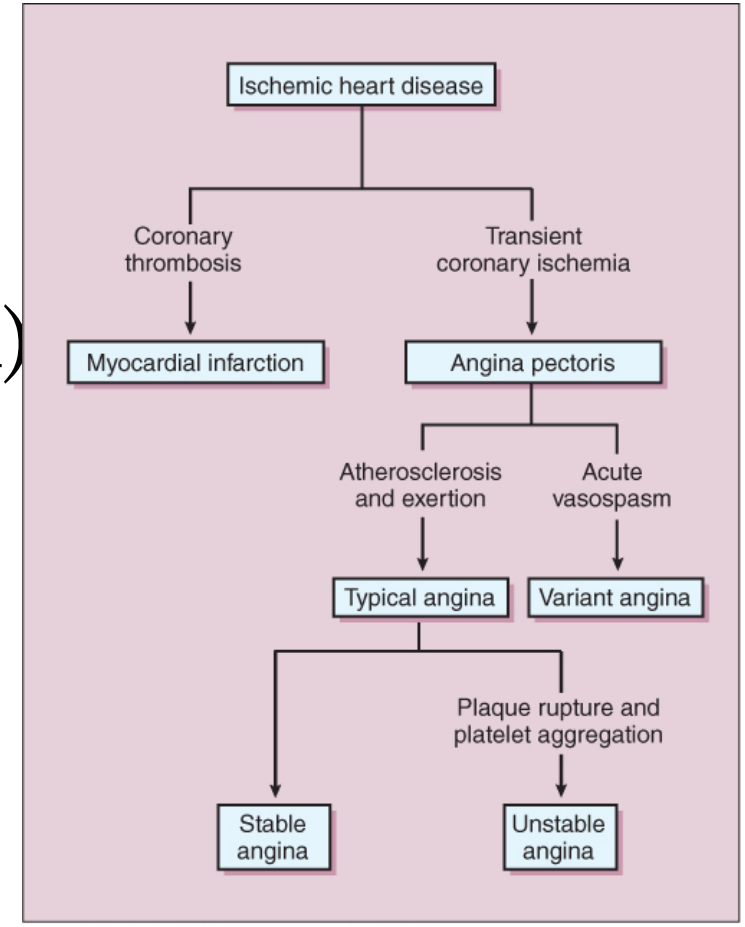
Antianginal drugs

Types of angina

- Stable
- Unstable
- Variant (Prinzmetal)

Typical



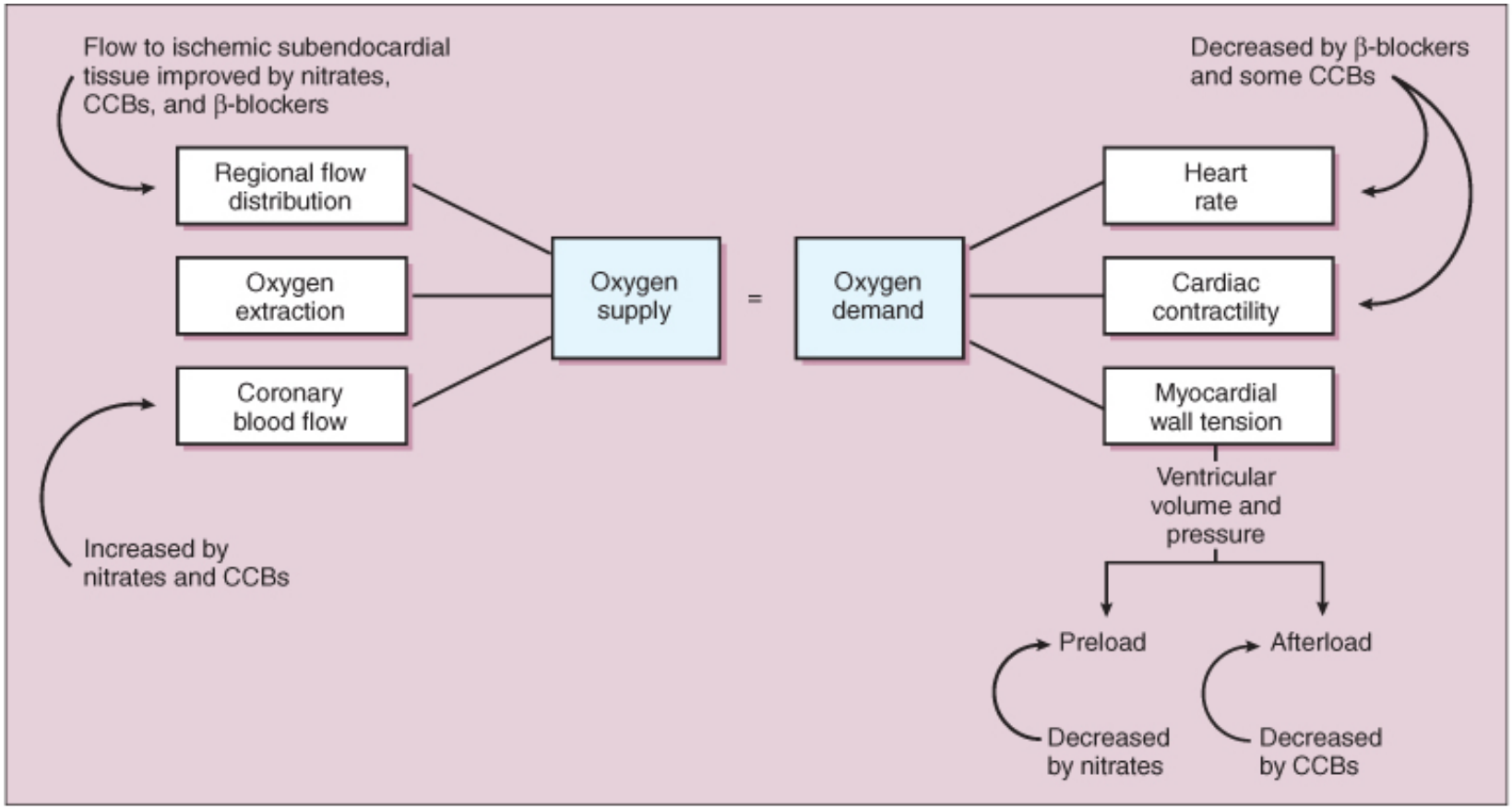
Groups of antianginal drugs

- ANTIPLATELETS
- BETA BLOCKERS
- **NITRATES**
- **CALCIUM ANTAGONIST**
- ACEI
- STATINS
- **NEW THERAPIES**

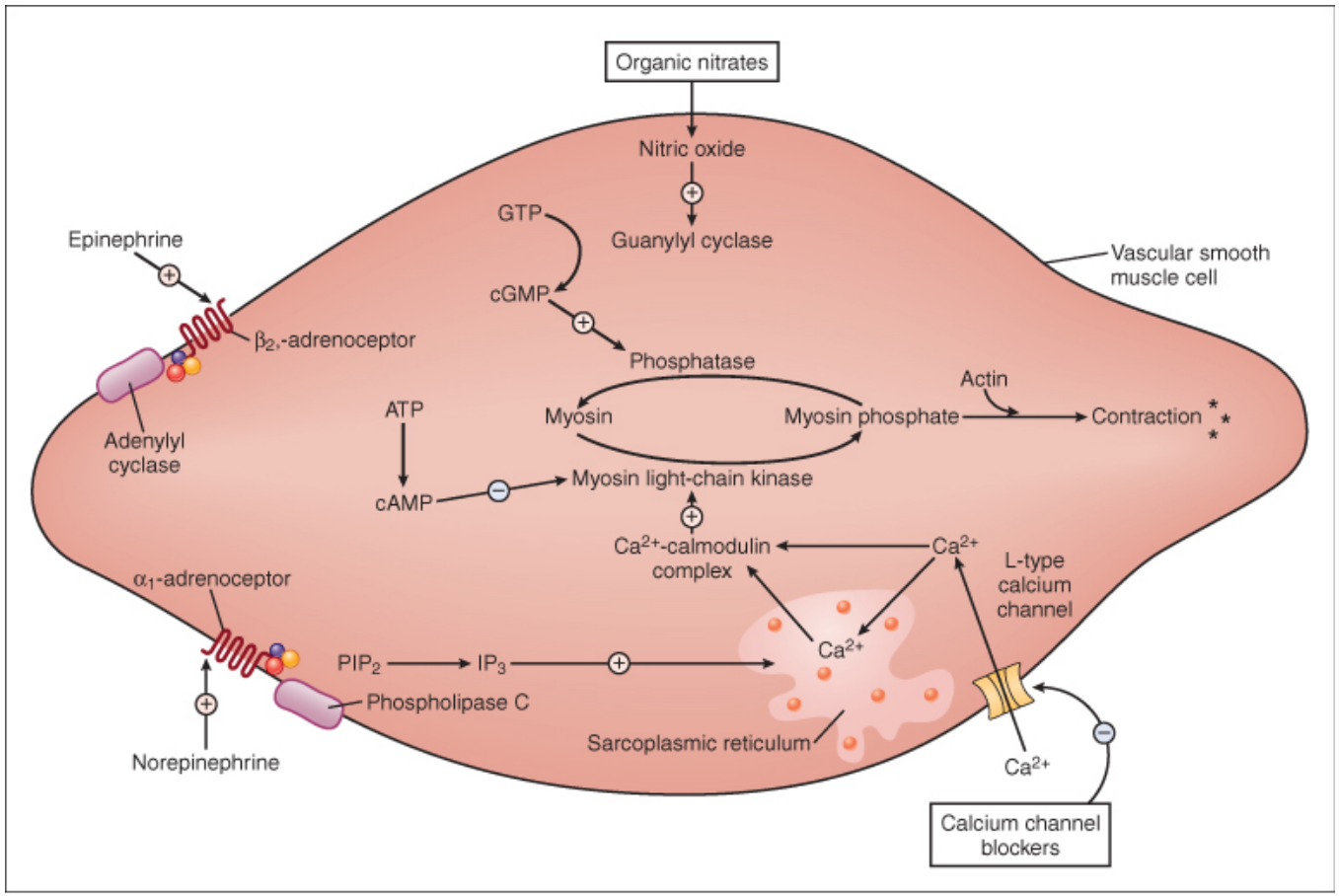
Table 11-1. Efficacy of Drugs Used in the Treatment of Coronary Heart Disease*

	TYPICAL ANGINA PECTORIS			
Drug Class	**Stable Angina**	**Unstable Angina**	**Variant Angina Pectoris**	**Myocardial Infarction**
Anti-ischemic Agents				
Organic nitrites and nitrates	++	++	++	+
Calcium channel blockers	++	0 to ++	+++	0
ß-adrenoceptor antagonists	++	++	0	+++
Preventive Agents				
Antithrombotic drugs (e.g., aspirin)†	+++	+++	0	++++
Cholesterol-lowering agents	+++	+++	0	+++

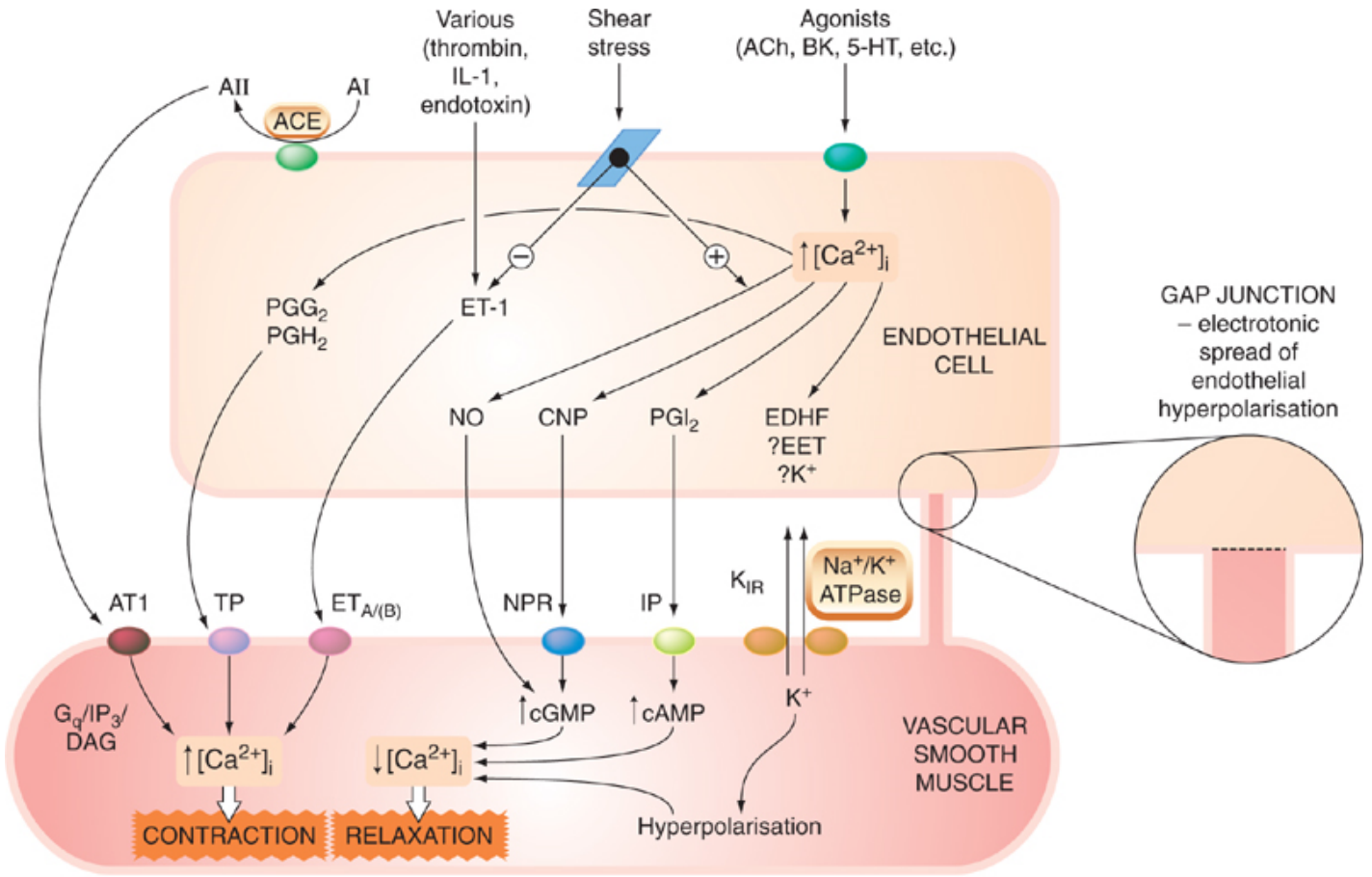
*Ratings range from 0 (not efficacious) to +++ (highly efficacious).
†Includes antiplatelet, anticoagulant, and fibronolytic drugs.



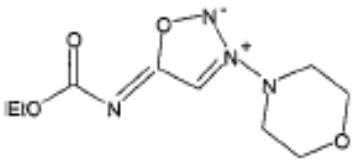
Regulation of vascular smooth muscle contraction



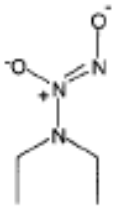
Endothelium-derived mediators



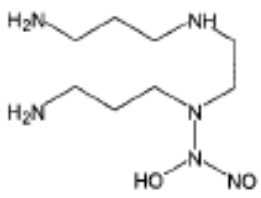
NO donor compounds



Molsidomine

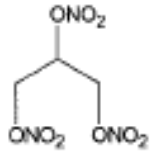


Diethylamino-NONOate

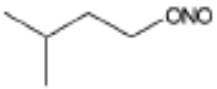


Spermine NONOate

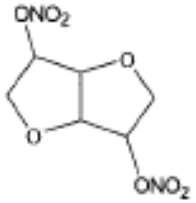
Direct NO donors



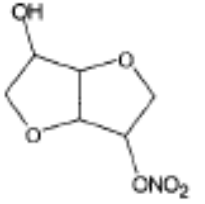
Nitroglycerin



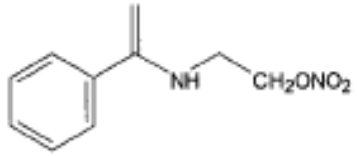
Amyl nitrite



Isosorbide dinitrate

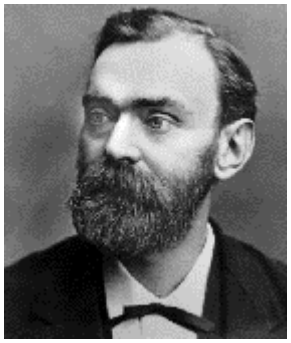


Isosorbide mononitrate

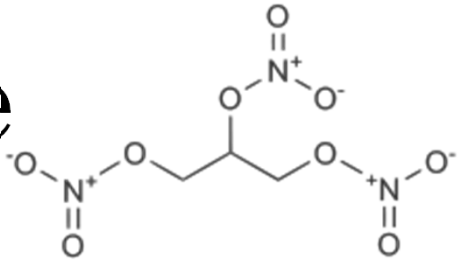


Nicorandil

Enzymatic NO donors



Glyceryl trinitrate



Nitroglycerin and Dynamite

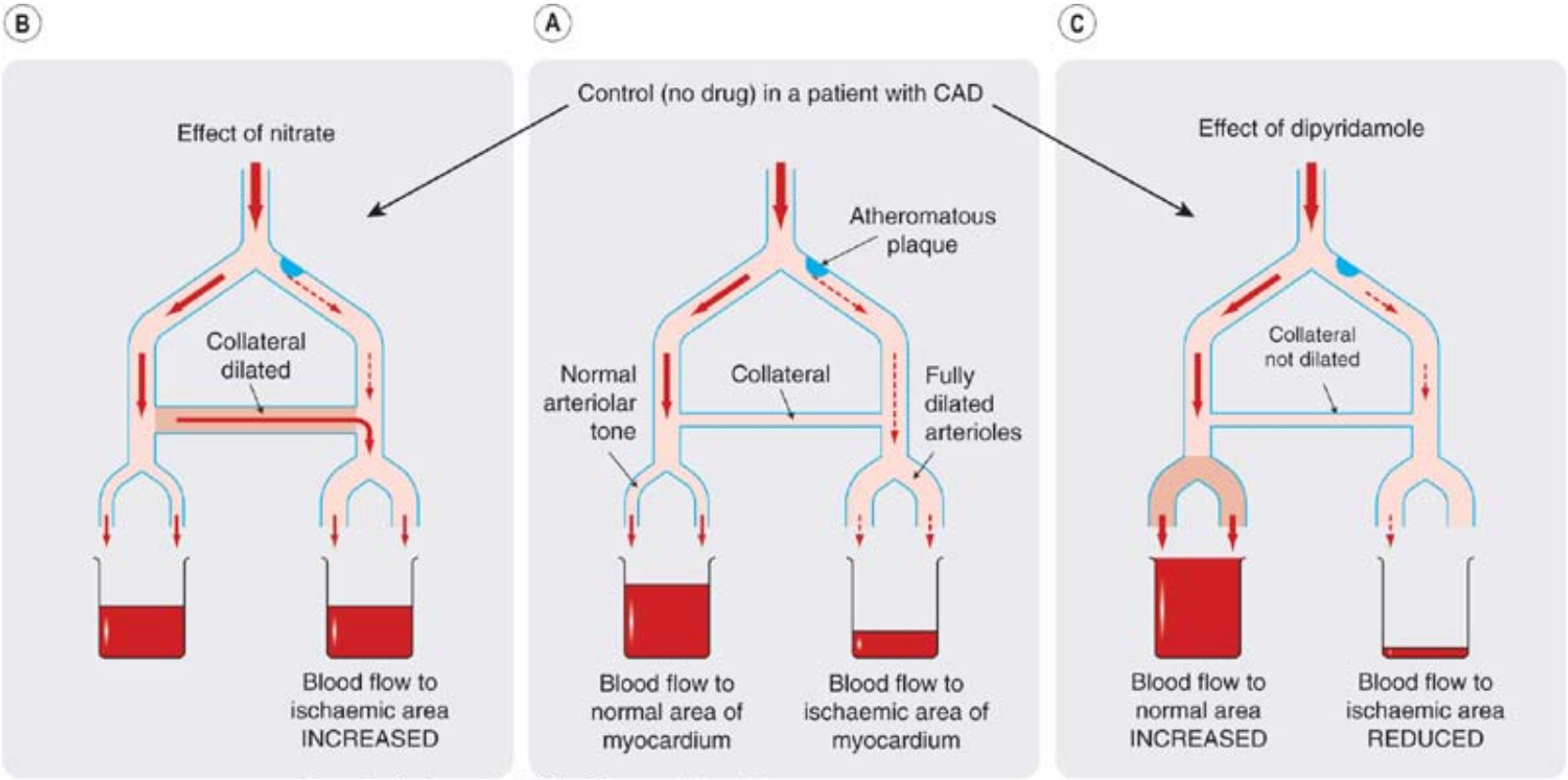
- Nitroglycerin was first invented by Italian chemist Ascanio Sobrero in 1846.
- In its natural liquid state, nitroglycerin is very volatile. Alfred Nobel experimented with several safer ways to handle the dangerous nitroglycerin after his younger brother Emil Oskar Nobel and several factory workers were killed in a nitroglycerin explosion at the Nobel's armaments factory in 1864 in Heleneborg, Sweden. Alfred Nobel understood this and in 1866 he discovered that mixing nitroglycerine with silica would turn the liquid into a malleable paste, called dynamite. One advantage of dynamite over nitroglycerin was that it could be cylinder-shaped for insertion into the drilling holes used for mining.

Denitration of GTN

Some believe that nitrates produce NO

- by reacting with sulfhydryl groups
- by glutathione S-transferases
- by cytochrome P450 (CYP)
- by xanthine oxidoreductase
- by mitochondrial aldehyde dehydrogenase (mtALDH).

Comparison of the effects of organic nitrates and an arteriolar vasodilator (dipyridamole) on the coronary circulation



Treatment of cyanide poisoning

- $NaNO_2$ iv. → methaemoglobin (binds and inactivates cyanide)
- $Na_2S_2O_3$

Nitrate containing preparations

- Glyceryl trinitrate
  - NITRODERM TTS (5-10-15 mg/24h)
  - NITRO-DUR (0,2-0,4 mg/h)
  - NITROLINGUAL (0,4 mg/ dose)
  - NITROMINT (0,5 mg tabl. subl., 2,6 mg – 6,5 mg retard tabl., 8 mg/g oral spray, 10 mg/24h TTS)

Nitrate containing preparations

- Isosorbide mononitrate (ISMN)
  - ISOSPAN SR (40 mg, 60 mg caps.)
  - MONO MACK DEPOT (100 mg tabl.)
  - OLICARD (40 mg, 60 mg caps.)
  - RANGIN (40 mg, 60 mg tabl.)
- Molsidomine (active metabolite: linsidomine)
  - CORVATON (2 mg tabl., 8 mg retard tabl.)
  - CORVATON FORTE (4 mg tabl.)

Old nitrate compounds

- Amylnitrate
- Pentaerythritol tetranitrate
- Isosorbiddinitrate (ISDN)

Unwanted effects of nitrates

- Nitrate tolerance development (organic nitrates
  - Low-molecular-weight thiols, ascorbate, L-arginine, tetrahydrobiopterin, hydralazine, ACE inhibitors, and folate can be used for reversal
- Throbbing headache
- Veretigo, dizziness
- Palpitation, tachicardia
- Postural hypotension
- Flushing, rash
- Exfoliative dermatitis

Groups of Ca^{2+} entry blockers

Smooth muscle

- *dihydropyridines* (e.g. **nifedipine**, **amlodipine**)
- *benzothiazepines* (e.g. **diltiazem**)
- *phenylalkylamines* (e.g. **verapamil**)

Heart

Nimodipine (subarachnoid haemorrhage)

Ca^{2+} entry blockers

- Block Ca^{2+} entry by preventing opening of voltage-gated L-type calcium channels.
- There are three main L-type antagonists, typified by verapamil, diltiazem and dihydropyridines (e.g. nifedipine).
- Mainly affect heart and smooth muscle, inhibiting the Ca^{2+} entry caused by depolarisation in these tissues.
- Selectivity between heart and smooth muscle varies: verapamil is relatively cardioselective, nifedipine is relatively smooth muscle selective, and diltiazem is intermediate.
- Vasodilator effect (mainly dihydropyridines) is mainly on resistance vessels, reducing afterload. Calcium antagonists dilate coronary vessels, which is important in variant angina.
- Effects on heart (verapamil, diltiazem): antidysrhythmic action (mainly atrial tachycardias), because of impaired atrioventricular conduction; reduced contractility.
- Clinical uses:
  - ***- antidysrhythmic (mainly verapamil)***
  - ***- angina (e.g. diltiazem)***
  - ***- hypertension (mainly dihydropyridines).***
- Unwanted effects include headache, constipation (verapamil) and ankle oedema (dihydropyridines). There is a risk of causing cardiac failure or ***heart block***, especially with verapamil.

PD & PK of CCBs

Table 11-2. Pharmacokinetic Properties of Calcium Channel Blockers Used in the Treatment of Coronary Heart Disease*

Drug	Oral Bioavailability	Excreted Unchanged in Urine	Elimination Half-Life (Hours)
Dihydropyridines			
Amlodipine	75%	10%	40
Felodipine	20%	1%	14
Nicardipine	35%	1%	3
Nifedipine	60%	1%	3
Other Calcium Channel Blockers			
Bepridil	60%	5%	25
Diltiazem	55%	3%	5
Verapamil	25%	3%	5

*Values shown are the mean of values reported in the literature.

Table 11-3. Cardiovascular Effects of Calcium Channel Blockers Used in the Treatment of Coronary Heart Disease

Drug	Coronary Blood Flow	Sinoatrial Node Automaticity*	Cardiac Contractility*	Atrioventricular Node Conduction Velocity*
Dihydropyridine Drugs				
Amlodipine	Increases	None	None	None
Nicardipine	Increases	None	None	None
Nifedipine	Increases	None	None	None
Felodipine	Increases	None	None	None
Other Calcium Channel Blockers				
Bepridil	Increases	Decreases slightly	Decreases slightly	Decreases slightly
Diltiazem	Increases	Decreases	Decreases slightly	Decreases
Verapamil	Increases	Decreases	Decreases	Decreases

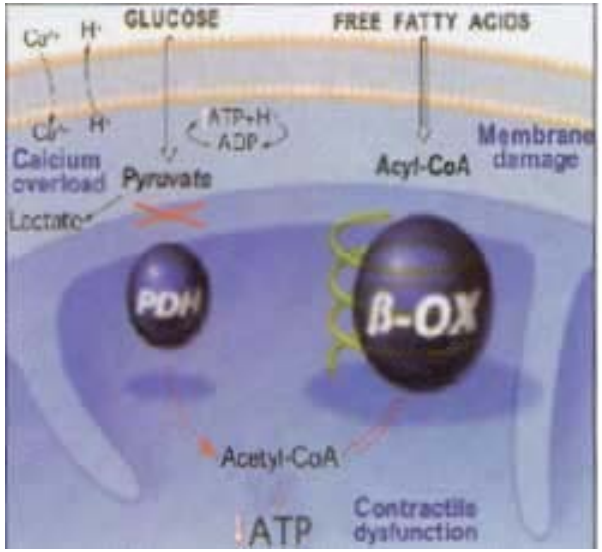
*Direct effects may be counteracted by reflex activity.

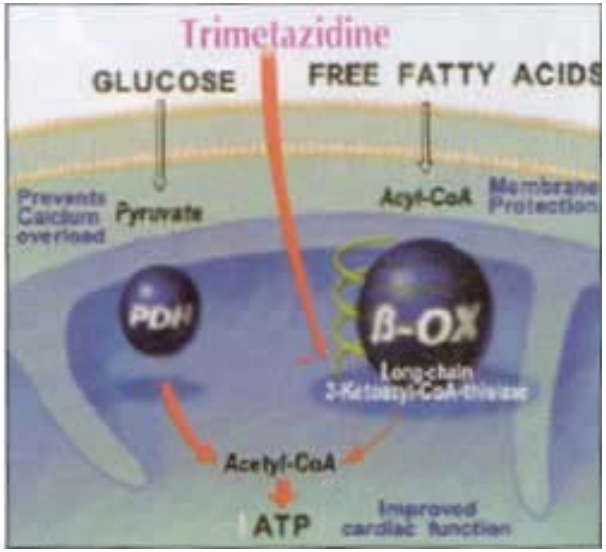
Potassium channel opener

- K^+ ions control the resting membrane potential → K^+ channel opening → efflux of K^+ & Hyperpolarisation → opposes the opening of Ca^{+2} channels (due to no depolarization) → fall of cystolic Ca^{+2} conc resulting in a reduction of cellular contractile activity at the myocardial & vascular level
- **Nicorandil**
  - Combines activation of the potassium K_{ATP} channel with nitrovasodilator (nitric oxide donor) actions.
  - It is both an arterial and a venous dilator, and causes the expected unwanted effects of headache, flushing and dizziness.
  - It is used for patients who remain symptomatic despite optimal management with other drugs, often while they await surgery or angioplasty.

Newer therapies

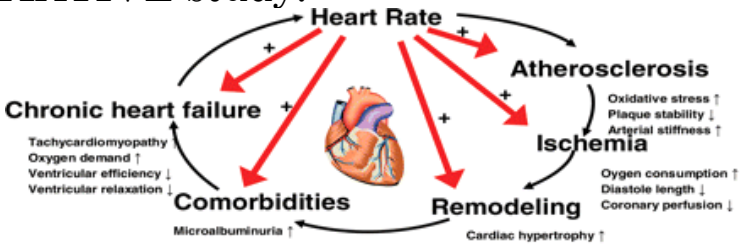
- Trimetazidine
  - partial inhibition of fatty acid ß-oxidation by reducing the mitochondrial activity of an enzyme, 3-ketoacyl coenzyme A thiolase.
  - It increases coronary reserve, although its antianginal effect is not due to reduced heart rate, myocardial depression or vasodilatation.





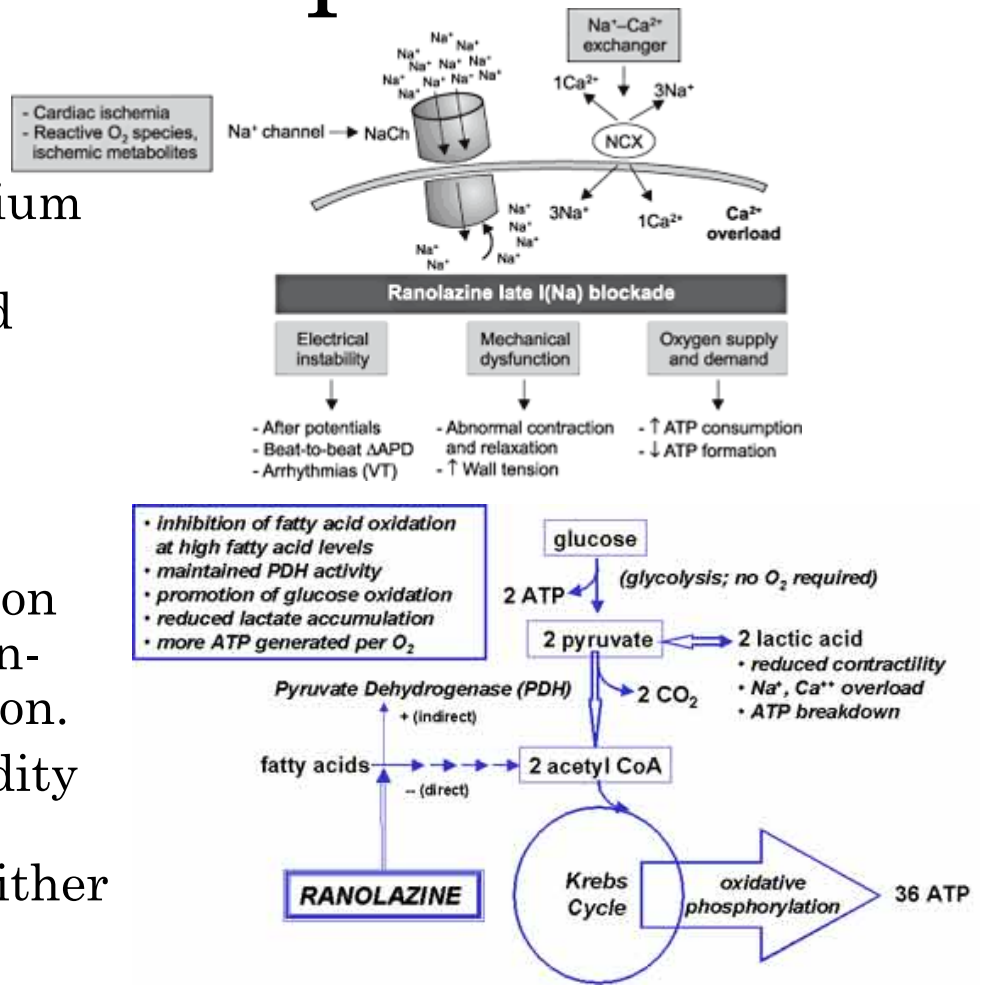
Newer therapies

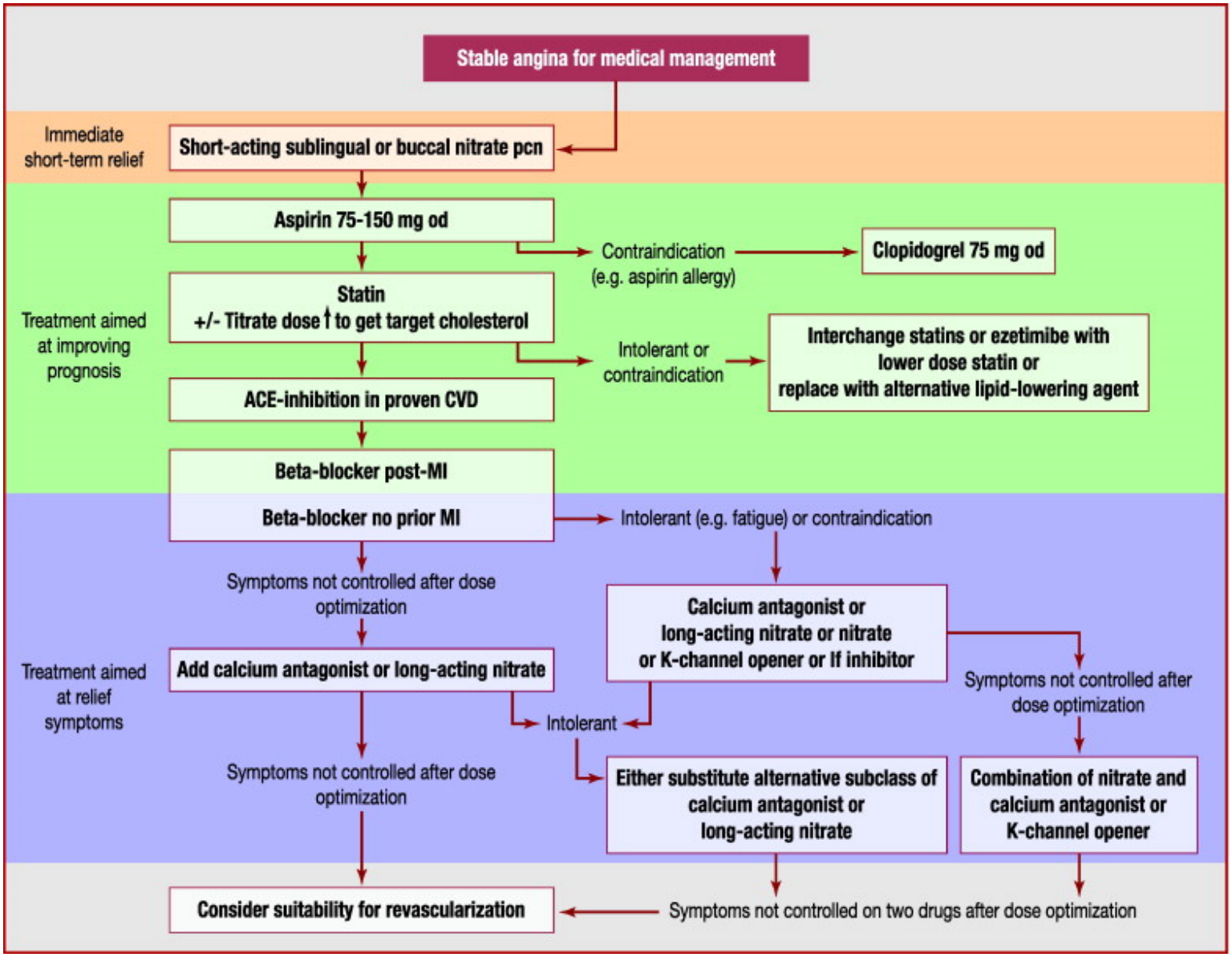
- ***Ivabradine (PROCOROLAN)***
  - Ivabradine acts purely by decreasing heart rate through a **blockade of sinoatrial node I_f (funny) entry currents**.
  - If is a mixed Na^+–K^+ inward current activated by hyperpolarization and modulated by the autonomic nervous system. It is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial (SA) node. Ivabradine selectively inhibits the pacemaker I_f current in a dose-dependent manner. Blocking this channel reduces cardiac pacemaker activity, slowing the heart rate and allowing more time for blood to flow to the myocardium.
  - It was first shown to be effective as an antianginal against placebo (superiority) in coronary artery disease patients with stable angina, and then against atenolol (non-inferiority) in the INITIATIVE study.
  - Other studies: BEAUTIFUL, SHIFT
  - Side effects: Luminous phenomena (I_h channel in retina), bradycardia, headache, AV-block, VES, dizziness, blurred vision
  - Contraindication: SSS, CYP3A4 inhibitors



Newer therapies

- ***Ranolazine (RANEXA)***
  - Selective inhibitor of late sodium current, which prevents the intracellular calcium overload that has been implicated as a negative factor in myocardial ischaemia.
  - Partial fatty acid oxidation inhibitor, shifts ATP production from fatty acid to more oxygen-efficient carbohydrate oxidation.
  - Reduces myocardial wall rigidity and improves myocardial perfusion without changing either heart rate or blood pressure.




Stable angina for medical management
Immediate short-term relief
Short-acting sublingual or buccal nitrate pcn
Aspirin 75-150 mg od
Contraindication (e.g. aspirin allergy)
Clopidogrel 75 mg od
Treatment aimed at improving prognosis
Statin
+/- Titrate dose ↑ to get target cholesterol
Intolerant or contraindication
Interchange statins or ezetimibe with lower dose statin or replace with alternative lipid-lowering agent
ACE-inhibition in proven CVD
Beta-blocker post-MI
Beta-blocker no prior MI
Intolerant (e.g. fatigue) or contraindication
Symptoms not controlled after dose optimization
Calcium antagonist or long-acting nitrate or nitrate or K-channel opener or If inhibitor
Treatment aimed at relief symptoms
Add calcium antagonist or long-acting nitrate
Symptoms not controlled after dose optimization
Intolerant
Symptoms not controlled after dose optimization
Either substitute alternative subclass of calcium antagonist or long-acting nitrate
Combination of nitrate and calcium antagonist or K-channel opener
Consider suitability for revascularization
Symptoms not controlled on two drugs after dose optimization