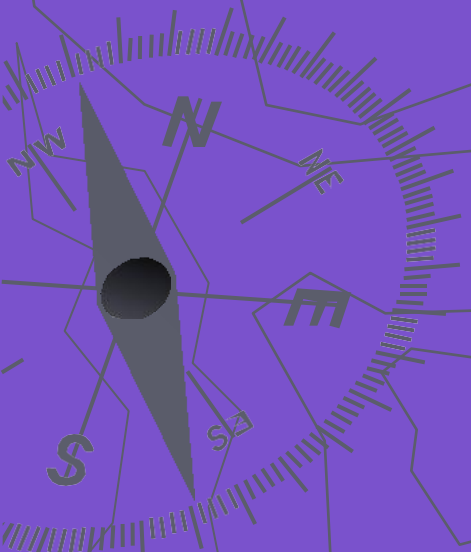
Drug Treatment of Ischemic Heart Disease



Angina pectoris

- Sudden, severe, pressing chest pain and radiating to the neck, jaw, back, and arms. The episodes are transient, stay between 15 sec to 15 min.

- Caused by a reduction in the coronary blood flow to a level that does not meet the requirements of the myocardium, leading to what is called ischemia.

- This oxygen supply imbalance may caused by:
  a. a spasm of the vascular smooth muscles
  b. obstruction of blood vessels caused by atherosclerosis.

Types of angina

- Angina has three overlapping patterns, which are caused by varying combination of increased myocardial demand and decreased myocardial perfusion.

A. Stable angina, the most common form, and characterized by a burning heavy or squeezing feeling in the chest.

Caused by reduction of coronary perfusion due to coronary atherosclerosis. So the heart become susceptible to ischemia whenever there is demand, such as exercise, emotional excitement.

This type is rapidly relieved by rest or nitroglycerin.

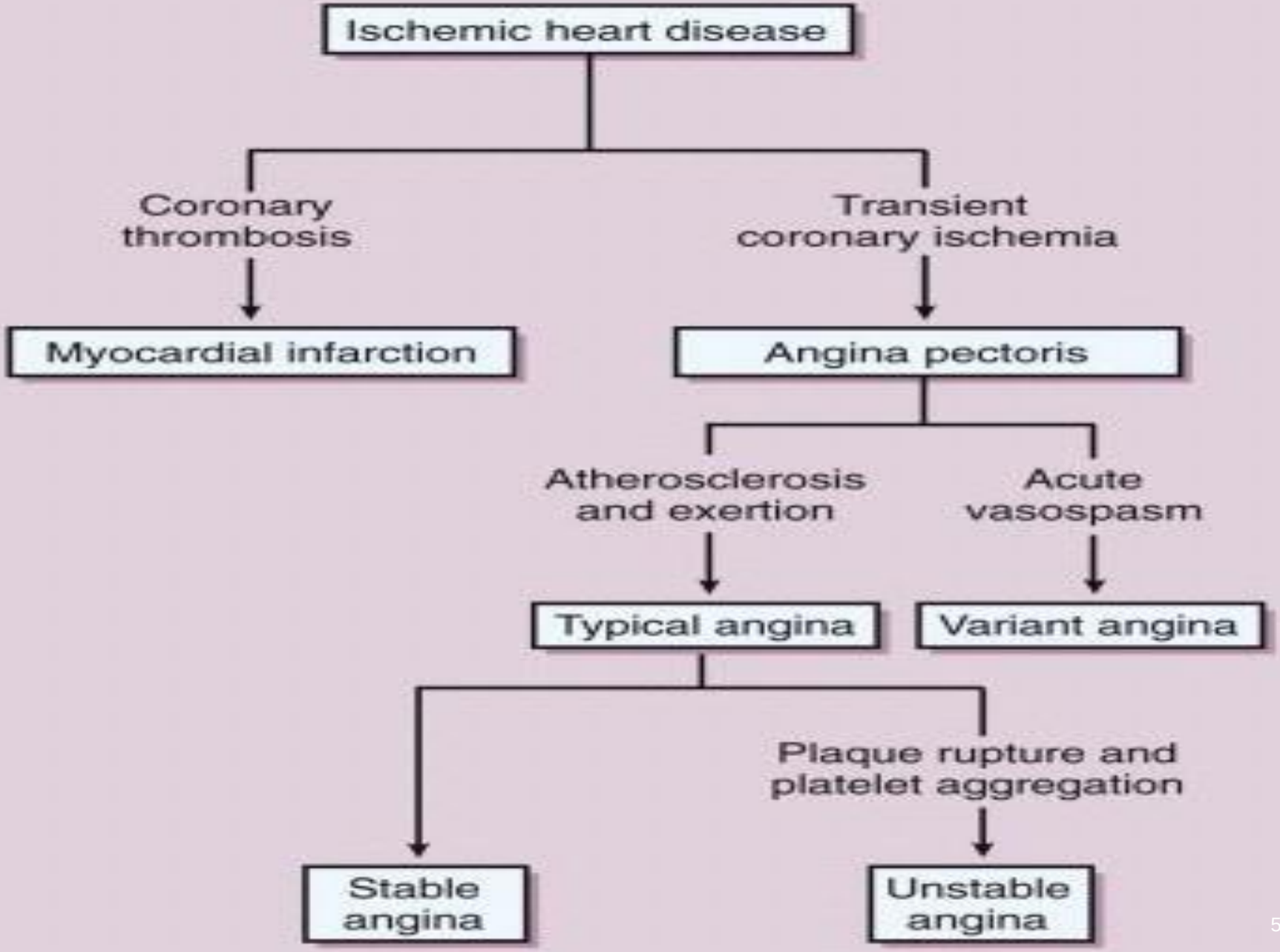
Types of angina

B. Unstable angina, lies between stable angina and myocardial infarction, Often unrelated to exercise.

unstable angina require more aggressive therapy, for example treatments of dyslipidemias, hypertension.

C. Variant angina, occurs at rest and caused by coronary artery spasm (i.e. caused by contraction of the smooth muscle tissue in the vessel walls rather than directly by atherosclerosis(

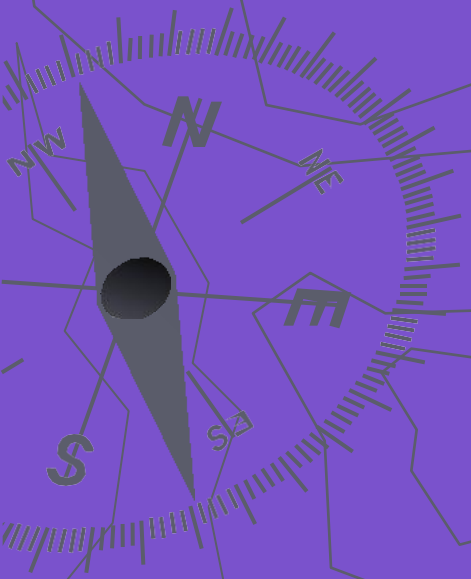
Generally, this type rapidly responds to nitroglycerin and calcium channel blockers.


Ischemic heart disease
Coronary thrombosis
Transient coronary ischemia
Myocardial infarction
Angina pectoris
Atherosclerosis and exertion
Acute vasospasm
Typical angina
Variant angina
Plaque rupture and platelet aggregation
Stable angina
Unstable angina

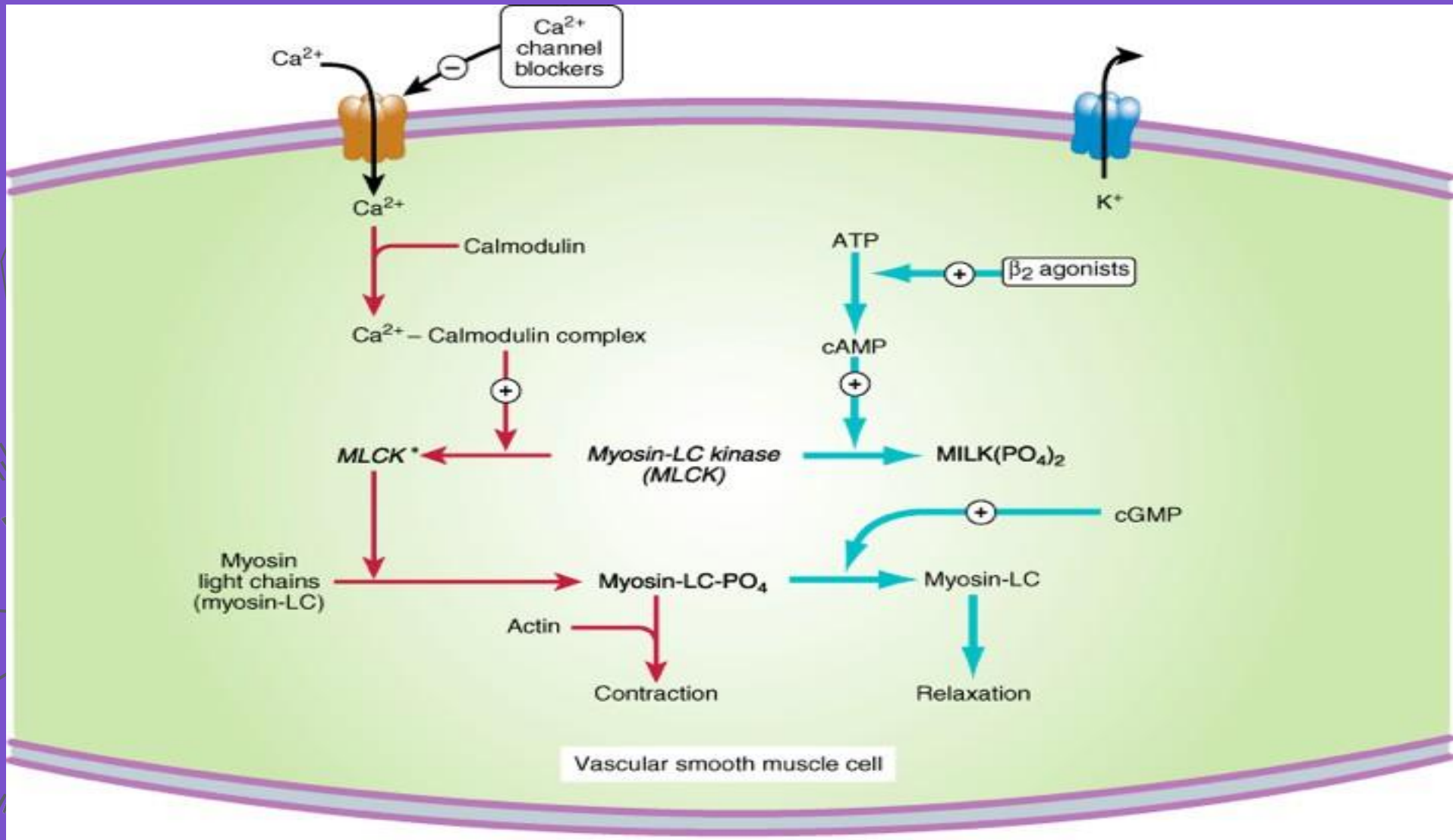
Mechanism of IHD

Due to an imbalance of the ratio:

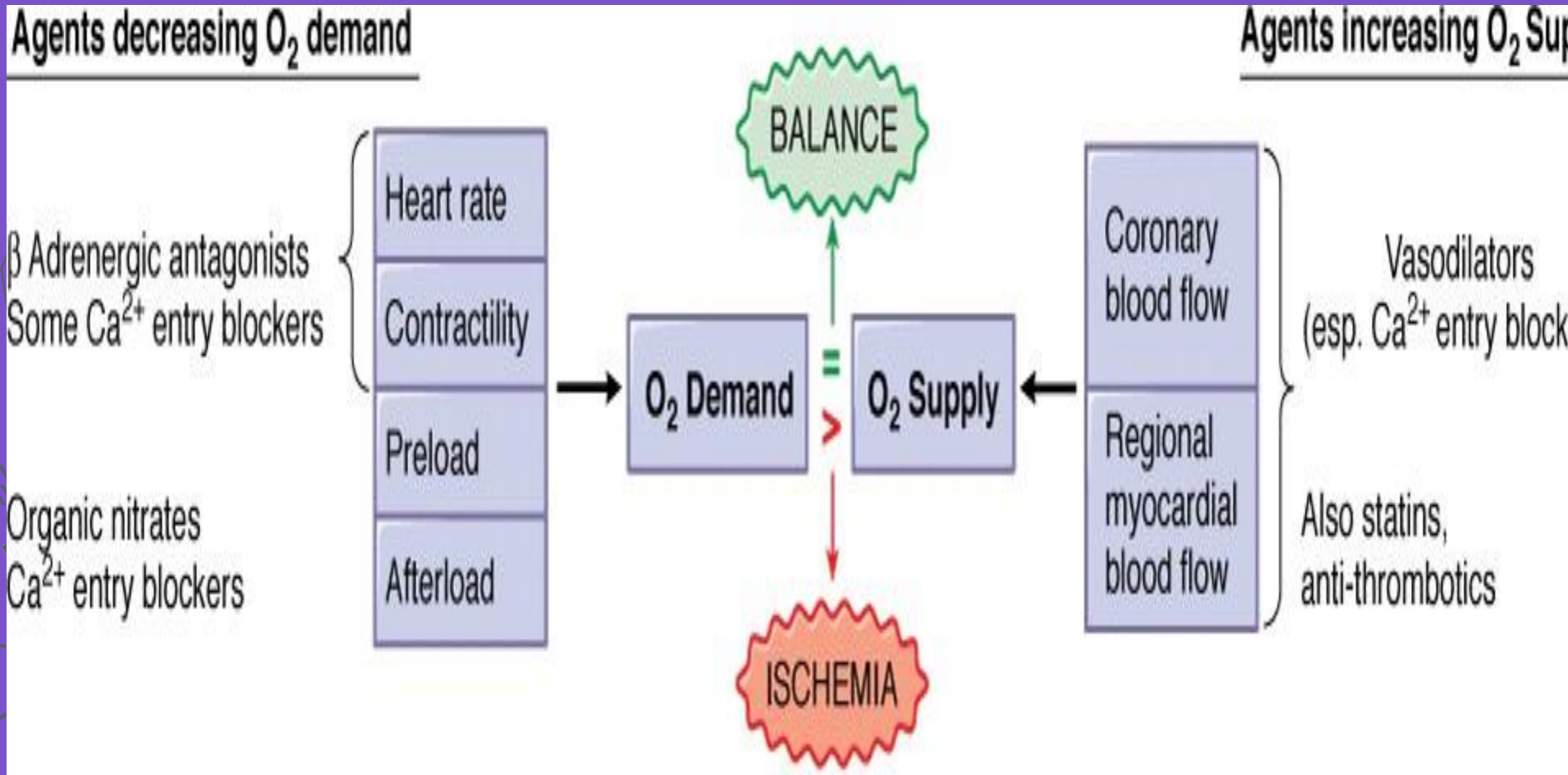
$$\frac{O_2 \text{ Supply (Coronary Blood Flow(}}{O_2 \text{ Demand (Work of the Heart(}}$$



Control of vascular smooth muscle contraction



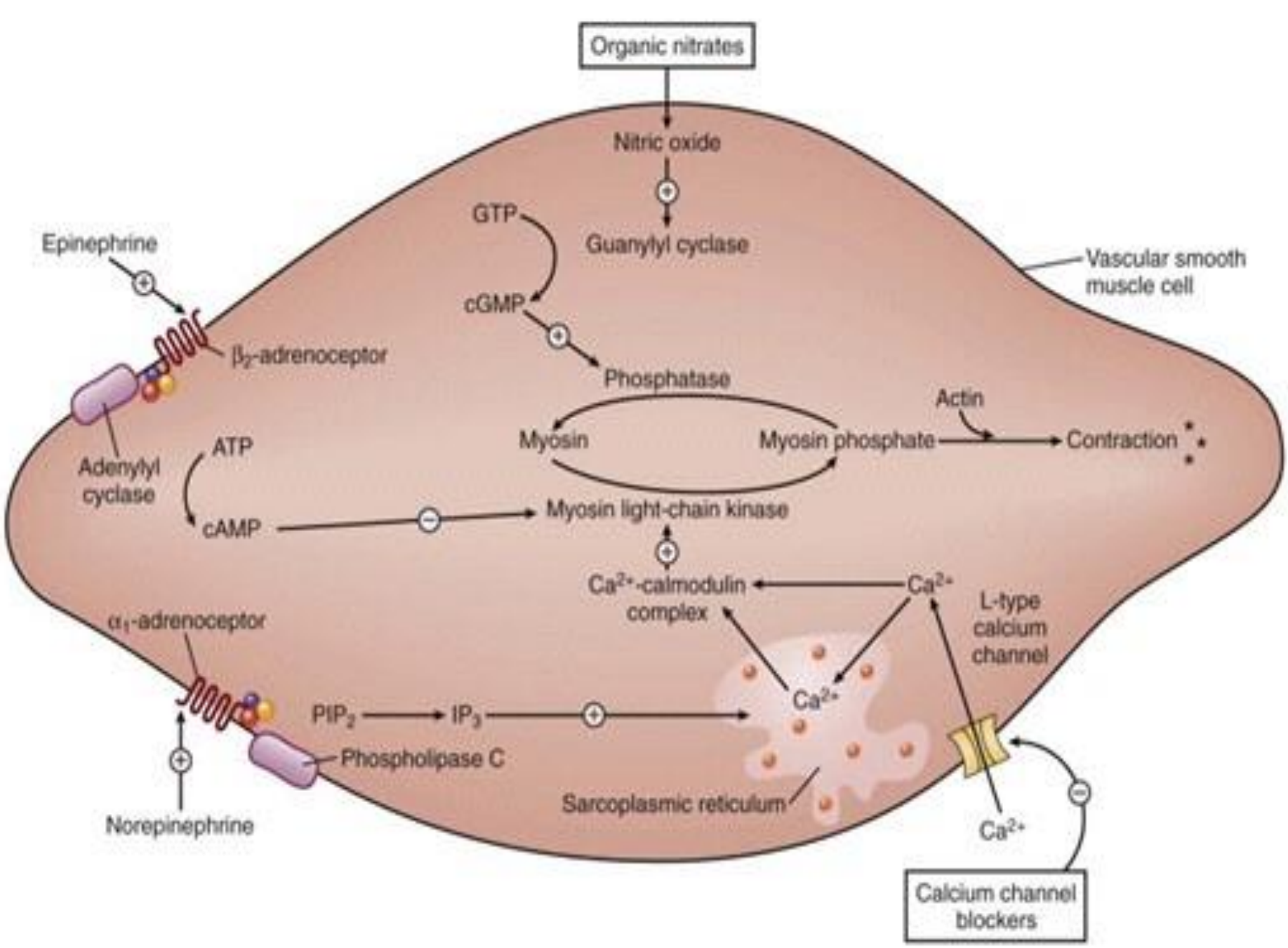
Pharmacological modification of the major determinants of myocardial O2 supply



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Drug effects on vascular smooth muscle contraction.

- Calcium influx is inhibited by CCBs, leading to muscle relaxation.
- Organic nitrates release nitric oxide, which activates guanylyl cyclase and increases formation of cyclic guanosine monophosphate.
  - cGMP causes smooth muscle relaxation by activating kinases that increase myosin phosphatase activity and decrease myosin phosphate levels.
- α 1-Adrenoceptor agonists activate phospholipase C (PLC), which increases formation of inositol triphosphate (IP 3) from phosphatidylinositol bisphosphate (PIP 2), leading to increased release of calcium from the sarcoplasmic reticulum.
- β 2-Adrenoceptor agonists increase formation of cyclic adenosine monophosphate (cAMP), which activates kinases that inhibit myosin light-chain kinase.


Organic nitrates
Nitric oxide
GTP
Guanylyl cyclase
Epinephrine
Vascular smooth muscle cell
cGMP
β_2-adrenoceptor
Phosphatase
Actin
Myosin
Myosin phosphate
Contraction
Adenylyl cyclase
ATP
cAMP
Myosin light-chain kinase
Ca^{2+}-calmodulin complex
Ca^{2+}
L-type calcium channel
α_1-adrenoceptor
PIP_2
IP_3
Ca^{2+}
Phospholipase C
Sarcoplasmic reticulum
Norepinephrine
Ca^{2+}
Calcium channel blockers

Organic nitrates

- They are effective in the three types of angina pectoris.
- Members of this group include: isosorbide dinitrate, isosorbide mononitrate, Pentaerythritol tetranitrate and Nitroglycerine.
- Their mechanism of action summarised in a decrease coronary spasm or vasoconstriction and in an increase perfusion of the myocardial by relaxing the coronary arteries.

2.Pharmacological mechanism

Organic nitrates

↓

NO

↓

guanylyl cyclase

↓

cGMP ↑

↓

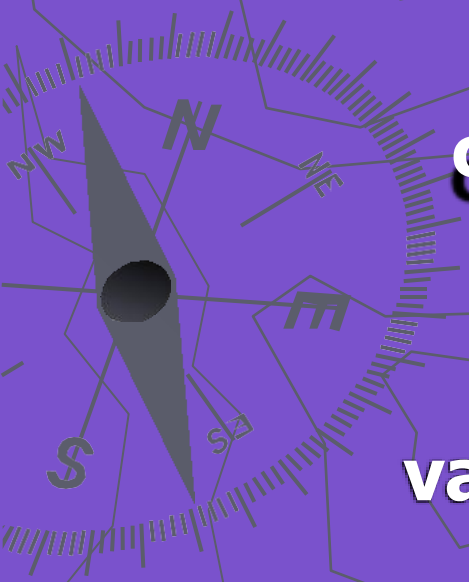
cGMP dependent protein kinase

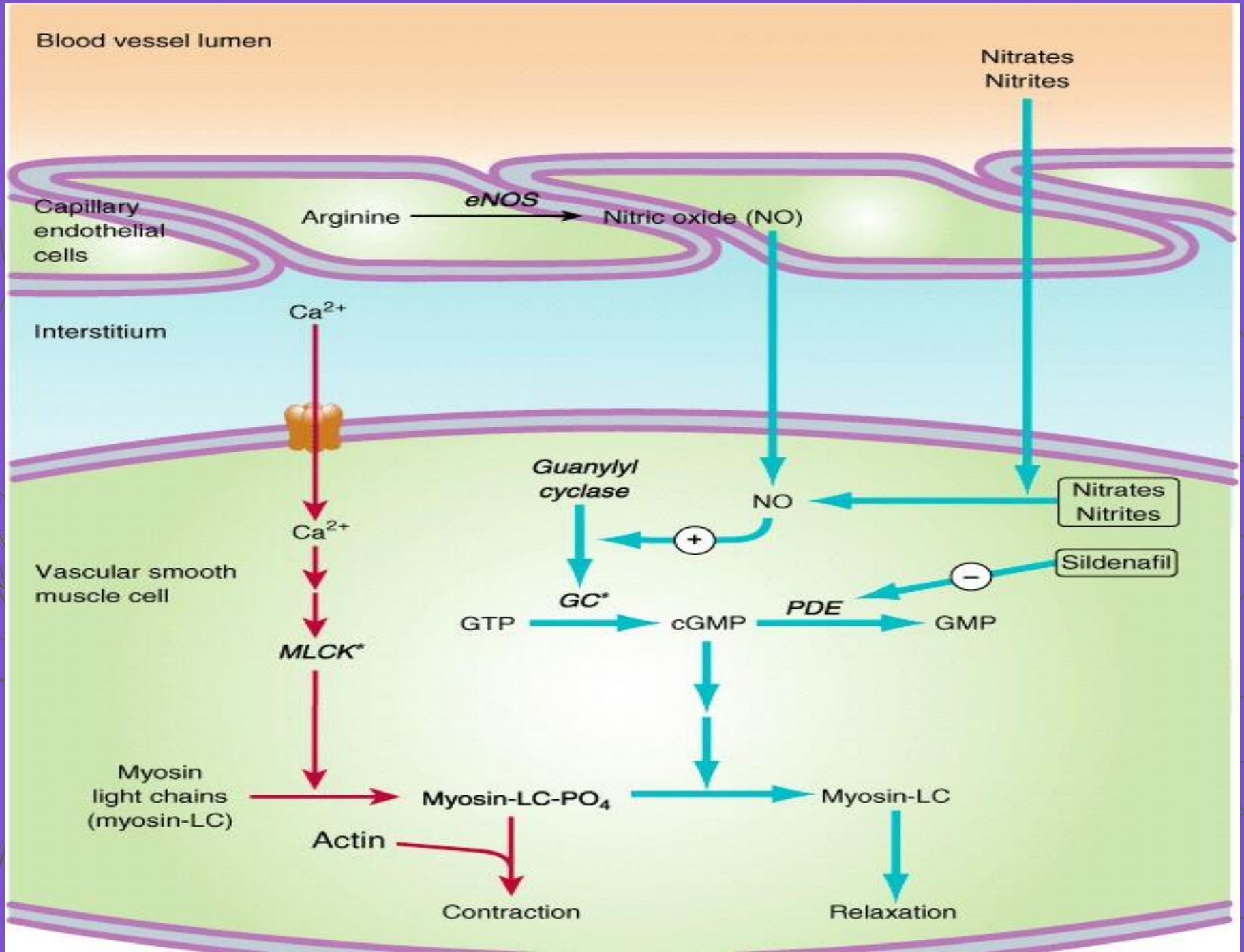
↓

intracellular Ca^{2+} ↓

↓

vascular smooth muscle relaxation




Blood vessel lumen
Nitrates
Nitrites
Capillary endothelial cells
Arginine
eNOS
Nitric oxide (NO)
Interstitium
Ca2+
Guanylyl cyclase
NO
Nitrates
Nitrites
Ca2+
+
Vascular smooth muscle cell
Sildenafil
−
GC*
PDE
GTP
cGMP
GMP
MLCK*
Myosin light chains (myosin-LC)
Myosin-LC-PO4
Myosin-LC
Actin
Contraction
Relaxation

Organic Nitrates

- **Nitroglycerine (GTN):**
- Prototype, used for more than 140 years.
- Nonspecific smooth muscle relaxant.
- Action not antagonized by any known antagonist.

Nitroglycerine (GTN)

- Usually administered sublingually.
- Can be administered by various routes.
- Fast onset of action(1-3minutes, Peaks at 10 minutes).
- Short duration (15-30minutes).
- Reductase enzyme in liver will breakdown the drug.

Nitroglycerine)GTN(

- Causes general vasodilation:
- Arteriolar dilation: short lived (5-10 min(
  - Decreases systemic blood pressure (afterload) and causes reflex tachycardia and increased contractility, ?might increase MVO.2
- Venous dilation: more intense, even with low doses, lasts for 30 minutes.
  - Decreases venous return (preload) and decreases MVO.2

Nitroglycerine)GTN(

- **Side Effects:**
- Headache.
- Hypotension and tachycardia.
- Increased intraocular and intracranial pressures.
- Methemoglobinemia.
- Tolerance: only for the arteriolar effects.
- Withdrawal: in workers in ammunition industry.

Organic nitrates

- All of the three agents are effective but they differ in the onset and duration of action.
- For rapid relief of an ongoing attack that precipitate by exercise and emotional stress, sublingual nitroglycerine is the drug of choice.
- At therapeutics dose nitroglycerine has two major effects:

a. dilation of the large veins, resulting in pooling of blood in the veins (diminish preload and reduce the work of heart.(

b. dilates the coronary arteries.

Organic nitrates

- The time to onset the action varies from 1 min for nitroglycerine to 1 hr for isosorbide mononitrate. .
- Significant first pass metabolism of nitroglycerine occurs so it administrated sublingually or transdermally (patch.(
- Isosorbide mononitrate has long duration of action due to its ability to avoid first pass effect (so it is administrated orally.(
- Adverse effect:

  a. headache is a common early side effect of nitrates, which is usually decrease after the first few days (patient develop tolerance.(

Organic nitrates

b. high doses can cause postural hypotension syncope can result and tachycardia.

- Sildinafil (Viagra) potentiates the action of nitrates, and to avoid the dangerous hypotension, an interval of six hour between the two agents is recommended.
- Tolerance to the action of the nitrates develops rapidly, the blood vessels become desensitized to the vasodilation.
- The tolerance can be overcame by providing a daily "nitrate free intervals" to restore sensitivity to the drug (this interval are usually 10 – 12 hr at night(

Nitrate and Nitrite Drugs Used in the Treatment of Angina.

Drug	Duration of Action
Short-acting:	
Nitroglycerin, sublingual	10–30 minutes
Isosorbide dinitrate, sublingual	10–60 minutes
Amyl nitrite, inhalant	3–5 minutes
Long-acting:	
Nitroglycerin, oral sustained-action	6–8 hours
Nitroglycerin, 2% ointment, transdermal	6–3hours
Nitroglycerin, slow-release, buccal	6–3hours
Nitroglycerin, slow-release patch, transdermal	10–8hours
Isosorbide dinitrate, sublingual	2–1.5hours
Isosorbide dinitrate, oral	6–4hours
Isosorbide dinitrate, chewable oral	3–2hours
Isosorbide mononitrate, oral	10–6hours

Beta Adrenergic Blockers

- Prevent actions of catecholamines, so more effective during exertion.
- Do not dilate coronary arteries.
- Do not increase collateral blood flow.
- Cause subjective and objective improvement: decreased number of anginal episodes, nitroglycerine consumption, enhanced exercise tolerance, and improved ECG.

β-adrenergic blocking agents

- They suppress the heart by blocking β1 receptors, and so reduce the work of the heart by decreasing the cardiac output and blood pressure.
- They reduce the frequency and the severity of angina attack.
- The cardioselective β 1agents, such as acebutolol and atenolol and metoprolol are preferred.

β-adrenergic blocking agents

Clinical uses

Stable and unstable angina

Myocardia infarction

Contraindication

Variant angina,

Bronchial asthma,

Bradycardia

Calcium channel blockers

- Inhibiting the entrance of calcium into cardiac and smooth muscles cells of the coronary arteries

A. Nifidipine, arterioles vasodilation effect with minimal effect on the heart, and is useful in the treatments of angina caused by spontaneous coronary spasm (Variant angina.(

B. Verapamil, slow cardiac conduction directly, and thus decrease oxygen demand, so should be avoided with patient with a congestive heart failure due to its negative inotropic effect on the heart.

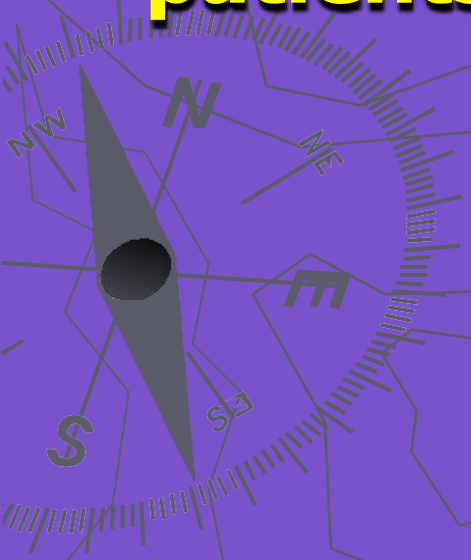
C. Diltiazem has similar effect on the heart to Verapamil.

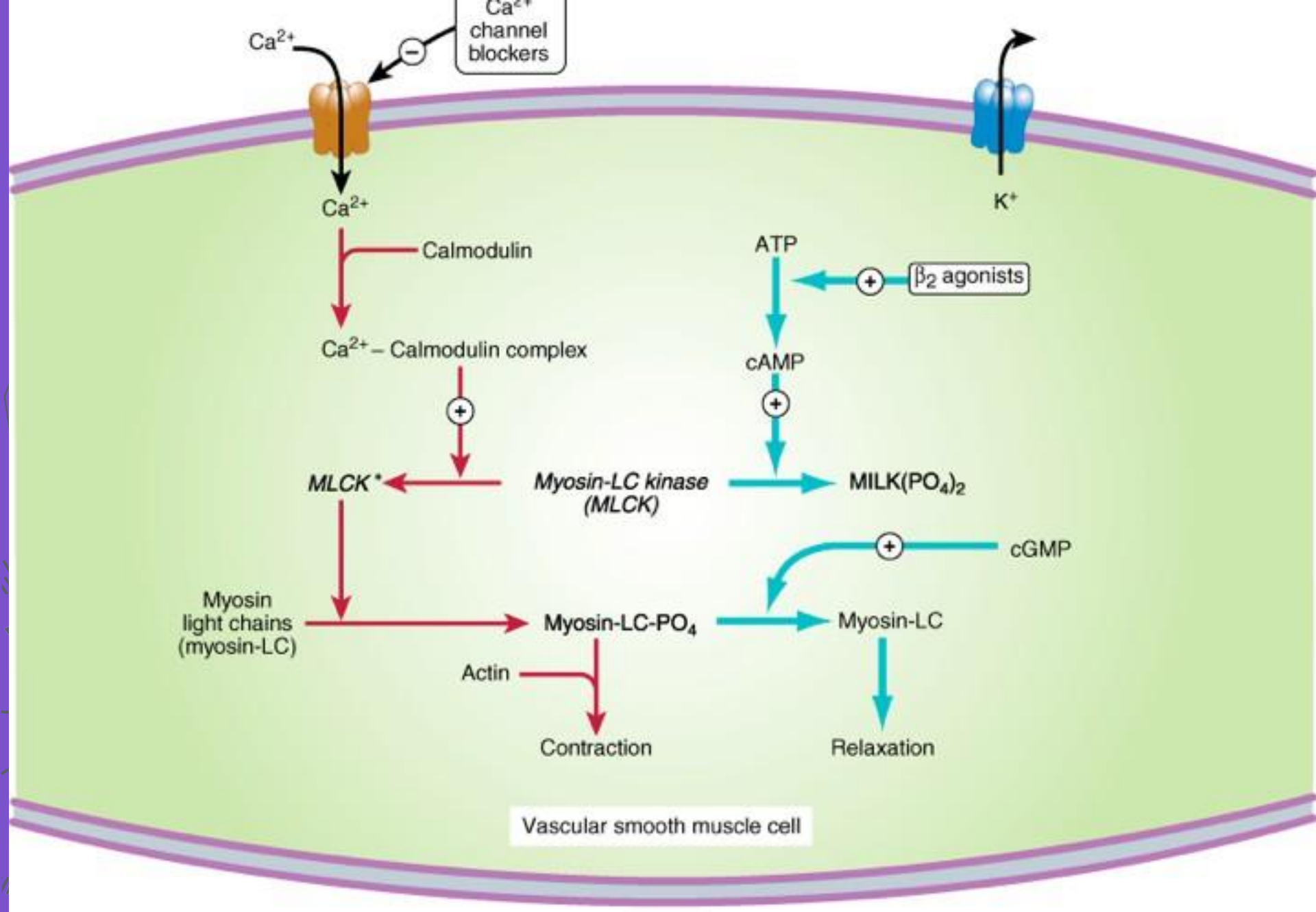
Calcium Channel Blockers

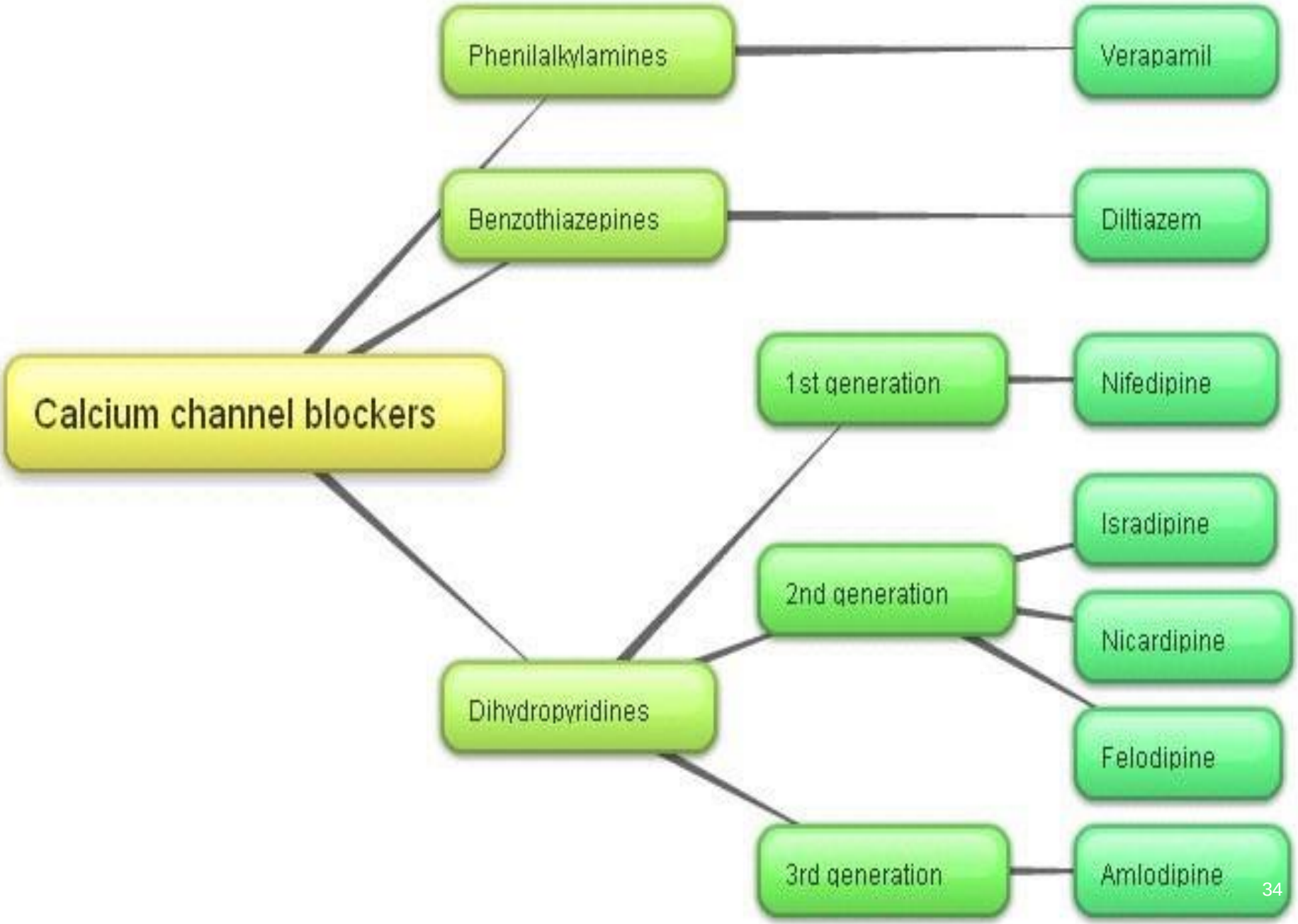
Particularly beneficial in vasospasm.

Can affect platelets aggregation.

May be dangerous in heart failure and in patients susceptible to hypotension.






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

Verapamil and Diltiazem

- In patients with relatively low blood pressure, dihydropyridines can cause further deleterious lowering of pressure. Verapamil and diltiazem appear to produce less hypotension and may be better tolerated in these circumstances.
- In patients with a history of atrial tachycardia, flutter, and fibrillation, verapamil and diltiazem provide a distinct advantage because of their antiarrhythmic effects.

Drug	Oral Bioavailability (%)	Half-Life (hours)	Indication
Dihydropyridines			
Amlodipine	65–90	30–50	Angina, hypertension
Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon
Isradipine	15–25	8	Hypertension
Nicardipine	35	2–4	Angina, hypertension
Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon
Nimodipine	13	1–2	Subarachnoid hemorrhage
Nisoldipine	< 10	6–12	Hypertension
Nitrendipine	10–30	5–12	Investigational
Miscellaneous			
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine

Calcium Channel Blockers

- **Side Effects:**
- Hypotension.
- Headache, dizziness.
- Flushing.
- Peripheral edema.

Effects of Nitrates Alone and with Beta Blockers or Calcium Channel Blockers in Angina Pectoris.

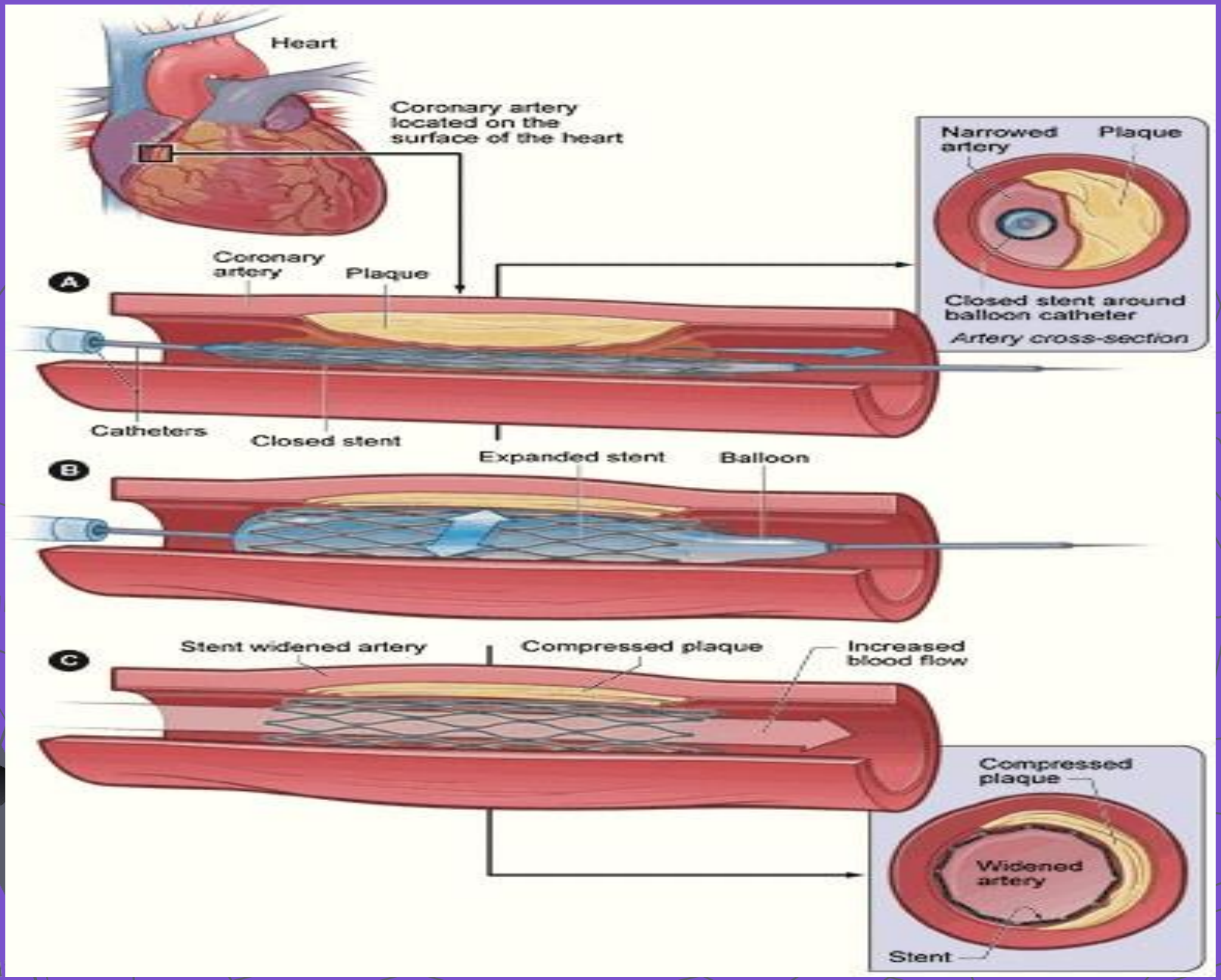
	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	Reflex[1]increase	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	Increase	Non or decrease
Contractility	Reflex[1]increase	Decrease	Non
Ejection time	Decrease	Increase	Non

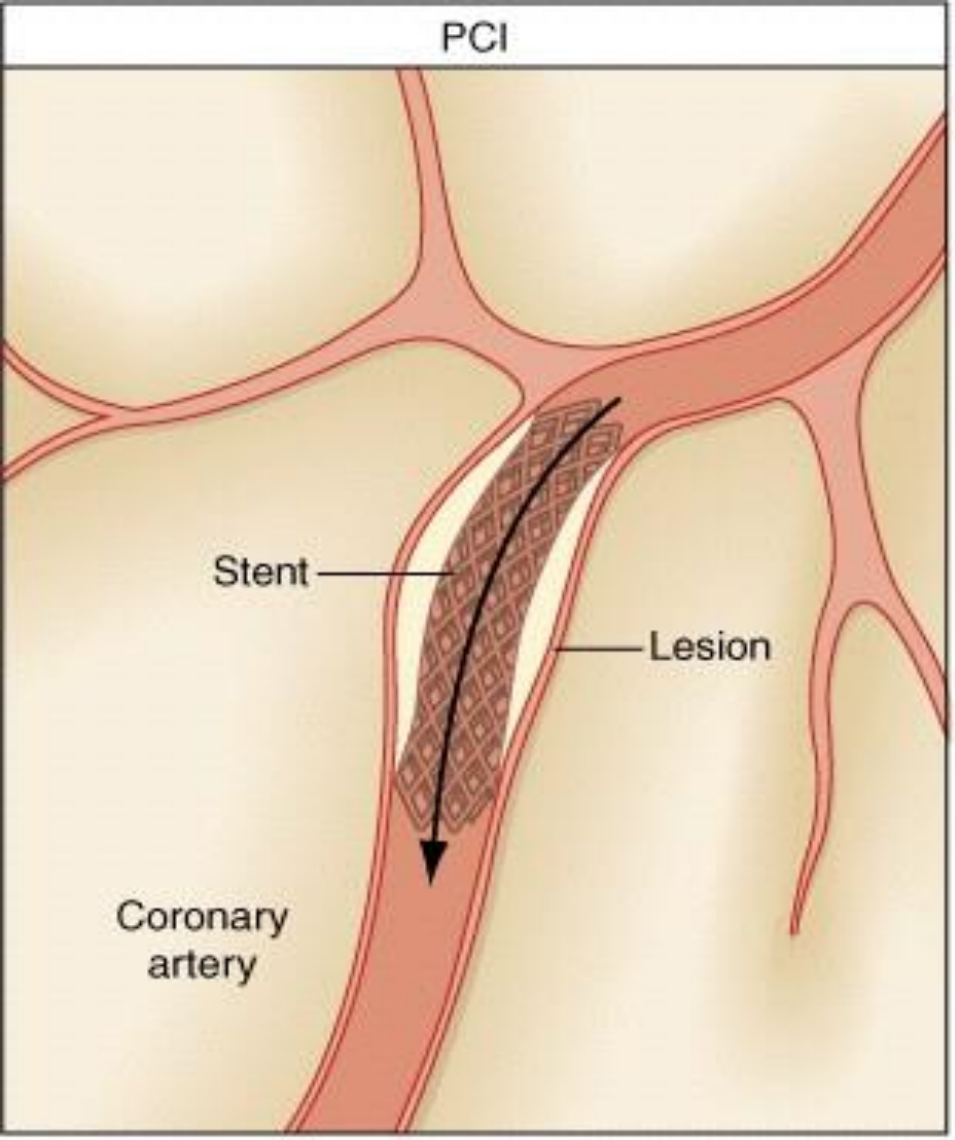
Dipyridamole

- Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme.
- Thought to be a good coronary dilator.
- Increases the blood flow to the normal area i.e. "Coronary Steal Phenomenon."
- Still used as an antiplatelet drug (in TIAs), but not better than aspirin.

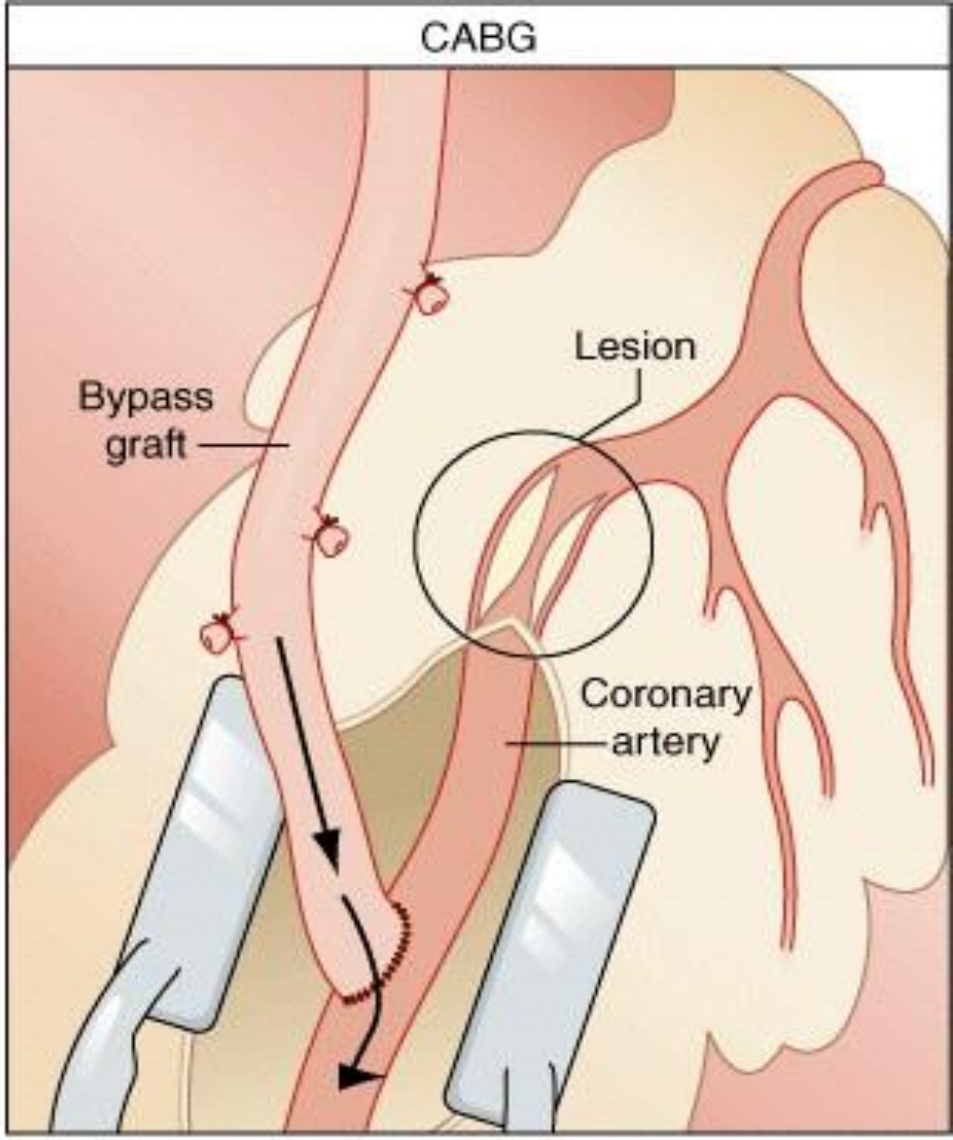
Others

- ACEI.
- Anticoagulants and/or Thrombolytic Therapy.
- Cholesterol Lowering Agents.
- Angioplasty
- Surgery.


Heart
Coronary artery located on the surface of the heart
Narrowed artery
Plaque
Closed stent around balloon catheter
Artery cross-section
A
Coronary artery
Plaque
Catheters
Closed stent
B
Expanded stent
Balloon
C
Stent widened artery
Compressed plaque
Increased blood flow
Compressed plaque
Widened artery
Stent



Stent addresses the existing lesion but not future lesions.



Bypass grafting addresses the existing lesion and also future culprit lesions.

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Newer Antianginal Drugs

- Metabolic modulators: Ranolazine.
- Direct bradycardic agents: Ivabradine.
- Potassium channel activators: Nicorandil.
- Rho-kinase inhibitors: Fasudil.
- Vasopeptidase inhibitors.
- Nitric oxide donors: L- arginine.
- Capsaicin.
- Amiloride.

Newer Antianginal Drugs

- Metabolic modulators: Ranolazine.
- Direct bradycardic agents: Ivabradine.
- Potassium channel activators: Nicorandil.
- Rho-kinase inhibitors: Fasudil.
- Sulfonylureas: Glibenclamide.
- Thiazolidinediones.
- Vasopeptidase inhibitors.
- Nitric oxide donors: L- arginine.
- Capsaicin.
- Amiloride.

Newer Antianginal Drugs

- Ranolazine is a newer antianginal drug that appears to act by reducing a late sodium current (I Na) that facilitates calcium entry via the sodium-calcium exchanger.
- The resulting reduction in intracellular calcium concentration reduces cardiac contraction.

Newer Antianginal Drugs

- trimetazidine: metabolic modulators are known as pFOX inhibitors because they partially inhibit the fatty acid oxidation pathway in myocardium.
- Because metabolism shifts to oxidation of fatty acids in ischemic myocardium, the oxygen requirement per unit of ATP produced increases.

Newer Antianginal Drugs

- Ivabradine: relatively selective I f sodium channel the hyperpolarization
  - -activated sodium channel in the sinoatrial reported (inhibition of pace maker current(
- Ivabradine appears to reduce anginal attacks with an efficacy similar to that of calcium channel blockers and β blockers.

Newer Antianginal Drugs

- The Rho kinases comprise a family of enzymes that inhibit vascular relaxation and diverse functions of several other cell types. Excessive activity of these enzymes has been implicated in coronary spasm, pulmonary hypertension, apoptosis, and other conditions. Drugs targeting the enzyme have therefore been sought for possible clinical applications.
- Fasudil is an inhibitor of smooth muscle Rho kinase and reduces coronary vasospasm in experimental animals. In clinical trials in patients with CAD,

ivabradineit has improved performance in stress tests.

Newer Antianginal Drugs

- allopurinol , represents another type of metabolic modifier. Allopurinol inhibits xanthine oxidase, an enzyme that contributes to oxidative stress and endothelial dysfunction.
- A recent study suggests that high-dose allopurinol prolongs exercise time in patients with atherosclerotic angina.