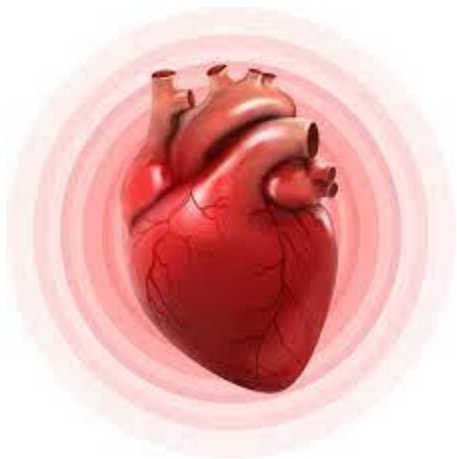




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Depart. of Pharmacology and Toxicology

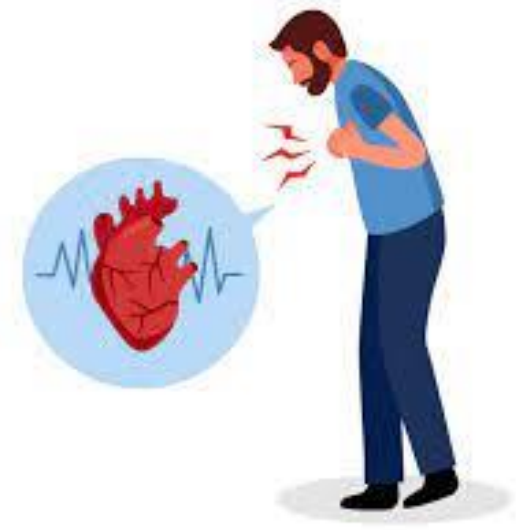


Antianginal Drugs



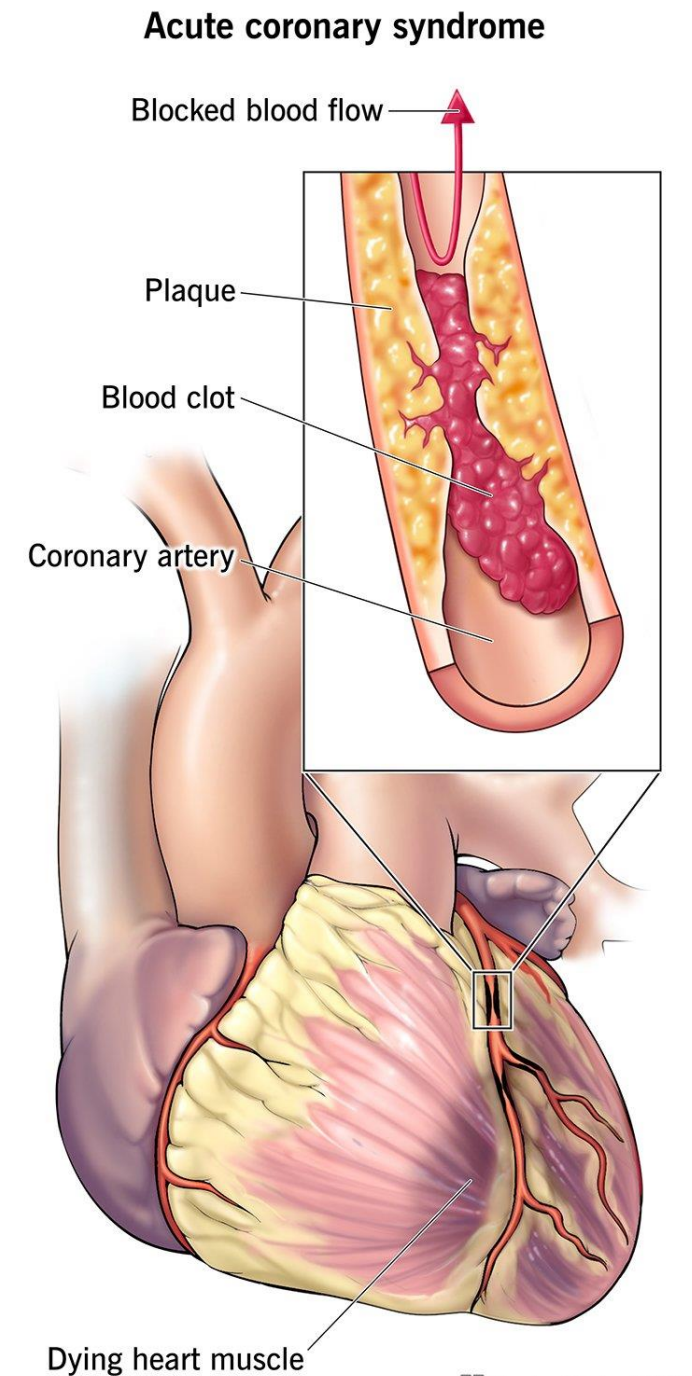
Pharmacology 4th Stage
November , 2025

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Angina Overview

- Atherosclerotic disease of the coronary arteries, also known as coronary artery disease (CAD) or ischemic heart disease (IHD).
- Atherosclerotic lesions 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).
- Spasms of vascular smooth muscle may also impede cardiac blood flow, reducing perfusion and causing ischemia and angina pain.



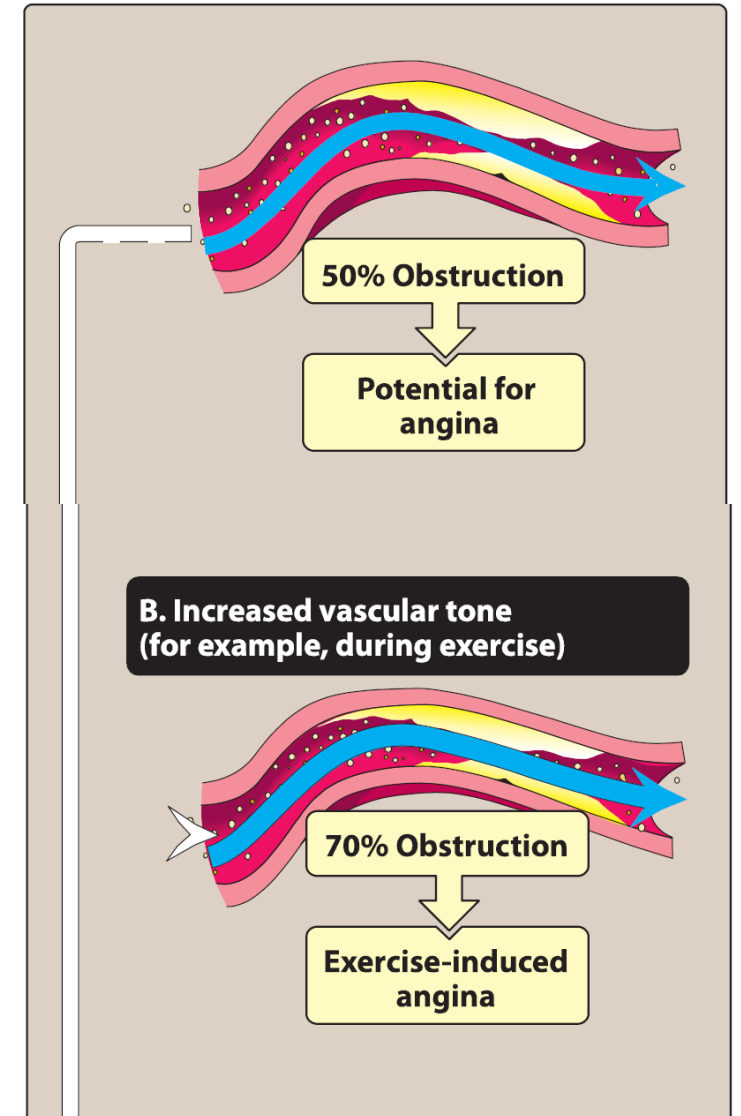
Types of Angina

A) Stable angina, effort-induced angina, classic or typical angina

- It is the most common form of angina and usually characterized by a short-lasting burning, heavy, or squeezing feeling in the chest.
- Some ischemic episodes may present "atypically"-with extreme fatigue, nausea, or diaphoresis-while, others may not be associated with any symptoms (silent angina).
- Classic angina is caused by the reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis.

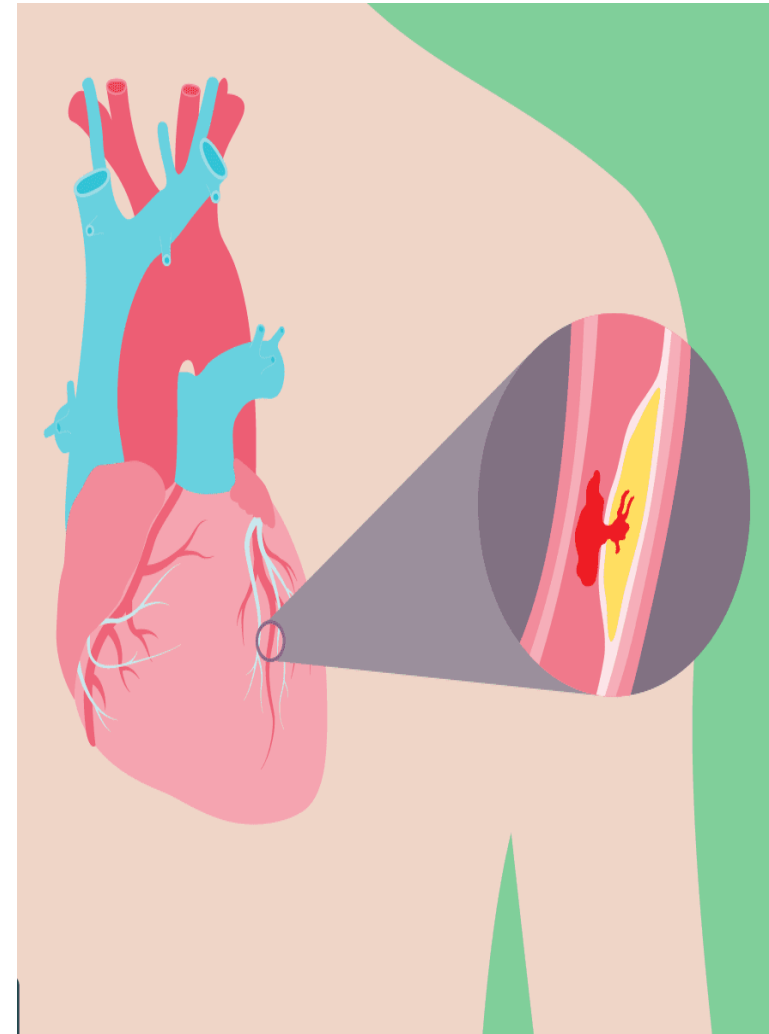
A) Stable angina Cont..

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



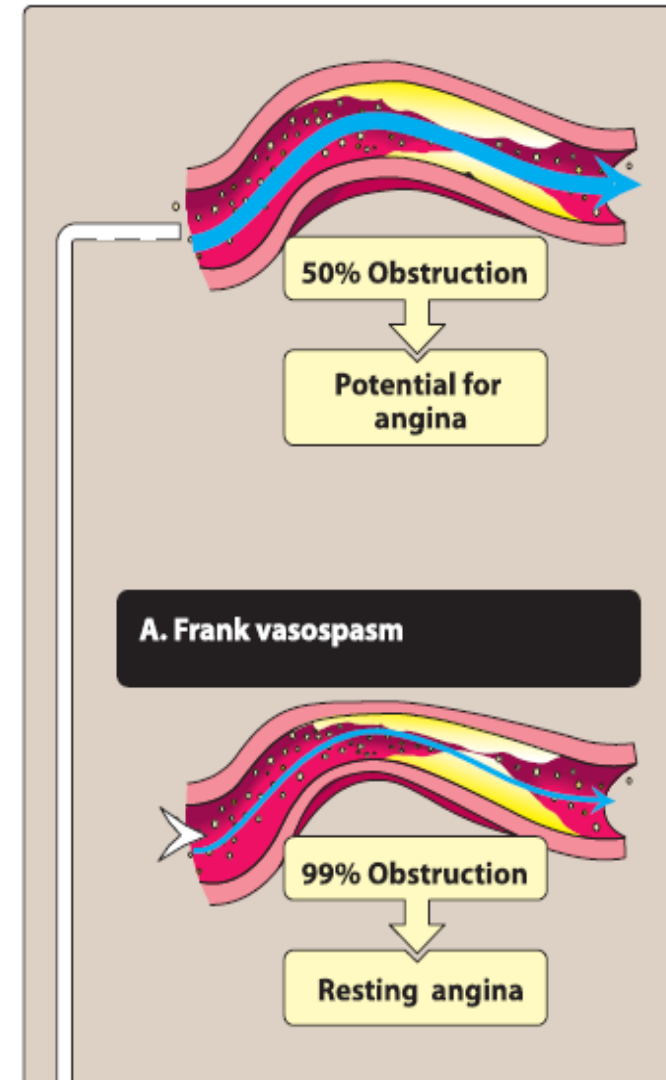
B) Unstable Angina

- Unstable angina is chest pain with increased frequency, duration, and intensity and can be precipitated by progressively less effort. (longer than 20 minutes, new onset, any crescendo angina, or sudden development of shortness of breath).
- 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.



C. Prinzmetal, variant, vasospastic, or rest angina

- 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.



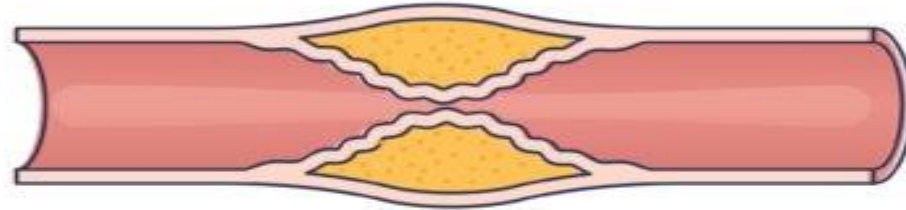
TYPES OF ANGINA

NORMAL



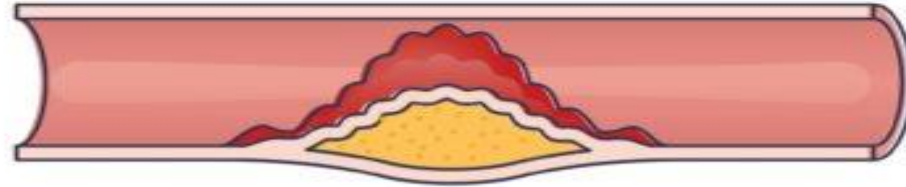
Normal Coronary Artery

STABLE ANGINA



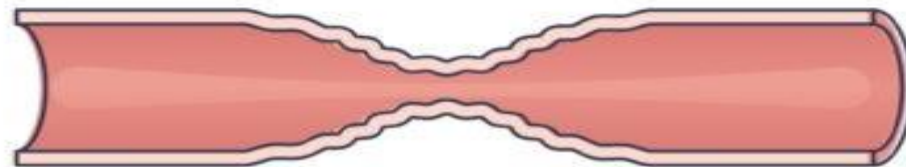
Atherosclerosis

UNSTABLE ANGINA



Atherosclerosis with Blood Clot

VARIANT ANGINA



Coronary Spasm

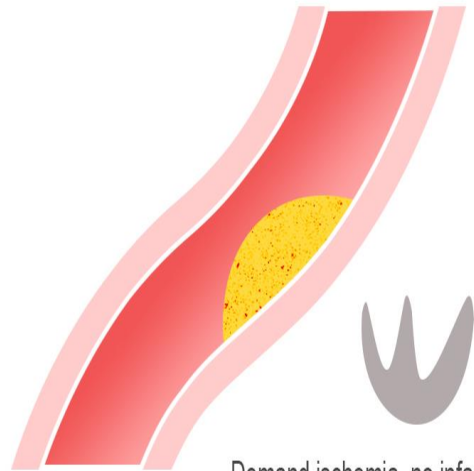
D) Acute coronary syndrome

- It 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 untreated, necrosis of the cardiac muscle may ensue (MI).
- 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.

ACUTE CORONARY SYNDROME

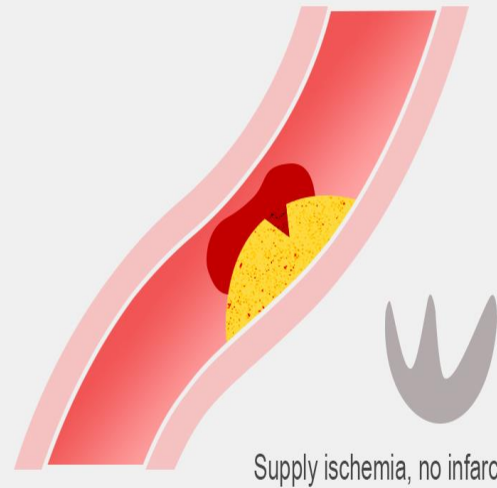
1 STABLE ANGINA

Angina pain develops when there is increased demand in the setting of a stable atherosclerotic plaque. The vessel is unable to dilate enough to allow adequate blood flow to meet the myocardial demand.



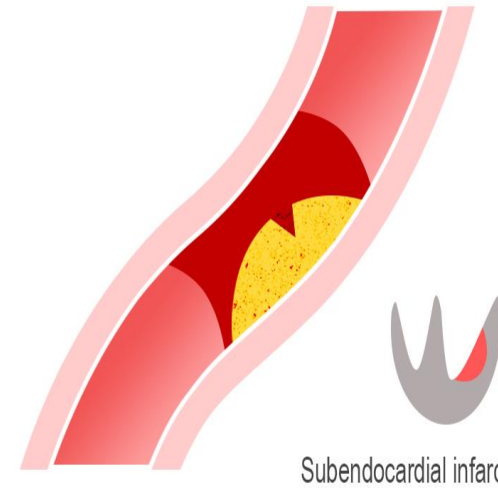
2 UNSTABLE ANGINA

The plaque ruptures and a thrombus forms around the ruptured plaque, causing partial occlusion of the vessel. Angina pain occurs at rest or progresses rapidly over a short period of time.



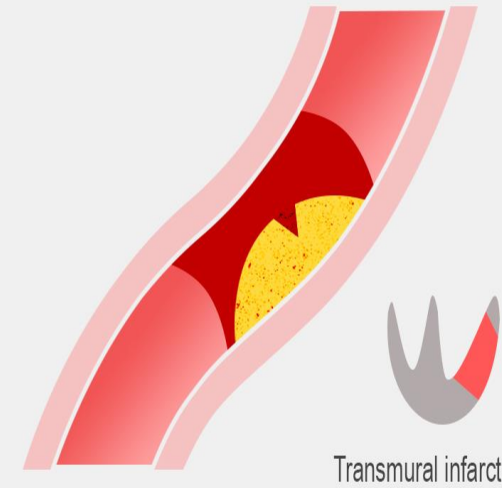
3 NSTEMI

During an NSTEMI, the plaque rupture and thrombus formation causes partial occlusion to the vessel that results in injury and infarct to the subendocardial myocardium.



4 STEMI

A STEMI is characterized by complete occlusion of the blood vessel lumen, resulting in transmural injury and infarct to the myocardium, which is reflected by ECG changes and a rise in troponins.



ECG



Normal



Normal, Inverted T waves, or ST depression



Normal, Inverted T waves, or ST depression



Hyperacute T waves or ST elevation

TROPONINS

Normal

Normal

Elevated

Elevated

Treatment Strategies

- Lifestyle modifications (smoking cessation, physical activity, weight management) and management of modifiable risk factors (hypertension, diabetes, dyslipidemia) are important to reduce cardiovascular morbidity and mortality.
- Four types of drugs, used either alone or in combination, are commonly used to balance the cardiac oxygen supply and demand equation by affecting blood pressure, venous return, heart rate, and contractility.

β-BLOCKERS (NONSELECTIVE)

Nadolol CORGARD

Propranolol INDERAL, INNOPRAN XL

Sotalol BETAPACE, SORINE

β₁-BLOCKERS (CARDIOSELECTIVE)

Atenolol TENORMIN

Bisoprolol GENERIC ONLY

Metoprolol LOPRESSOR, TOPROL-XL

Nebivolol BYSTOLIC

CALCIUM CHANNEL BLOCKERS (DIHYDROPYRIDINES)

Amlodipine NORVASC

Felodipine PLENDIL

Nifedipine ADALAT, PROCARDIA

CALCIUM CHANNEL BLOCKERS (NONDIHYDROPYRIDINE)

Diltiazem CARDIZEM, CARTIA, TIAZAC

Verapamil CALAN, VERELAN

NITRATES

Nitroglycerin MINITRAN, NITRO-DUR, NITROSTAT

Isosorbide dinitrate DILATRATE-SR, ISORDIL

Isosorbide mononitrate GENERIC ONLY

SODIUM CHANNEL BLOCKER

Ranolazine RANEXA

1- β -Adrenergic Blockers

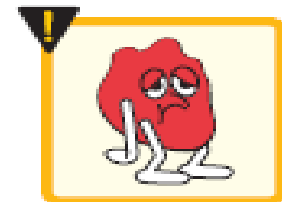
- **MOA:** β -adrenergic blockers decrease the oxygen demands of the myocardium (at exertion and rest) by blocking β_1 receptors, resulting in decreased heart rate and contractility, which subsequently decreases cardiac output and blood pressure.
- **Uses:** increase exercise duration and tolerance in patients with effort-induced angina. They can reduce both the frequency and severity of angina attacks and the risk of death and MI inpatient with previous MI and HFrEF. β -Blockers are recommended as first-line antianginal therapy in all patients unless specifically contraindicated (except vasospastic angina) .

1- β -Adrenergic Blockers Cont..

- **PK:** Selectivity, high doses, ISA, α -blocking effects.
- **A.E:** Hypotension, insomnia, decrease libido, hypertriglyceridemia, decrease HDL, dizziness, tiredness, blurred vision, cold hands and feet, and slow heartbeat.
- **Caution and Avoidance:** Bradycardia, PVD, COPD, asthma, hypoglycemia.
- It is important not to discontinue β -blocker therapy abruptly.



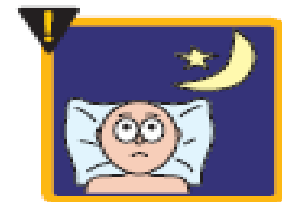
Hypotension



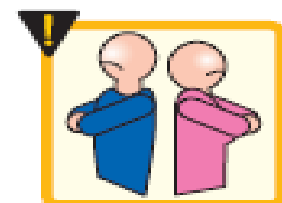
Bradycardia



Fatigue



Insomnia

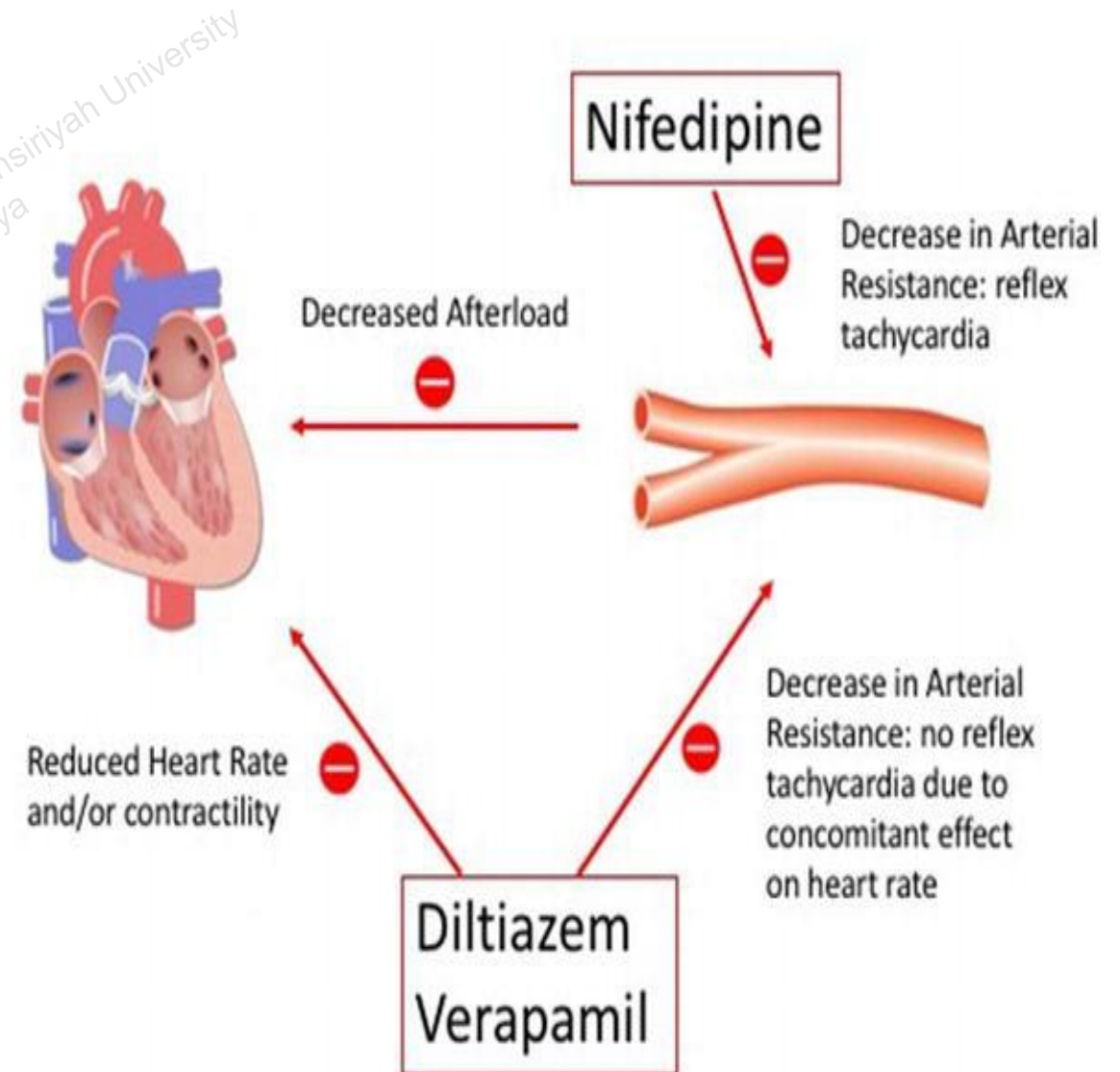
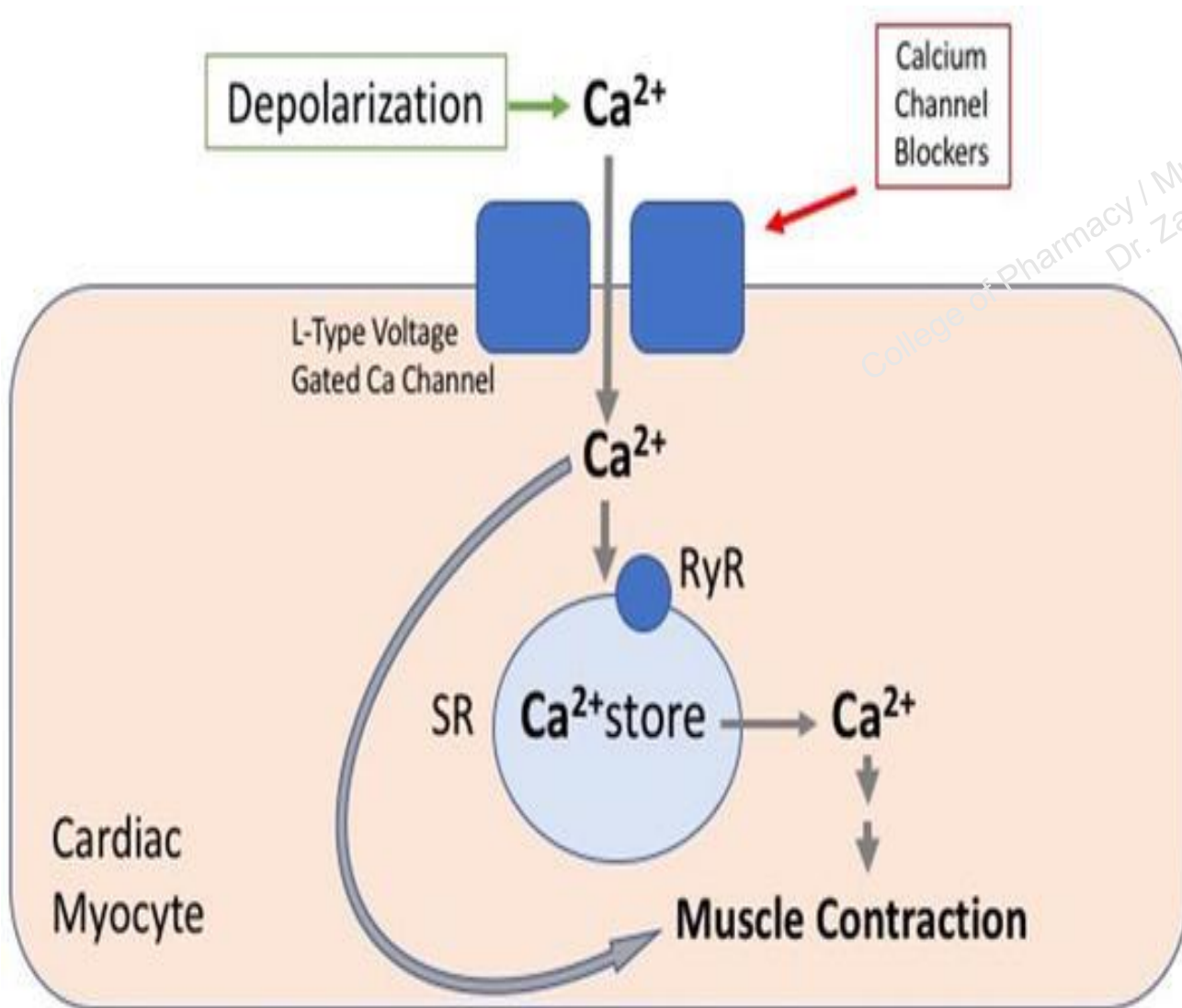


Sexual dysfunction

2- Calcium Channel Blockers

- Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces which promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia.
- **MOA:** CCB protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All CCBs are, therefore, arteriolar vasodilators that decrease smooth muscle tone and vascular resistance.
- **Uses:** In the treatment of effort-induced angina, CCBs reduce myocardial oxygen consumption by decreasing vascular resistance, thereby decreasing afterload. Their efficacy in vasospastic angina is due to relaxation of the coronary arteries.

2- CCB: A) Dihydropyridine B) Non-dihydropyridine



A) Dihydropyridine CCBs

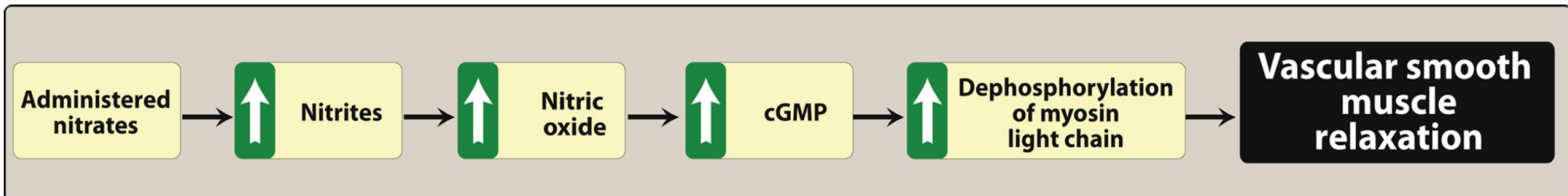
- **Amlodipine**, an oral dihydropyridine, has minimal effect on cardiac conduction and functions mainly as an arteriolar vasodilator. The vasodilatory effect of amlodipine is useful in the treatment of variant angina caused by spontaneous coronary spasm.
- **Nifedipine** is another agent in this class; it is administered as an extended-release oral formulation. Short-acting dihydropyridines should be avoided in CAD.

B) Nondihydropyridine CCBs

- **Verapamil** slows atrioventricular (AV) conduction (dromotropy) directly and decreases heart rate (chronotropy) and contractility (inotropy), which all decrease blood pressure and the corresponding oxygen demand. Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator. Verapamil is contraindicated in patients with preexisting AV conduction abnormalities.
- **Diltiazem** slows AV conduction, decreases the rate of firing from the SA node pacemaker, and is also a coronary artery vasodilator. Diltiazem can relieve coronary artery spasm and is particularly useful in patients with variant angina.
- These CCBs can worsen heart failure (avoided) in patients with HFrEF due to their negative inotropic effect.

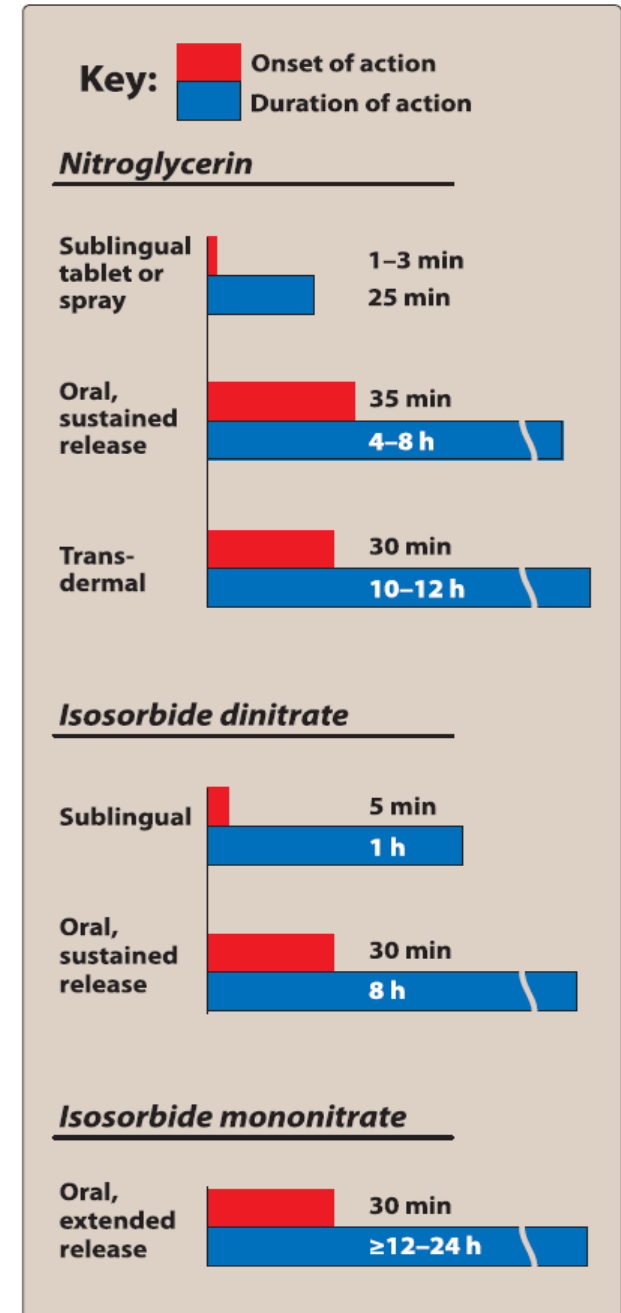
3- Organic Nitrates

- These compounds cause a reduction in myocardial oxygen demand, followed by relief of symptoms. They are effective in stable, unstable, and variant angina.
- **MOA:** Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitric oxide, which activates GCs and increases synthesis of cGMP. Nitrates such as **nitroglycerin** cause dilation of the large veins, which reduces preload and myocardial oxygen demand. Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.



3- Organic Nitrates Cont..

- **PK:** Onset, routes, Drug of Choice, first pass effect, prodrug. Need by all patient?
- **A.E:** Headache, high doses (postural hypotension, facial flushing, and tachycardia). Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation, can overcome by "nitrate-free interval"
- **C.I:** with sildenafil (PDE5 inhibitors) risk of dangerous hypotension.



4- Sodium Channel Blocker

- **Ranolazine** inhibits the late phase of the sodium current (late I_{Na}), improving the oxygen supply and demand equation. Inhibition of late I_{Na} reduces intracellular sodium and calcium overload, thereby improving diastolic function (lusitropy).
- Ranolazine has antianginal as well as antiarrhythmic properties. It is used in patients who have failed other antianginal therapies.
- **PK:** Gender, metabolism, CYP3A and CYP2D6, P-gp, ranolazine can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.

Stable Ischemic Heart Disease



Guideline-directed medical therapy including emphasis on lifestyle modifications for cardiovascular risk reduction

Anginal symptoms present



Sublingual *nitroglycerin* for immediate relief



β -Blocker



ADD

Calcium channel blocker

OR

Long-acting nitrate



ADD

Ranolazine

If inadequate relief after titration

If inadequate relief

MEDICAL CONDITIONS

ANTIANGINAL DRUG THERAPY CONSIDERATIONS

RECENT MYOCARDIAL INFARCTION	β-Blockers	Ca ²⁺ channel blocker	Long-acting nitrate	Ranolazine
VASOSPASTIC ANGINA	β-Blockers	Ca ²⁺ channel blocker	Long-acting nitrate	
HYPERTENSION	β-Blockers	Ca ²⁺ channel blocker	Long-acting nitrate	Ranolazine
HYPOTENSION	β-Blockers	Ca ²⁺ channel blocker	Long-acting nitrate	Ranolazine
HEART FAILURE WITH REDUCED EJECTION FRACTION	β-Blockers	Ca ²⁺ channel blocker Dihydropyridine	Long-acting nitrate	Ranolazine
		Ca ²⁺ channel blocker Nondihydropyridine		
DIABETES	β-Blockers	Ca ²⁺ channel blocker	Long-acting nitrate	Ranolazine
ASTHMA	β-Blockers Nonselective	Ca ²⁺ channel blocker	Long-acting nitrate	Ranolazine
	β-Blockers Selective			
COPD	β-Blockers	Ca ²⁺ channel blocker	Long-acting nitrate	Ranolazine

KEY:

- Preferred
- Neutral
- Use with caution/
close monitoring
- Generally avoid

DRUG CLASS	COMMON ADVERSE EFFECTS	DRUG INTERACTIONS	NOTES
<p>β-Blockers</p> <p><i>atenolol</i> <i>metoprolol</i> <i>propranolol</i></p>	<p>Bradycardia, worsening peripheral vascular disease, fatigue, sleep disturbance, depression, blunt hypoglycemia awareness, inhibit β₂-mediated bronchodilation in asthmatics</p>	<p>β₂ Agonists (blunted effect); non-dihydropyridine calcium channel blockers (additive effects)</p>	<p>β₁-Selective agents preferred (<i>atenolol, metoprolol</i>). Avoid agents with ISA for angina therapy (<i>pindolol</i>).</p>
<p>Dihydropyridine calcium channel blockers</p> <p><i>amlodipine</i> <i>felodipine</i> <i>nifedipine</i></p>	<p>Peripheral edema, headache, flushing, rebound tachycardia (immediate-release formulations), hypotension</p>	<p>CYP 3A4 substrates (will increase drug concentrations)</p>	<p>Avoid short-acting agents as they can worsen angina (may use extended-release formulations)</p>
<p>Nondihydropyridine calcium channel blockers</p> <p><i>diltiazem</i> <i>verapamil</i></p>	<p>Bradycardia, constipation, heart failure exacerbations, gingival hyperplasia (<i>verapamil</i>), edema (<i>diltiazem</i>)</p>	<p>CYP 3A4 substrates (will increase drug concentrations); increase <i>digoxin</i> levels; β-blockers and other drugs affecting AV node conduction (additive effects)</p>	<p>Avoid in patients with heart failure</p> <p>Adjust dose of both agents in patients with hepatic dysfunction</p>
<p>Organic nitrates</p> <p><i>isosorbide dinitrate</i> <i>isosorbide mononitrate</i> <i>nitroglycerin</i></p>	<p>Headache, hypotension, flushing, tachycardia</p>	<p>Contraindicated with PDE5 inhibitors (<i>sildenafil</i> and others)</p>	<p>Ensure nitrate-free interval to prevent tolerance</p>
<p>Sodium-channel inhibitor</p> <p><i>ranolazine</i></p>	<p>Constipation, headache, edema, dizziness, QT interval prolongation</p>	<p>Avoid use with CYP 3A4 inducers (<i>phenytoin, carbamazepine, St. John's wort</i>) and strong inhibitors (<i>clarithromycin, azole antifungals</i>) and agents that prolong QT interval (<i>citalopram, quetiapine, others</i>)</p>	<p>No effect on hemodynamic parameters</p>