

# Newer antianginal drugs

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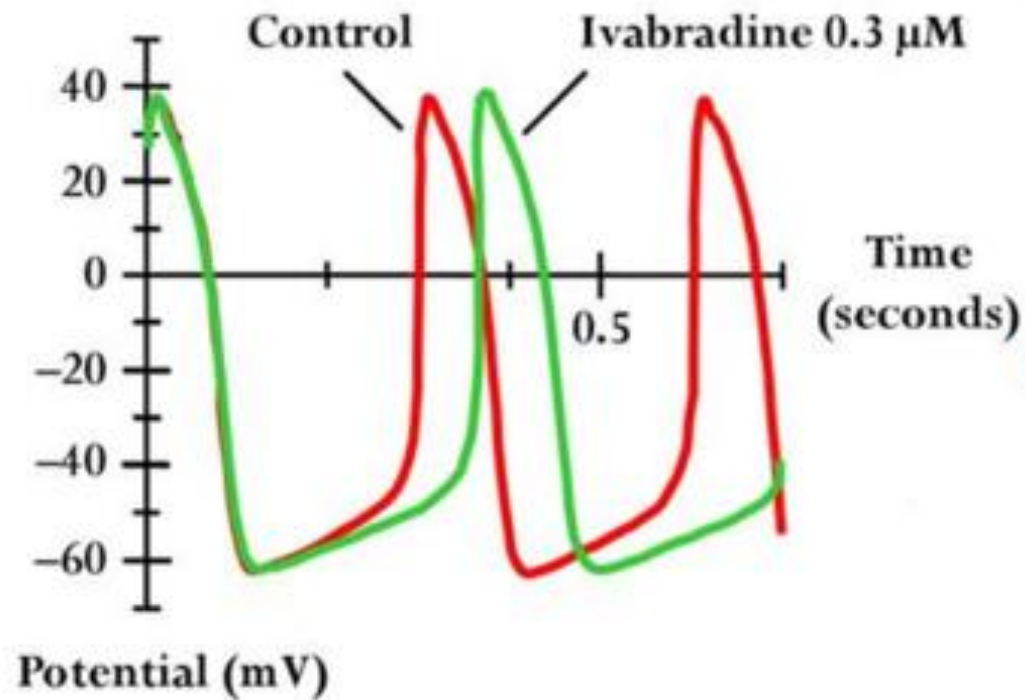


# Ivabradine

- Ivabradine selectively inhibits the  $I_f$  current, an important current involved in generating the early phase of spontaneous diastolic depolarization in sino-atrial cells, reducing the frequency of action potential initiation and lowering heart rate.
- It decreases the body's demand for myocardial oxygen, without any effect on blood pressure or myocardial contractility or conduction times, and results in a reduction in angina symptoms
- Ivabradine is metabolised by CYP3A4, there is drug interaction with CYP3A4 inhibitors and inducers.
- It is contraindicated to be used with verapamil and diltiazem.
- Used in HF



# Sinus node inhibition: Ivabradine



- $I_f$  current is an inward  $\text{Na}^+/\text{K}^+$  current that activates pacemaker cells of the SA node
- Ivabradine
  - Selectively blocks  $I_f$  in a current-dependent fashion
  - Reduces slope of depolarization, slowing HR



# Ivabradine

- It is 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 beats per minute.
- In people not sufficiently managed with beta blockers for their heart failure adding ivabradine decreases the risk of hospitalization for heart failure.



# Adverse effect

- Overall, 14.5% of patients taking ivabradine experience luminous phenomena, in which the patients described as sensations of enhanced brightness in a fully maintained visual field.
- This is probably due to blockage of  $I_h$  ion channels in the retina, which are very similar to cardiac  $I_f$ .
- In a large clinical trial, bradycardia occurred in 2% and 5% of patients taking ivabradine at doses of 7.5 and 10 mg respectively (compared to 4.3% in those taking atenolol).
- 2.6–4.8% reported headaches.
- blurred vision.

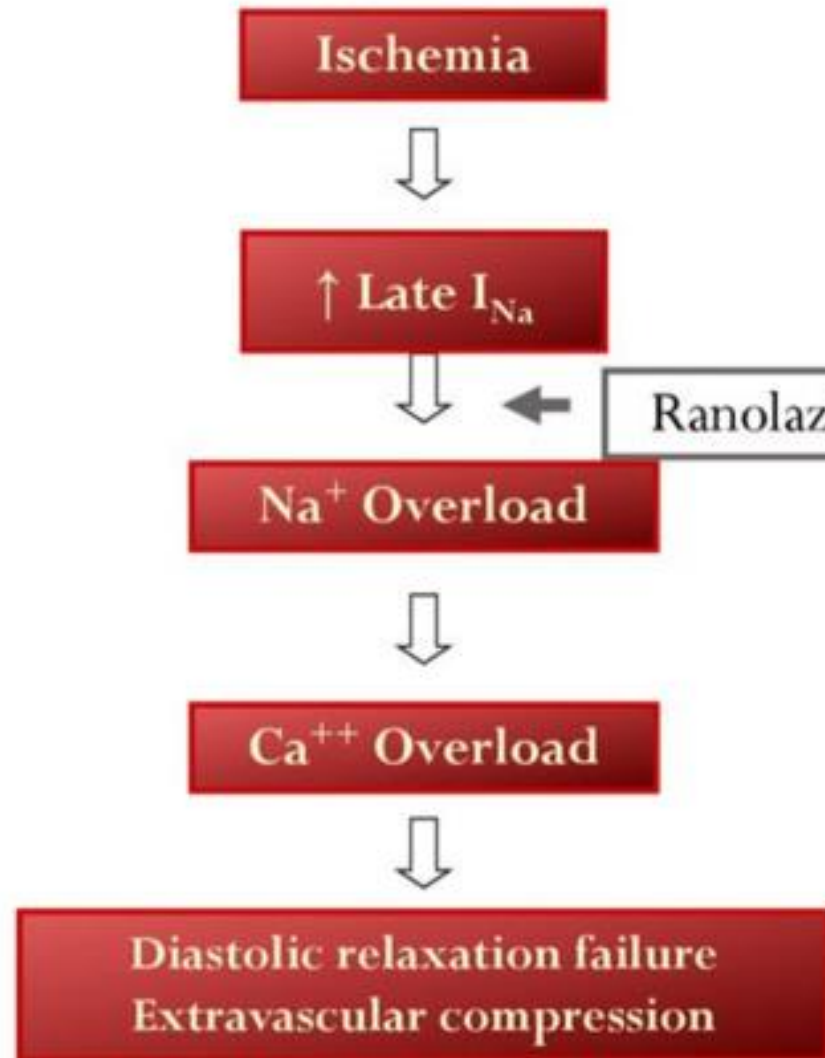


# Ranolazine

- It selectively inhibits the late sodium influx in the myocardium, reducing calcium overload, attenuating the ischaemic abnormalities of ventricular repolarisation and the resulting reduced contractility.
- It improves exercise tolerance while reducing the frequency of angina episodes.
- Can improve myocardial ischaemia without affecting heart rate or blood pressure.



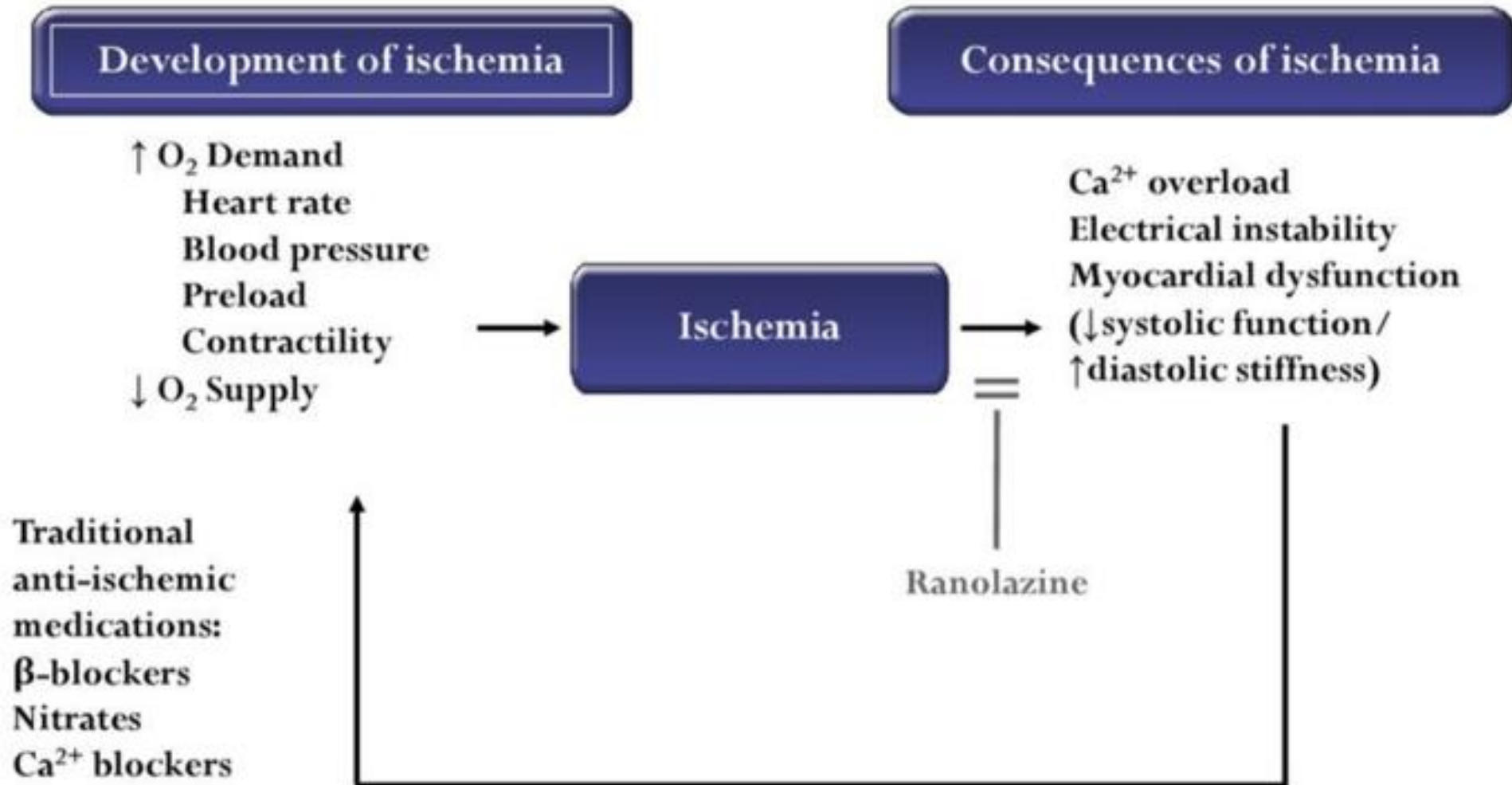
# Understanding Angina at the Cellular Level



- Ischemia impairs cardiomyocyte sodium channel function
- Impaired sodium channel function leads to:
  - Pathologic increased late sodium current
  - Sodium overload
  - Sodium-induced calcium overload
- Calcium overload causes diastolic relaxation failure, which:
  - Increases myocardial oxygen consumption
  - Reduces myocardial blood flow and oxygen supply
  - Worsens ischemia and angina



# Myocardial ischemia: Sites of action of anti-ischemic medication





## Pharmacologic Classes for Treatment of Angina

Medication Class	Impact on HR	Impact on BP	Physiologic Mechanism
Beta Blockers	↓	↓	Decrease pump function
Calc Channel Blockers	↓	↓	Decrease Pump function + Vaso-dilatation
Nitrates	↑	↓	Vaso-dilatation
Ranolazine	—	—	Reduced Cardiac Stiffness



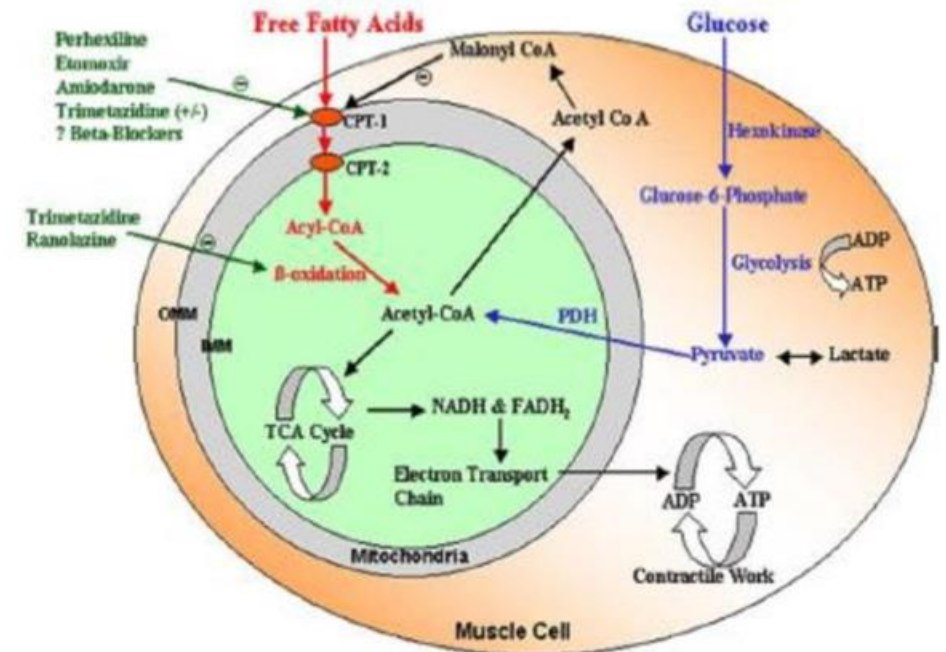
# Ranolazine and QT

- Ranolazine slightly increased QT interval in some patients and the FDA label contains a warning for this effect.
- The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of  $I_{Kr}$ , which prolongs the ventricular action potential.
- The drug's effect on the QT interval is increased in the setting of liver dysfunction; thus it is contraindicated in persons with mild to severe liver disease.

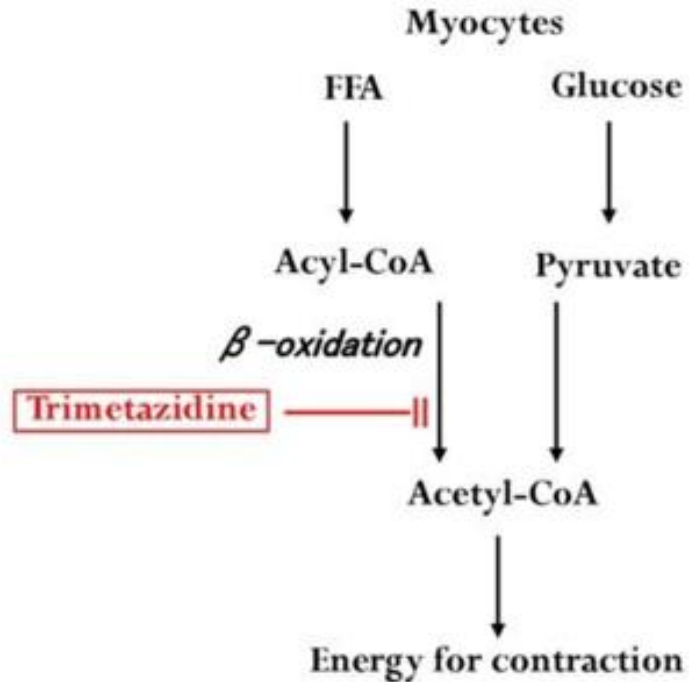


# Trimetazidine

- Inhibition of the reduction of adenosine triphosphate, stimulation of glucose consumption by the myocardium
- It has very limited haemodynamic effect but can cause symptoms of Parkinsonism. Therefore, among its main contraindications is Parkinson's disease.



# Metabolic modulation (pFOX): Trimetazidine



- O<sub>2</sub> requirement of glucose pathway is lower than FFA pathway
- During ischemia, oxidized FFA levels rise, blunting the glucose pathway

pFOX = partial fatty acid oxidation  
FFA = free fatty acid



# Trimetazidine

- Parkinsonian
- 
- Extrapyrarnidal: symptoms such as tremor, rigidity, akinesia, hypertonia.

Restless leg syndrome

- Not to prescribe to patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome.



# Nicorandil

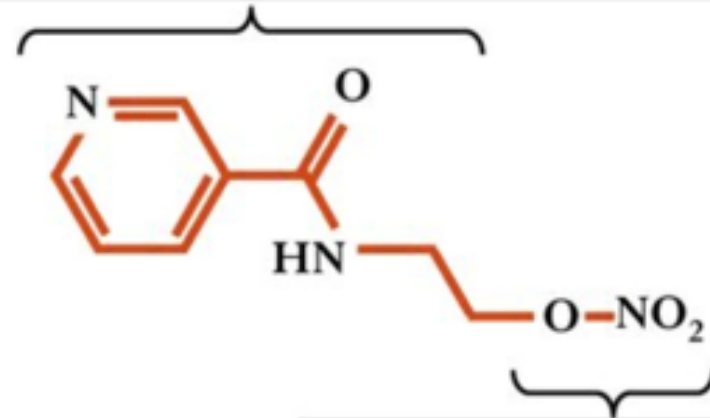
- It increases cyclic guanosine monophosphate and facilitates the opening of mitochondrial potassium adenosine triphosphate channels.
- Nicorandil is considered as a second-line option to treat patients with stable angina when they do not tolerate or cannot use beta-blockers (or calcium channel antagonists such as verapamil and diltiazem) or when they do not respond enough to first-line medications.
- Among the adverse effects are gastrointestinal, skin and mucosal ulcerations (especially if there is concomitant use of acetylsalicylic acid or non-steroidal anti-inflammatory drugs). In this case, the drug should be discontinued permanently



# Preconditioning: Nicorandil

Activation of ATP-sensitive  $K^+$  channels

- Ischemic preconditioning
- Dilation of coronary resistance arterioles



Nitrate-associated effects

- Vasodilation of coronary epicardial arteries

