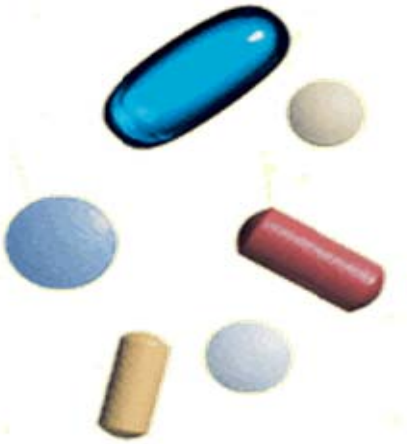
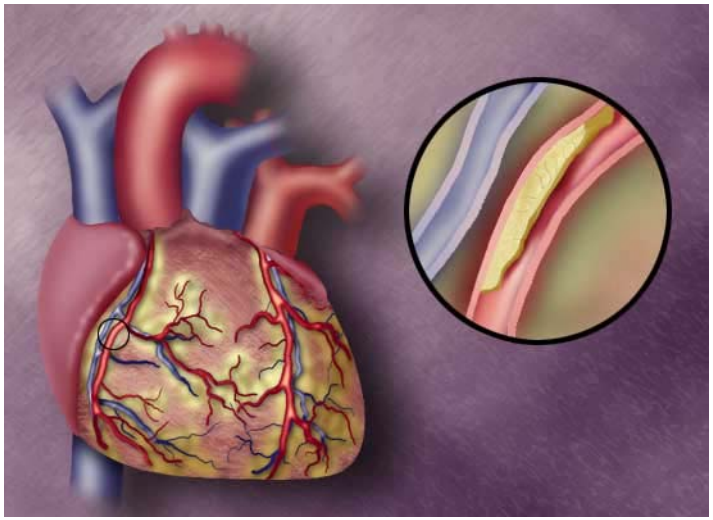
Drug therapy of Angina Pectoris





Coronary Artery Disease

- **Coronary Artery Disease /Coronary atherosclerotic heart disease/ Ischaemic heart disease.**
- **Risk factors for CAD/CHD**
- **Clinical manifestations of CAD**

Angina pectoris

◆ Definition

Angina pectoris is a primary symptom of myocardial ischemia, which is the severe chest pain that occurs when coronary blood flow is inadequate to supply the oxygen required by the heart.

Angina pectoris

◆Typical Symptoms

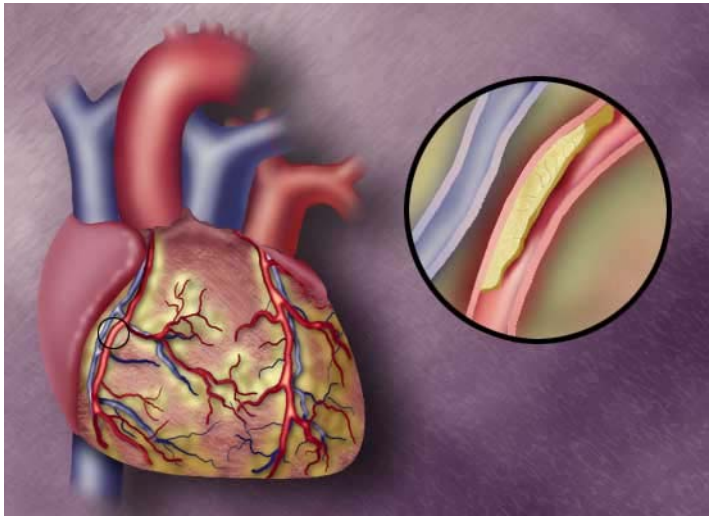
a heavy strangulation or pressure-like sensation, sometimes may feel like indigestion, usually located in retrosternal area , often radiating to the left shoulder, left arm, jaw , neck, epigastrium or back.

Clinical Classifications of angina

- Stable angina pectoris
- Unstable angina pectoris
- Prinzmetal's /Variant angina pectoris

1.Stable angina

- Is caused by narrowed arteries due to atherosclerosis
- Occurs when there is exertion /effort
- Episodes of pain tend to be alike
- Usually lasts a short time
- Is relieved by rest or antianginals



2. Prinzmetal, Variant ,vasospastic angina

- **Usually occurs at rest**
- **Tend to be severe**
- **Is caused by a transient spasm in a coronary artery**
- **Is relieved by anti-anginal drugs.**

3. Unstable angina

- Often occurs at rest
- Is more severe and lasts longer than stable angina
- Episodes of pain tend to be changing in the character,ie increasing severity (cresendo angina) , frequency, duration as well as precipitating factors

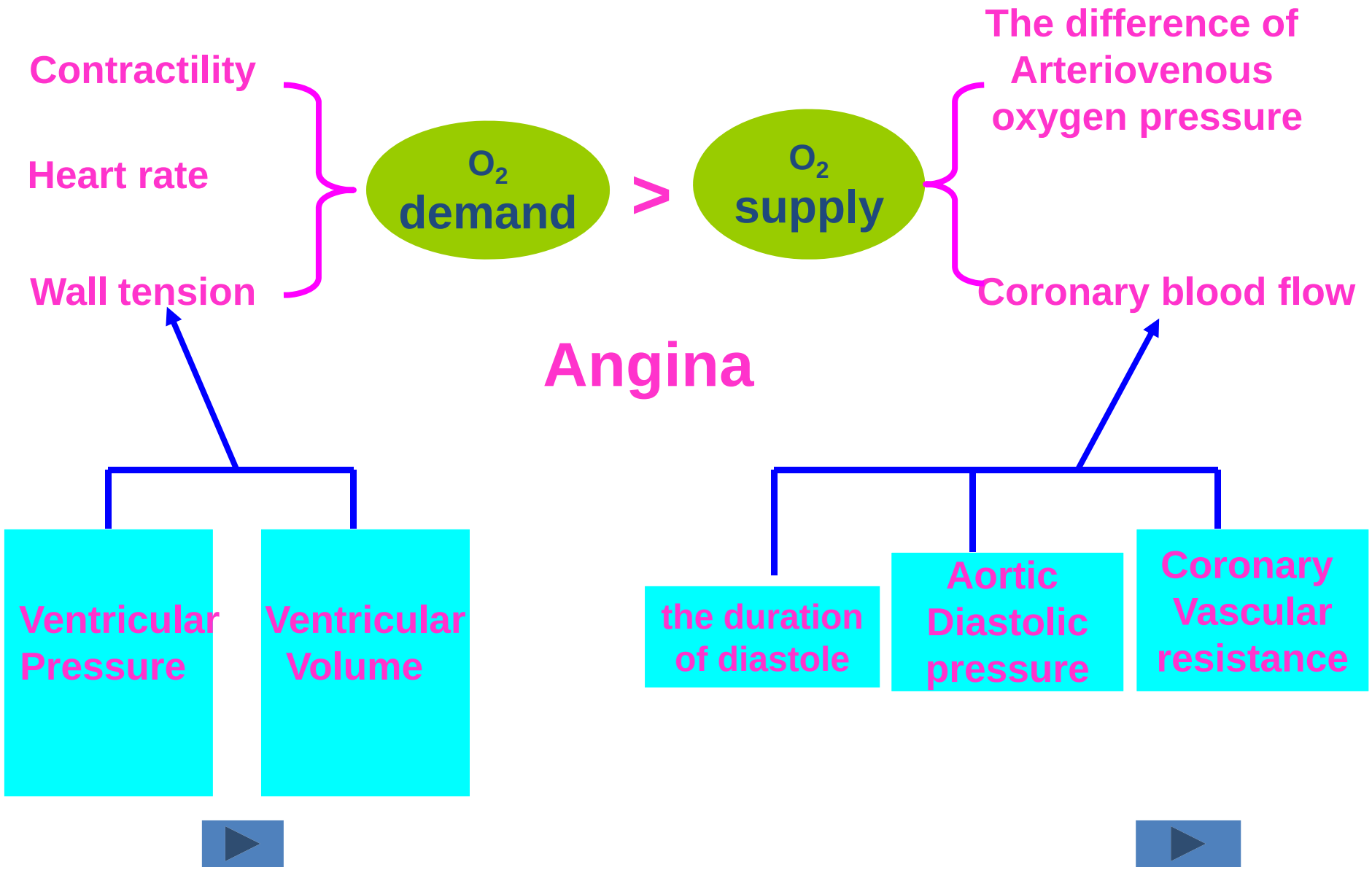
Acute Coronary Syndromes

- Is an emergency
- Occurs due to rupture of an atherosclerotic plaque& partial/complete thrombosis of a coronary artery.
- If thrombus occludes coronary vessel signif.--- necrosis of cardiac ms: MI
- May present as Unstable angina or Myocardial infarction.

Pathophysiology of angina

◆ **An imbalance between the myocardial oxygen supply and demand.**

Factors affecting myocardial oxygen demand and oxygen supply



Indirect measure of myocardial oxygen consumption

- **Double product:**

  heart rate x systolic blood pressure

- **Triple product:**

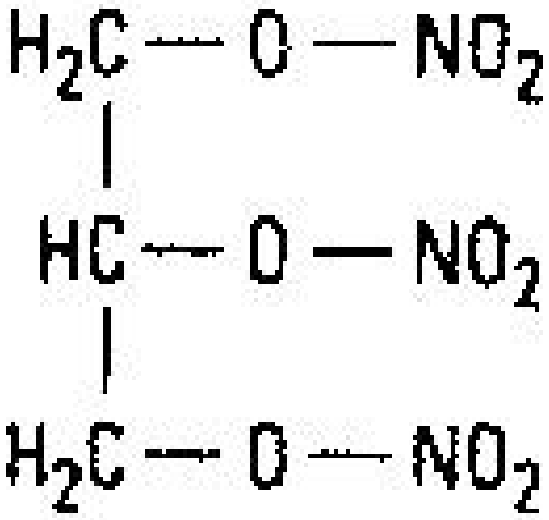
  systolic blood pressure × heart rate x ejection time

Treatment of angina pectoris

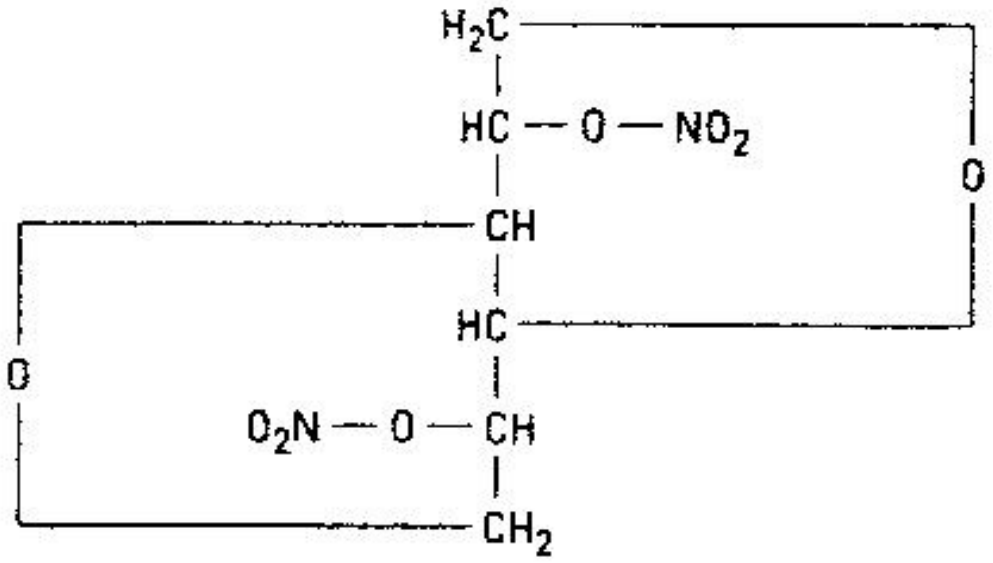
- **Lifestyle changes**
- **Drugs:**
- **Nitrates**
- **β-blockers**
- **Calcium channel blockers**
- **Misc:**
- **Potassium ch openers, Trimetazidine, Ranolazine, Ivabradine**
- **Surgery :**
- **CABG (coronary artery bypass graft)**
- **PTCA (percutaneous transluminal coronary angioplasty)**

Organic Nitrates/ Nitrovasodilators

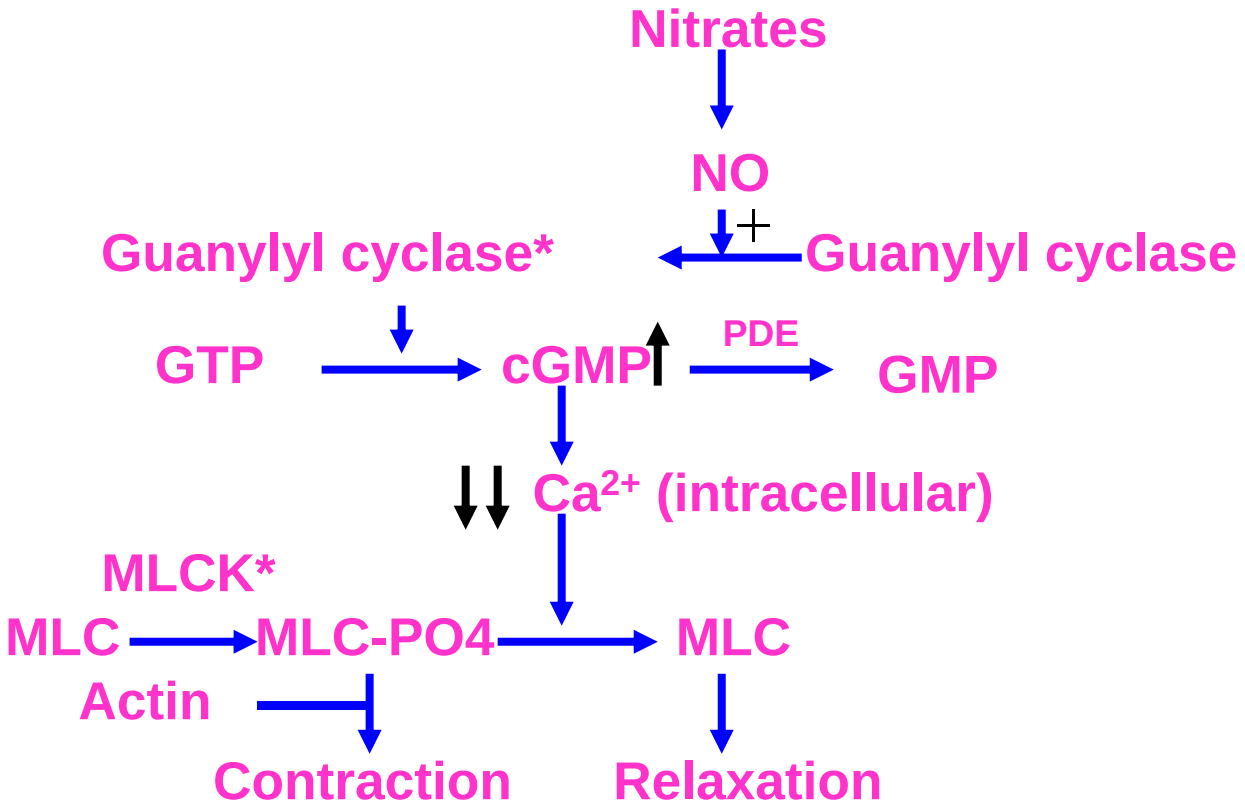
Nitroglycerine



Isosorbide dinitrate



Mechanisms of action



(MLCK-myosin light chain kinase

Pharmacokinetics

Absorption oral bioavailability 10-20%

ISMN- 100%

Metabolism liver by glutathione –organic nitrate reductase.

Excretion kidney

Table 20.1 Dosage Forms, Onset of Action and Duration of Effect of Organic Nitrates used in Angina

Drug & Route	Dose (mg)	Onset (min)	Duration (hrs)
NITROGLYCERINE			
- Sublingual	0.5	2–5	0.25–0.5
- Oral*	5–15	20–30	4–8
- Ointment (2%)	–	15–30	3–8
- Transdermal	5–10 mg/24 hr	30–40	Max. 24 hr
ISOSORBIDE DINITRATE			
- Sublingual	5–10	5–15	1–2
- Oral*	10–20	30–60	2–4
ISOSORBIDE MONONITRATE			
- Oral*	20–40	15–30	6–10
ERYTHRITYL TETRANITRATE			
- Sublingual	5–10	5–15	2–4
- Oral	10–30	30	2–6
PENTAERYTHRITOL TETRANITRATE			
- Oral*	10–20	30	5–10

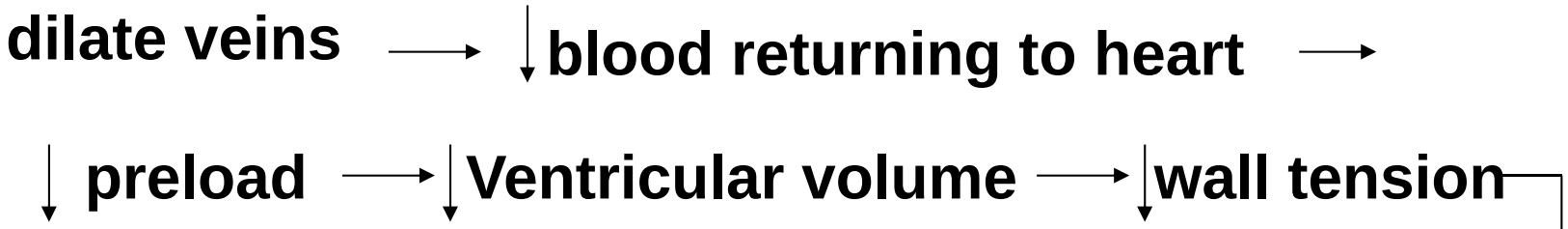
*Longer acting sustained release preparations are also available

Pharmacological actions of organic Nitrates

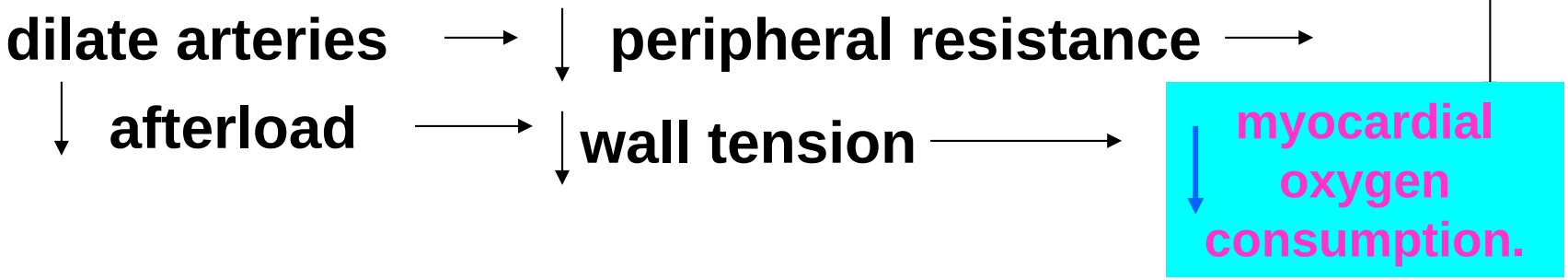
1. Dilate vascular smooth muscle, decrease myocardiac oxygen consumption

- dilate veins
- dilate arteries (higher conc)

at minimal effective dose:

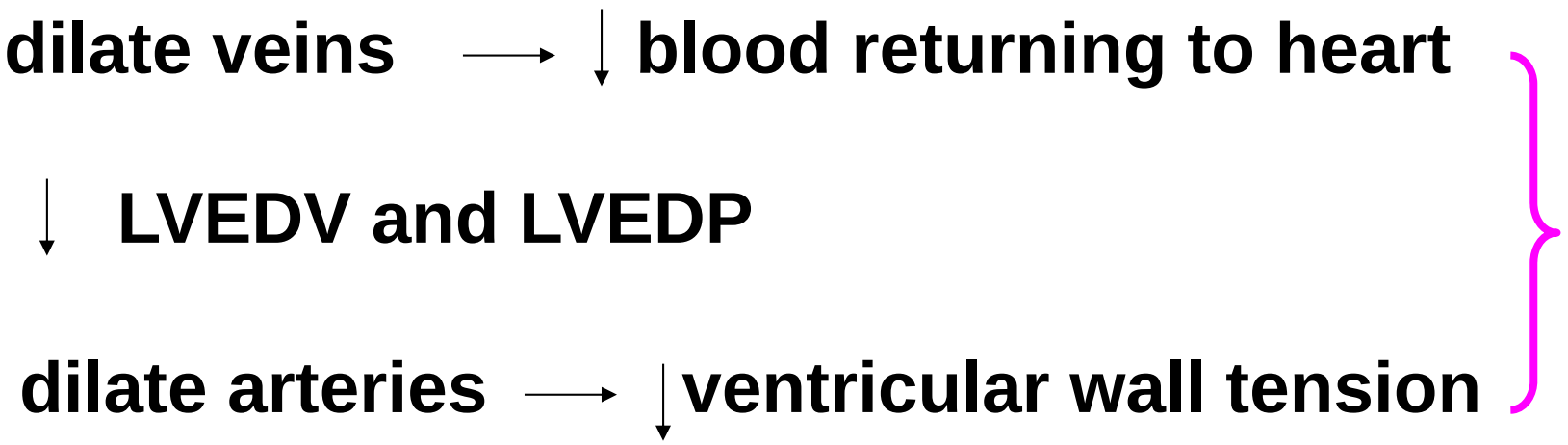


at higher dose:

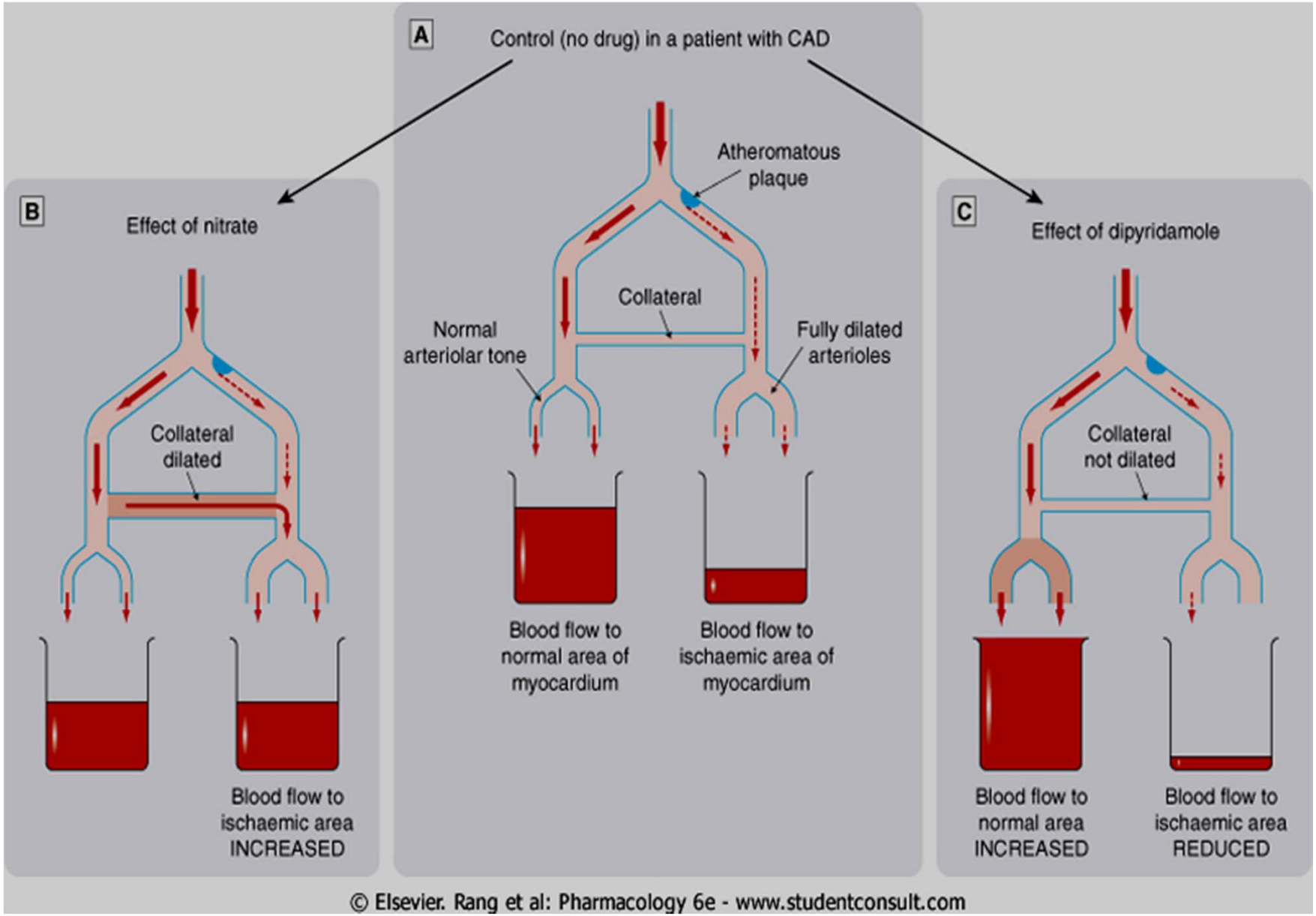


2. Increase blood supply to ischemic area

- **Increase subendocardium blood flow**
- **Redistribution of coronary blood flow**

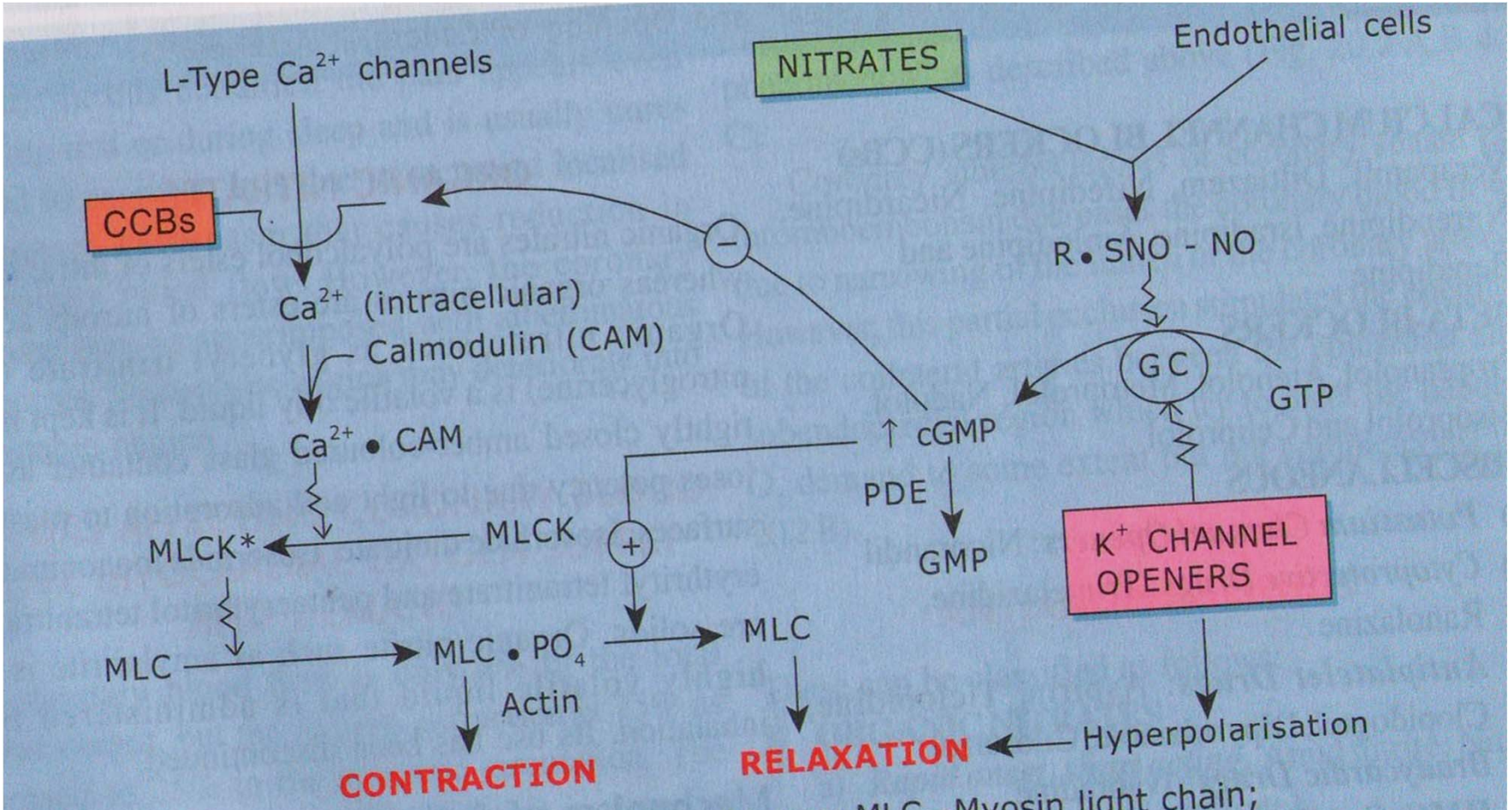


blood flows from epicardium to endocardium



Nitrates…

3. Protect the ischemic cardiac myocytes, inhibit platelet aggregation and adhesion，decrease ischemic damage

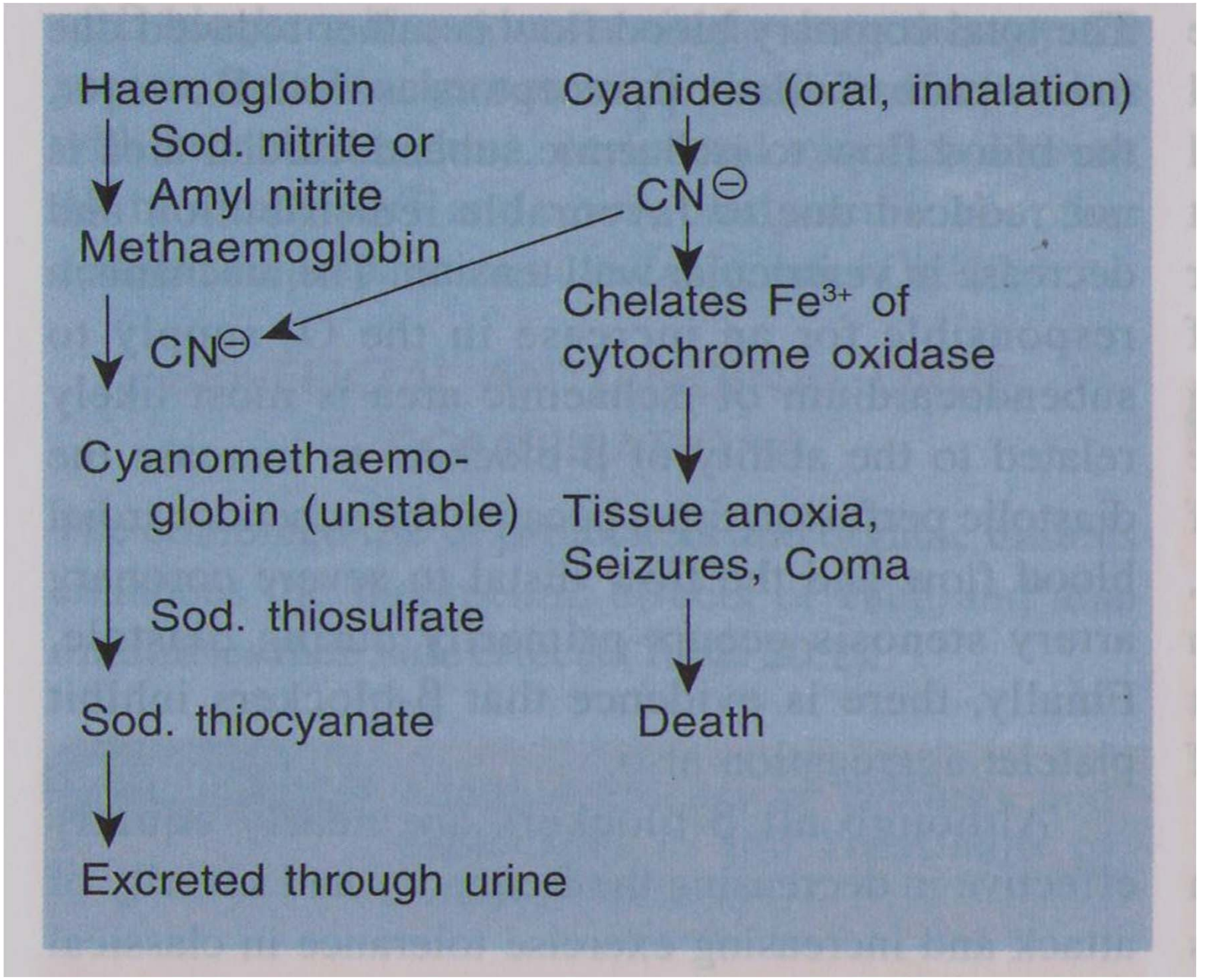


Key: MLCK*—Activated myosin light chain kinase; MLC—Myosin light chain; MLC • PO_4—Phosphorylated mysosin light chain; GC—Activated guanylyl cyclase; PDE—Phosphodiesterase enzyme

Fig 20.3 Mechanism of Action of Calcium Channel Blockers (CCBs), Organic Nitrates and Potassium Channel Openers.

Clinical uses

- **All types of angina**
- **Acute myocardial infarction**
- **Heart failure**
- Cyanide poisoning
- Biliary colic
- Esophageal spasm


Haemoglobin
Sod. nitrite or
Amyl nitrite
Methaemoglobin
CN⊖
Cyanomethaemo-
globin (unstable)
Sod. thiosulfate
Sod. thiocyanate
Excreted through urine
Cyanides (oral, inhalation)
CN⊖
Chelates Fe3+ of
cytochrome oxidase
Tissue anoxia,
Seizures, Coma
Death

Nitrates : ADRs

Throbbing headache ,Flushed appearance, Orthostatic hypotension ,Tachycardia

Methemoglobinemia

Monday disease (M morning sickness)

- Drug interactions

Sidenafil , Tadalafil, vardenafil (PDE V inhibitors) potentiate axn : dangerous hypotension.

Nitrate Tolerance

The requirement for the dose of a drug becomes higher to achieve the same pharmacological effect.

Develops rapidly when long acting prep. (oral, TTS) or continous IV inf used for more than a few hrs without interruption.

Mechanism:

- Vascular SH depletion
- Free radical hypoth.: peroxynitrite
- Neurohormonal hypoth.: venodilation--- compensatory vasoconstriction d/t activ. Of RAS

Tolerance: Prevention

"As is often true in matters of heart , absence makes the heart grow fonder"- *Opie,1991*

Interval dosing with eccentric doses providing a nitrate-free intreval of 10-12 hours should be observed to reduce or prevent tolerance.

- Others (less consistent effects) : Co-therapy with ACE inhibitors, Carvedilol, hydralazine, vit C .

Antianginals: Beta-adrenoceptor Blocking Drugs

- Not vasodilators
- Nonselective β-blockers:

  Propranolol, Pindolol, Timolol….

- Selective β_1-blockers:

  Atenolol, Metoprolol, Acebutolol….

Beta-adrenoceptor Blockers
Antianginal actions

Decrease myocardial oxygen consumption

- **blockβ- → decrease heart rate, contractility, and blood pressure → decrease myocardial oxygen consumption.**

Improve blood supply to the ischemic area

- **decrease myocardial oxygen consumption, promote the blood supply to the compensative dilating ischemic area**
- **decrease heart rate, increase diastolic perfusion time, blood flow from epicardium to endocardium**

Beta blockers:Antianginal action

Also Decrease myocardial free fatty acid production → improve myocardial metabolism

These agents decrease mortality of pt with recent MI & improve survival & prevent stroke in pt of HT.

Better outcomes than CCBs in pt with stable angina.

Disadvantages

- 1. decrease contractility → eject time ↑, ventricular volume ↑ → O_2consumption ↑
- 2. block **β_2- R** on coronary artery → coronary artery contract → coronary blood flow ↓
- These deleterious effects are balanced by using nitrates concomitantly

Clinical uses

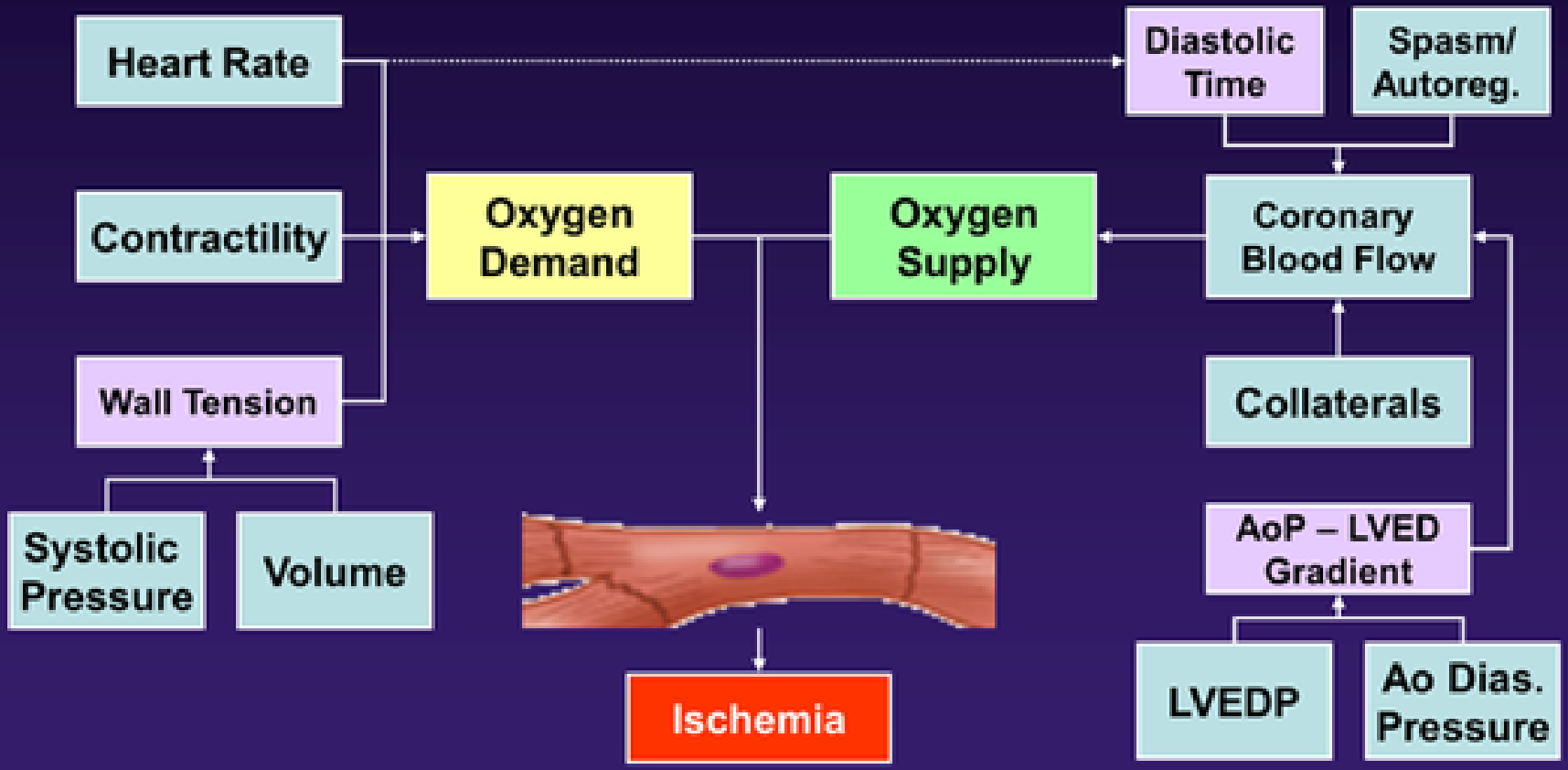
- Stable and unstable angina
- Myocardial infarction

  Combined with nitroglycerin
- Variant angina pectoris: CI
- Other Contraindications:
- Adverse Effects:

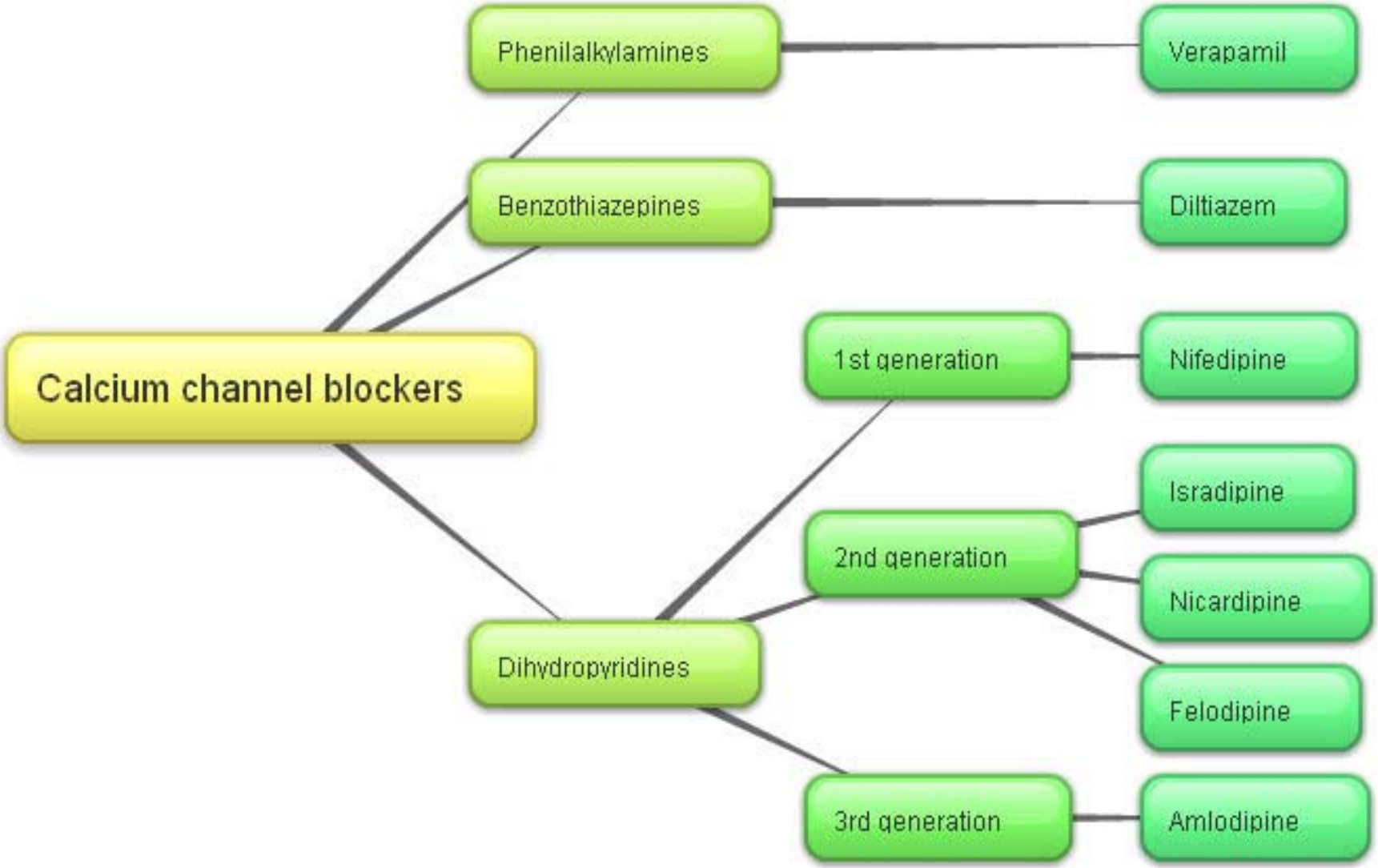
Table 20.2 Additive Efficacy of Nitrates and β-Blockers in the Treatment of Angina Pectoris

Parameters	Nitrates	β-Blockers	Combined Efficacy
1. Heart rate	↑	↓	± or ↓
2. Contractility	↑	↓	±
3. Arterial pressure	↓	↓	↓↓
4. End-diastolic volume	↓	↑	±
5. Ejection time	↓	↑	±
6. Coronary blood flow	↑	↓	± or ↑
7. Subendocardial ischaemic area blood flow	↑	± or ↑	↑
8. Collateral blood flow	↑	±	↑
9. Myocardial wall tension	↓	±	↓
10. Ventricular volume	↓	↑	±
11. Heart size	↓	↑	±

Factors Influencing the Development of Angina Pectoris: Targets for Therapy



Adapted from Morrow, Gersh, Braunwald. Chronic Coronary Artery Disease. *In Heart Disease*, 7th Ed. Zipes, Libby, Bonow, Braunwald, eds.


Calcium channel blockers
Phenilalkylamines
Verapamil
Benzothiazepines
Diltiazem
Dihydropyridines
1st generation
Nifedipine
2nd generation
Isradipine
Nicardipine
Felodipine
3rd generation
Amlodipine

Calcium channel-blocking drugs

Mechanisms of Antianginal actions

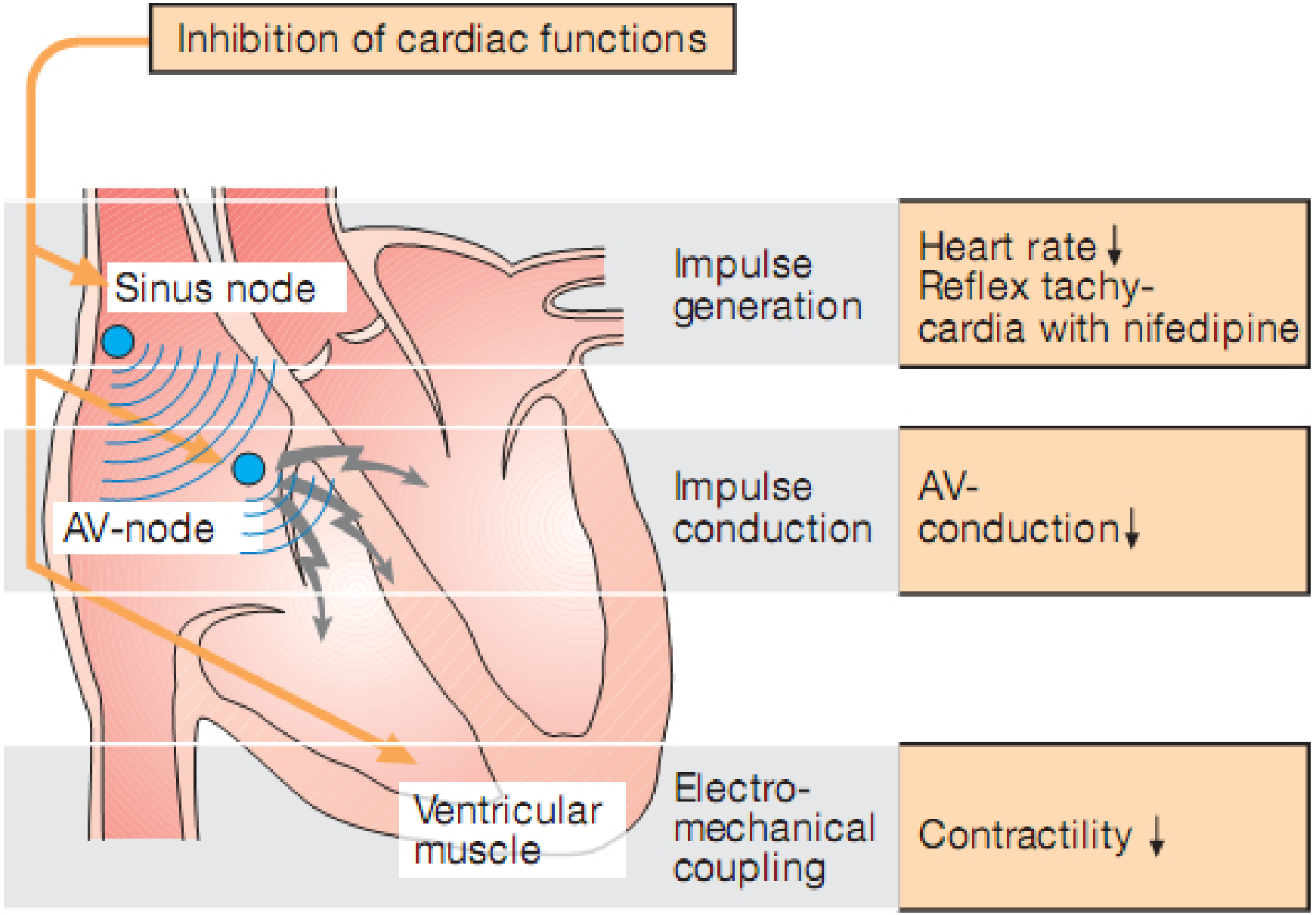
- **Decrease myocardial oxygen consumption**

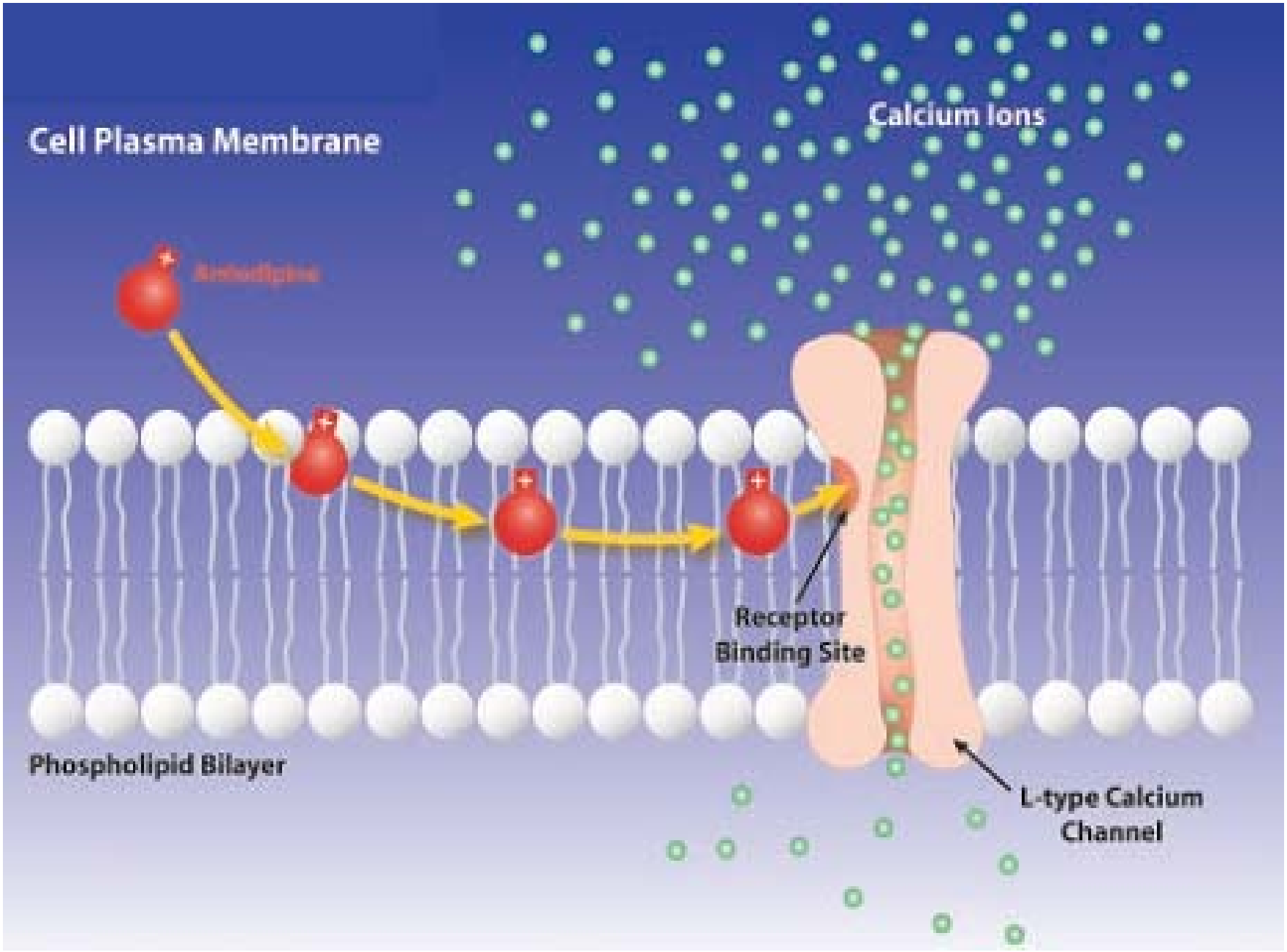
  ↓**heart rate and contractility; vasodilation; antisympathetic action**

- **Improve the blood supply to the ischemia**

  Dilate coronary artery, decrease the platelet aggregation

- **Protect ischemic cardiac myocytes**
- **Antiatherosclerosis**

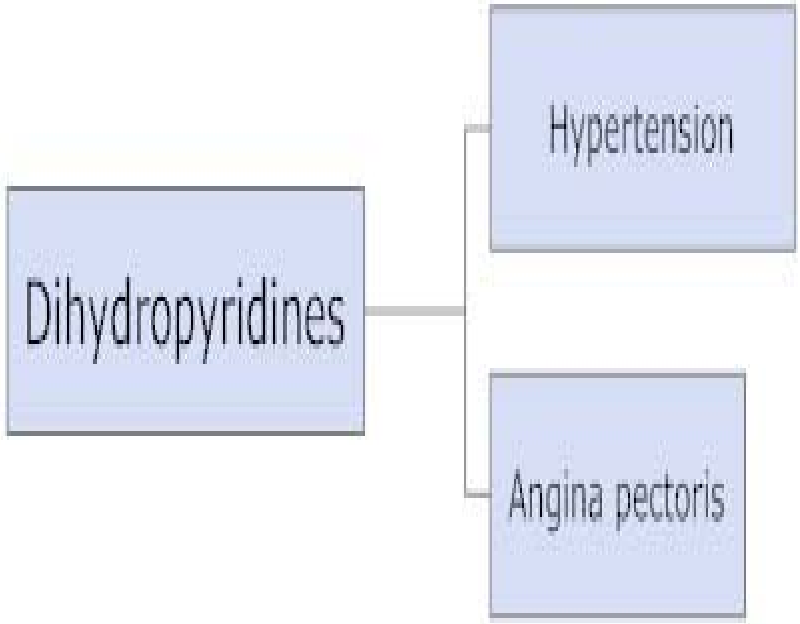

Inhibition of cardiac functions
Sinus node
AV-node
Ventricular muscle
Impulse generation
Impulse conduction
Electro-mechanical coupling
Heart rate ↓
Reflex tachy-cardia with nifedipine
AV-conduction ↓
Contractility ↓


Cell Plasma Membrane
Calcium Ions
Amlodipine
Receptor
Binding Site
Phospholipid Bilayer
L-type Calcium
Channel

Clinical uses

Antianginal effect is similar to β-blockers,

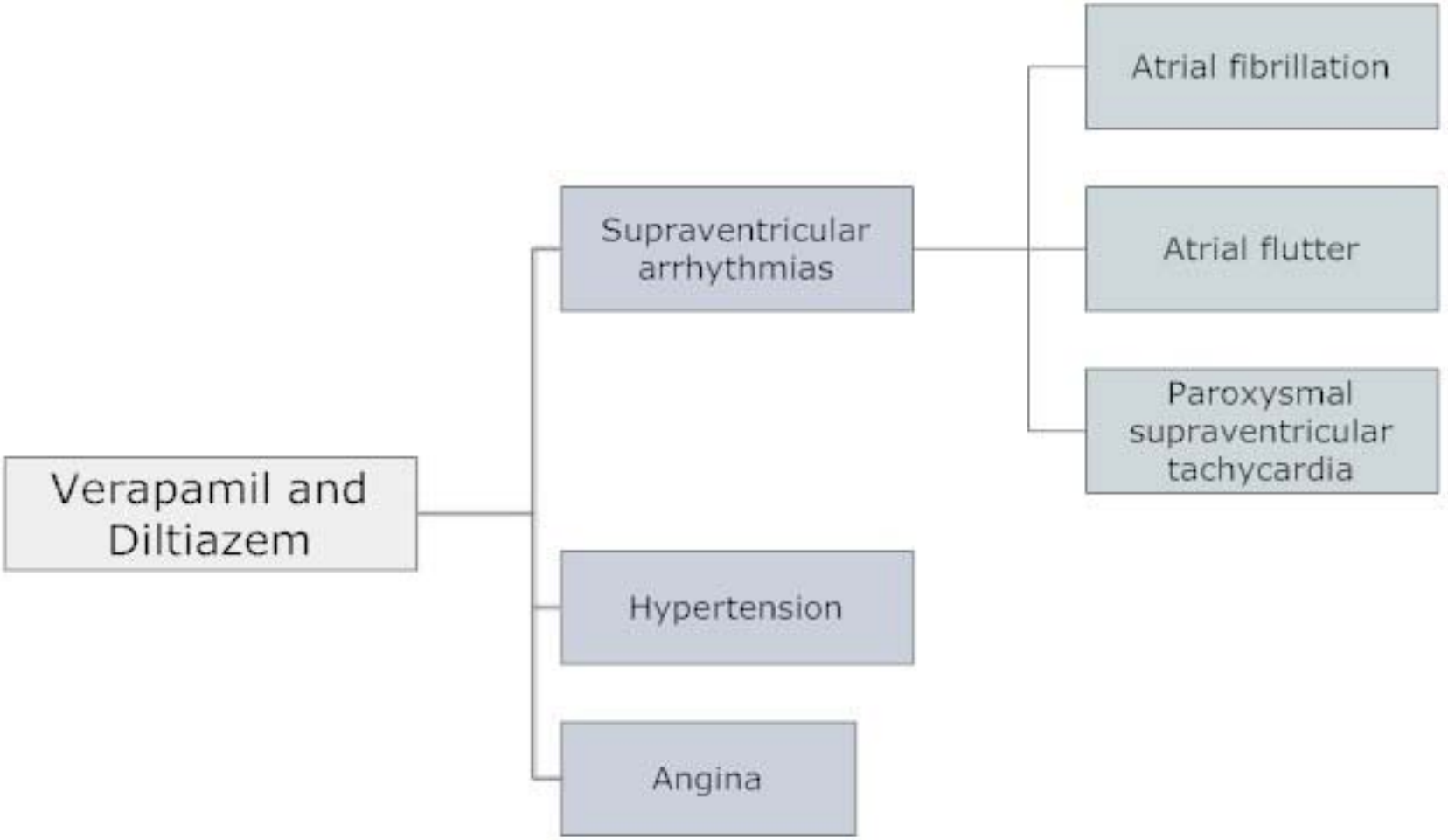
- **Suited for the anginal patient with asthma**
- **Variant angina first choice**
- **Suited for the anginal patient with surrounding blood vessel spasm**


Dihydropyridines
Hypertension
Angina pectoris

Nifedipine

- **Variant angina strongest action**
- **Stable angina**

  Combined with β-blokers


Verapamil and Diltiazem
Supraventricular arrhythmias
Atrial fibrillation
Atrial flutter
Paroxysmal supraventricular tachycardia
Hypertension
Angina

Verapamil

- Weaker for dilating peripheral vessels
- Inhibit the heart
- Used for stable angina and variant angina combined with other drugs
- Contraindications:
  - heart failure
  - atrioventricular blockade

Diltiazem

- **Moderate , used for all types of angina**
- **Anginal patient with heart failure, atrioventricular blockade caution**

Misc. Antianginal Drugs

- **Potassium channel openers**:
- Types of K ch: Voltage gated {vasular & other SM}, Ca activated, ATP activated{ cardiac ms & Beta cells of pancreas: opening causes hyperpolariz & relaxn of cardiac SM; others
- Nicorandil: Newer agent, Activates ATP sensitive K ch (K_{ATP}) & hyperpolarizes VSM. Decreases pre- & afterload & prod coronary dilation. Has nitrate –like moiety, also exerts nitrate like effect. Thus arteriodilator + venodilator. But no tolerance.

Nicorandil…

- Simulates “ischaemic preconditioning” d/t activ of mitochondrial $K_{ATP\ Ch.}$
- PK: Well absb PO, almost completely metab in liver,biphasic elimin. Used in vasospastic & chronic stable angina . Dose ; 10-20 mg BD PO
- A/E: flushing , palpitations ,dizziness, headache, stomatitis, N,V ,apthous ulcers
- DI :Not to be used with sildenafil
- CI: pt in cardiogenic shock, Hypotension

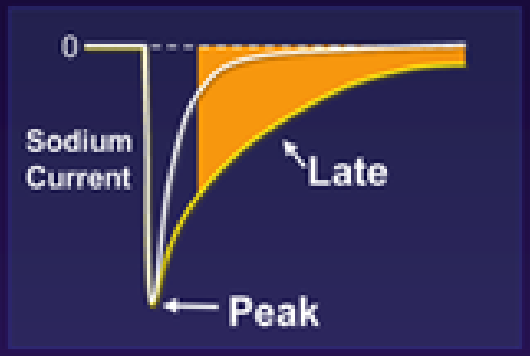
Cytoprotective agents

- Trimetazidine: Acts non-haemodynamically , prevents degradation of membrane unsaturated fatty acids by lipid peroxidation—reduces myo O2 demand- pFOX inhibitor
- Also inhibits superoxide cytotoxicity- protects myo from harmful effects of ischaemia.
- PK: Absb PO, partly metab in liver , mainly excreted unchanged in urine.
- A/E : GI irritation,fatigue,dizziness,reversible parkinsonism in elderly.Use : stable angina,

Ranolazine

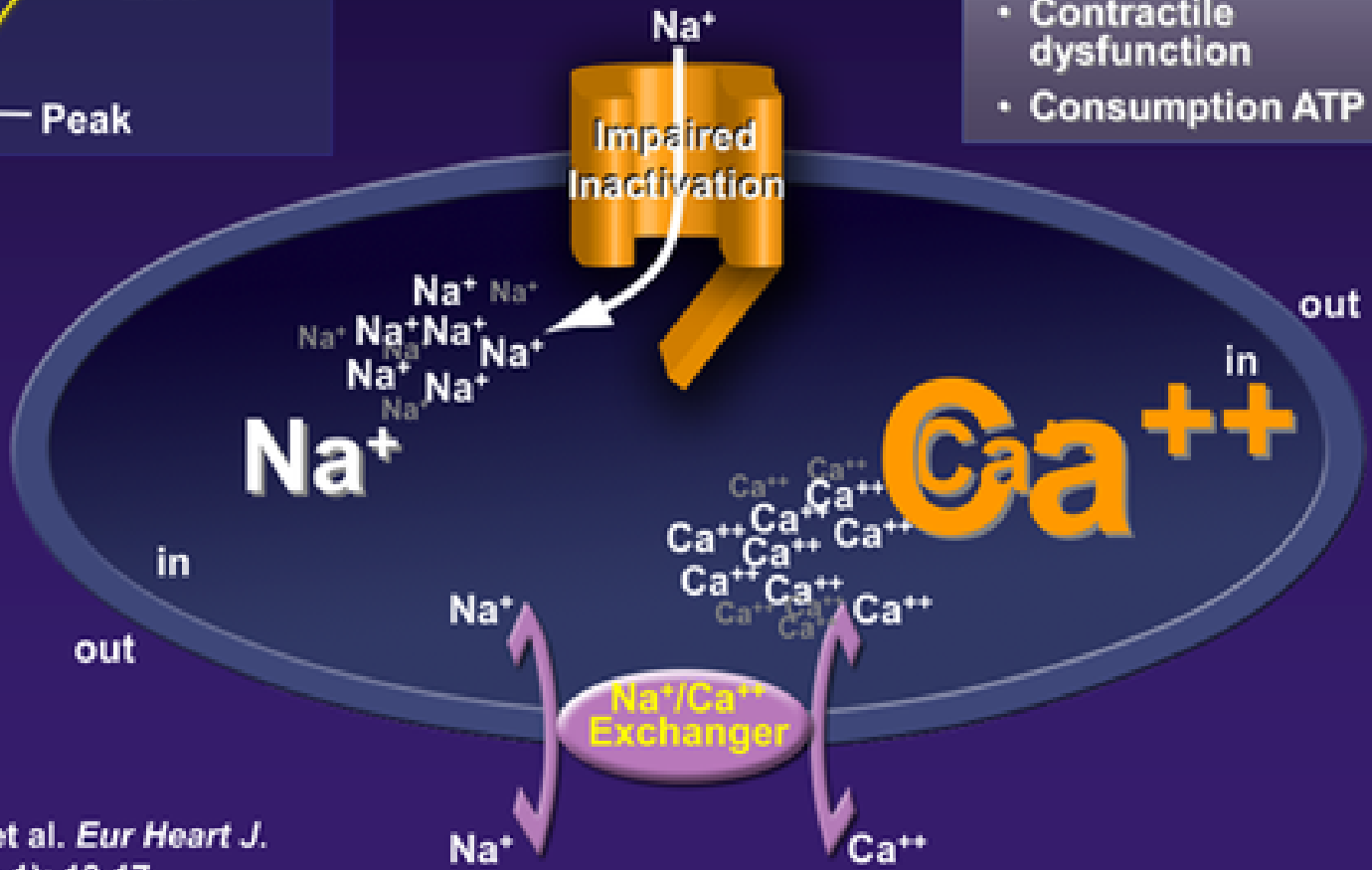
- Main axn: inhibition of late inward Na current (late I_{Na}) in myo. during ischaemia. Ca load in cardiac ms is reduced indirectly thru Na –ca exchanger: cardioprotective ; also inhibits fatty acid oxidation
- No effect on HR & BP prolongs exercise tolerance to angina but no effect on HR, BP.
- PK: BA- 30-50%,metab mainly in liver by CYP3A4,excreted in urine. T1/2 is 7hrs

Ranolazine is an Inhibitor of Late I_{Na}



Calcium overload causes:

- Electrical instability
- Contractile dysfunction
- Consumption ATP



Belardinelli, et al. *Eur Heart J.* 2004; 6 (supp 1): 13-17.

Ranolazine…..

- Dose 500mg BD PO. Can be combined with CCBs?, BB or nitrates
- A/E : dizziness,weakness,constipation,postural hypoT, dyspepsia, Headache, prolongation of QTc
- DI:Metab by CYP3A4 : caution with drugs like verapamil. Diltiazem, ketoconazole, macrolides, PI

Ivabradine

- Direct bradycardic agent or ‘pure’ HR lowering agent
- Blocks hyperpolarization-activated current (I_f) thru Na ch present in SA node which get activated during early part of slow distoloc depolariz(Ph4) during ischaemic episodes .--- HR decreased– myo oxygen demand decreases.

No negative inotropic or lusitropic effect effect or fall in BP

Ivabradine…

PK: Well absb PO, BA-40%, metab by CYP3A4, Excreted in urine, t1/2 is 2 hrs

Use: Chr stable angina in pt with sinus rhythm who can't tolerate BB or where BB are CI

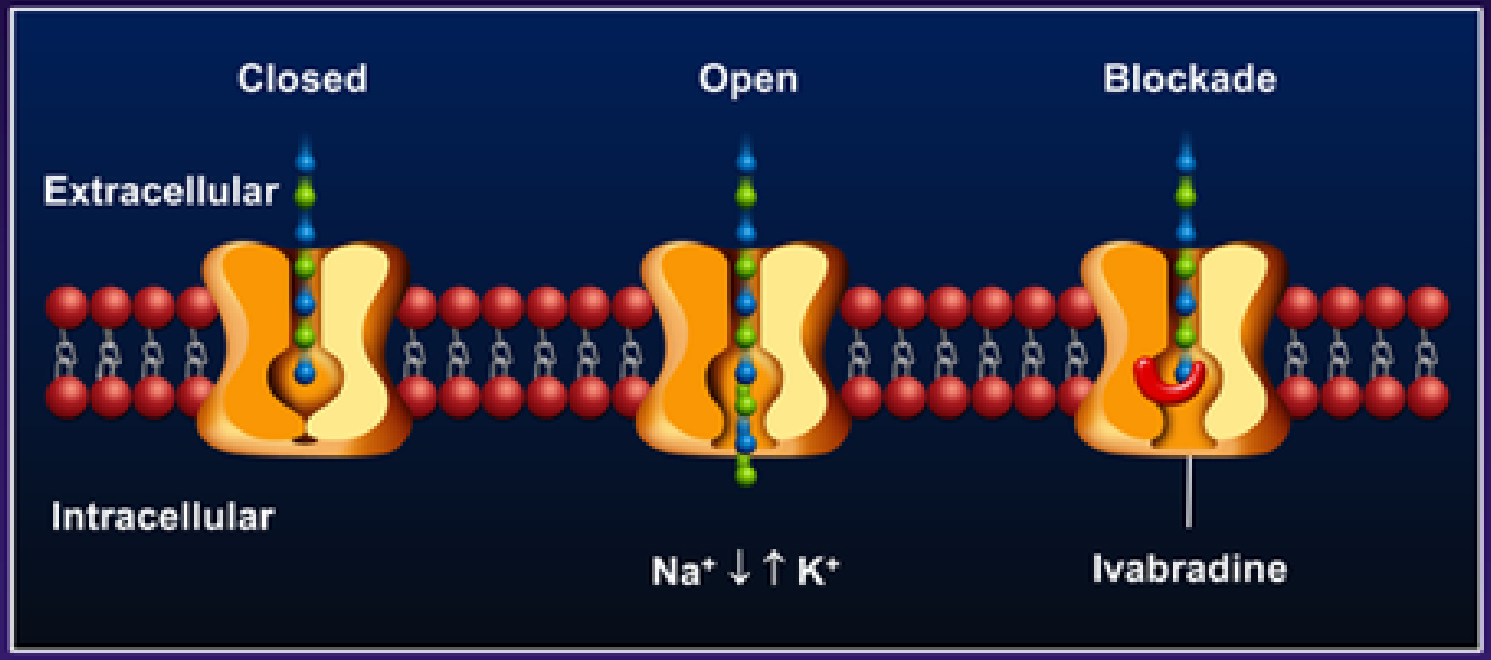
A/E ; disturbance in nocturnal vision with flashing lights, excess bradycardia, H D N

CI : HR < 60, Sick sinus synd, CYP3A4 inhibitors

•

Ivabradine: Specific and Selective Inhibitor of the I_f Ion Channel

Channel principally responsible for the SA Node Pacemaker Current



Di Francesco D, Camm JA. *Drugs*. 2004;64:1757–1765.

Unstable Angina

- **In patients with unstable angina，anticoagulant and antiplatelet drugs play a major role in therapy. Aggressive therapy with antilipid drugs, heparin, and antiplatelet agents is recommended.**

- **In addition, therapy with nitroglycerin and β-blockers should be considered; calcium channel blockers should be added in refractory cases.**

Treatment of peripheral artery disease

- d/t atherosclerosis of large & medium periph. arteries.
- S/S: Intermittent claudication: LL
- Trt.: directed at reversal or control of atherosclerosis & trt of hyperlipidemia ,HT, DM, smoking cessation.
- Antiplatelet agents
- Pentoxyphilline-xanthine deriv-dec. blood viscosity
- Cilostazol: PDE 3 inhib : sel antiplatelet & vasodilating axn. Both drugs increase exercise tolerance