MED441
KING SAUD UNIVERSITY

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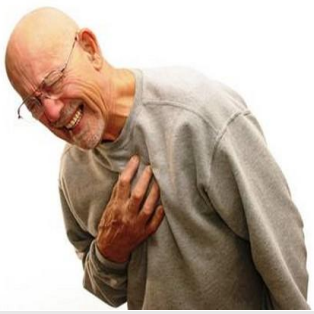
9,10
Antianginal drugs

Pharmacology
TEAM 441

Objectives:

- Recognize variables contributing to a balanced myocardial supply VS. demand.
- Expand on drugs used to alleviate acute angina attacks VS. Those meant for prophylaxis and survival improvement.
- Detail the pharmacology of nitrates, other vasodilators, and other drugs used in anti anginas therapy.



HELPFUL VIDEOS:

- **Antianginal drugs (Dr. Fouda)**
- **Action potential** (Boards & beyond)
- **Angina pathophysiology (osmosis)**

Editing file

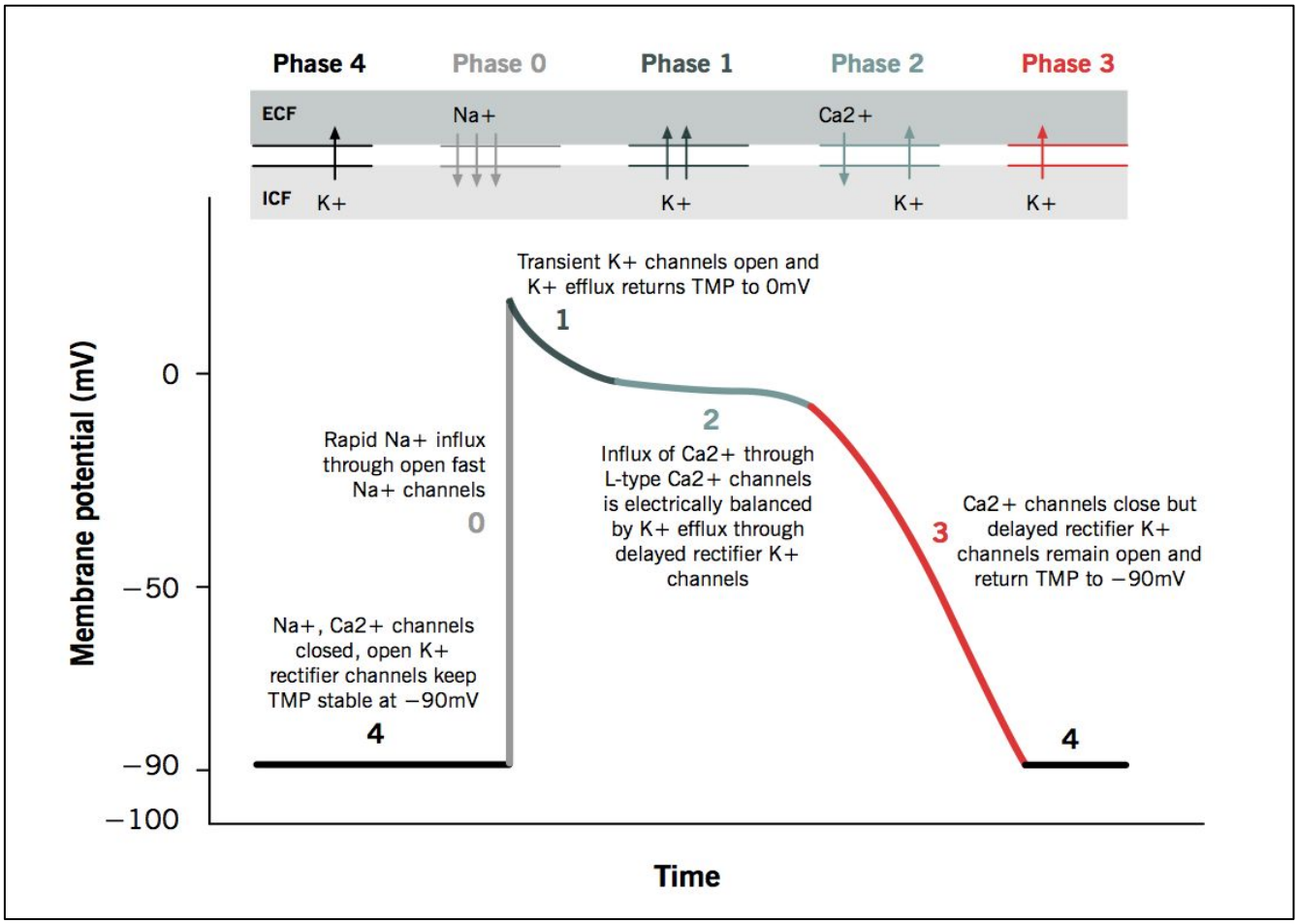
Color index:
Important
In male's slides only
In female's slides only
Extra information
Doctors' notes

REVIEW

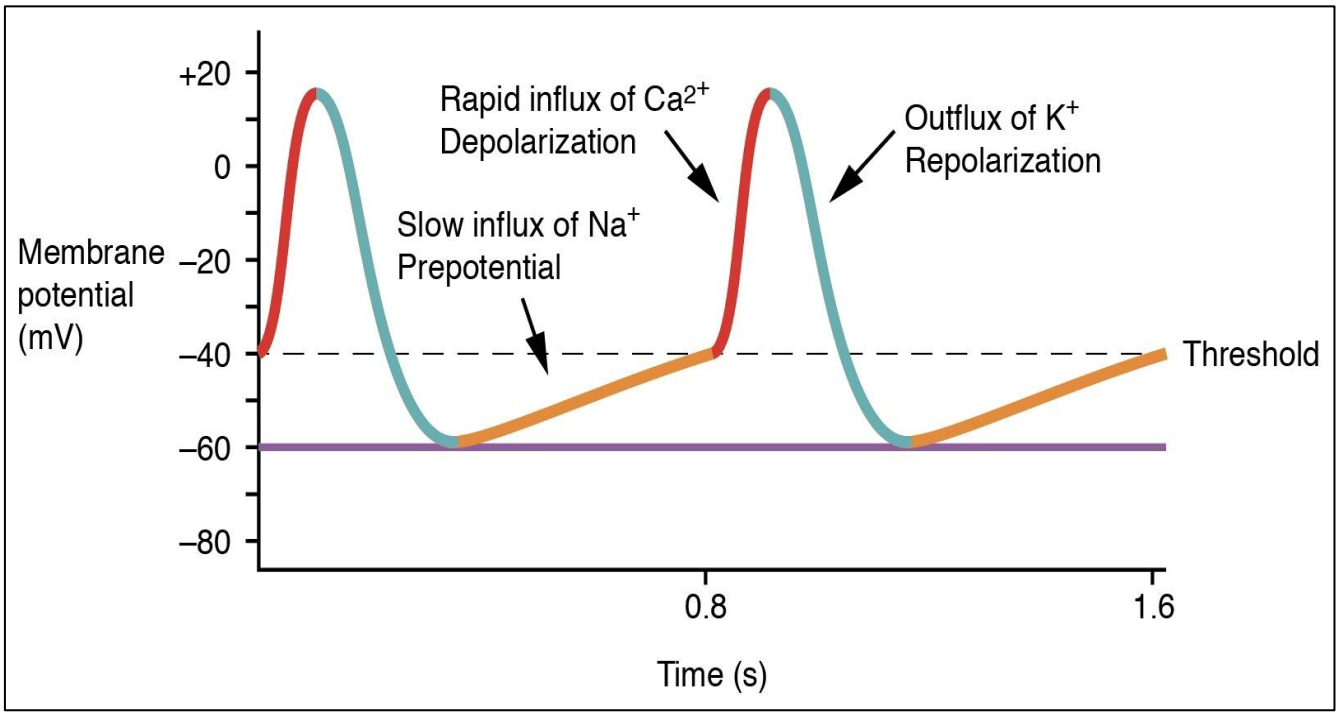
EXTRA SLIDE!!

You should be aware of this already, but try to read it thoroughly for a better and comprehensive understanding.

Action potential of cardiac contractile cells



Action potential of nodal cells (pacemaker)



Angina pectoris

Angina is a clinical syndrome of **chest pain** (varying in severity) due to ischemia of heart muscle. It may **radiate** to the left arm, neck, or jaw.

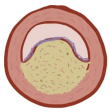
Coronary artery disease (CAD) is an ischemic heart disease most commonly caused by atherosclerosis. Acute retrosternal chest pain (**angina**) is the **cardinal** symptom of CAD. Patients with CAD usually become **symptomatic** when the degree of **coronary stenosis** reaches **≥ 70%**.

Signs & Symptoms

- Pain is caused either by: partial **obstruction** or **spasm**. "Reduced blood flow" Obstruction is the main cause; spasm is less common e.g. variant angina.
- Pain is due to: accumulation of **metabolites** (K^+, PGs, kinins, adenosine, lactic acid, etc.) secondary to ischemia"ischemia results in their formation". They are called **pain factors** as they activate pain receptors (nociceptors). Ischemia will lead to the release of ions (like K^+) because maintenance of such ions inside the cell needs energy.
- Other clinical features: dyspnea, dizziness, palpitations, restlessness.

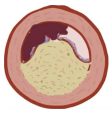
Types of Angina

Stable Angina (Effort, Typical, Classical)



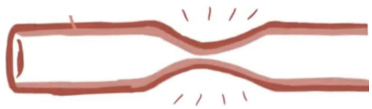
- Ischemia due to a **fixed obstruction** of a coronary artery by **atherosclerosis**.
- Common triggers:
  - Exercise
  - Emotions (↑ HR & contractility)
  - Heavy meal (GIT needs ↑ blood → dilatation → compensatory ↑ in sympathetic activity)
- **Treatment:** nitroglycerin, + subsides with rest

Unstable Angina (Accelerated, Crescendo)



- Ischemia caused by a **rupture** of an atherosclerotic plaque & **partial occlusion** of a coronary artery.
- There is an increase in the severity and frequency of anginal attacks.
- **Severe** type; pain can occur even at rest. High risk of development into MI. "a preload to MI"
- **Treatment**: hospital admission for a more aggressive therapy.

Variant Angina (Prinzmetal*, Vasospastic)



- Caused by **coronary spasms** (α-receptor mediated vasoconstriction) with or without atherosclerosis.
- Pain even at rest.
- More common in females.
- **Treatment**: nitroglycerin or Ca^{+2} channel blockers (β-blockers are contraindicated)

*Prinzmetal is the physician who discovered it

*There is a fourth type called **silent angina**, detected only by ECG (asymptomatic) and responds well to β-blockers

What is the basic mechanism of angina pectoris?

An **imbalance** between the supply of O_2 and its demand. "When the demand exceeds the supply ischemia will take place"
*The blood flows to the coronaries when the aortic pressure exceeds the ventricular pressure(the greater the difference the greater the BF), thus the blood only flows during diastole.

What are the determinants of O_2 **demand** & **supply?**

Factors affecting O_2 **SUPPLY** & **DEMAND**

O_2 Demand

O_2 demand is determined by:

1- Heart rate
2- Contractility
3- Wall tension, affected by:-
- **Afterload** (ventricular pressure)
- **Preload** (ventricular volume)

O_2 demand is DIMINISHED by:

1- Reducing **contractility**
2- Reducing **heart rate**
3- Reducing the **preload**
4- Reducing the **afterload**

1&2: Decreased by B-blockers & some CCBs
3: Decreased by nitrates
4: Decreased by CCBs

O_2 Supply

O_2 supply is determined by:

1- Coronary blood flow, affected by:
- Aortic pressure
- Coronary vascular resistance
-Diastolic period

2- Oxygen carrying capacity (Hb & RBCs)

O_2 supply is ENHANCED by:

1- Reducing coronary vascular resistance "by dilation of coronaries"
2- Reducing external compression "ischemia causes Ca accumulation in the cells →myocardium muscles do not relax fully during diastole →muscles will compress the blood vessels reducing the blood flow"
3- Prolong diastolic period "as coronary flow occurs during diastole"
4- Dilating collateral vessels (mechanism of nitrates & CCBs)
5- Optimizing Hb & RBCs

Treatment of Angina Pectoris

Agents that improve **prognosis**, (halt progression prevent acute insult & improve survival) ABAS عباس

- **A**CE inhibitors (Prevents remodelling of both myocardium and BVs/ reduces CVs events/ reduces myocardium size→ ↓O_2 demand)
- **B**eta-blockers (Reduce remodelling/ ↓O_2 demand/ Anti-arrhythmic → ↓ mortality(main cause of mortality in angina patients is arrhythmia)
- **A**spirin/other anti-platelets (the plaque causes damage to the endothelium →the endothelium does not prevent aggregation of platelets→ aggregation may take place)
- **S**tatins: "↓Cholesterol levels /Anti-inflammatory effect" ↓inflammation of BVs and formation of atheromatous plaque"

Lily **K**eeps her **M**outh **S**hut

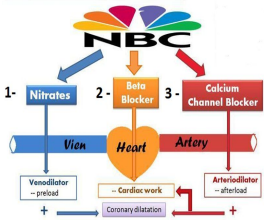
Ronaldo **N**ever **T**ries **I**mitating

Agents that improve **symptoms & ischemia**

"relieve pain"

Traditional approaches

No Body Cares (NBC) محد مهتم



- **N**itrates.
- **B**eta-blockers
- **C**a^{++} channel blockers

New approaches

- **L**ate Na^+ current inhibition, e.g. **R**anolazine
- **K**$^+$ channel openers, e.g. **N**icorandil
- **M**etabolic acting agents, e.g. **T**rimetazidine
- **S**inus node inhibition, e.g. **I**vabradine

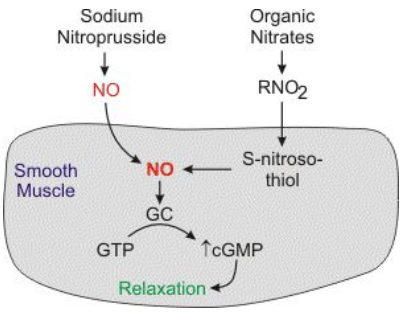
Traditional Approaches

1- Organic nitrates

Classification	Short acting	Long acting
Drugs	**Nitroglycerin**	**Isosorbide Mononitrate & Dinitrate**

M.O.A

- **NO** binds to **guanylate cyclase** in vascular smooth muscle cell to form **cGMP** → cGMP activates **protein kinase G** → relaxation
- **Organic nitrates** are enzymatically activated.
- **Sodium nitroprusside** spontaneously releases NO (faster). However, it is only used in ER hypertension and not in angina because it's given IV & requires hospital preparation.



Hemo-dynamics

1- Veno dilation (↓ preload)

2- Arterio dilation (↓ afterload)

(Nitrates are **mainly venodilators**, but at higher conc. they are **arteriodilators** as well).

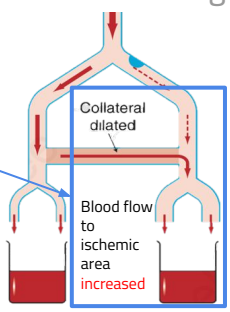
3- Coronary dilation (↑ myocardial perfusion) → especially beneficial in **variant** angina.

*Arterial dilation → **reflex tachycardia** & ↑ **contractility** → **pro-anginal**.

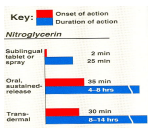
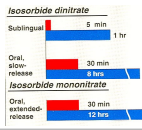
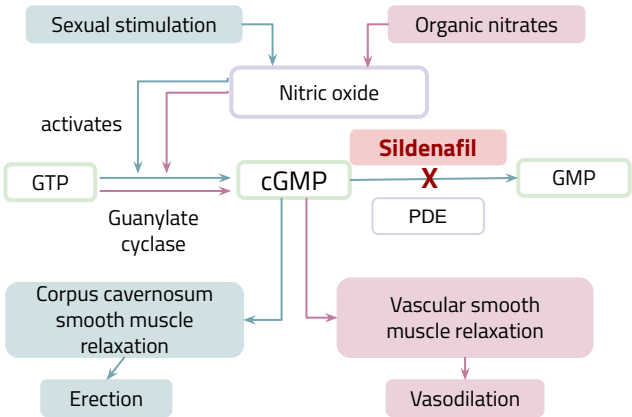
*__Venodilation__ & **coronary dilation** → **anti-anginal**.

4- Shunting of flow from normal to ischemic area by dilating **collateral** vessels.

Dilating **both coronary & collateral vessels** is important. If we dilate coronaries only, this will drive more blood towards the normal area "**coronary steal**". An example of such a drug is *Dipyridamole* (anti-platelet).



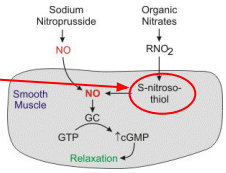
Organic Nitrates (cont.)

Drug	Nitroglycerin (GTN; glyceryl trinitrate)	Isosorbide Nitrates
Indications	• Sublingual: - **Stable** angina: acute symptom relief + **situational** prophylaxis* immediately before exertion (مثلاً قبل الطواف). - **Variant** angina • IV: - **Unstable** angina, Refractory acute HF, Acute MI	- **Stable** angina: **persistent** prophylaxis → Isosorbide mono or Dinitrate - **Congestive HF** if there's a contraindication to ACEIs (e.g. black Americans); combine: ○ Isosorbide mononitrate (venodilator) ○ Hydralazine (arteriodilator)
P.K.	• Undergoes significant first pass metabolism **if given orally** → only 10-20% bioavailability. • Given **sublingual** (to bypass portal circulation), **transdermal** patch or parenteral.	• **Mononitrate:** very well absorbed **(100% bioavailability).** • **Dinitrate:** undergoes **denitration** into: 2 **mononitrates**, both have antianginal activity & conjugate to glucuronic acid in liver. *Why 2 mononitrates?* We can remove nitrate from either side of the molecule. • $t_{1/2}$ = 3 hrs • Excreted in urine
Preparations	• **Sublingual tablets** or **sprays**: **rapid** & **short** duration of action. • **Transdermal** patch (8-14 hrs). • Oral or buccal sustained release. ○ Less effective. • **I.V.** preparations. 	• **Dinitrate**: ○ Sublingual tablets ○ Oral sustained release المستخدم حالياً ○ Infusion preparations • **Mononitrate:**: ○ Oral sustained release *Usually taken in the morning & at lunch to allow a nitrate-free period at night (when pts are not exerting themselves, to avoid tolerance). 
Contra-indications	• Known sensitivity to organic nitrates. • Glaucoma, nitrates increase synthesis of aqueous humor, thus increase IOP. • Head trauma or cerebral haemorrhage → Increased intracranial pressure. "dilate cranial BVs" • Hypotension: ○ Uncorrected hypovolemia. ○ Concomitant administration of **PDE_5 Inhibitors**. Sildenafil + nitrates → severe hypotension & death Sildenafil (Viagra) is indicated for erectile dysfunction. It inhibits the isoform of phosphodiesterase (type 5) that breaks down cGMP, potentiating the effect of organic nitrates.	 PDE: Phosphodiesterase enzyme

Organic Nitrates (cont.)

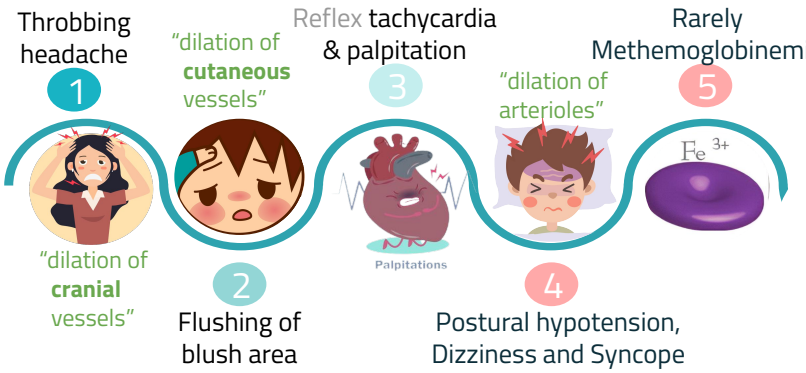
Nitrates Tolerance

- **When?** Loss of vasodilator response of nitrates on use of **long-acting** preparations (oral, transdermal) or **continuous** IV infusions, for more than a few hours without interruption.
- **How?** 4 postulated mechanisms
  1. Compensatory neurohormonal counter-regulation
     - Similar to vasodilators; activates both RAAS and sympathetic system.
  2. Depletion of free-SH groups
     - SH groups are are essential for the formation of NO.
  3. Dysfunction of aldehyde dehydrogenase (ALDH2) {antioxidants}
     - ALDH2 is one of the enzymes that are required to activate nitrates.
     - ALDH2 is completely absent in some Asians → not effective in these people.
  4. Enhanced endothelial production of O_2-derived free radicals (such as superoxide). This radical will degrade NO.



- **How to overcome tolerance?** by:
  1. Smaller doses at increasing intervals (nitrate-free periods twice a day).
  2. Giving drugs that maintain tissue SH group e.g. Captopril, cysteine amino acid.

ADRs

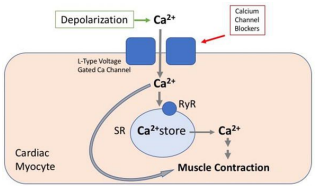


In methemoglobinemia, ferric iron replaces ferrous iron → Hb cannot carry oxygen → cyanosis. It occurs when nitrates are converted into **nitrites** (which are oxidizing agents; $Fe^{2+} \rightarrow Fe^{3+}$). But because the dose in angina is very low (3 mg), very small amount of nitrate becomes nitrite, so this rarely happens

#439 Effects of nitrates in treatment of angina & their results

Effects	Results
↓ Arterial pressure	↓ O_2 demand
↓ Ventricular volume	
↑ Collateral flow	Improved perfusion to ischemic myocardium
↓ Left ventricular diastolic pressure	Improve subendocardial perfusion
Vasodilatation of epicardial coronary arteries	Relief of coronary artery spasm
Unwanted (Pro-anginal) Effects	
Reflex ↑ contractility	↑ O_2 demand
Reflex tachycardia (reduced by combination with β-blockers)	
↓ Diastolic perfusion time due to tachycardia	↓ Myocardial perfusion

2- Calcium Channel Blockers (CCBs)

Classification	Dihydropyridines	Phenylalkylamines	Benzothiazepines
Chemical structure (Drugs)	• **Nifedipine** • Amlodipine • Nicardipine	**Verapamil**	**Diltiazem**
Selectivity	Vascular smooth muscle. (Nifedipine)	Cardiomyocytes	Intermediate (both)
M.O.A.	Binding of to the L-type Ca channels → ↓ frequency of opening in response to depolarization → ↓ entry of Ca → ↓ Ca release from internal stores → no stimulus-contraction coupling → **RELAXATION**		
Antianginal Action	• ↓ **Cardiomyocyte contraction** → ↓ cardiac work through their –ve inotropic & chronotropic → ↓ myocardial **O_2 demand** (for non-dihydropyridines only) • ↓ **Vascular smooth muscle cell contraction** → ↓ afterload (arteriodilators) → ↓ cardiac work →↓ myocardial **O_2 demand** • **Coronary dilation** → ↑ myocardial **O_2 supply** • **Collateral vessels dilation** (in a similar way to Nitrates)		
Indications in angina	**Variant (first choice)**	Attacks completely prevented in 70% of patients treated with nitrates & CCBS	
	Stable	Regular prophylaxis.	
	Unstable	Seldom (rarely) added in refractory cases.	

Should the short acting dihydropyridines (Nifedipine) be AVOIDED?

Yes; they cause vasodilation & hypotension → reflex tachycardia
→ increased O_2 demand → may result in anginal pain or myocardial infarction.

Can we combine calcium channel blockers with a beta blocker?

- **Dihydropyridines** (Nifedipine): can be combined with beta-blockers.
  - Reflex tachycardia الـ نقلل عشان ندمجهم أفضل بالعكس.
- **Non-dihydropyridines** (Verapamil): act on myocardium→ bradycardia (-ve chrono).
  - Must be careful about HR when combined with beta-blockers (كلهم يسوون brady).

Can we combine calcium channel blockers with nitrates?

- As we said, **nitrates** cause reflex tachycardia & ↑ contractility (**pro-anginal** effects), so:
  - **Dihydropyridines**: cause reflex tachycardia, so they make it worse.
  - **Non-dihydropyridines** (Verapamil): yes, can **block pro-anginal** effects of nitrates.
    - *Why?* Because they act on myocardium→ bradycardia & ↓ contractility.

Are calcium channel blockers useful antianginal in patients with congestive heart failure?

- **Dihydropyridines:** yes, because they will reduce the afterload (not preload because CCBs are **mainly arteriodilators**).
  - Do not work on cardiomyocytes → don't have -ve inotropic effect.
- **Non-dihydropyridines** (Verapamil):
  - Act on myocardium→ -ve inotropic → should NOT be given for heart failure.

3- β Adrenergic blockers (β_1 Selective)

Drugs	Atenolol	Bisoprolol	Metoprolol
Antianginal Mechanism	**Acts on cardiomyocyte by either:** Decreasing **heart rate** (- chronotropic effect) Increase duration of diastole Increase coronary blood flow Increase oxygen supply Decreasing **contractility** (- inotropic effect) Decrease workload Decrease O_2 consumption (demand)		
Indications in angina	**Stable**	• **Regular prophylaxis**. • Cardio**selective** (beta 1 blockers) are preferred to avoid involvement of lung (bronchiole) & blood vessels. • **First choice** for **chronic** use ○ *Why?* because they also improve the **prognosis** of angina in addition to relief of **pain** & **ischemia**.	
	Variant	**Contraindicated** • Even cardioselective β-blockers may cause vasoconstriction. This will make the vasospasm worse.	
	Unstable	Halts (stops) progression to MI, **improve survival**.	
Indication in acute MI	↓ morbidity & mortality (due to ↓ arrhythmia) ↓ Infarct size, ↓ O_2 demand		

Can beta blockers be combined with nitrates?

Yes, they can block the pro-anginal effects of nitrates, which is desirable.

Can beta blockers be combined with dihydropyridine CCBs?

Yes, because dihydropyridines cause reflex tachycardia & β-blockers will block this action.

Can beta blockers be combined with Verapamil?

No, both cause -ve inotropic effect ⟶ can lead to heart failure.

Should Beta blocker be withdrawn gradually?

Yes, because sudden stoppage will give rise to a **withdrawal syndrome** (Increased pain, rebound angina, MI, arrhythmia & hypertension).
What is the reason? due to stimulation or up-regulation of β-receptors.

Can we give a beta blocker to a diabetic patient with ischemic heart disease?

They should be cautiously used because we have to balance between the **risks** & **benefits** of β-blockers. Their risks in diabetic patients are: **masking hypoglycemia** symptoms (e.g. tremor & palpitations) in addition to **hypoglycemia**.

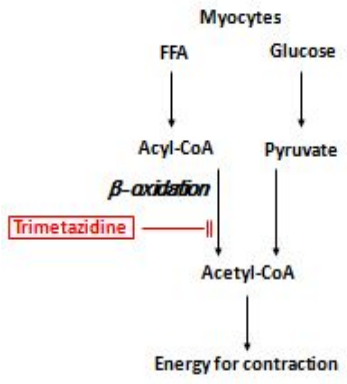
New Approaches

1- Potassium Channel Openers

Drug	**Nicorandil**	
M.O.A.	**Dual action** mechanism	
	As a **K channel opener** (arteriodilator)	As a **Nitric Oxide donor** (venodilator).
	• On **VSM:** opening of K channels → hyperpolarization → vasodilatation • On **cardiomyocytes:** opening of K channels → repolarization → ↓ cardiac work	↑ NO → cGMP/PKG → vasodilation
Indications	**Prophylactic 2nd line therapy** in: • Stable angina • Refractory variant angina	
ADRs	• Flushing, Headache, Hypotension, Palpitation, Weakness (due to nitric oxide) Mouth & peri-anal ulcers (special to Nicorandil), nausea & vomiting	

2- Metabolically Acting Agents

Drug	**Trimetazidine** (ترا ما تزيدين)
Pharmaco dynamics Has **dual-action mechanism**	• The O_2 we need to utilize glucose is **less** than the O_2 we need to metabolize fatty acids. • During ischemia: the metabolism shifts to oxidation of fatty acids, which yields more energy but consumes more O_2 & diminishes the glucose pathway. • So, to ↓ oxygen consumption & demand we ↑ the utilization of glucose by giving **partial FFA oxidation inhibitors** (e.g. Trimetazidine) → reduces oxygen demand without altering hemodynamics.
Indications	Used as an **add on** therapy
ADRs	GIT disturbances (keep in mind that it does **not** cause hypotension)
Contra-indications	1. Hypersensitivity reaction 2. Pregnancy & lactation *"more studies are needed"*



3- Late Na^+ Current Inhibition

Drug	Ranolazine
M.O.A.	Inhibits the **late sodium current** which increases during ischemia. ● Late sodium current (I_{Na}) develops in phase 4 of action potential (thus called "late"). It only occurs during ischemia. ○ During ischemia: ↑ late I_{Na} → Na^+ overload → activation of Na/Ca exchanger (Na out & Ca In) → Ca^{++} overload → diastolic relaxation failure (myocardium cannot relax fully due to Ca) → extravascular compression → ↓ blood flow to myocardium
Indications	● Used in chronic angina concomitantly **with other drugs** ● Used in **diastolic heart failure** (when heart cannot relax) and arrhythmia.
Precautions	● It **prolongs the QT interval** so contraindicated with **Class Ia** (e.g. Quinidine) & **III** (e.g. Ibutilide) antiarrhythmics ○ In spite of that, it does not cause *torsades de pointes* عكس antiarrhythmics. ● Toxicity develops due to interaction with **CYT 450 inhibitors** as: Diltiazem, Verapamil, Ketoconazole, Macrolide antibiotics, Grapefruit juice
ADRs	Dizziness, Constipation

4- Sinus Node Inhibition

Drug	Ivabradine
M.O.A.	Selectively **blocks funny current (I_f)** *I_f current is an inward Na^+/K^+ current that activates pacemaker cells of SA node.
Pharmaco dynamic Effect	↓ Slope of diastolic depolarization (phase IV) → longer time for AP to reach threshold → ↑ diastolic duration → ↓ HR → ↓ myocardial work & O_2 demand
Indications	● Used in treatment of chronic stable angina in patients with normal sinus rhythm **who cannot take β-blockers** (e.g. asthma or COPD) ● Used in combination with beta blockers in people with **heart failure** with LVEF < 35 inadequately controlled by beta blockers alone and whose **heart rate** exceeds 70/min. * Ivabradine decreases heart rate ONLY; it does not affect the contractility. Thus, it is good for HF.
ADRs	Luminous phenomena (transient brightness in a limited area of the visual field) ● *How?* The **retina** has an **I_f current** that is similar to that of the SA node.

*Mnemonic: **IV**abradine slows depolarization in phase **IV.**

SAQs:

Q1- What are the ADRs of using Nitrates?

Q2- Why should Beta blockers be used cautiously in patients with diabetes and IHD?

Click here!

SUMMARY

Answers:

A1-Throbbing headache, Flushing, Postural hypotension dizziness & syncope, Reflex tachycardia & palpitation, methemoglobinemia

A2- They mask hypoglycemic manifestations

Test yourself

From our amazing Qbank team

Good luck!

Pharmacology
TEAM 441

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Subleader

Leen Alhadlaq

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Arwa Almobeirek

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