ANTIANGINAL DRUGS

LEARNING OUTCOMES

Recognize variables contributing to a balanced myocardial supply versus demand

Expand on the drugs used to alleviate acute anginal attacks versus those meant for prophylaxis & improvement of survival

Detail the pharmacology of nitrates, other vasodilators, and other drugs used as antianginal therapy .

Calcium channel blockers

Classification

Dihydropyridines:- Nifedipine , Nicardipine, Amlodepine

Phenylalkylamines:- Verapamil

Benzthiazepines:- Diltiazem

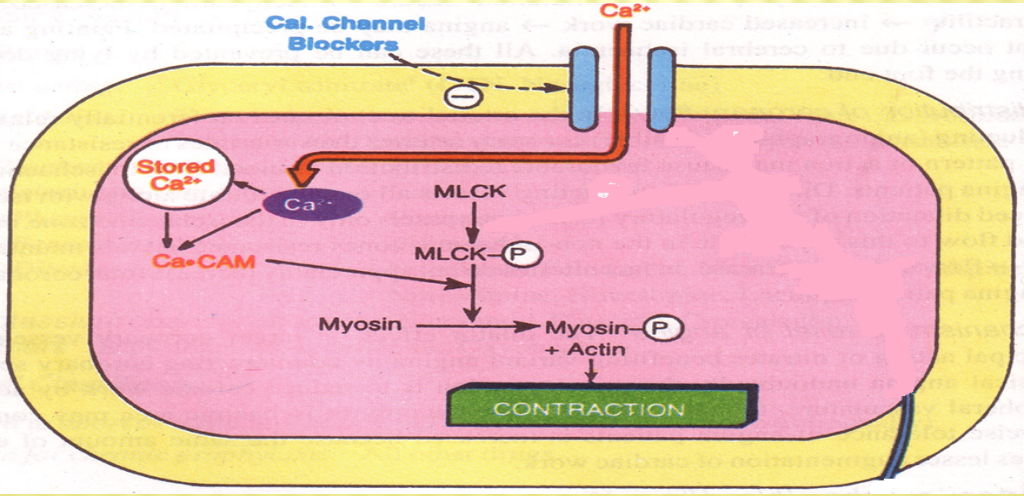
Calcium channel blockers

Selectivity	
Nifedipine ,	Vascular smooth muscle
Verapamil	Cardiomyocytes
Diltiazem	Intermediate

Mechanism of Action

Binding of calcium channel blockers [CCBs] to the L-type Ca channels ↓ their 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 action (verapamil & diltiazem) → ↓myocardial oxygen demand

↓VSMC Contraction → ↓ Afterload → ↓cardiac work → ↓myocardial oxygen demand

Coronary dilatation → ↑myocardial oxygen supply

Therapeutic Uses

IN VARIANT ANGINA

➔ Attacks prevented (> 60%) / sometimes variably aborted

IN UNSTABLE ANGINA;

Seldom added in refractory cases

IN STABLE ANGINA;

Regular prophylaxis

Therapeutic Uses

Short acting dihydropyridine should be avoided ??

Can be combined to β-AR blockers???

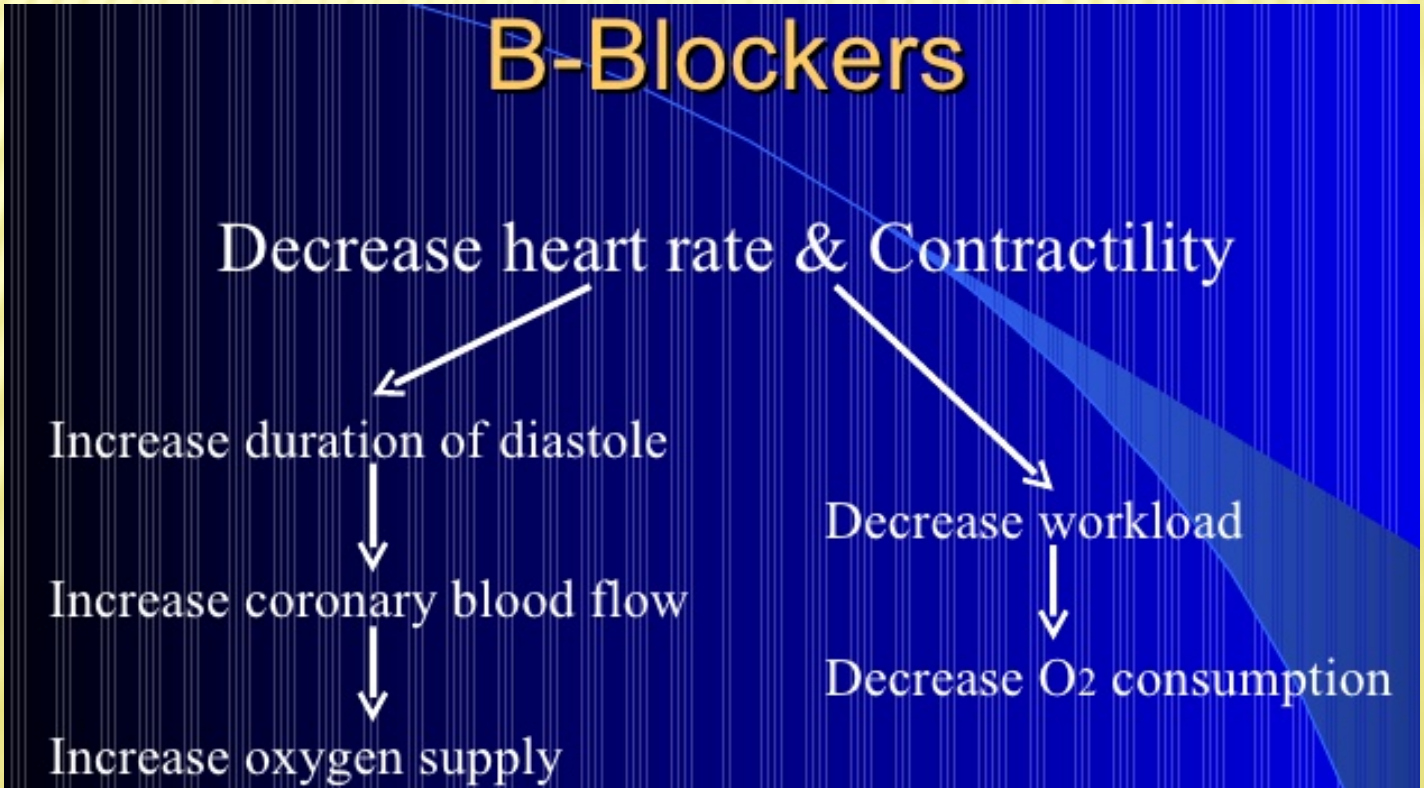
Can be combined with nitrates???

Dihydropyridenes useful antianginal if with CHF??

Beta Adrenoceptor Blockers

Examples Atenolol, Bisoprolol, Metoprolol (β_1 – Selective)

Antianginal Mechanism



Beta Adrenoceptor Blockers

Indications in angina

In stable angina

Regular prophylaxis, selective are preferred?

First choice for chronic use?

Can be combined with nitrates?

Can be combined with dihydropyridine CCB?

Verapamil?

In variant angina

Beta Adrenoceptor Blockers

Indications in angina

In Unstable angina

Halts progression to MI, improve survival

In Myocardial infarction

Reduce infarct size

Reduce morbidity & mortality

→reduce O2 demand

→reduce arrhythmias

Beta Adrenoceptor Blockers

β- blockers should be withdrawn gradually?

Given to diabetics with ischemic heart disease?

MINICASE

Which antianginal drug is the best choice for the case of Helmi? And Why?

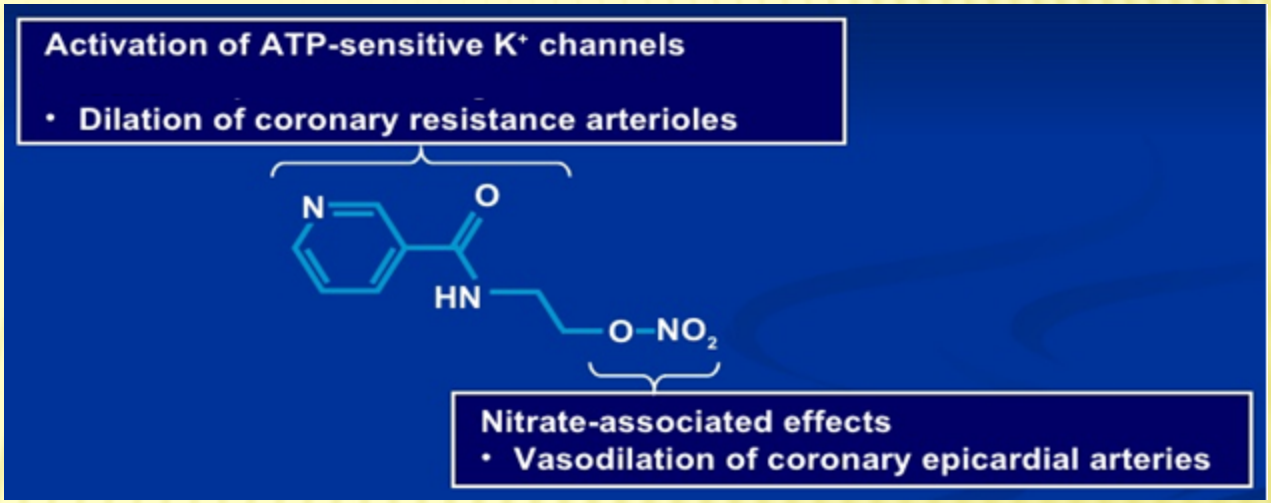
MINICASE

If Helmi does not respond to monotherapy, what other drug should be added to his regimen?

Potassium channel openners

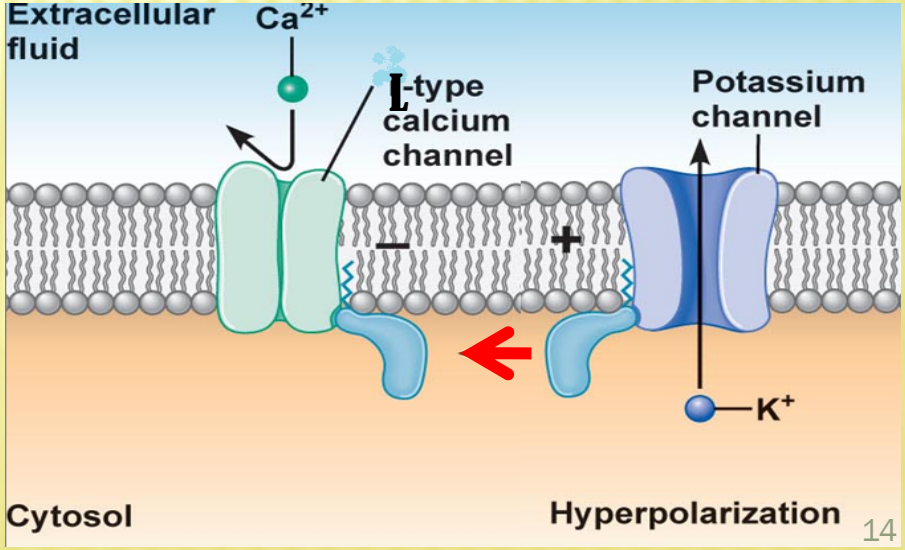
Nicorandil

Mechanism



It has dual mechanism of action;

1. Opens K_{ATP} channels (> arteriolar dilator)
2. NO donor as it has a nitrate moiety (> venular dilator)



Pharmacodynamic Effects

As K channel openner

On vascular smooth muscles opening of K channels ➔hyperpolarization ➔ vasodilatation

On cardiomyocytes opening of K channels ➔repolarization ➔↓ cardiac work

As nitric oxide donor

NO ↑ 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.

THINK-PAIR-SHARE

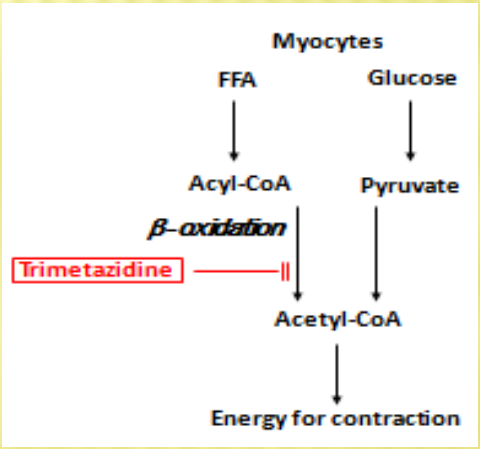
A 55 - year - old woman complained to her physician of palpitations, flushing of the face, and vertigo. The woman, suffering from diabetes mellitus, was giving herself three daily doses of insulin. She had been recently diagnosed with exertional angina for which nitrate therapy was started with transdermal nitroglycerin and oral isosorbide mononitrate.
After 3 weeks of therapy, her anginal attacks were less frequent but not completely prevented. Which would be an appropriate next therapeutic step for this patient?

Metabolically Acting Agents

e.g. Trimetazidine

O2 requirement of glucose pathway is lower than FFA pathway

During ischemia, oxidized FFA levels rise, blunting the glucose pathway



Reduces O2 demand without altering hemodynamics

Trimetazidine

Indications

Used as an add on therapy

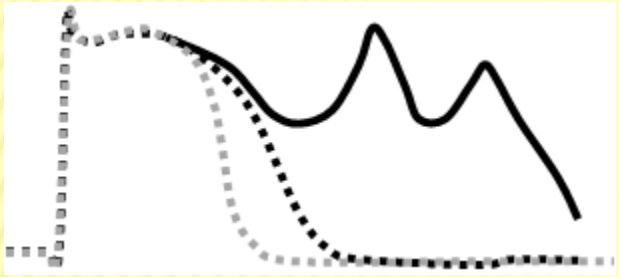
ADRs

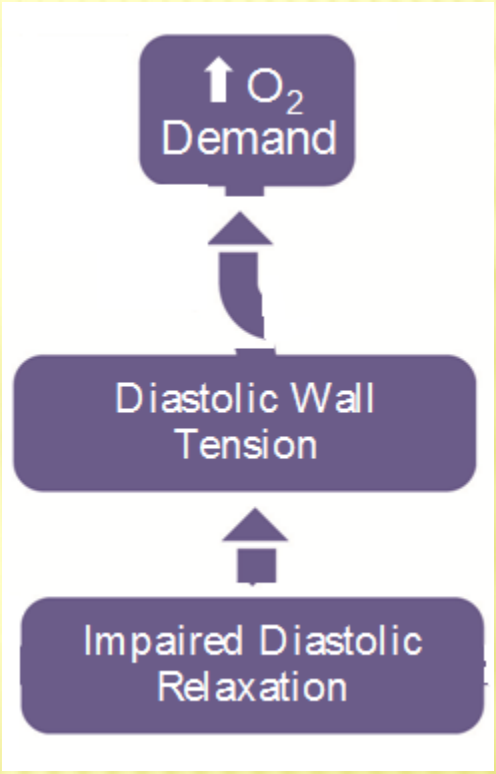
GIT disturbances

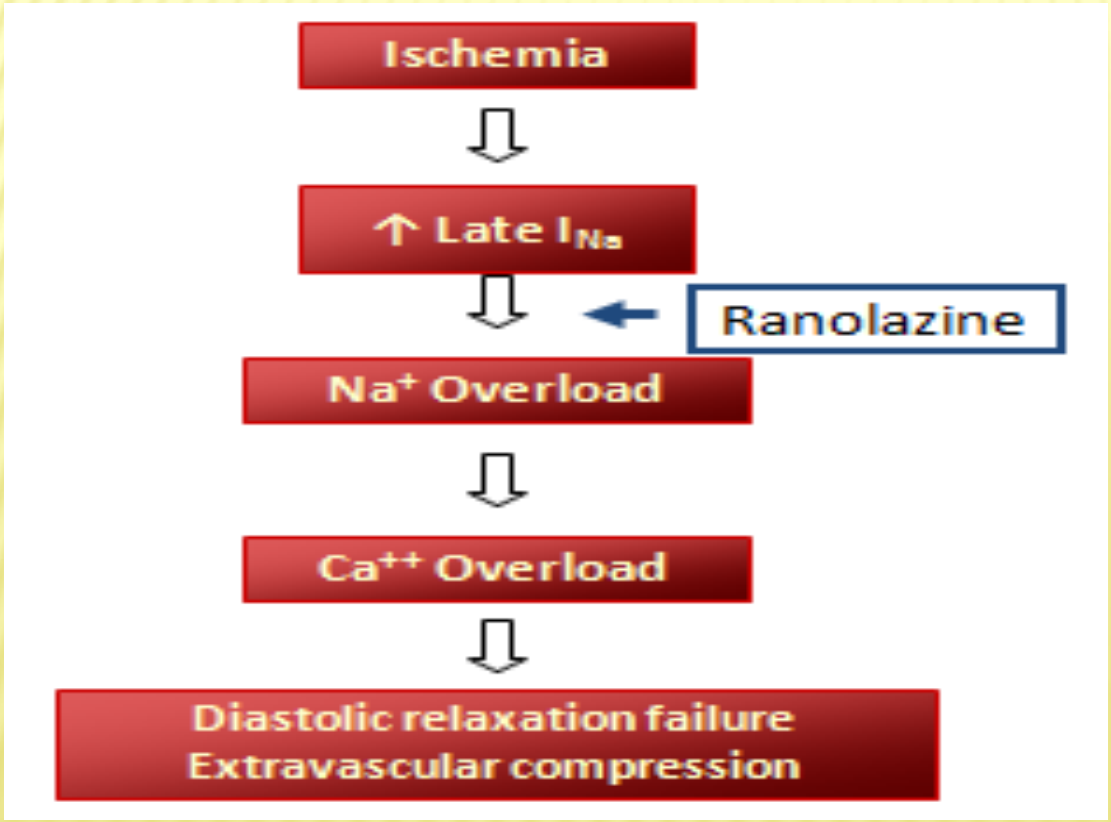
Contraindications

Hypersensitivity reaction

Pregnancy & lactation




↑ O_2 Demand
Diastolic Wall Tension
Impaired Diastolic Relaxation


Ischemia
↑ Late I_{Na}
Ranolazine
Na^+ Overload
Ca^{++} Overload
Diastolic relaxation failure
Extravascular compression

Ranolazine

Inhibits the late sodium current which increases during ischemia

It prolongs the QT interval so contraindicated with; Class Ia & III antiarrhthmics

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

ADRs:- dizziness & constipation

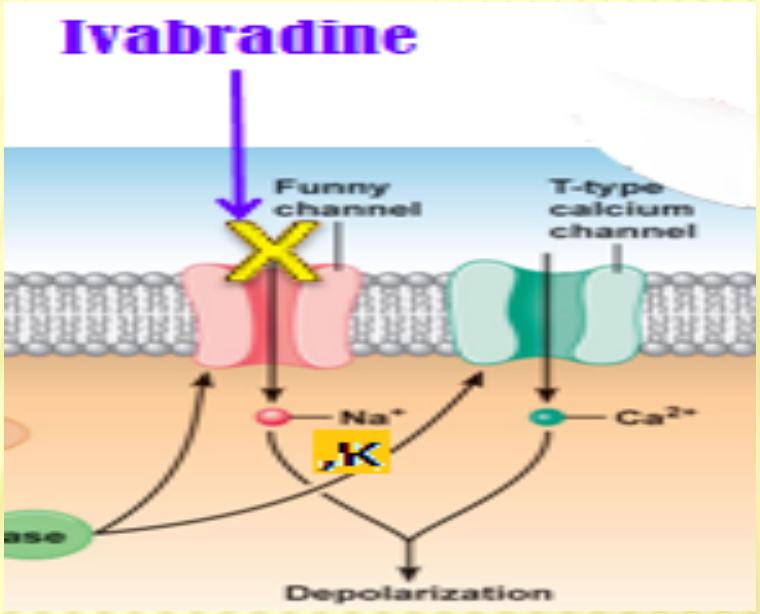
Used in chronic angina concomitantly with other drugs

MINICASE

Which antihyperlipidemic drug should be prescribed to Helmi?

Ivabradine

Ivabradine Selectively blocks I_f



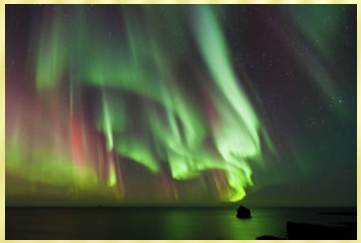
I_f current is an inward Na+/K+ current that activates pacemaker cells of the SA node

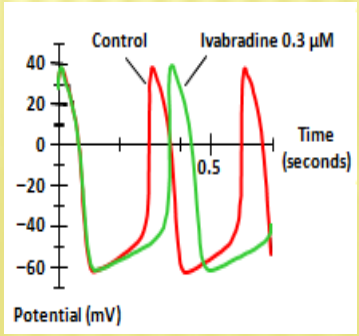
Ivabradine

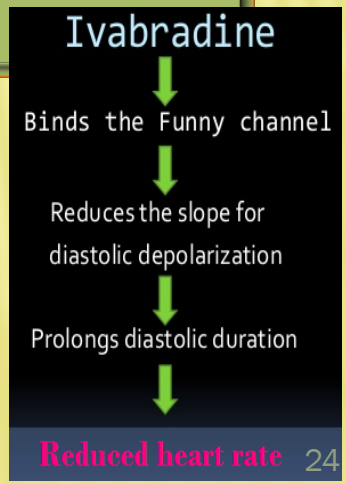
Ivabradine reduces slope of depolarization, slowing HR, reducing myocardila work & O2 demand

Used in treatment of chronic stable angina in patients with normal sinus rhythm who cannot take ß-blockers

Used in combination with beta blockers in people with heart failure with LVEF lower than 35 percent inadequately controlled by beta blockers alone and whose heart rate exceeds 70/min







ADR:- luminous phenomena

Agents that improve prognosis

-Aspirin / other antiplatelet agents
-ACE inhibitors
-Statins
-β -blockers

Halt progression
Prevent acute insult
Improve survival

MEMORY MATRIX

In the following table indicate increase, decrease or no effect with signs ↑, ↓, – respectively

Drug/Class	HR	BP	Wall Tension	Contract-ility	O_2 Supply
Beta-blockers					
CCBs					
Verap/Dilt					
Dihydropyridines					
Nitrates					
Ranolazine					