King Saud University
College of Medicine
1st Year, 4th block

Anti-anginal Drugs 11&12

Cardiovascular Block

Objectives :

- 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.

Ischemic Heart Disease (IHD)

It is an obstruction in the coronary blood flow because of the narrowing that happens in the coronary arteries.
-Functionally: coronary artery spasm
-Structurally: Atherosclerotic plaque
This is all caused either by: decreased the coronary supply, or increased oxygen demand.

Stable

Angina*
Decreased exercise tolerance

Unstable

Acute MI
Acute coronary syndrome

***Angina:**
Caused: by a spasm or stabilized plaque
Symptoms: chest pain (constricting & tight, oppressive, crushing)
Reasons of the pain: accumulation of metabolites K^+, PGs, Kinins, Adenosine
Types:
1-Prinzmetal's Angina: occurs at rest cyclic (vasospasm) due to contraction of VSMC.
2-Stable Angina: develops by exertion, resolves at rest.
3-Unstable Angina: occurs at rest.

Drugs in treatment of Angina

Agents that improve symptoms & ischemia

1. Organic nitrates
2. Calcium channel blockers
3. Potassium channel openers
4. β-adrenoceptor blockers
5. Metabolically acting agents
6. Others

Vasodilators

Agents that improve prognosis

1. Aspirin / Other antiplatelets
2. Statins
3. ACE Inhibitors
4. β-AD blockers

NITRODILATORS

Release NO via enzymatic reaction

Organic Nitrates

Antianginal drugs

Release NO spontaneously

Na Nitroprusside

Antihypertensives

	Short acting	Long acting
Drug	- Nitroglycerine (GTN). - Amyl nitrate.	Isosorbide mono & dinitrate
Onset of action	Rapid	Slower
Indication	acute attack	long-term prophylaxsis
Rout of administration*	Sublingual	-Sustained release. -Transdermal patches.

*The indication of the drugs is changed according to the rout of administration, if sublingual → emergencies (acute attacks).
These drugs could be used in both situations according to the rout.

Organic Nitrates

Origin	Nitrates → Nitrosothiols → Nitrite ion in endothelial cell → acts as NO donner → mimic action of endogenous NO
Mechanisms of action	1. Vasodilation: Relaxation of VSMC ↓Ca → -ve Myosin Light Chain Kinase → relaxation 2. Cytoprotection: to endothelium
Pharmacodynamic Actions	1. Anti-Anginal Actions: ↑ Myocardial oxygen supply: - 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 → decrease the preload → decrease central venous p → ↓ CO - Arteriolar vasodilatation: ↓ peripheral resistance & ↓ afterload → ↓BP at high dose ↓Platelet Aggregation: Endothelial protective action by ↓leukocyte-endothelial interactions (anti-inflammatory) antiatherogenic potentials
	2. Other Pharmacodynamic Actions: Smooth muscle relaxation of ▪ Bronchi ▪ Gastrointestinal tract & biliary system ▪ Genitourinary tract
Pharmacokinetics	1. Nitroglycrine [GTN]: Has first pass metabolism occurs in the liver (10-20%) bioavailability so given sublingual or via 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.

Organic Nitrates

Indications

- In stable angina:

1. Acute symptom relief → sublingual GTN
2. Prevention:
   - Persistent prophylaxis → Isosorbide mono or dinitrate
   - Situational prophylaxis (as before exercising, climbing…etc) → sublingual GTN

- In variant angina → sublingual GTN

- In unstable angina → IV GTN

Adverse reactions

- Postural hypotension with reflex tachycardia.
- Nitrite syncope with fainting and collapse due to ↟ dilatation of venous capacitance vessels.
- Flushing of blush area (face, neck and upper trunk).
- Throbbing headache.
- Drug rash.
- Visual disturbance.
- Carcinogenesis.
- Met-hemoglobinemia.

Nirate tolerance

*What is it?

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

-Pseudo-tolerance: After 1st day, compensatory counter-regulation → low therapeutic efficacy.

-Tolerance: After 3 days, mainly due to partial depletion of free-SH gps ➜ little formation of nitrosothiols from organic nitrate ➜↓NO

*Nitrate tolerance can be overcomed by:

1. Nitrate free periods once or twice a day.
2. Giving drugs that maintain tissue SH group e.g. Captopril.

Organic Nitrates

Precautions	Give free period of Nitrates (10 hours) Never stop nitrate therapy suddenly. Do not take double dose. Do not use after expiry date Must be stored in cool, tightly capped, dark container.
Contraindication	-Pateints who are known of sensitivity to organic nitrates. -Glaucoma; nitrates ↑ aqueous formation -Head trauma or cerebral haemorrhage. -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 Inhibitors [Evening].

Ca channel blockers

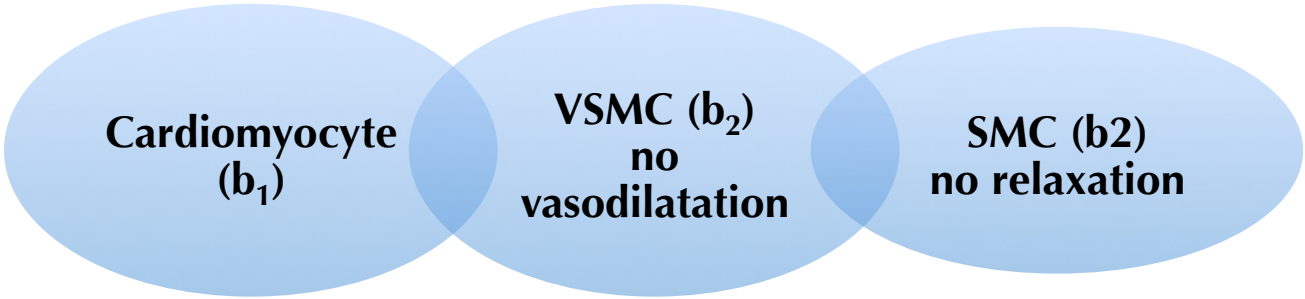
Classification	1- Dihydropyridines: Nifedipine(short acting), Nicardipine, Amlodepine (long acting) 2- Phenylalkylamines: Verapamil 3- Benzthiazepines: Diltiazem
Mechanism	1- bind to L-type Ca channels. 2- decrease their frequency of opening in response to depolarization. 3- decrease the entry of Ca, so ↓ Ca from internal stores → Relaxation.
Selectivity	• Nifedipine → VSMCs • Verapamil → Cardiomyocyte • Diltaizem → Intermediate action on both.
Pharmacodynamics	1- cardiomyocyte contraction: cardiac work through their –ve inotropic & chronotropic action (Verapamil & diltiazem) decrease the myocardial oxygen demand. 2- VSMC contraction: *Decrease afterload→ decrease the cardiac work → decrease the oxygen demand. *Coronary dilatation (Nifedipine & Nicardipine(short acting) / Amlodipine(long acting) → increase the myocardial oxygen supply.
Indications	**1- in stable angina:** -Regular prophylaxis: *Long acting Dihydropyridines (Amlodipine & slow release formulation Nifedipine, Diltiazem > Verapamil). *Short acting Dihydropyridine are avoided. **2- in variant angina:** Attacks prevented (> 60%) / sometimes variably aborted **3- in unstable angina:** Seldom added in refractory cases

K-CHANNEL OPENERS

e.g. Nicorandil

Mechanism	**It has dual mechanism of action**; 1. Opens K_{ATP} channels (is more arteriolar dilator) 2. NO donor as it has a nitrate moiety (is more venular dilator)
Pharmacodynamics	1. Opening of K_{ATP} channels: - On VSMC: K channel opening → Hyperpolarization → vasodialtion - On Cardiomyocyte: K channel opening → Repolarization → Low cardiac work. 2. Acting as NO donor: - On VSMC NO donner → high cGMP/ PKG → vasodilation
Indications	**Prophylactic 2nd line** therapy in stable angina & refractory variant angina
Adverse effects	• Flushing, headache, • Hypotension, palpitation, weakness • Mouth & peri-anal ulcers, nausea and vomiting.

β- AR Blockers



↓ cardiac work

b_1 – Selective > Non – Selective

Atenolol

Bisoprolol

Metoprolol

Pharmacodynamic Action

1. Anti-anginal action:

↓ cardiac work through;
-ve inotropic & chronotropic action
↓afterload
↓renin angiotensin release
↓myocardial oxygen deman

Though no coronary dilatation, yet:
prolonged diastole
↑ perfusion time
↑ coronary filling & flow
↑myocardial oxygen supply

Indications As Antianginal

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

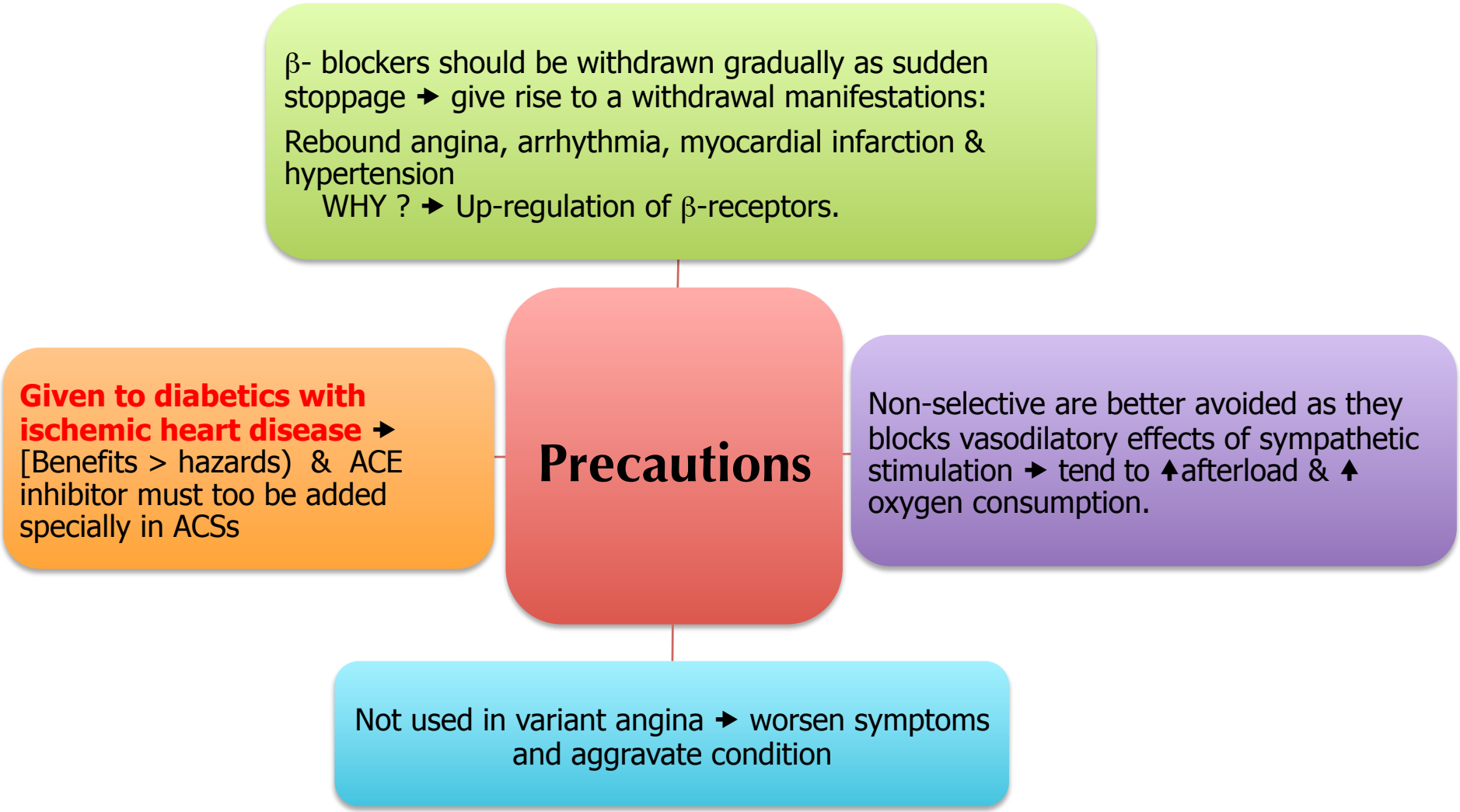
- contraindicated (it has no vasodilator action)

In Unstable Angina

- halts progression to AMI → improve survival

In Myocardial Infarction

- given early → ↓infarct size,
- morbidity & mortality → CARDIOPROTECTIVE


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

Metabolically Acting Agents

FFA=free fatty acid

1-Trimetazidine

Mechanism	During ischemia, metabolism shifts to oxidation of FFA. Glucose utilization needs less O_2 requirement than FFA utilization i.e. oxidation of FFA requires more oxygen per unit of ATP generated than oxidation of CHO. So, to treat we can enhance more utilization of CHO (less energy cost); by giving ➜ **Partial FFA Oxidation Inhibitors (pFOX Inhibitors)**
Pharmacological Effects	↓ fatty acid metabolism by → **-ve 3 Ketoacyl Thiolase** [3KAT] ↓oxygen demands without altering hemodynamic
Indication	Used when ever needed as add on therapy to nitrates, Ca channel blockers or b-blockers.
ADRs	GIT disturbances.
Contraindications	1. Hypersensitivity reaction. 2. In pregnancy & lactation.

2- Ranolazine

Mechanism	• Newly introduced. Considered one of the metabolically acting agents like trimetazedine. • Also affects Na dependent-Ca Channels ➜ prevents Ca load ➜ ↓ apoptosis ➜ cardioprotective.
	It prolongs the QT interval so not given with Class IA(Quinidine) & III antiarrhthmics(Amiodarone)
	Toxicity develops due to interaction with CYT 450 inhibitors as; diltiazem, verapamil, ketoconazole, macrolide antibiotics, grapefruit juice.

Other agents that improve symptoms & ischemia

e.g. **Ivabradine**

Not classified; claimed to be cardiotonic agent.

Mechanism:

Acts on the "Funny Channel" a special Na channel in the SAN

↓HR

↓myocardial work

↓Myocardial O_2 demand

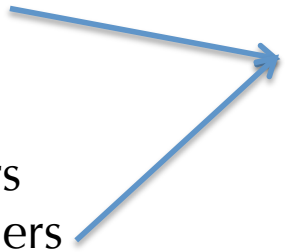
Indications:

-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 combination

	Mechanism of action	Drug's name	preparations or mechanism	Uses	ADRs	Contraindication	Important notes
Organic Nitrates	In VSMC, Binds soluble GC, Formation of cGMP , Activation of PKG >>> RELAXATION Dilation of veins MORE than arteries : 1- Decreased Myocardial Demand (main action) 2- Increased myocardial supply	Nitroglycerine [GTN] Amyl nitrate	Short Acting (sublingual in ER + Rapid acting)	1-For emergency e.g. terminating an acute attack 2-in situational prophylaxes i.e. if a person will exercise	1- Hypotension and reflex tachycardia 2- Nitrite syncope 3- Flushing of blush area 4- Nitrate tolerance: Solution is spacing the doses, have a Nitrate free periods twice a day, or give a –SH donor	Concomitant administration of PDE5 Inhibitors that are used for the treatment of erectile dysfunction e.g. Sildenafil >>>↑Myocardial Ischemia The solution: so we must space doses i.e. Nitrates [morning], PDE5 Inhibitors [Evening]	changes in the preparations changes the indications, nitroglycerine patches and isosorbide sublingual, so now according to the preparation the onset of action changes. The nitroglycerine patches are slower in action, and the isosorbide is rapid in action.
		Isosorbide mono & dinitrate	Long Acting (Oral For long-term prophylaxis + slow acting)	Prophylaxis (on a daily basis)			
Ca CHANNEL BLOCKERS	block the L-Ca channel > no depolarization > relaxation (arteriolar dilators more than venodilator)	Nifedipine , Amlodepine	> VSMCs – they mostly increase the supply (coronary dilation) more than decreasing the work of the heart though it doesn't work on the heart (Nife:short-acting (Aml:long-acting Note: Nifedipine is not given in ER.. Unless if its sustained release but it's ok to give Aml	- with β-blockers - drug number 1 in spastic angina - with CHF because it has nothing to do with contractility) - Regular prophylaxis not situational: amlodipine & SR formulation nifedipine		- with nitrates - in hypotension	-The one that works more on blood vessels SHOULD NOT be combined with nitrates -The ones that work on the heart more SHOULD NOT be combined with B-blockers
		Verapamil	> Cardiomyocytes – they mostly decrease the demand	- with nitrates - in hypotension		- with β-blockers	
		Diltaizem	**> Intermediate action on both**	**- in hypotension**		- with β-blockers	

	Mechanism of action	Drug's name	Uses	ADRs	Contraindication
K CHANNEL OPENERS	It has dual mechanism of action; 1. Opens K_{ATP} channels (> arteriolar dilator) 2. NO donner as it has a nitrate moiety (> venular dilator	Nicorandil	-It's a 2nd line of therapy -Not in ER -Given with B-blockers and Verapamil & Diltaizem	Mouth & peri-anal ulcers	- in situational prophilacxis - with nitrates
β-blockers	-depress the cardiac work (O demand) mainly) -increase the supply	We should choose selective β blockers: (BAM) Bisoprolol Atenolol Metoprolol	-With nitrate -With Nifedipine , Amlodepine - Unstable angina it improve survival -CARDIOPROTECTIVE - Given to diabetic patient and has ischemic heart diseas		- in spastic angina
Metabolically acting agents	1- ↓Oxygen Demand Without Altering Hemodynamics 2- PFOX inhibitors 3- act on level of 3 ketoacyl Thiolase (3KAT).	Trimetazidine	Used as an add on therapy		
	affects Na dependent-Ca Channels → prevents Ca load → ↓ apoptosis → cardioprotective.	Ranolazine			- It prolongs the QT interval so not given with; Class Ia & III antiarrhthmics - interaction withs; diltiazem, verapamil, ketoconazole, macrolide antibiotics, grapefruit juice
Others	Acts on the " Funny Channel" a special Na channel in SAN →↓HR→↓myocardial work →↓Myocardial O_2 demand	Ivabradine			

MCQs

1- 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)

2- 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

3- Which of the following drugs is contraindicated in variable angina?
A. Isosorbide mononitrate
B. Atenolol
C. Amlodipine
D. Slow-release formulation nifedipine

4- Which of the following antianginal drugs mainly targets the heart muscles?
a) Nifedipine
b) Amlodepine
c) Diltiazim
d) Verapamil

5- Which of the following drugs should be avoided when treating stable angina?
A. Isosorbide mononitrate
B. Atenolol
C. Amlodipine
D. Nicardipine

6- 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

7- 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

8- 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

9- In stable angina, Atenolol can be taken along with:
A. Verapamil
B. Diltiazim
C. Amlodipine
D. Nifedipine

10- Which of the following is best given in unstable angina and myocardial infarction?
a) Verapamil
b) Isosorbide mononitrate
c) Amlodipine
d) Bisoprolol

11- Inhibiting 3 Ketoacyl Thiolase is the mechanism of action of:
A. Ivabradine
B. Trimetazidine
C. Statins
D. Nitroglycerine

12- 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

1-B 2-D 3-B 4-D 5-D
6-A 7-C 8-A 9-C 10-D
11-B 12-A

We hope we made this lecture easier for you
Contact us for any questions or comments
Good Luck !

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