Antianginal Drugs

Pharmacology Team

Objective:

- **Recognize variables contributing to a balanced myocardial supply vs demand**
- **Identify etiopathogenic cascades contributing to ischemic heart disease**
- **Justify the different related clinical presentations of ischemic heart disease**
- **Expand on the drugs used to alleviate acute anginal attacks vs those meant for prophylaxis & improvement of survival**
- **Detail the pharmacology of nitrates, other vasodilators, and other drugs used as antianginal therapy**
- **Sum up the varied therapeutic recommendations for treatment of different clinical presentations of ischemic heart disease**

Here are some notes about the pathophysiology of Angina

***Coronary supply (filling) occurs during Diastole , so when there is tachycardia the diastole period will be shortened and thus coronary filling decreases. SO "once the Period of diastole is decreased or pressure increase, coronary filling is decreased "**

1. **We should have balance between the demand of myocardium and coronary supply. And once this balance is disrupted by increase the demand of myocardium or decrease in the coronary supply we get the ischemic heart diseases.**
2. **The coronary supply is decreased when there is a narrowing in a vessel either by Atherosclerosis (Functional), Vasospasm or Thrombosis (Structural).**

***development of atherosclerotic plaque is variable between the patients , but normally at 20 years of age there is a deposition of fatty acids on the vessels (Fatty streak). Ultimately it forms a plaque by increase the deposition overtime and life style play role on it.**

3. **An atherosclerotic plaque has 2 forms; "STABILIZED" or "VULNERABLE" = crack and fissuring of the plaque.**
4. **The Angina which caused by functional change " Vasospasm" it's called: Spastic Angina OR prinzmetal's Angina OR Variant Angina = All are the same**
5. **When the atherosclerotic plaque is stabilized it leads to "Stable Angina".**
6. **When the atherosclerotic plaque is vulnerable "crack and fissuring" it leads to "unstable Angina", and once it progress to complete closure it will lead to Acute Myocardial infarction. * Unstable angina and acute myocardial infarction are considered from acute coronary syndrome.**

To sum up:
ANGINA = insidious such as Stable angina and Spastic angina
Acute coronary syndrome = ACUTE such as Unstable angina which may progress to Acute MI.

Angina pectoris: **by a spasm or stabilized plaque.**

Chest pain (varying in severity) due to ischemia of heart muscle (accumulation of metabolites K^+, PGs, Kinins, Adenosine….) caused by obstruction or spasm of coronary arteries.
This chest pain Starts in the centre behind the sternum or on left side of the front of chest & spread out to shoulder arm.

1. prinzmatal's Angina (Variant Angina) :

Occurs at REST Cyclic (vasospasm) due to contraction of VSMC. More in younger women
***cyclic means " comes and goes " ATTACKS**

2. stable Angina " Effort Angina":

Develops by exertion Resolves at rest and lasts ~5 min Insidious onset.

3-unstable Angina " crescendo Angina":

Occurs at REST / minimal exertion and Severe / Lasting >10 min and Crescendo pattern, once it becomes acute leads to MI. ➔ Acute coronary syndrome.

4. Vulnerable plaque ➔ Acute occlusion. This occlusion may be TOTAL "complete" or Subtotal "Partial "➔ Acute coronary syndrome.

1. Rupture / erosion / fissuring ➔ exposure of thrombogenic surface ➔platelets adhere ➔thrombosis ➔ OCCLUSION
2. Internal haemorrhage ➔ sudden growth ➔ OCCLUSION

What is Acute coronary syndrome?
Its an umbrella term that covers a spectrum of acute clinical conditions ranging from
1. Unstable angina (38%) No cardiac markers release (negative)
2. NSTEMI (25%) = Non S-T segment Elevation Myocardial Infarction. cardiac markers are release (positive)
3. STEMI (30%) = S-T segment Elevation Myocardial Infarction. cardiac markers are release(positive)

Drugs used in TREATMENT OF ANGINA (ANTIANGINAL DRUGS):

Agents that treat symptoms and ischemia:

Organic nitrates

Calcium channel blockers

Potassium channel openers

β-adrenoceptor blockers

Metabolically acting agents

Others

Agents that improve prognosis:

They just control, they don't have action on coronary vasodilation. Aspirin / Other antiplatelet

Statins

ACE Inhibitors

β-adrenoceptor blockers

ANTIANGINAL DRUGS:

1-Agents that treat symptoms &ischemia:

Nitodilators:

1. **Nitoprusside :**

***Release NO spontaneously** which acts on arterial system and Nitroprusside used as an **Antihypertensive**.

***Release NO (nitric oxide) via enzymatic reactions** known as **organic nitrates** which used as **anti angina**

Divided in to 2 groups of drugs;

1. Short Acting : e.g.Nitroglycerine [GTN] Amyl Nitrite

Rabidly in the acute cases (sublingual). *sublingual administration gives rapid effect because under the tongue reach in blood capillaries so it enters to systemic circulation directly and thus gives RAPID effect .

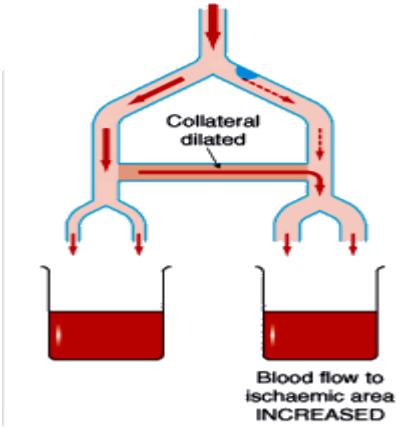
2.Long Acting : e.g. Isosorbide mono & dinitrate

Slowly as long term prophylaxis (oral sustained release transdermal patches).

But they applied some preparations on Isosorbide to be given sublingually so give Rapid action. And preparation to Nitroglycerine to be given orally sustained release or transdermal pathches so give slow action.
So the preparations can influence a change in indications. => I.V or infusion => in unstable angina and Heart failure.

Mechanism of action:

In Vascular smooth muscle cells binds to soluble CG (Guanylyl cyclase) lead to formation of cGMP which will activate PKG (protein kinase G) and causes Relaxation.



Pharmacodynamic actions:

1-Antianginal actions:

↑ Myocardial Oxygen Supply :

***Dilatation of large coronary vessels.**

***Redistribution of coronary flow from normal 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 (reflex tachycardia) => because of no appropriate coronary filling → ↓BP at high dose.**

↓Platelet Aggregation

Endothelial protective action → ↓leukocyte-endothelial interactions (anti-inflammatory); antiatherogenic potentials.

2-Other pharmacodynamic actions:

SMC Relaxation of

1. Bronchi →NO activates cGMP in BSMC → bronchodilatation

2. Gastrointestinal tract & biliary system

3. Genitourinary tract

Pharmacokinetics:

1. Nitroglycrine [GTN]

Significant first pass metabolism occurs in the liver (10-20%) bioavailability (so sublingual or transdermal patch)

2. 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:

A-In stable Angina :

***Acute symptom relief → sublingual GTN**

***Prevention; Persistant prophylaxis → Isosorbide mono or dinitrate**

Situational prophylaxis → as before exercising, climbing…etc

→ sublingual GTN

***situational means if the patient knows that he will do an effort now , so he can take it to prevent the anginal attack.**

B-In variant Angina: →sublingual GTN

***Because variant Angina caused by Vasospasm and Organic nitates has arteriolar dilatation action.**

C-In unstable Angina: → IV GTN.

Refractory AHF → IV GTN

CHF → Isosorbide mononitrate + hydralazine *[if contraindication to ACE Is]*

AMI →IV GTN

Preparations:

Nitroglycerine

1. Sublingual tablets or spray
2. Transdermal patch
3. Oral or bucal sustained release
4. I.V. Preparations

Isosorbide dinitrate & mononitrate

1. **Dinitrate** Sublingual tablets
2. **Dinitrate** Oral sustained release
3. **Mononitrate** Oral sustained release
4. Infusion Preparations

Adverse effects:

1-Postural hypotension with reflex tachycardia: especially if the patient is standing stationary.

2-Nitrite syncope with fainting & collapse → due to ↑ dilatation of venous capacitance vessels + severe ↓ of venous return →↓ CO & BP. * Nitrite syncope is treated by putting the patient in a low head position.

3-Flushing of blush area (face, neck and upper trunk) is unpleasant

4-Throbbing headache (>common)& tendency to ↑intra-cranial pressure →used cautiously in cerebral bleeding & head trauma

5-drug rash.

6-Visual disturbance.

7- Carcinogenesis (rarely happens)

8-Met-hemoglobinemia (in overdose & accidental poisoning).

Nitarte 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.

***Magnitude of tolerance is a function of dosage & frequency of use.**

Causes:

1. After 1st day of continuous nitrates, compensatory neurohormonal counter-regulation occurs (*RAAS, NE, Vasopressin ….etc activation*)→ ↓therapeutic efficacy (PSEUDOTOLERANCE).

2. After 3 days, dysfunction of ECs & VSMC occur by many different molecular mechanisms, aside the partial depletion of free-SH groups that permits formation of nitrosothiols from the organic nitrate to give NO➔ (TOLERANCE).

Nitrate tolerance can be overcomed by: to prevent the Nitrate tolerance by 2 ways:

1- Smaller doses at increasing intervals (Nitrate free periods twice a day).

2-Giving drugs that maintain tissue SH group e.g. Captopril.

precautions during Nitrate therapy:

1. **10 hours nitrate free period.**
2. **Never stop nitrate therapy suddenly.**
3. **Do not take double dose. (to prevent Nitate syncope from happening only in case combined with Nitoglycerine in attacks otherwise we don't give double dose.)**
4. **Do not use it after expiry date; GTN is volatile; shelf-life ~6w after opening must be stored in cool, tightly capped, dark container.**

Contraindication:

1- Known sensitivity to organic nitrates.

2-Glaucoma; nitrates➔ ↑ aqueous formation

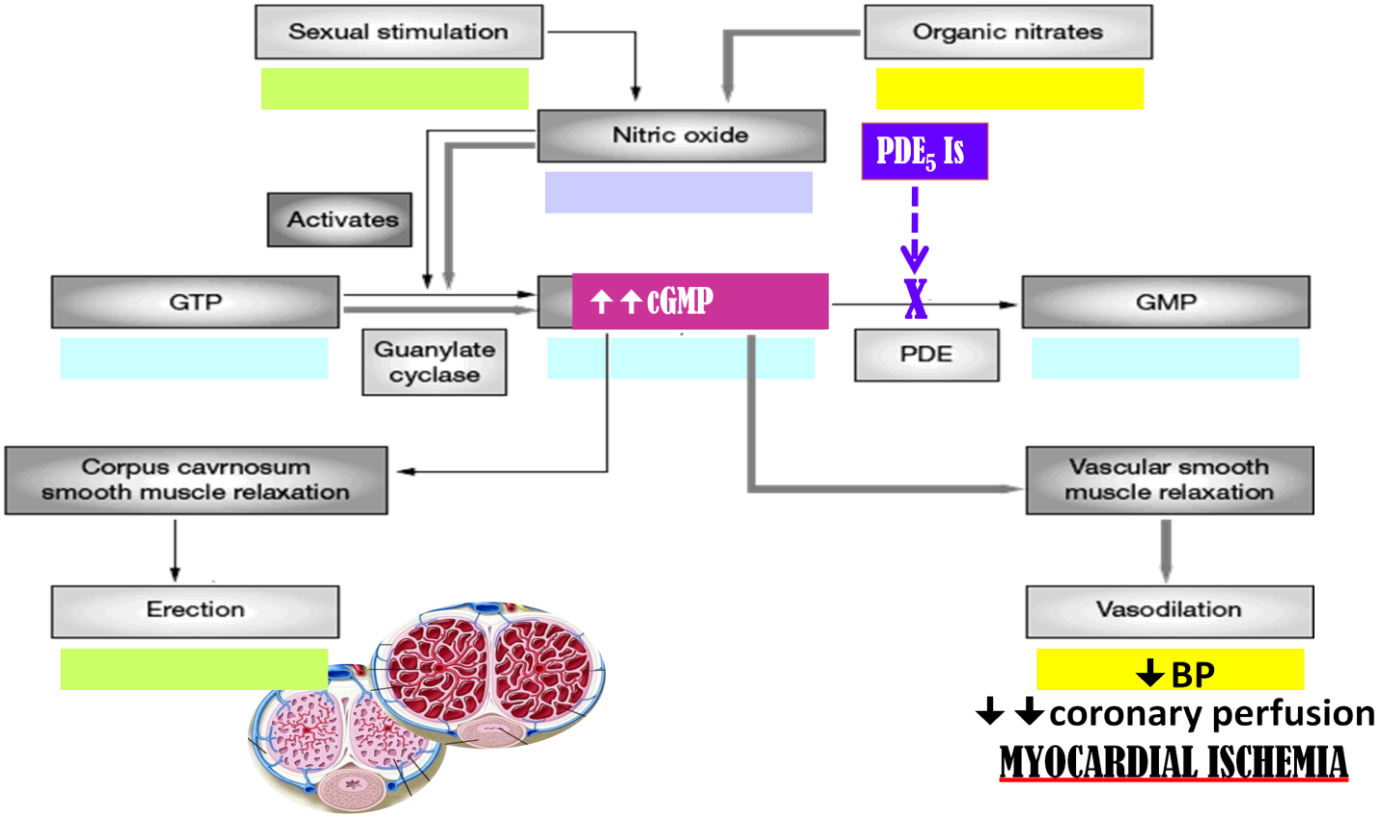
3-Head trauma or cerebral haemorrhage increase ➔intracranial pressure .

4- Uncorrected hypovolemia

5- 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].

***PDE_5 Inhibitors:Phosphodiesterase-5- inhibitors.**

***Nitrates and Phosphodiesterase inhibitors are both vasodilatror and we cant take them together because they will lead to syncope and sever drop in blood pressure and thus lead to reflect tachycardia and impairment of coronary syndrome so it can precipitate acute attack.**


Sexual stimulation
Organic nitrates
Nitric oxide
PDE5 Is
Activates
GTP
↑↑cGMP
GMP
Guanylate cyclase
PDE
Corpus cavrnosum smooth muscle relaxation
Vascular smooth muscle relaxation
Erection
Vasodilation
↓BP
↓↓coronary perfusion
MYOCARDIAL ISCHEMIA

Ca CHANNEL BLOCKERS

- **Classification : Heterogeneous**
  - ✓ **Dihydropyridines:-** Nifedipine , Nicardipine, Amlodepine
  - ✓ **Phenylalkylamines:-** Verapamil
  - ✓ **Benzthiazepines:-** Diltiazem

- **Ca Channel Types & Distribution**

Type	Distribution
L	Cardiac & VSMCs / neurons
T	Heart / neurons
N	Neurons
P	Cerebellar Purkinje neurons

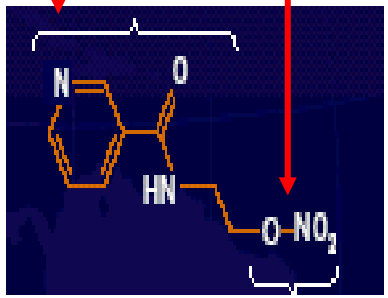
N.B. Selectivity of Ca channel blockers

- ✓ Nifedipine ➔ VSMCs
- ✓ Verapamil ➔ Cardiomyocytes > VSMCs
- ✓ Diltaizem ➔ Intermediate action on both

Mechanism	Pharmacodynamic Actions (Anti-Anginal Actions)		Indications AS ANTIANGINAL
Binding of calcium channel blockers [CCBs] to the L-type Ca channels ↓ their frequency of opening in response to depolarization ↓entry of Ca → ↓ Ca from internal stores → No Stimulus-Contraction Coupling → RELAXATION	**Dihydropyridines** ○ ↓VSMC contraction ○ ↓ After load → ↓cardiac work → ○ ↓myocardial oxygen demand ○ Coronary dilatation (nifedipine & nicardipine *(short acting)* / amlodipine *(long acting)* > diltiazem & verapamil → ↑myocardial oxygen supply	**Phenylalkylamines & Benzthiazepines** **↓ Cardiomyocyt Contraction** ↓cardiac work through their –ve inotropic & chronotropic action (verapamil & diltiazem) → ↓myocardial oxygen demand	IN STABLE ANGINA; Regular prophylaxis → Long acting dihydropyridines ; amlodipine & SR formulation nifedipine, diltiazem > verapamil Short acting dihydropyridine avoided →↓ BP →↑symathetic activation →refelx tachycardia +syncope →impair coronary filling→ischemia ….. ◆Can be combined to b-AR blockers??? Which group is much safer??? Yes , but only with **Dihydropyridines group** ◆ Can be combined with nitrates??? Which group is much safer??? Yes , but only with **Phenylalkylamines group** ◆ Dihydropyridenes → no ↓ contractility → useful antianginal if with CHF ◆ Verapamil & diltiazem → < vasoactivity → as antianginal if hypotension IN VARIANT ANGINA→ Attacks prevented (> 60%) / sometimes variably aborted (**Nifedipine** most potent) IN UNSTABLE ANGINA; Seldom added in refractory cases

K CHANNEL OPENERS

Nicorandil

Mechanism	Pharmacodynamic	Indications	ADRs
It has dual mechanism of action; 1. Opens K_{ATP} channels (> arteriolar dilator) 2. NO donner as it has a nitrate moiety (> venular dilator)  	1.Opening of K_{ATP}channels 1. On VSMC K channel opening→ Hyperpolarization → VASODILATATION 2. On Cardiomyocyte K channel opening→ Repolarization →↓Cardiac work 2. Acting as NO donner On VSMC NO donner → ↑ cGMP/ PKG → VASODILATATION	Prophylactic 2nd line therapy in stable angina & refractory variant angina **(coz not that much potent)** **(Give it combine with other drug but not with ORGANIC NITRATES)**	Flushing, headache, Hypotension, palpitation, weakness Mouth & peri-anal ulcers, nausea and vomiting.

β - AR BLOCKERS

- CARDIOMYOCYTE (B_1)→ ↓ Cardiac Work
- VSMC(B_2)→ NO Vasodilatation
- SMC (B_2)→ NO Relaxation

β_1 – Selective > Non – Selective: Atenolol , Bisoprolol ,Metoprolol

Pharmacodynamic Actions Anti-Anginal Actions	Indications as antianginal	Precautions
↓cardiac work through their ✓ -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 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 & allow unopposed α-adrenergic coronary vasoconstriction to occur. IN UNSTABLE ANGINA → halts progression to AMI → improve survival 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.	1.β- blockers should be withdrawn gradually as sudden stoppage → give rise to a withdrawal manifestations: Rebound angina, arrhythmia, myocardial infarction ,hypertension WHY ? → Up-regulation of β-receptors. 2.Non-selective are better avoided as they blocks vasodilatory effects of sympathetic stimulation → ↑afterload & ↑ oxygen consumption. 3.Not used in variant angina → worsen symptoms and aggrevate condition 4.Given to diabetics with ischemic heart disease → [Benefits > hazards) & 5.ACE inhibitor must too be added specially in ACSs

Metabolically Acting Agents

TRIMETAZIDINE

Mechanism	Pharmacol Effects	Indication	ADRs	Contraindications
✓ O_2 requirement for glucose utilization is < 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	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	Used when ever needed as add on therapy to nitrates, CCBs or b-blockers (Not use it alone)	GIT disturbances	➢ 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*

OTHERS

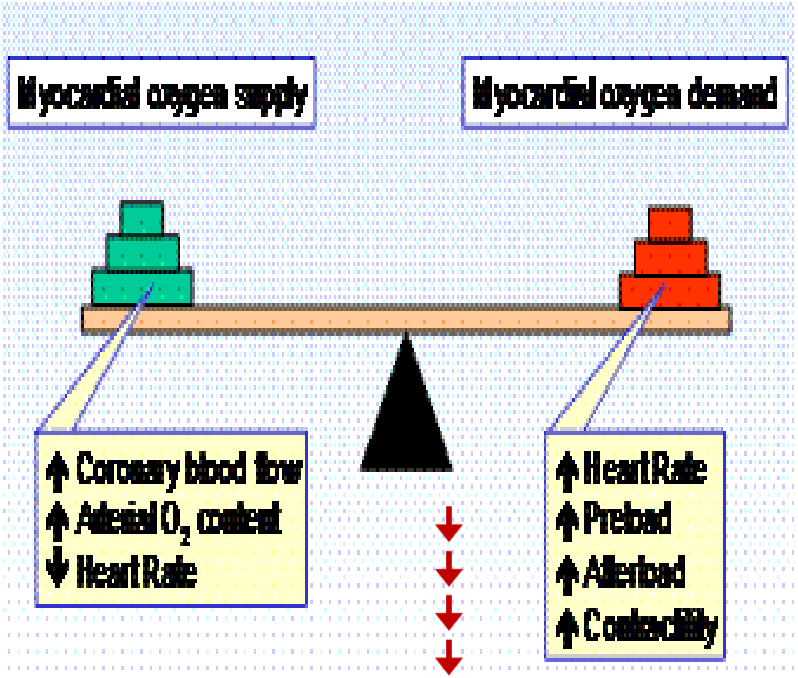
Ivabradine

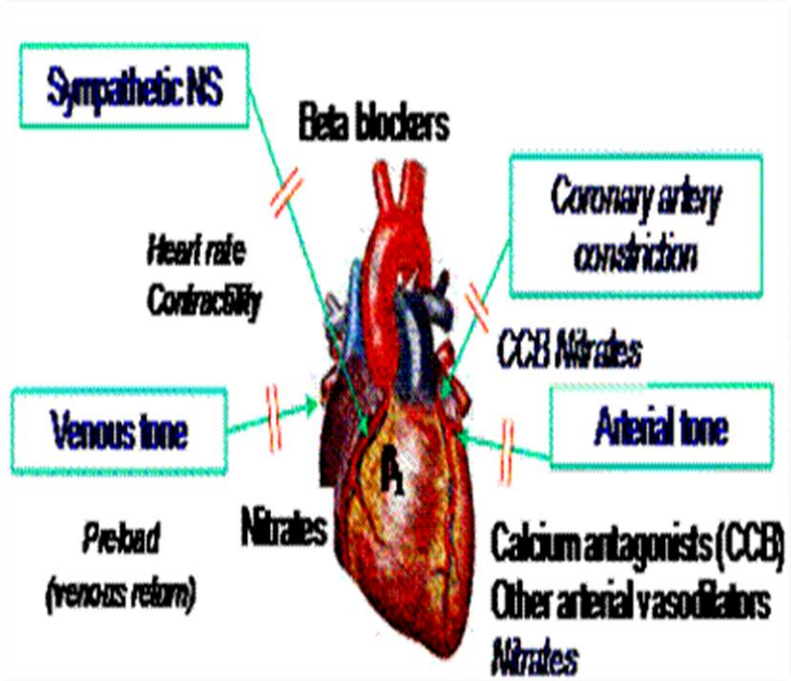
Not classified ➔ claimed to be *CARDIOTONIC agent*

Acts on the "Funny Channel" a special Na channel in SAN ➔↓HR➔↓myocardial work ➔↓Myocardial O_2 demand

Summary:

ANTIANGINAL DRUGS SET THE BALANCE BACK





In attack & situational prophylaxis

- **Short acting nitrates**

For prophylactic therapy

- **β-adrenoceptors blockers.**
- **Calcium channel blockers**
- **Long - acting nitrates.**
- **Potassium channel openers**

Metabolic modifiers & others

In Combinations

Agents that improve prognosis

- Aspirin / Other antiplatelets
- Statins
- ACE Inhibitors
- β-AD blockers

Main Stay of Prophylactic Treatment

- **Halt progression**
- **Prevent acute insults**
- **Improve survival**

THERAPEUTIC GUIDELINES FOR ISCHEMIC HEART DISEASES

Stable Angina:

- **Acute symptoms by short acting nitrates**
- **Maintain therapy by a suitable antianginal drug (Nitrates and/or β-Blockers and/or CCB ± metabolic modifiers).**

Vasospastic Angina:

- **Prevention and even abortion of an attack of coronary artery spasm is achieved by Nitrates and/or CCB.**
- **Propranolol is contraindicated.**

ACS **Unstable angina: ➔ Better transfer to ICU or CCU.**

- **Antianginal drugs (Nitrates &/or B-blockers, CCB in refractory cases) + Aspirin or Antiplatelets & IV Heparin.**

- **IF THERAPY FAIL to any➔ REVASCULARIZATION ? ➔ OPENING OF OCCLUDED VESSEL either by;**
  - **Percutaneous coronary intervention;** PCI
  - **Surgical coronary artery bypass grapht;** CABG
- **ACS**:

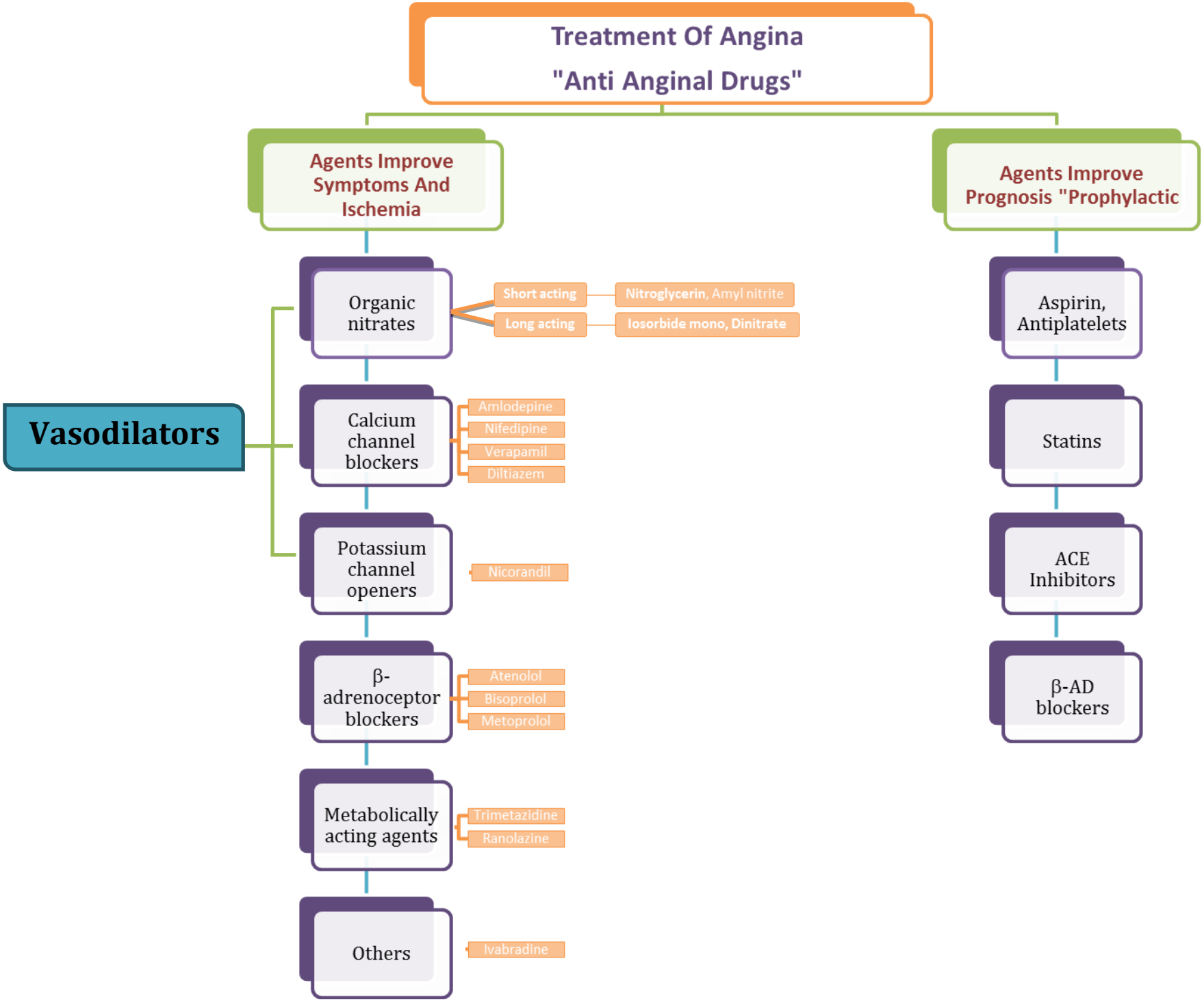
AMI: Transfer to CCU & apply the following measures:

Before & During Transfer:

- **Cardiopulmonary resuscitation / Oxygen & I.V fluids.**
- **Nitroglycrine sublingual up to 3 doses with 5 minutes intervals**
- **Analgesics, as morphine, for severe pain.**
- **Chewable aspirin 160 mg**.

In ICU or CCU units:

- Thrombolytics: **to induce clot lysis & restore blood flow**
- **Anti-coagulant: IV Heparin, continue on aspirin orally**
- **O_2 & Opiates: IV morphine or meperidine.**
- **Nitrates: IV infusion of GTN + early b-blockers → ↓myocardial damage.**
- **ACE Inhibitors →start early →↓postmyocardial fibrosis & improve survival**
- **Statin therapy →start early →stabilize plaque**


Treatment Of Angina
"Anti Anginal Drugs"
Agents Improve Symptoms And Ischemia
Agents Improve Prognosis "Prophylactic
Vasodilators
Organic nitrates
Short acting
Nitroglycerin, Amyl nitrite
Long acting
Isorbide mono, Dinitrate
Calcium channel blockers
Amlodepine
Nifedipine
Verapamil
Diltiazem
Potassium channel openers
Nicorandil
β-adrenoceptor blockers
Atenolol
Bisoprolol
Metoprolol
Metabolically acting agents
Trimetazidine
Ranolazine
Others
Ivabradine
Aspirin, Antiplatelets
Statins
ACE Inhibitors
β-AD blockers

ORGANIC NITRATE	Nitroglycrine "GTN" In Acute attack	Oral isosorbide dinitrate & mononitrate As prophylactic
M.O.A	In VSMC: Binds to soluble GC →Formation of cGMP →Activation of PKG →RELAXATION 1. Anti-Anginal Actions -↑ Myocardial Oxygen Supply by; Dilatation of large coronary vessels. Redistribution of coronary flow from normal to ischemic region. Dilatation collaterals -↓ Myocardial Oxygen Demand→ **by** ↓cardiac work indirectly **;** **Venodilatations: of capacitance vessels →↓preload → ↓ central venous P →↓ CO** **Arteriolar vasodilatation: ↓ peripheral resistance & ↓ afterload (reflex tachycardia) → ↓BP at high dose** -↓Platelet Aggregation -Endothelial protective action	
Pharmacokinetics	If given orally first pass metabolism occurs in the liver (10-20%BV) So it's given sublingual or via transdermal patches or IV	Orally is Very well absorbed & 100% BV The dinitrate undergoes denitration to two mononitrates, both are anti-anginal
Uses "indications"	(sublingual): -In Stable Angina:- Acute symptom relief - situational prophylaxis - In variant angina (IV): -Unstable angina, Refractory AHF* and Acute MI	-In Stable Angina:-Persistant prophylaxis
Adverse Effects	- **Postural hypotension** with **reflex tachycardia**. - **Nitrite syncope** with fainting & collapse due to ↑ dilatation of venous capacitance vessels + severe ↓of venous return leading to ↓CO & BP. **Nitrite syncope is treated by putting the patient in a low head position.** - **Flushing** of blush area (face, neck and upper trunk) and **drug rash** - Throbbing **headache** - ***Nitrate tolerance*** (loss of VD** response after continuous use) can be overcome by smaller doses at increasing intervals **(Nitrate free periods twice a day)** or use it with other drugs "captopril"	
Precautions during use	-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.	
Contraindications	-Organic nitrates sensitivity - Head trauma or cerebral hemorrhage - Glaucoma - Uncorrected hypovolemia -Concomitant administration of PDE_5 Inhibitors for the treatment of erectile dysfunction →↓BP →↑Myocardial Ischemia	

***AHF=acute heart failure**

****** VD= vasodilatation**

Ca Channel Blockers "L-type"	Dihydropyridine group (**Amlodepine ,Nifedipine**, Nicardipine)	Verapamil	Diltiazem
MAIN EFFECT	act mainly on vascular smooth muscles "VSMC" and used as vasodilators "coronary"	act more on the Cardiomyocytes and used as anti-arrhythmic drug	intermediate effect
M.O.A	Anti anginal action: On VSMC: -↓VSMC Contraction **-↓**myocardial oxygen demand **by: ↓ After load → ↓cardiac work** - ↑myocardial oxygen supply by vasodilatation of coronary vessels **(nifedipine & *(short acting)* / amlodipine *(long acting)*** ***diltiazem & verapamil have very week vasoactivity** **On the heart:** ↓ Cardiomyocyte Contraction ↓myocardial oxygen demand by:**↓cardiac work through their –ve inotropic & chronotropic action (verapamil & diltiazem)**		
INDICATION	- stable angina - antianginal with CHF (no ↓ contractility) - drug of choice **IN VARIANT ANGINA due to their VD effect** **Safer in combination with b-AR blockers**	- stable angina - anti-anginal with hypotension (less vasoactivity) **Safer in combination with with nitrates**	

K CHANNEL OPENERS	Nicorandil
M.O.A	1. Opens KATP channels (> arteriolar dilator) 2. NO donner as it has a nitrate moiety (> venular dilator)
INDICATION	Prophylactic 2nd line therapy for stable angina & refractory variant angina Cant combined with
Adverse Effects	Flushing, headache, Hypotension, palpitation, weakness, Mouth & peri-anal ulcers, nausea and vomiting "not important"
Drug interaction	Can not be used with NITRATE and it is better to avoid using it with CCB vasodilator

β- blockers	Atenolol, Bisoprolol, Metoprolol (selective)
M.O.A	- **decrease O2 demand** (by decreasing the cardiac work through their –ve inotropic and chronotropic effect and decrease rennin angiotensin release) - **increase O2 supply** (increasing diastole, which give more time for perfusion and lead to increased coronary blood flow)
INDICATION	- **stable angina** (used as prophylaxis, β-selective blockers are 1st choice on prolonged use, they prevent ventricular arrhythmias) - **unstable angina** (stop its progression to Acute MI or reduce infarct size "CARDIOPROTECTIVE") -contraindicated in variant angina because it doesn't have vasodilatation action➔ **worsen symptoms and aggrevate condition**
Precautions	- should be withdrawn gradually (if not -receptors are up-regulated, and it gives rise to Rebound angina, arrhythmia, MI & hypertension) - Non-selective are better avoided (they blocks vasodilator effects of sympathetic stim.) - Given to diabetics with ischemic heart disease ➔ [Benefits > hazards) & ACE inhibitor must too be added specially in ACSs
Drug interaction	Can be combined with nitrates Can be combined with dihydropyridene CCBs but not verapamil nor diltiazem

Metabolically acting agents	TRIMETAZIDINE
M.O.A	↓OXYGEN DEMAND WITHOUT ALTERING **HEMODYNAMICS** by: - -O2 requirement for glucose utilization is less than that required for FFA "free fatty acids" utilization - During ischemia, metabolism shifts to oxidation of FFA. However still, the ↑FFA➔blunts glucose utilization. - Partial FFA oxidation inhibitors - Restores energy balance in the cell (↓fatty acid metabolism "by **inhibiting 3 Ketoacyl Thiolase [3KAT]"**, inhibiting anaerobic glycolysis, Allowing only aerobic glycolysis)
Pharmacokinetics	- Rapidly absorbed, Peak concentration= 2 hrs - t1/2 = 6hrs - Excretion, mainly unchanged in urine
Uses	Used when ever needed as add on therapy to nitrates, Ca Channel Blockers or β-blockers
Adverse Effects	GIT disturbances
Contraindications	Hypersensitivity reaction and 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*

Ivabradine not classified drug
Acts on the "Funny Channel" a special Na channel in SAN ➔↓HR➔↓myocardial work ➔↓Myocardial O_2 demand

MCQs

1- **Ahmad Abdullah is having angina and he lives in an apartment in the 5th floor. the elevator is out of order so, he has to climb up the stairs.**
the Situational prophylaxis that he has to take it before he climbs the stairs is:
   A. GTN sublingual administration
   B. Oral isosorbide dinitrate
   C. GTN IV administration
   D. Nicorandil

2- **Which one of the following drugs will prescribe for A patient has angina and hypotension as an anti angina drug:**
   a. GTN sublingual administration
   b. Amlodepine
   c. GTN IV administration
   d. Verapamil

3- **For The patient described in Question2 which one of the following drugs must be avoided while he is taking his anti anginal drug?**
   A. GTN
   B. Atenolol
   C. Nicorandil
   D. isosorbide mononitrate

4- **A patient who was taking Nitrate, he suddenly had Nitrate syncope, what is the best way to treat him?**
   A. Putting him in lower head position
   B. Administration of small GTN dose (IV)
   C. Administration of small GTN dose (sublingual)
   D. Gastric lavage.

5- **Nitroglycerin , either directly or through reflexes, result in which one of the following effects?**
   A. Decreased heart rate.
   B. Decreased venous capacitance.
   C. Increased afterload .
   D. Increased cardiac forced.
   E. Increased preload.

6- **An active metabolite of another drug and an active antianginal drug for oral administration in its own right.**

A. isosorbide dinitrate.
B. Amylnitrite.
C. isosorbide mononitrate
D. Nitroglycerin.
E. Pentaerythritol tetranitrate .

7- **A side effect least likely to be seen with Nitroglycerin.**

A. Headache
B. Dizziness.
C. Palpitation.
C. Cancer of oesophagus.
D. Flushing
E. Flushing

Answers:

1-A, 2-D, 3-B, 4-A,5-D, 6-c,7-D