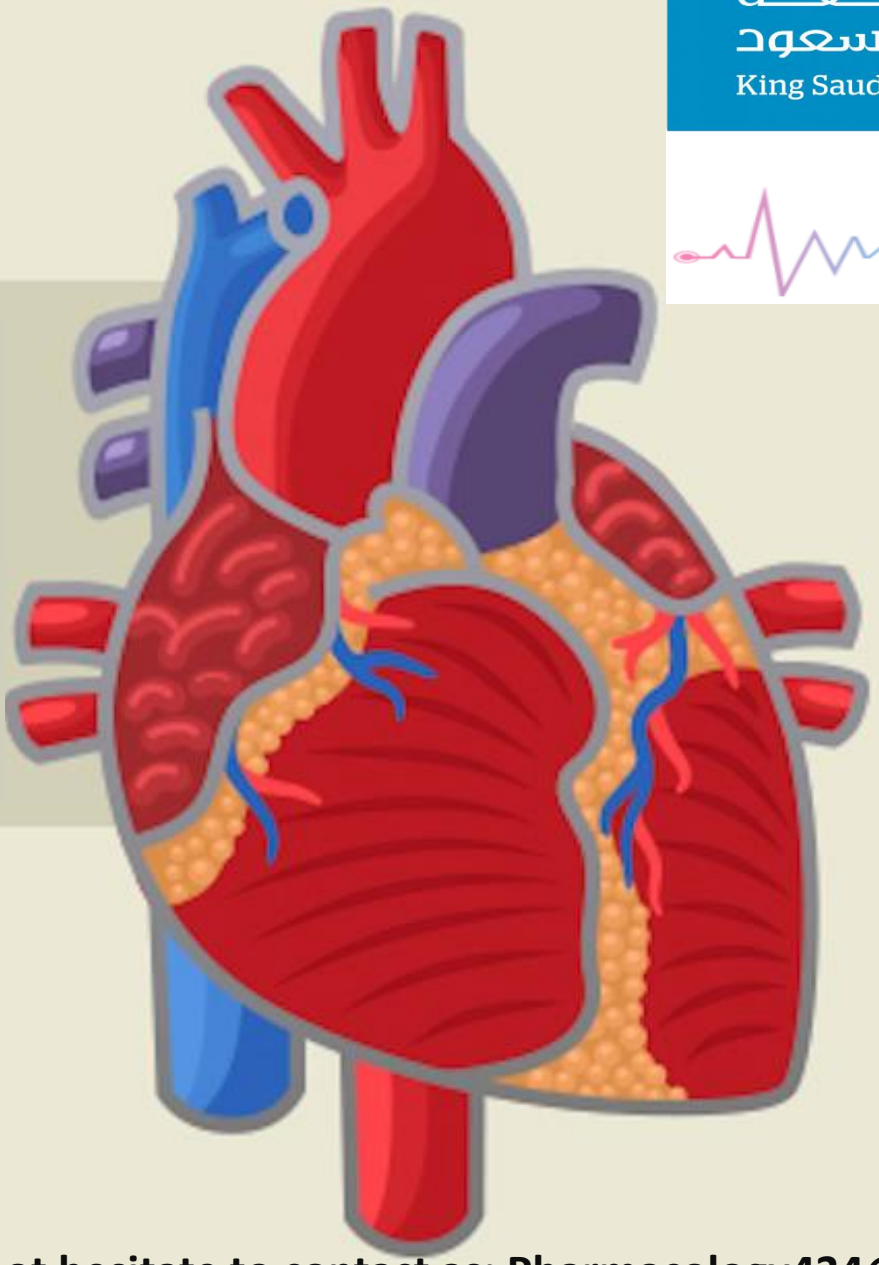
9&10

Antianginal drugs



Cardiovascular Block.

For any correction, suggestions or any useful information do not hesitate to contact as: Pharmacology434@gmail.com

DRUGS USED IN TREATMENT OF ANGINA

Agents that improve symptoms & ischemia

- Organic nitrates
- Calcium channel blockers
- Potassium channel openers
- Beta-adrenoreceptor blockers
- Metabolically acting agents
- Others

→ Vasodilators.

Agents that improve prognosis

VASODILATORS

NITRODILATORS

1- Na NITROPRUSSIDE (ANTIHYPERTENSIVES): Release NO spontaneously

2- ORGANIC NITRATES (ANTIANGINAL DRUG): Release NO via enzymatic reaction { by: Nitrates → Nitrosothiols → Nitrite Ion in endothelial cell (EC) → Acts as NO donner → Mimick action of Endogenous NO}, two types:

- Short Acting: Nitroglycerine [GTN]* & Amyl nitrate*, Rapid For terminating an acute attack

- Long Acting*: Isosorbide mono* & dinitrate*, slower For long-term prophylaxis

* Both will be given SUBLINGUAL in emergency or TRANSDERMAL PATCH as prophylaxis.

❖ Preparations: can influence a change in indications, e.g. I.V or infusion GTN / Amyl nitrate used in Unstable angina Heart Failure

Mechanism	1. Vasodilatation: Relaxation of [VSMC] by: Binds soluble GC Formation of cGMP Activation of PKG ↓Ca ➔ -ve MLCK ➔ RELAXATION 2. Cytoprotection; to endothelium.
Pharmacodynamic Actions	1. Anti-Anginal Actions: ↑ Myocardial Oxygen Supply: (on coronaries) Dilatation of large coronary vessels. Redistribution of flow to ischemic region. Dilatation of collaterals. ↓ Myocardial Oxygen Demand:➔ by ↓cardiac work indirectly ; Venodilatations: of capacitance vessels ➔↓preload ➔ ↓ central venous P ➔↓ CO Arteriolar vasodilatation: ↓ peripheral resistance & ↓ afterload ➔ ↓BP at high dose ↓Platelet Aggregation. Endothelial protective action: ➔ ↓leukocyte-endothelial interactions (anti-inflammatory); antiatherogenic potentials 2. Other Pharmacodynamic Actions: Smooth Muscle Relaxation of: • Bronchi ➔ NO activates cGMP in BSMC ➔ bronchodilatation • Gastrointestinal tract & biliary system • Genitourinary tract
Pharmacokinetics	- Nitroglycrine [GTN]: Significant first pass metabolism occurs in the liver (10-20%) bioavailability - Oral isosorbide dinitrate & mononitrate: Very well absorbed & 100% bioavailability The dinitrate undergoes denitration to two mononitrates➔ both possess antianginal activity ➔($t_{1/2}$ 1-3 hours) ➔ Further denitrated metabolites conjugate to glucuronic acid in liver. Excreted in urine.
Indications	IN STABLE ANGINA: Acute symptom relief: ➔ sublingual GTN Prevention: - Persistent prophylaxis ➔ Isosorbide mono or dinitrate - Situational prophylaxis as before exercising …etc ➔ sublingual GTN IN VARIANT ANGINA: ➔ sublingual GTN IN UNSTABLE ANGINA: ➔ IV GTN

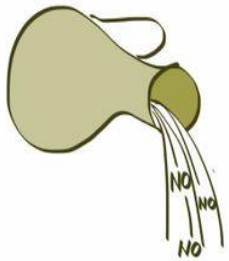
Preparations	- Nitroglycerine: • Sublingual tablets or spray • Transdermal patch • Oral or bucal sustained release • I.V. Preparations -Isosorbide dinitrate & mononitrate: • Dinitrate Sublingual tablets • Dinitrate Oral sustained release • Mononitrate Oral sustained release • Infusion Preparations
ADRs	- Postural hypotension with reflex tachycardia. - Nitrite syncope with fainting & collapse: → due to ↑ dilatation of venous capacitance vessels → ↓ of venous return → ↓ CO & BP. Nitrite syncope is treated by putting the patient in a low head position. - Flushing of blush area: (face, neck and upper trunk). - Throbbing headache: (>common) → tendency to ↑ intra-cranial pressure → used cautiously in cerebral bleeding & head trauma. - Drug rash. - Visual disturbance. - Carcinogenesis. - Met-hemoglobinemia. (in overdose & accidental poisoning)
Nitrate Tolerance	- Loss of vasodilator response of nitrates on use of long-acting preparations (oral, transdermal) or continuous intravenous infusions, for more than a few hours without interruption. - **Causes**: • After 1st day , compensatory counter-regulation → ↓therapeutic efficacy (PSEUDOTOLERANCE). • After 3 days, mainly due to partial depletion of free-SH gps → little formation of nitrosothiols from organic nitrate → ↓NO→ (TOLERANCE) - Nitrate tolerance can be overcomed by: • Nitrate free periods once or twice a day. • Giving drugs that maintain tissue SH group e.g. Captopril.
Precautions During Nitrate Therapy	• 10 hours nitrate free period. • Never stop nitrate therapy suddenly. • Do not take double dose. • Do not use after expiry date; GTN is volatile; shelf-life ~6w after opening Must be stored in cool, tightly capped, dark container.
Contraindication	• Known sensitivity to organic nitrates • Glaucoma; nitrates→ ↑ aqueous formation. • Head trauma or cerebral hemorrhage: Increase →intracranial pressure. • Uncorrected hypovolemia. • Concomitant administration of PDE_5 Inhibitors that are used for the treatment of erectile dysfunction → ↓BP → ↑Myocardial Ischemia→ so we must space doses i.e. Nitrates [morning], PDE_5 Is [Evening].

Antianginal Drugs → 3 main groups: → Organic Nitrates | Beta-Blockers | Ca2+ Channel Blockers

Organic Nitrates

- Nitroglycerin
- Isosorbite dinitrate
- Isosorbite mononitrate

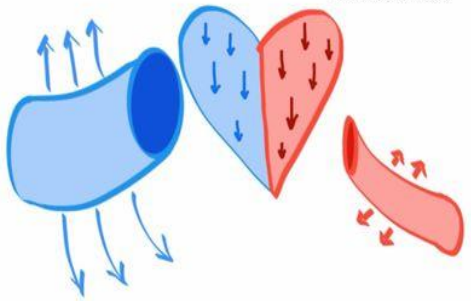
Mechanism of action:



Nitric oxid (powerful vasodilator agent) is released

Very powerful dilatator effect on veins: They relax veins, decreasing preload and myocardial oxygen consumption

Less dilatator effect on arterial peripheral system and coronaries

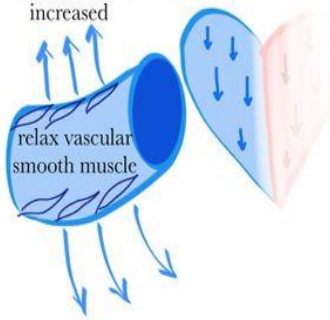


Effects

Effect on veins:

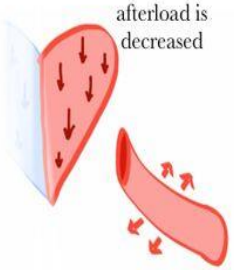
vascular capacitance is increased

afterload is decreased

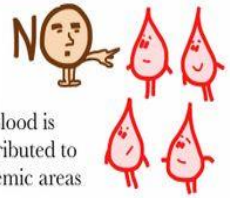


Effects on arteries:

afterload is decreased

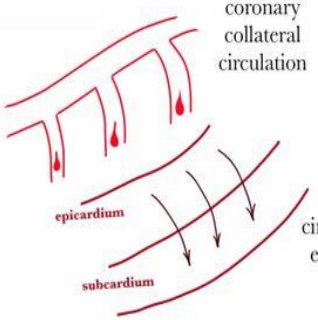


Effects on coronaries



Blood is distributed to ischemic areas

opening of coronary collateral circulation



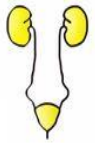
increase of blood circulation from epicardium to subcardium

Effects on other smooth muscles:

Relaxation of :

Bronchi

urogenital system



gastrointestinal tract

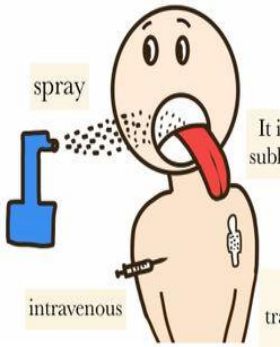
biliary system

moderate decrease of platelet aggregation

Pharmacokinetics

Significant first-pass metabolism of nitroglycerin occurs in the liver.

So Nitroglycerine is not administered orally.



Sublingual Nitroglycerine (Onset : 1-3 minutes after administration, duration: 20-30 min. Not suitable for chronic usage)

Nitroglycerin trans dermal patch. Duration :24 hours -24 hours

Nitroglycerine's metabolites → Isosorbite mononitrate : effect lasts for 6-12 hours | Isosorbite dinitrate : effect lasts for 4-6 hours

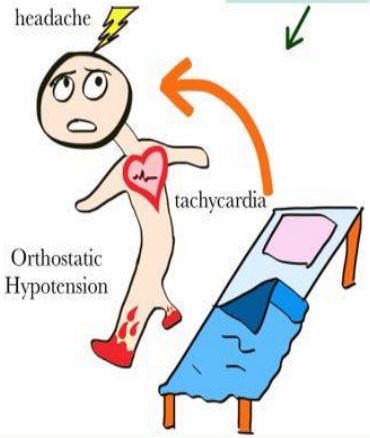
Usage: All types of Angina

Adverse effects:

- Pharmacological tolerance :
- Due to excessive vasodilation

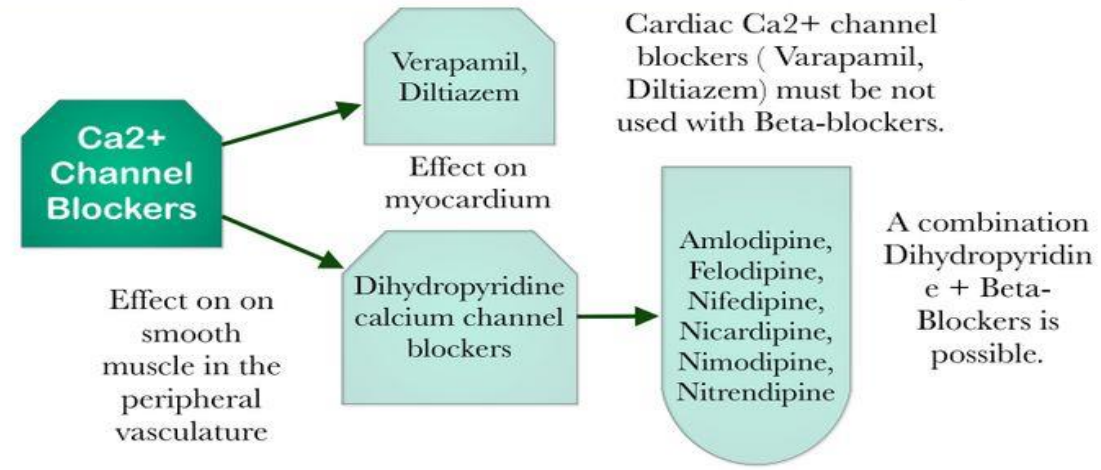
It develops quickly: The blood vessels become desensitized to vasodilation.

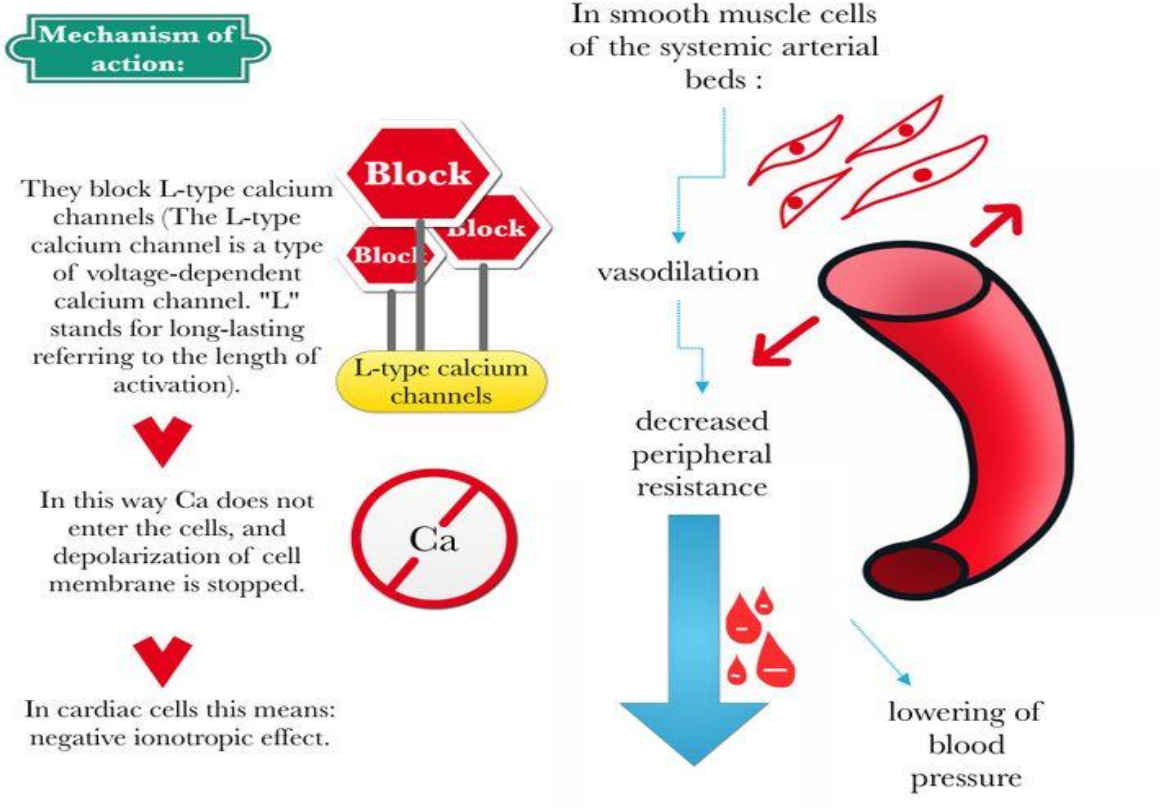
To avoid tolerance, nitrates should not be taken continuously, but a daily administration free interval should be provided.



Ca CHANNEL BLOCKERS

Classification	**Heterogeneous.** • **Dihydropyridines:- Nifedipine , Nicardipine, Amlodepine** • **Phenylalkylamines:- Verapamil** • **Benzthiazepines:- Diltiazem**
Mechanism	- Calcium channel blockers [CCBs] ➔ Bind to L Type Ca channels ➔ their frequency of opening in response to depolarization ➔entry of Ca ➔ ➔ Ca from internal stores ➔ No Stimulus-Contraction Coupling ➔ RELAXATION. - N.B. Selectivity of Ca channel blockers • Nifedipine ➔ VSMCs • Verapamil ➔ Cardiomyocytes > VSMCs • Diltaizem ➔ Intermediate action on both
Pharmacodynamic Actions	Anti-Anginal Actions: - ➔ Cardiomyocyte Contraction: ➔cardiac work through their –ve inotropic & chronotropic action (verapamil & diltiazem) ➔ ➔myocardial oxygen demand. - ➔VSMC Contraction: ➔ After load ➔ ➔cardiac work ➔ ➔myocardial oxygen demand. Coronary dilatation (nifedipine & nicardipine (short acting) / amlodipine (long acting) > diltiazem & verapamil ➔ ➔myocardial oxygen supply. • All Ca channel blockers are good in treating angina (If they are working on VSMC they will decrease myocardial O2 demand and increase myocardial O2 supply, but if they are working on cardiomyocyte they will decrease myocardial O2 demand.
Indications AS ANTIANGINAL	**- IN STABLE ANGINA:** **Regular prophylaxis ➔ Long acting dihydropyridines ; Amlodipine & SR Formulation nifedipine, diltiazem > verapamil** **Short acting dihydropyridine AVOIDED ➔➔ BP ➔➔symathetic activation** **➔reflex tachycardia +syncope ➔impair coronary filling➔ischemia …..** **◆Can be combined to b-AR blockers??? Which group is much safer ?** ***Just Amlodipine who's working on VSMC alone.** **◆ Can be combined with nitrates??? Which group is much safer ?** *** It's better to avoid vasodilators but if it's necessary we combine Verapamil and Diltiazem with the Nitrate because they works on the heart.** ○ **Dihydropyridenes ➔ no ➔ contractility ➔ useful antianginal if with CHF** ○ **Verapamil & diltiazem ➔ < vasoactivity ➔ as antianginal if hypotension** **- IN VARIANT ANGINA:➔ Attacks prevented (> 60%) / sometimes variably aborted. * Mainly Amlodipine.** **- IN UNSTABLE ANGINA: Seldom added in refractory cases**





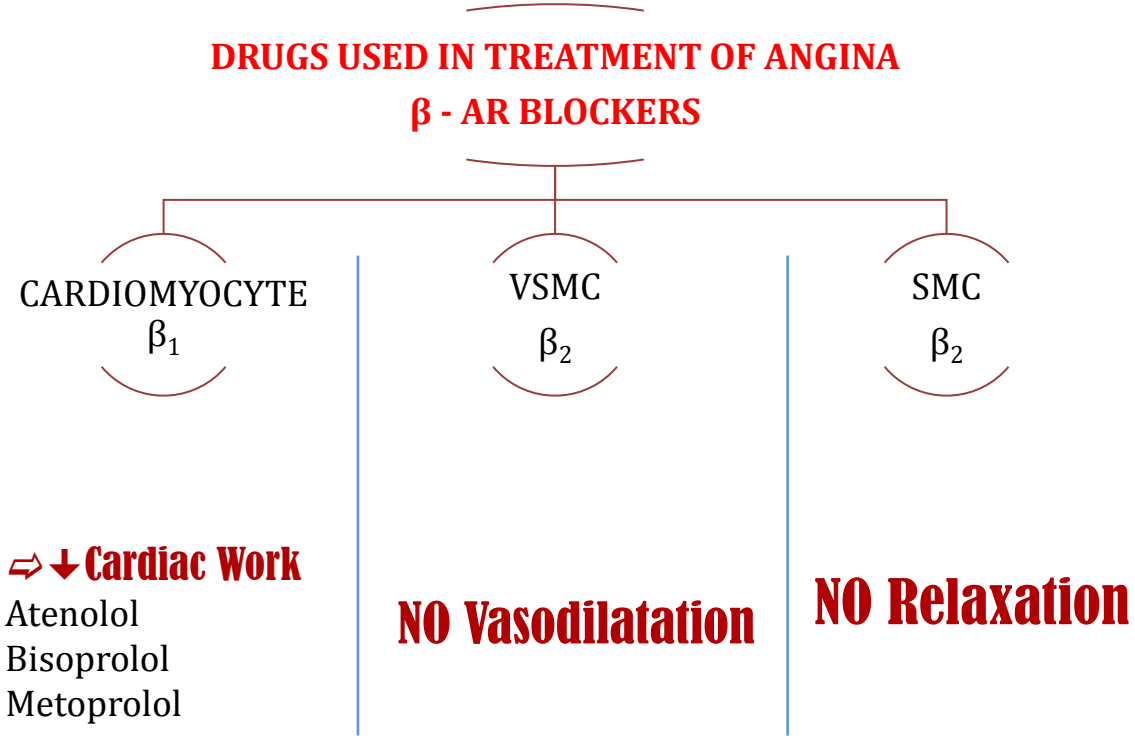
K CHANNEL OPENERS

Nicorandil

Mechanism	It has dual mechanism of action: 1. Opens K_{ATP} channels (> arteriolar dilator). 2. NO donner as it has a nitrate moiety (> venular dilator).
Pharmacodynamic	1. On VSMC: K channel opening ➔Hyperpolarization ➔ VASODILATATION On Cardiomyocyte: K channel opening ➔Repolarization ➔ ↓Cardiac work 2. Acting as NO donner On VSMC: NO donner ➔ ↑ cGMP/ PKG ➔ VASODILATATION
Indications	Prophylactic 2nd line therapy in stable angina & refractory variant angina.
ADRs	• Flushing, headache. • Hypotension, palpitation, weakness. • Mouth & peri-anal ulcers, nausea and vomiting.

DRUGS USED IN TREATMENT OF ANGINA

β - AR BLOCKERS



IN STABLE ANGINA;

Regular prophylaxis → Cardio-selective are better. Why??? → to spare B_2-AR

They are 1st choice on prolonged use → ↓incidence of sudden death specially due to ventricular tachycardia → by their antiarrhythmic action.

◆Can be combined with nitrates → abolish its induced reflex tachycardia.

◆Can be combined with dihydropyridene CCBs but not verapamil nor diltiazem→ for fear of conduction defect (bradycardia, heart block)

IN VARIANT ANGINA→ contraindicated → as it has no vasodilator action

IN UNSTABLE ANGINA → halts progression to AMI → improve survival

1. Anti-Anginal Actions

↓cardiac work through;

-ve inotropic & chronotropic action

↓afterload

↓renin angiotensin release

→↓myocardial oxygen demand

Though no coronary dilatation, yet

→ prolonged diastole

→ ↑ perfusion time

→ ↑ coronary filling & flow →

↑myocardial oxygen supply

In Myocardial Infarction; given early →↓infarct size, morbidity & mortality → CARDIOPROTECTIVE

↓ myocardial O_2 demand.

↑ Redistribution of blood flow in the myocardium.

⬇ free fatty acids.

Anti-arrhythmic action.

↓ incidence of sudden death.

Precautions

B- blockers should be withdrawn gradually as sudden stoppage ➔ give rise to a withdrawal manifestations:

Rebound angina, arrhythmia, myocardial infarction & hypertension

WHY ? ➔ Up-regulation of B-receptors.

Non-selective are better avoided as they blocks vasodilatory effects of sympathetic stimulation ➔ tend to ↑ afterload & ↑ oxygen consumption.

Not used in variant angina ➔ worsen symptoms and aggravate condition

Given to diabetics with ischemic heart disease ➔ [Benefits > hazards) & ACE inhibitor must too be added specially in ACSs

Metabolically Acting Agents

TRIMETAZIDINE

Glucose utilization needs less O2 requirement than FFA utilization i.e. oxidation of FFA requires > oxygen per unit of ATP generated than oxidation of CHO.

During ischemia, metabolism shifts to oxidation of FFA.

So, to treat we can enhance > utilization of CHO (less energy cost) ; by giving

Partial FFA Oxidation Inhibitors

(pFOX Inhibitors), TRIMETAZIDINE

Pharmacol Effects

Restores energy balance in the cell.

↓ fatty acid metabolism by ➔ -ve 3 Ketoacyl Thiolase [3KAT]

-ve anaerobic glycolysis

Allowing only aerobic glycolysis

-ve acidosis & FR accumulation ➔

↓ apoptosis ➔ Cytoprotective

Thus shift myocardial metabolism to ➔

↓OXYGEN DEMAND WITHOUT ALTERING HEMODYNAMICS

Indication of Metabolically Acting Agents

Used when ever needed as add on therapy to nitrates, CCBs or B-blockers

GIT disturbances ➔ **ADRs**

Contraindications

Hypersensitivity reaction

In pregnancy & lactation

Ranolazine

Newly introduced. Considered one of the metabolically acting agents like trimetazedine.

+ affects Na dependent-Ca Channels ➡ prevents Ca load ➡ ⬇apoptosis ➡ cardioprotective.

It prolongs the QT interval so not given with; Class Ia & III antiarrhthmics

Toxicity develops due to interaction with CYT 450 inhibitors as; diltiazem, verapamil, ketoconazole, macrolide antibiotics, grapefruit juice

OTHER DRUGS USED IN TREATMENT OF ANGINA

Ivabradine

Not classified➡ claimed to be CARDIOTONIC agent

Acts on the " Funny Channel" a special Na channel in SAN➡ ⬇HR ➡ ⬇myocardial work ➡ ⬇ Myocardial O2 demand

ANTIANGINAL DRUGS SET THE BALANCE BACK

In attack & situational prophylaxsis

Short acting nitrates

For prophylactic therapy

B-adrenoceptors blockers. ⟷ In Combinations
Calcium channel blockers

Long - acting nitrates.

Potassium channel openers

Metabolic modifiers & others

Agents that improve prognosis

Aspirin / Other antiplatelets

Statins

ACE Inhibitors

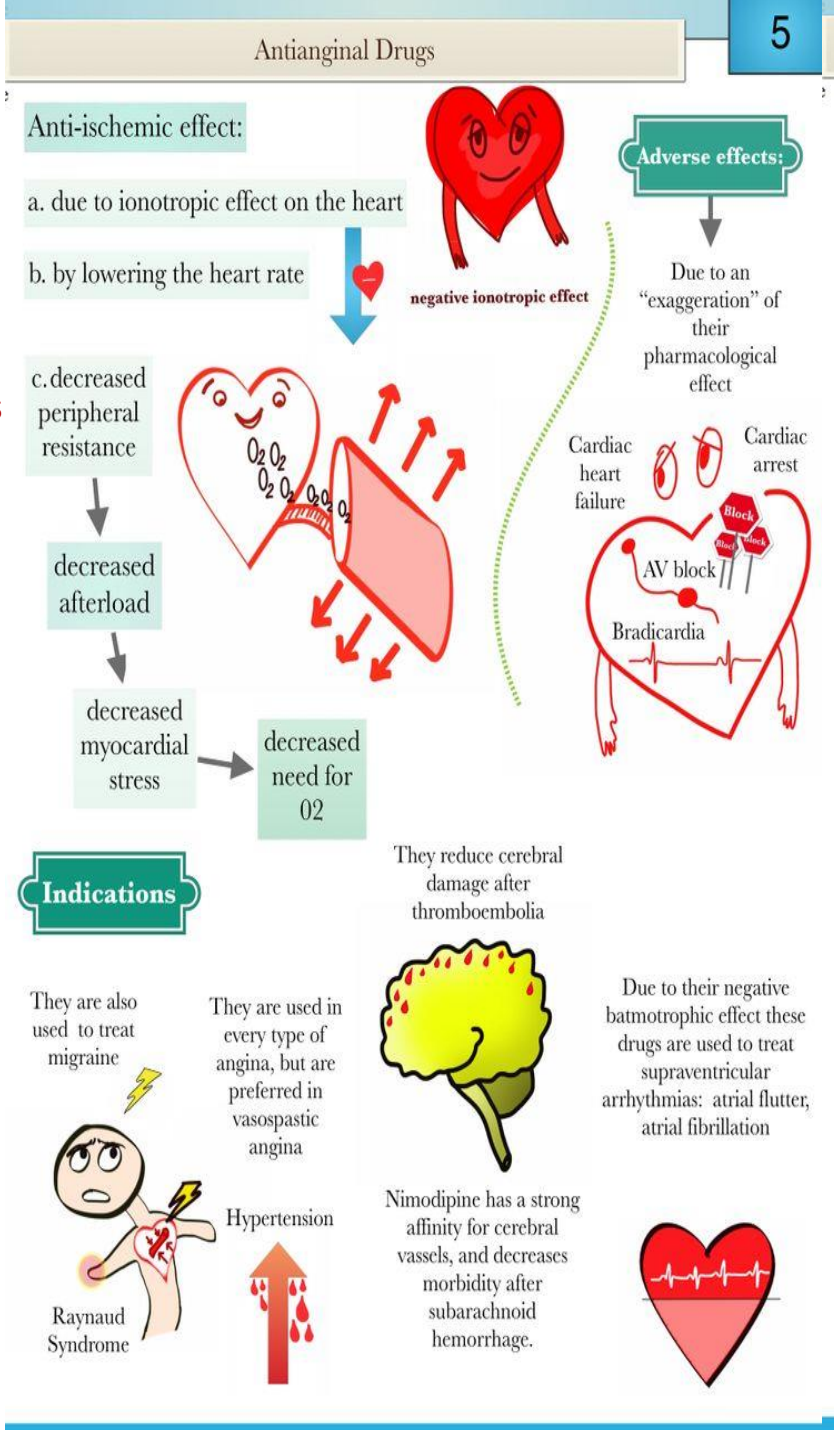
Beta -AD blockers

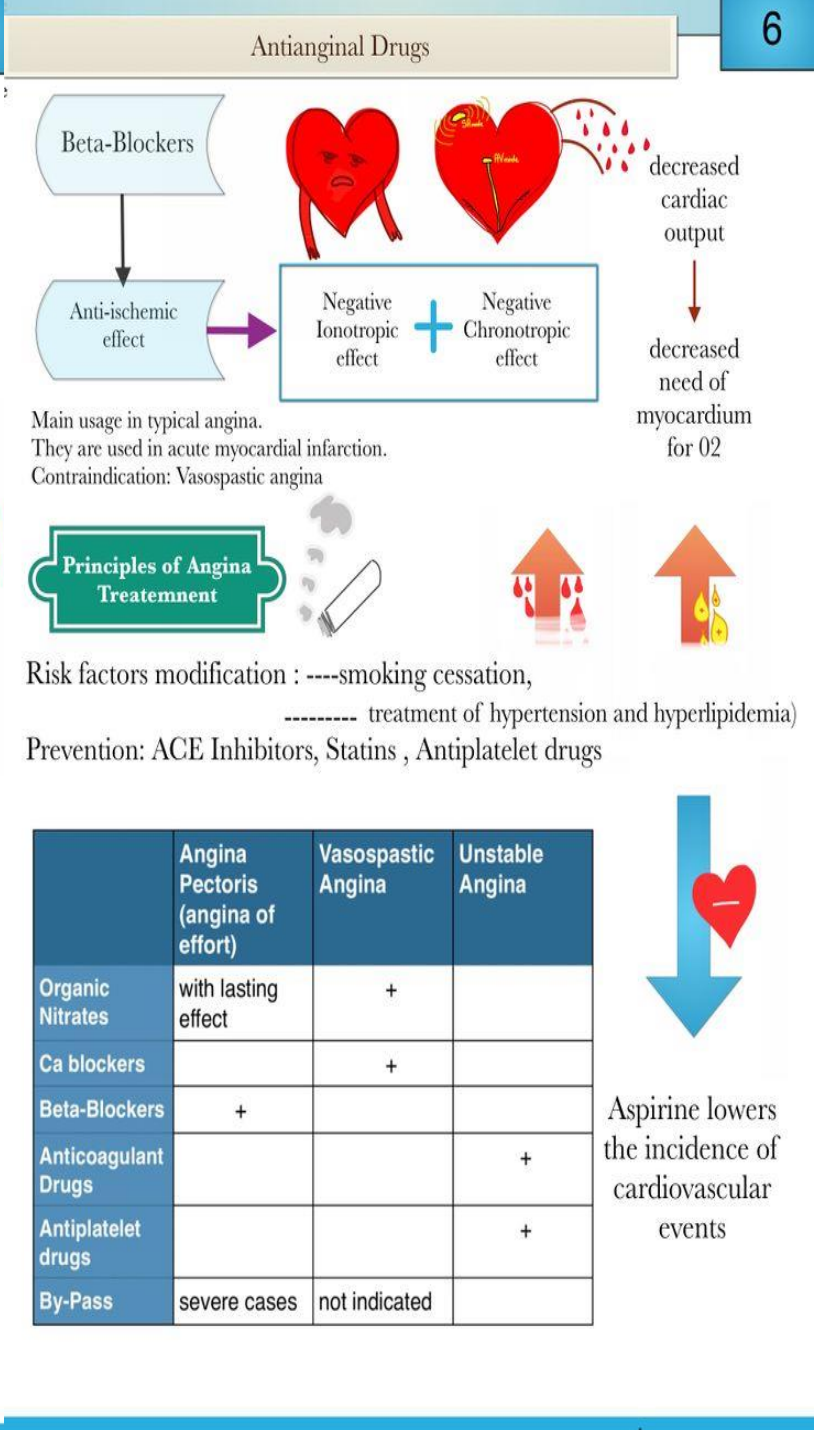
Main Stay of Prophylactic Treatment

Halt progression

Prevent acute insults (ACSs)

Improve survival





	Angina Pectoris (angina of effort)	Vasospastic Angina	Unstable Angina
Organic Nitrates	with lasting effect	+	
Ca blockers		+	
Beta-Blockers	+		
Anticoagulant Drugs			+
Antiplatelet drugs			+
By-Pass	severe cases	not indicated	

Aspirine lowers the incidence of cardiovascular events

Summary

Drugs used in treatment of Angina

- **Agents that improve symptoms & ischemia**
  - **Vasodilators**
    - **Organic nitrates**
    - **Calcium channel blockers**
    - **Potassium channel openers** — **Nicorandil**
  - **Metabolically acting agents** — **TRIMETAZIDINE & Ranolazine**
  - **B-adrenoceptor blockers**
  - **Others** — **Ivabradine:**
    - 1-Acts on the " **Funny Channel**" a special Na channel in SAN.
    - **2-decreased Myocardial O2 demand**
    - **(dynamic effect).**
- **Agents that improve prognosis**
  - **Beta-AD blockers**
  - **Aspirin / Other antiplatelet**
  - **Statins**
  - **ACE Inhibitors**

Ca channel Blockers (CCBs) Selectivity

- Dihydropyridines — **Nifedipine &Amlodipine On (VSMCs)**
- Phenylalkylamines — **Verapamil Cardiomyocytes > VSMCs**
- Benzthiazepines — **Diltaizem Intermediate action on both**

MCQs

1. A 63 year old woman comes to the clinic complaining of sever squeezing pain on her chest she said "my pain stays for 5 minutes whenever I do some activity climbing the stairs for example " she also said that after taking a few minutes rest she become much better and can complete what she was doing . What is the best every day medication to prevent such attacks.

a) Sublingual nitrate GTN b)Amlodipine

c) Na nitroprusside d) Nifedipine

2. Which of the following drugs cannot be combined with Nitroglycerin :

a) Diltiazem b)Verapamil

c) PDEs inhibitors d) capatopril

3. Which of the following Ca++ chanel blockers is best to be given for variant angina :

a) Amlodepine b) Diltiazem

b) Verapamil d) GTN

4. Which of the following is never given in angina :

a) Captopril b) Na nitroprusside

c) Nifedipine d) β – blockers

5. Organic nitrates decrease the cardiac oxygen demand through :

a) Decreasing the preload b) Decreasing the after load

c) Decreasing the contractility d)Both a&b

6. (Pathology question) A 58 year old male has come to the ER with acute ischemic heart disease symptoms. ECG does not indicate any change on ST segment. Laboratory findings also does not indicate any markers. What is the diagnosis?

a) Stable angina b)Unstable angina

c) Acute myocardial infraction d) Sudden heart death

7. A 70 year old male who has a congestive heart failure .recently developed stable angina which of the following drugs is save for him : (choose the best one):

a) Atenolol b) Verapamil

c) Amlodepine d) Diltiazem

8. A 36 healthy female has come to the ER with a severe chest pain radiated to her neck, left shoulder, her chin and her left arm. She cannot breathe properly. Her husband said she has just received bad news about their only son who studies abroad. He adds (she has never have such attack). Her doctor immediately gave her an IV line. He prescribed her a prophylactic drug. what is the drug :

a) Bisoprolol b) Verapamil

c) Niphedipine d) Amlodipine

9. A 56 year old male has been suffering of angina for about 6 months and he takes nitroglycerin, but when he went to see his doctor this time he complained that his pain does not relieved even after taking his medications. His doctor prescribed him another drug to combine and so enhance his first drug. What is that drug ?

a) Na nitropresside b) Nifedipine

c) β – blockers d) Captopril

MCQs

10. Which of the following is metabocally acting drug used in angina : (choose the best one)

a) Ranolazine b) Ivabradine

c) Trimetazidine d)Aspirin

11. Ivabradine is a drug that has an action on :

a) Ca channels b)K channels

c) L-type ca channels d)Funny channels

12. A patient with stable angina went to Makkah to perform Omrah. Which of the following is best to be taken before doing this high-effort work?

a) Nitroglycerine (transdermal patch) b) Nitroglycerine (sublingual)

c) Isosorbide dinitrate (oral) d) Isosorbide mononitrate (oral)

13. A patient with cerebral hemorrhage was diagnosed with stable angina. Which of the following drugs should be avoided when treating stable angina?

a) Bisoprolol b) Trimetazidine

c) Statins d)Nitroglycerine

14. Which of the following drugs is contraindicated in variable angina?

a) Isosorbide mononitrate b) Atenolol

c) Amlodipine d)Slow-release formulation nifedipine

15. Which of the following antianginal drugs mainly targets the heart muscles?

a) Nifedipine b) Amlodepine

c) Diltiazim d)Verapamil

16. Which of the following drugs should be avoided when treating stable angina?

a) Isosorbide mononitrate b) Atenolol

c) Amlodipine d)Nicardipine

17. A patient had angina that has been complicated by heart failure. Which of the following antianginal drugs can be given in this case?

a) Amlodipine b) Nifedipine

c) Verapamil d)Deltiazim

18. A patient has stable angina. His physician wants to prevent the progression of his stable angina into unstable angina and myocardial infarction. Which of the following drugs should be given to fulfill this purpose?

a) Bisoprolol b) Ranolazine

c) Statins d) Nitroglycerine

MCQs

19. A patient had severe hypotension and fainted after taking one of the antianginal drugs. Which of the following is probably this drug?

a) Isosorbide dinitrate b) Nicorandil

c) Atenolol d)Ivabradine

20. 9- In stable angina, Atenolol can be taken along with:

a) Verapamil b) Diltiazim

c) Amlodipine d) Nifedipine

21. Which of the following is best given in unstable angina and myocardial infarction?

a) Verapamil b) Isosorbide mononitrate

c) Amlodipine d) Bisoprolol

22. Inhibiting 3 Ketoacyl Thiolase is the mechanism of action of:

a) Ivabradine b) Trimetazidine

c) Statins d)Nitroglycerine

23. A patient had angina that has been complicated by heart failure. Which of the following antianginal drugs can be given in this case?

a) Amlodipine b) Nifedipine

c) Verapamil d) Deltiazim

Answers:

1: **B**, she needs a prophylaxis drug. We choose Ca++ channel blockers (dihydropyridine) amlodipine is much preferred than Nifedipine which can cause severe hypotension and reflex tachycardia.

2: **C**, PDEs inhibitors cause vasodilation and Nitroglycerin cause vasodilation it can cause a syncope

3: **A**, variant angina is caused by spasm of (smooth muscle cell) so , we need a drug that specifically work on that which is Amlodepine.

4: **B** 5: **D** 6: **B** 7: **C**

8: **D**, from the given scenario we can figure out she is on a prinzmetals angina (spasm). And we know that Bisoprolol is a selective β 1-blocker which has no effect on the VSC . Verapamil work better on decreasing the demand so won't give the action we want.

9: **D** 10: **C** 11: **D** 12: **B**

13: **D** 14: **B** 15: **D** 16: **D**

17: **A** 18: **C** 19 : **A** , one of the side effects because it is a vasodilator

20 : **C** 21: **D** 22: **A** 23: **A**

Long video but it is helpful

GOOD LUCK!

Done By Pharmacology Team

Lulu aldaej .
Sarah aljasser .
Rana aljunidel .
Najla alsubeeh .
Malak alkhathlan.
Malak alzhrani .
Fetoon alnemari.

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