Treatment of Ischemic Heart Disease

	Mechanism	Categories	Angina		Control of SM Contraction
Ischemic Heart Disease	**Imbalance** of the ratio of O2 **Supply** (Coronary Blood Flow) & O2 **Demand** (Work of the Heart) ✸**Factors of O2 Supply:** O2 extraction (%), coronary blood flow, aortic diastolic pressure, coronary arteriolar resistance, metabolic autoregulation, Endocardial-epicardial flow, coronary collateral blood flow, large coronary artery diameter ✸**Factors of O2 Demand:** Wall tension, ventricular volume, radius or heart size, ventricular pressure, systolic pressure (afterload), diastolic pressure (preload), heart rate, contractility	**A. Transient coronary ischemia:** -**Fixed "Stable", Effort Angina** → Atherosclerosis -**Unstable Angina** → Atherosclerosis + plaque rupture & platelet aggregations (can transform to MI) -**Variant Angina "Primary Angina"** → Vasospasm **B. Coronary thrombosis:** -Myocardial Infarction	**Secondary** Classical Angina of Effort Typical Small vessels Single or multiple vessels Atherosclerosis ECG: ST depression	**Primary** Variant (Prinzmetal's) Angina at Rest Atypical Large vessels Single vessel Vasospasm ECG: ST elevation	**1.** Influx of calcium through L-type channels **2.** Ca^{+2} combines with calmodulin to form a complex that converts the enzyme myosin light-chain kinase to its active form (MLCK*) **3**. MLCK* phosphorylates myosin → myosin can now interact with actin → contraction ✸ß2- agonists (substances that ↑ cAMP) cause relaxation in SM by accelerating the **inactivation** of MLCK and facilitating the **expulsion** of Ca^{+2} from the cell
Myocardial stunning is the reversible reduction of function of heart contraction after reperfusion not accounted for by tissue damage or reduced blood flow					

Drug	MOA	Uses & Desired Effects	Side Effects	Notes
ß-Adrenergic Blockers				
ß-Adrenergic Blockers	-Prevent actions of catecholamines, so more effective during exertion (stress) -Work by **decreasing** heart rate and contractility → **decreasing** O2 **demands** **-Decreases** the afterload -↑endocardial Blood flow, ↓epicardial BF	-Cause subjective and objective improvement: decreased number of anginal episodes, nitroglycerine consumption, enhanced exercise tolerance, and improved ECG		- **Do not dilate** coronary arteries, might **constrict** them -**Do not increase** collateral blood flow
Calcium Channel Blockers				
Verapamil **Diltiazem** **Nifedipine** **Nicardipine** **Amlodipine**	-Block calcium channels -Increases collateral vessel diameter -Increases stenosis diameter -Increase HR in the standing position, decrease it in the supine position (negative inotropic and chronotropic) -Decreases the afterload but doesn't affect the preload	-Particularly beneficial in vasospasm -Can affect platelets aggregation	-Hypotension -Headache, dizziness -Flushing -Peripheral edema	-May be dangerous in the presence of heart failure and in patients susceptible to hypotension (because they are used in treatment of hypertension)

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Organic Nitrates				
Nitroglycerine (GTN)	❋Releases NO → activation of guanylyl cyclase (nonspecific smooth muscle relaxant) → general dilation -Causes arteriolar dilation (↓afterload) then venous dilation (↓preload) -**Increases** endocardial blood flow and **decreases** epicardial blood flow -**Increases** collateral vessels diameter -**Increases** stenosis diameter -**Decreases** preload (↓↓↓) -**Decreases** afterload (↓) -**Decreases** wall tension (↓↓↓) ❋**Arteriolar dilation**: short lived (5-10 min): decreases systemic blood pressure (afterload) → can elicit the baroreceptor reflex to cause reflex tachycardia and increased contractility, and might increase MVO2 ❋**Venous dilation** (**Main**): more intense, even with low doses, lasts for 30 minutes: decreases venous return (preload) & decreases MVO2	-Treatment of Angina ❋Potential beneficial effects: ▫**Decreases** O2 requirement by: -Decreasing ventricular volume -Decreasing arterial pressure -Decreasing ejection time ▫**Relief** of coronary artery spasm by: -Vasodilation of epicardial coronary arteries ▫**Improves** perfusion to ischemic myocardium by: -Increasing collateral flow ▫**Improves** subendocardial perfusion by: -Decreasing left ventricular diastolic pressure	-Headache -Hypotension and tachycardia -Increased intraocular and intracranial pressures -Methemoglobinemia -Tolerance: only for the arteriolar effects -Withdrawal: in workers in ammunition industry ❋Potential deleterious effects: ▫Increases O2 requirement by the reflex tachycardia and increase in contractility ▫Decreases coronary perfusion by decreasing diastolic perfusion time due to tachycardia	- Prototype, used for more than 150 years - Action not antagonized by any known antagonist -Usually administered **sublingually** by can be administered by various routes -Fast onset of action (1-3minutes, Peaks at 10 minutes) -Short duration (15-30minutes) -Reductase enzyme, in liver, breaks down the drug -Amyl nitrite is an **inhalant** preparation *If you want to memorize the preparations refer to slide 21
A Nucleoside Transport Inhibitor				
Dipyridamole	Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme	-Increases the blood flow to the normal area (**Coronary Steal Phenomenon**: the normal area steals from the ischemic area) -Used as an antiplatelet (not better than aspirin)		-Thought to be a good coronary dilator

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	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Ca-Channel Blockers
Heart rate	Reflex: increase	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	Increase	Non or Decrease
Contractility	Reflex: increase	Decrease	Non
Ejection time	Decrease	Increase	Non

Other Treatment of Ischemic Heart Disease
▫ACEI
▫Anticoagulants and/or Thrombolytic Therapy
▫Cholesterol Lowering Agents
▫Angioplasty
▫Surgery
Newer Antianginal Agents
▫Metabolic modulators: Ranolazine
▫Direct bradycardic agents: Ivabradine
▫Potassium channel activators: Nicorandil
▫Rho-kinase inhibitors: Fasudil
▫Sulfonylureas: Glibenclamide
▫Thiazolidinediones
▫Vasopeptidase inhibitors
▫Nitric oxide donors: L- arginine
▫Capsaicin
▫Amiloride

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