD and angina should:
 1. **Receive** guideline-directed medical therapy
 2. Emphasis on **lifestyle modifications** (smoking cessation, physical activity, weight management)
 3. Management of **modifiable risk factors** (hypertension, diabetes, dyslipidemia) to reduce cardiovascular morbidity and mortality.



TYPES OF ANGINA

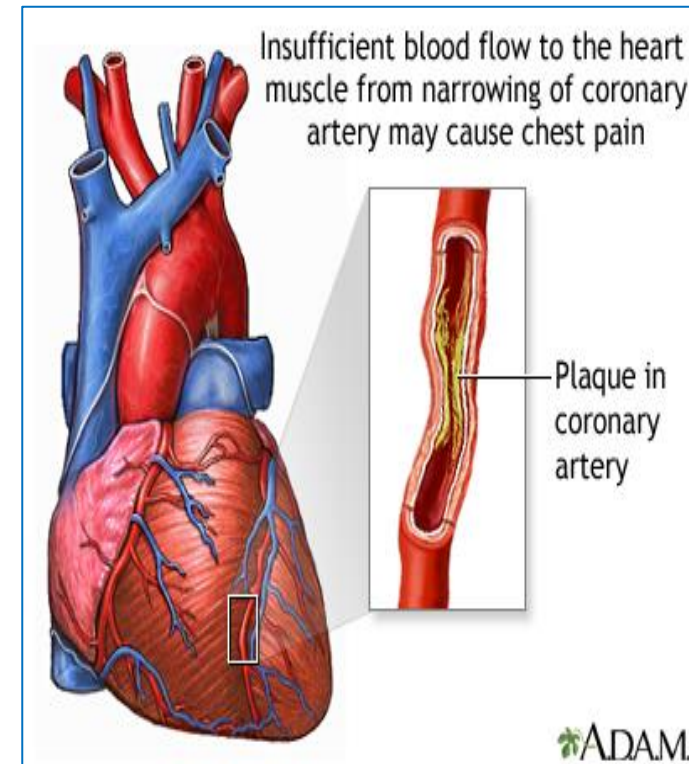


1. Prinzmetal, variant, vasospastic, or rest angina

- Prinzmetal angina is an **uncommon** pattern of episodic angina that **occurs at rest** and is due to **decreased blood flow** to the heart muscle caused by **spasm of the coronary arteries**.
- 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 angina 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

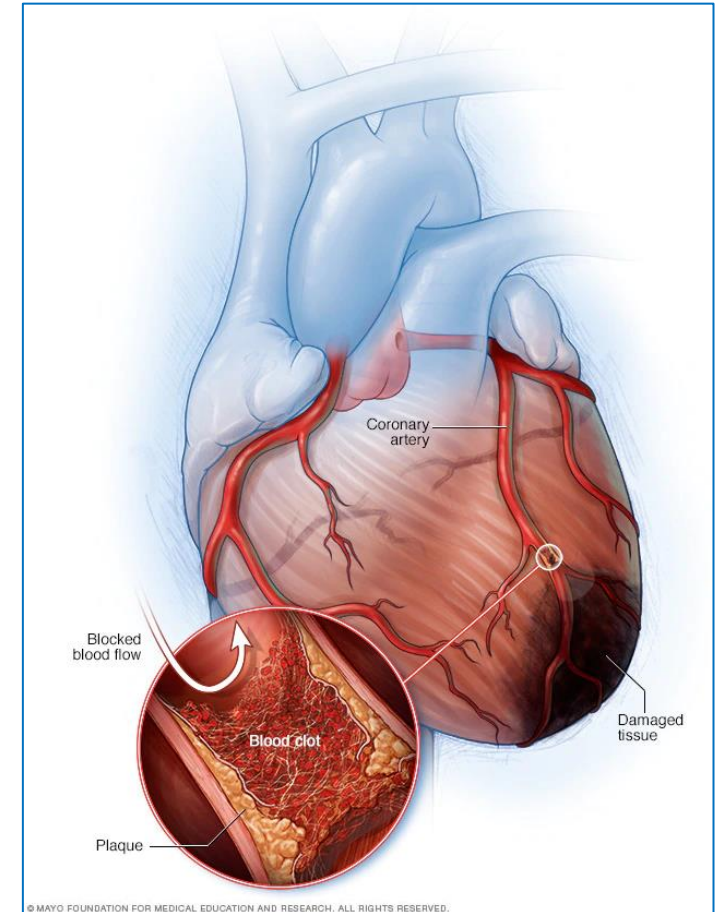
When the **pattern of chest pain** and the **amount of effort** needed to **trigger** the chest pain does **not vary** over time, the angina is named "**stable angina**".

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 women, diabetic patients, and the elderly.

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**, any new onset angina, any increasing (crescendo) angina, 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**.

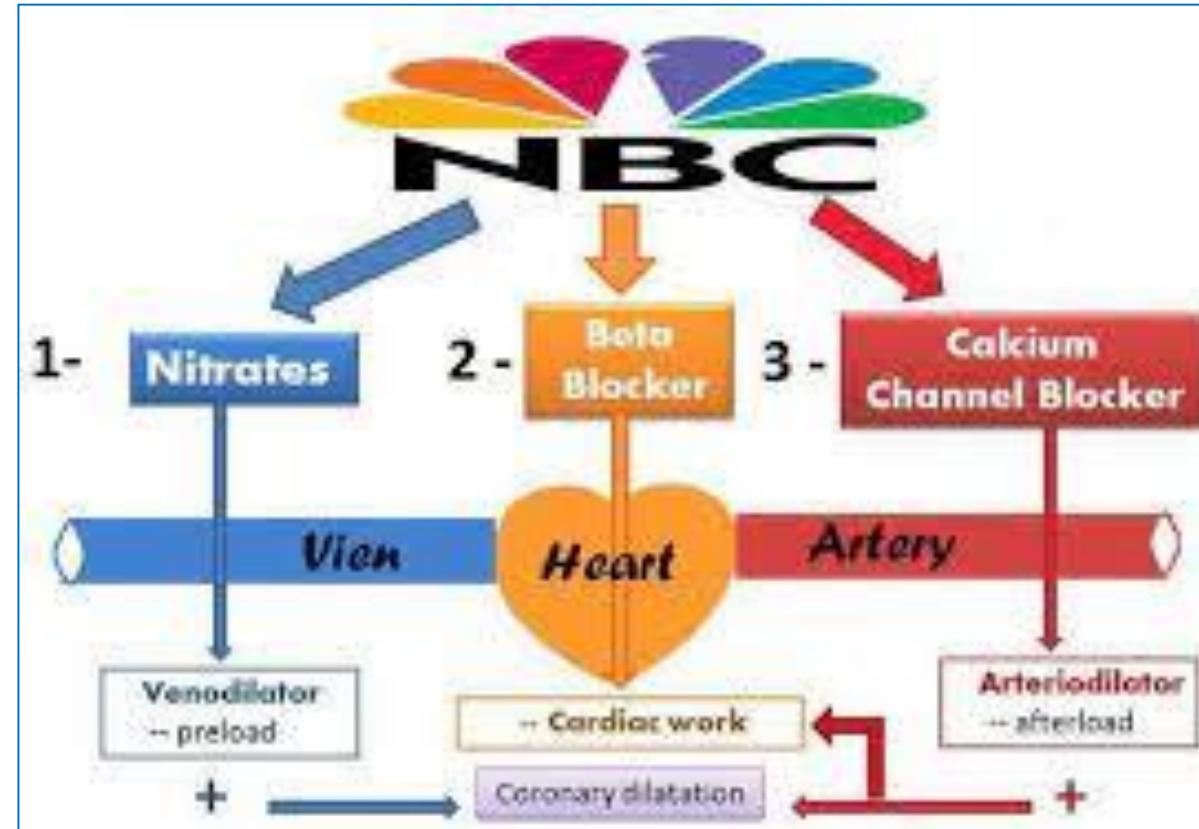


4. Acute coronary syndrome

- 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**.

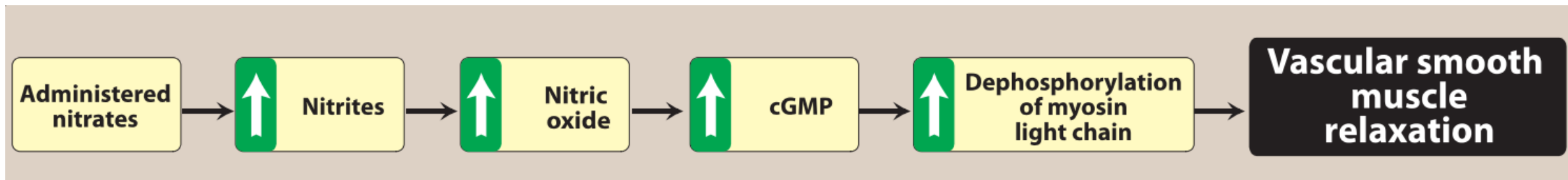
TREATMENT STRATEGIES

- **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.



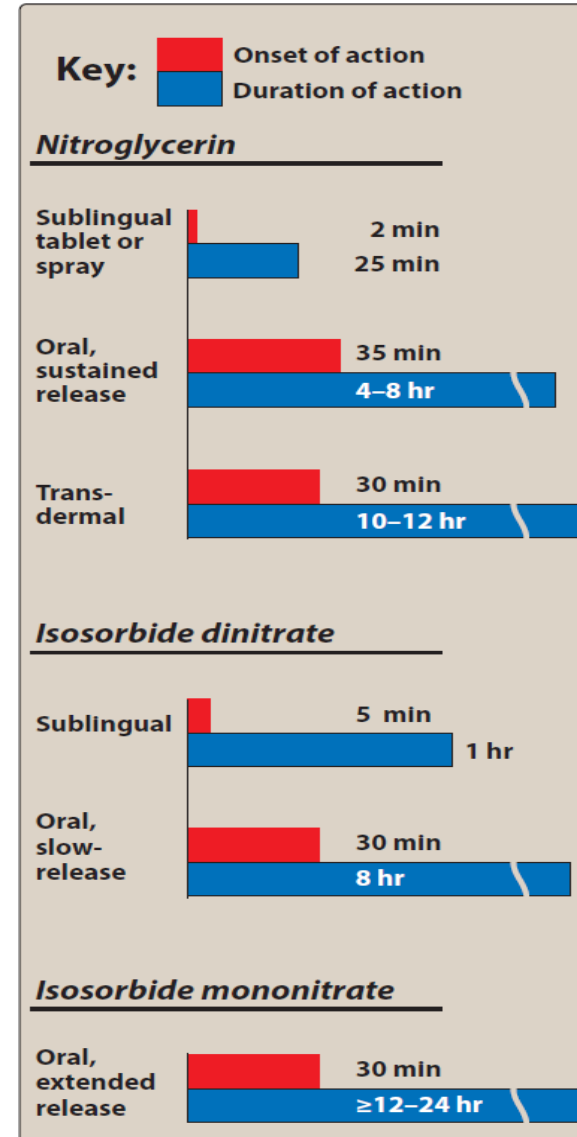
1. ORGANIC NITRATES

- 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

- The beta-adrenergic blockers **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** a **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:
 - A. Dihydropyridine** calcium channel blockers
 - B. 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.
- **Shortacting** dihydropyridines should be **avoided** in **CAD** because of evidence of increased mortality after an MI and an increase in acute M in hypertensive patients.

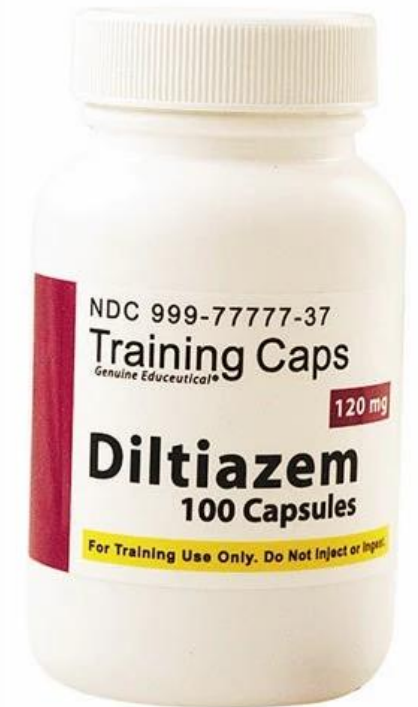
B. Nondihydropyridine calcium channel blockers

- **Verapamil** (phenylalkylamine) **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.



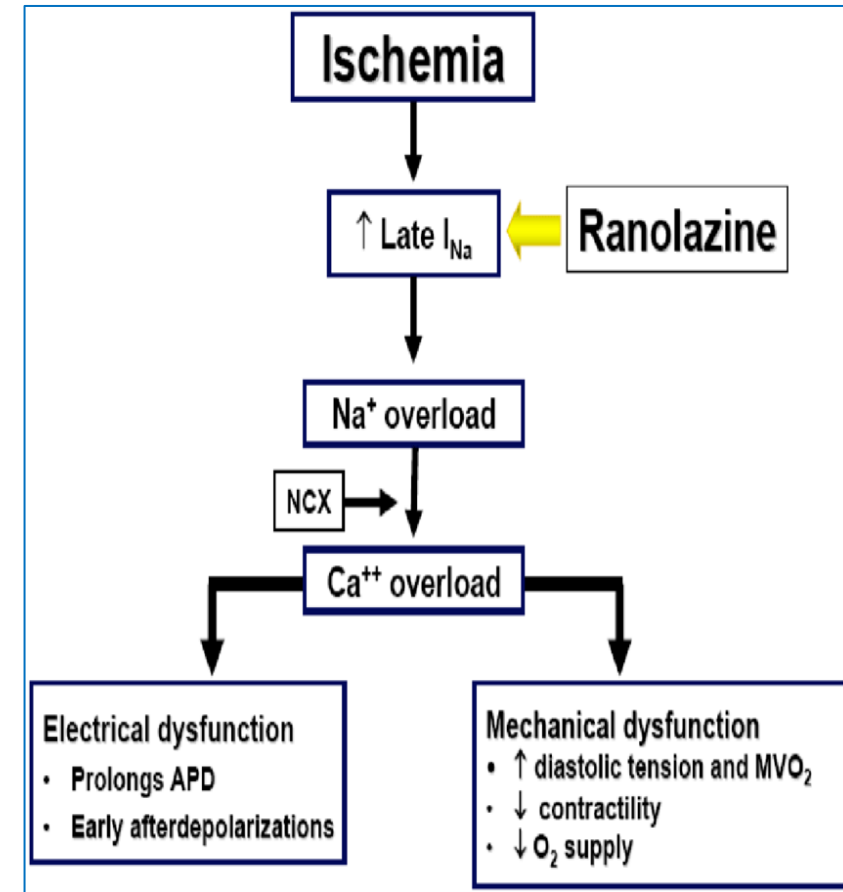
B. Nondihydropyridine calcium channel blockers

- **Diltiazem** (Benzothiazepine) 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**.
- Nondihydropyridine 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.
- 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