Drug Treatment of Ischemic Heart Disease

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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.

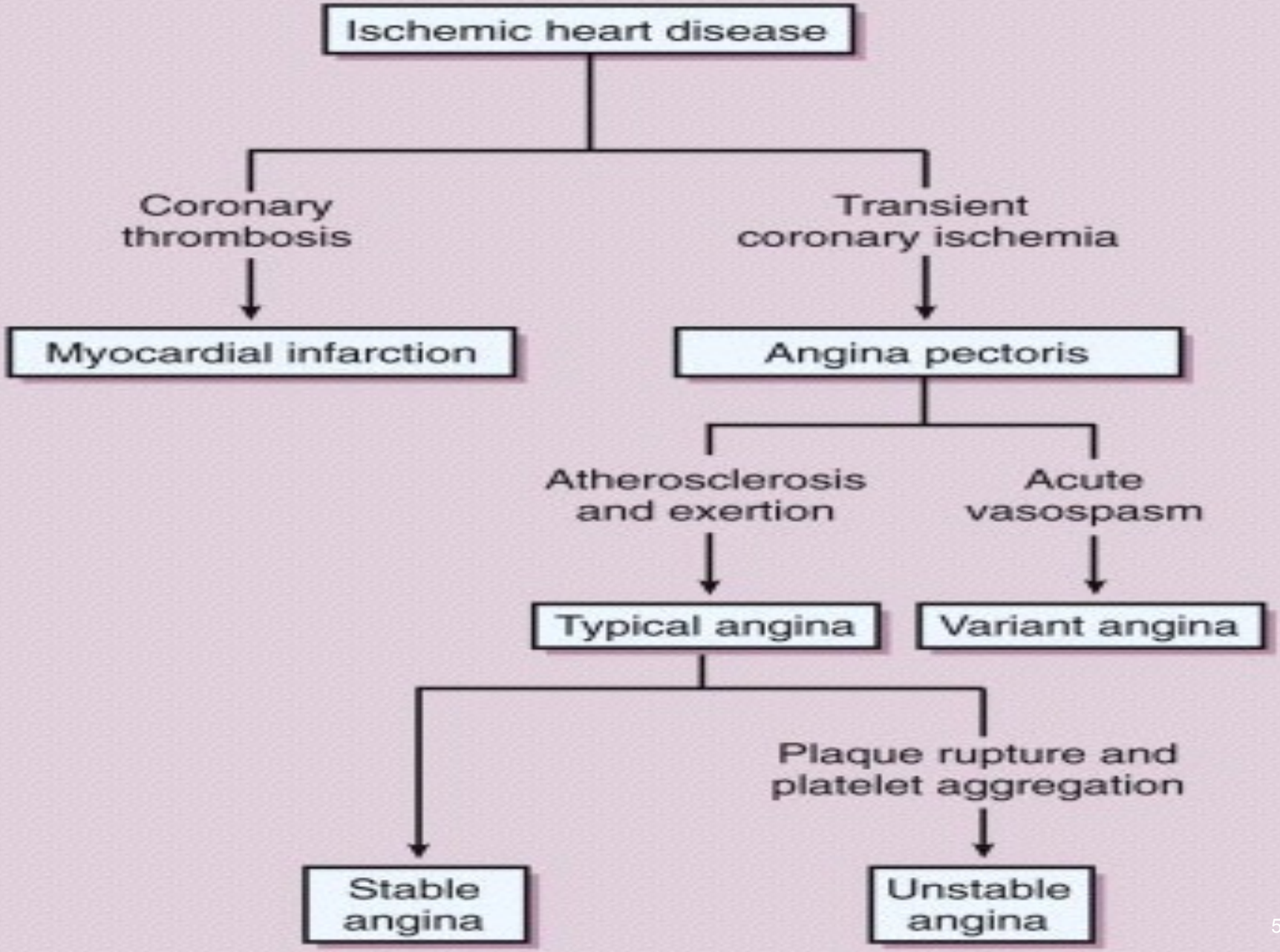
Types of angina

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.

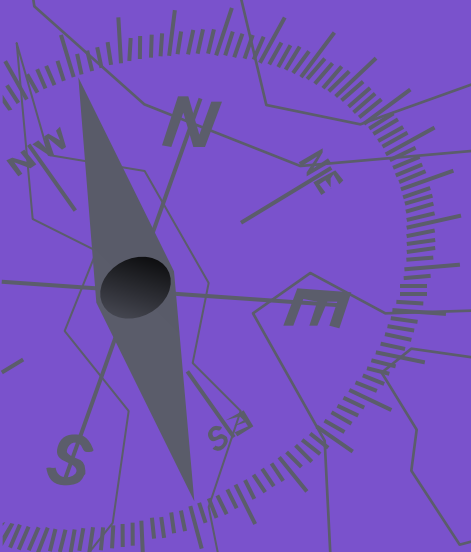

Ischemic heart disease
Coronary thrombosis
Transient coronary ischemia
Myocardial infarction
Angina pectoris
Atherosclerosis and exertion
Acute vasospasm
Typical angina
Variant angina
Plaque rupture and platelet aggregation
Stable angina
Unstable angina

Secondary Angina	Primary Angina
Classical	Variant (Prinzmetal's)
Angina of Effort	Angina at Rest
Typical	Atypical
Small vessels	Large vessels
Single or multiple	Single
Atherosclerosis	Vasospasm
ST depression	ST elevation

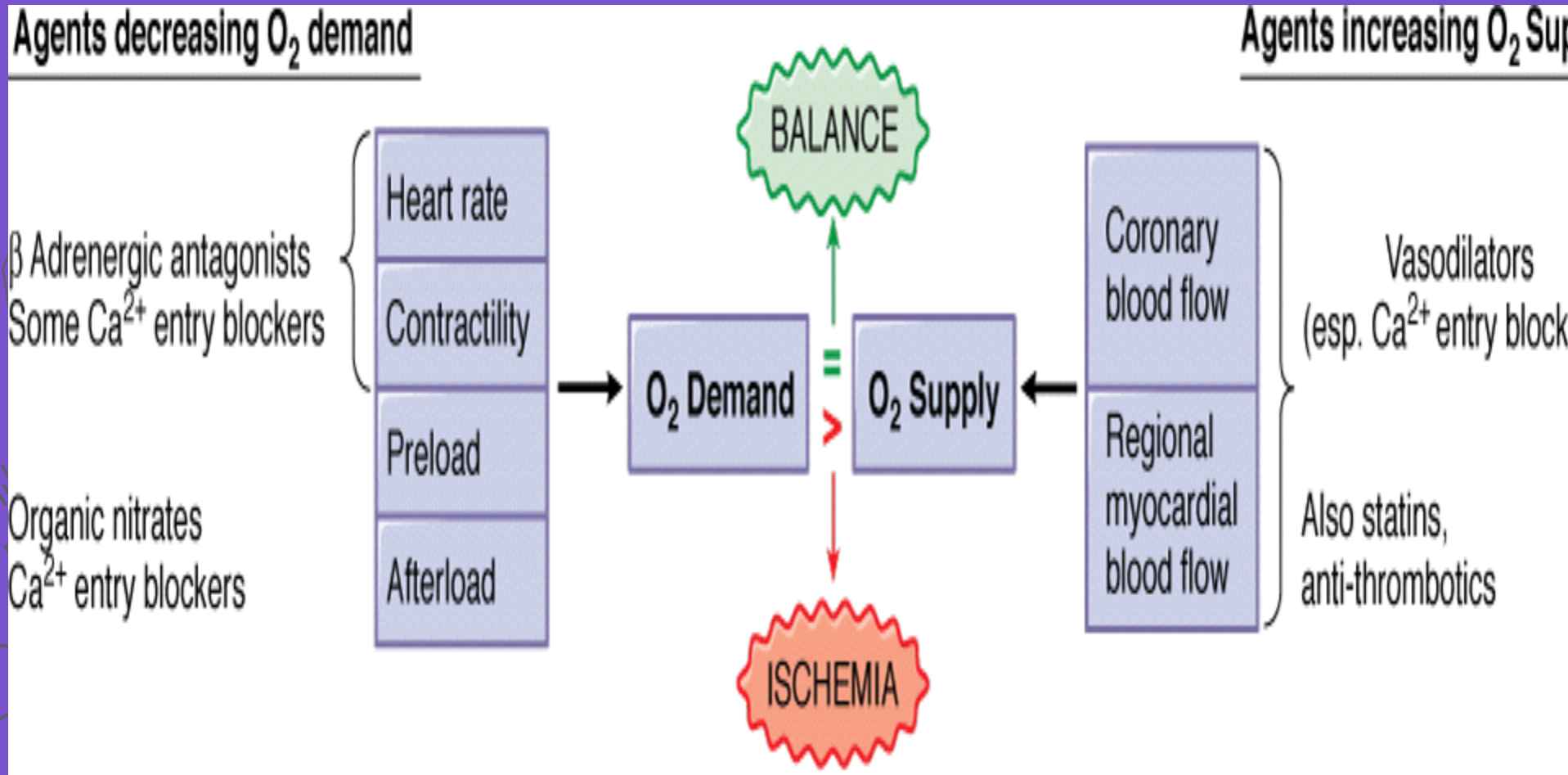
Mechanism of IHD

Due to an imbalance of the ratio:

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



Pharmacological modification of the major determinants of myocardial O2 supply

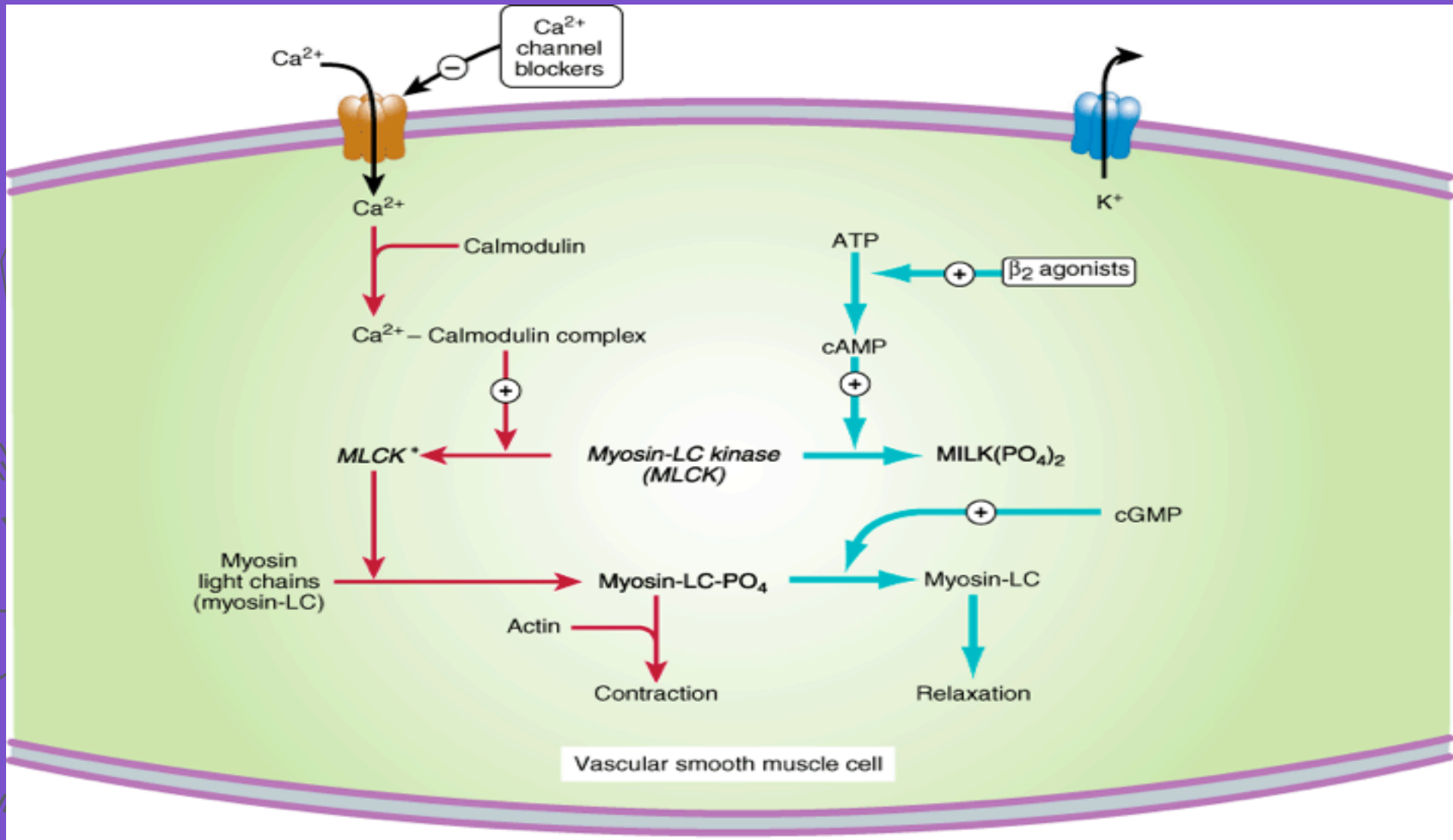


Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Control of smooth muscle contraction

- Contraction is triggered by influx of calcium through L-type transmembrane calcium channels.
- The calcium combines with calmodulin to form a complex that converts the enzyme myosin light-chain kinase to its active form (MLCK*).
- MLCK phosphorylates the myosin light chains, thereby initiating the interaction of myosin with actin.
- Beta2 agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle by accelerating the inactivation of MLCK and by facilitating the expulsion of calcium from the cell.

Control of vascular smooth muscle contraction



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://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.

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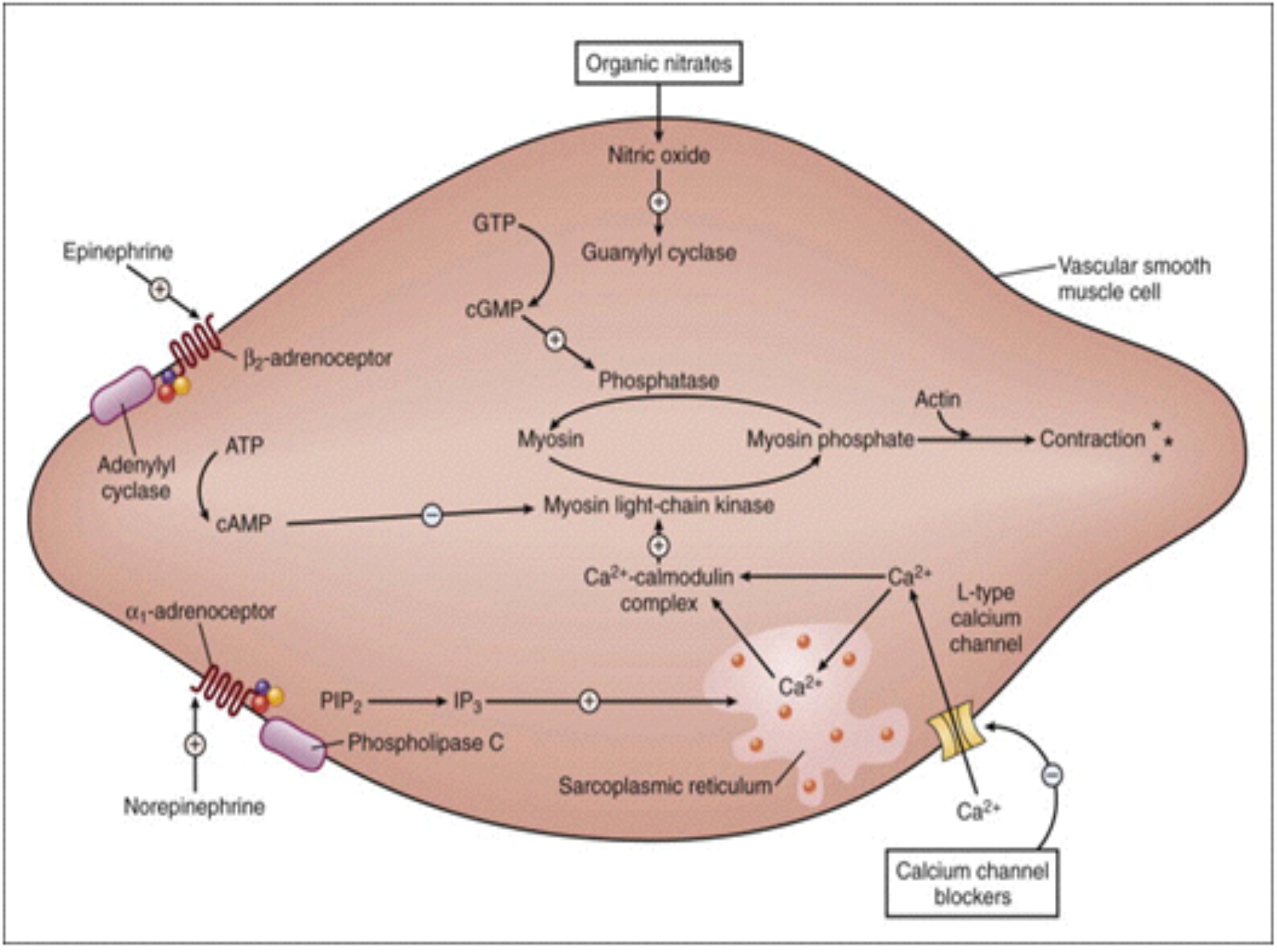
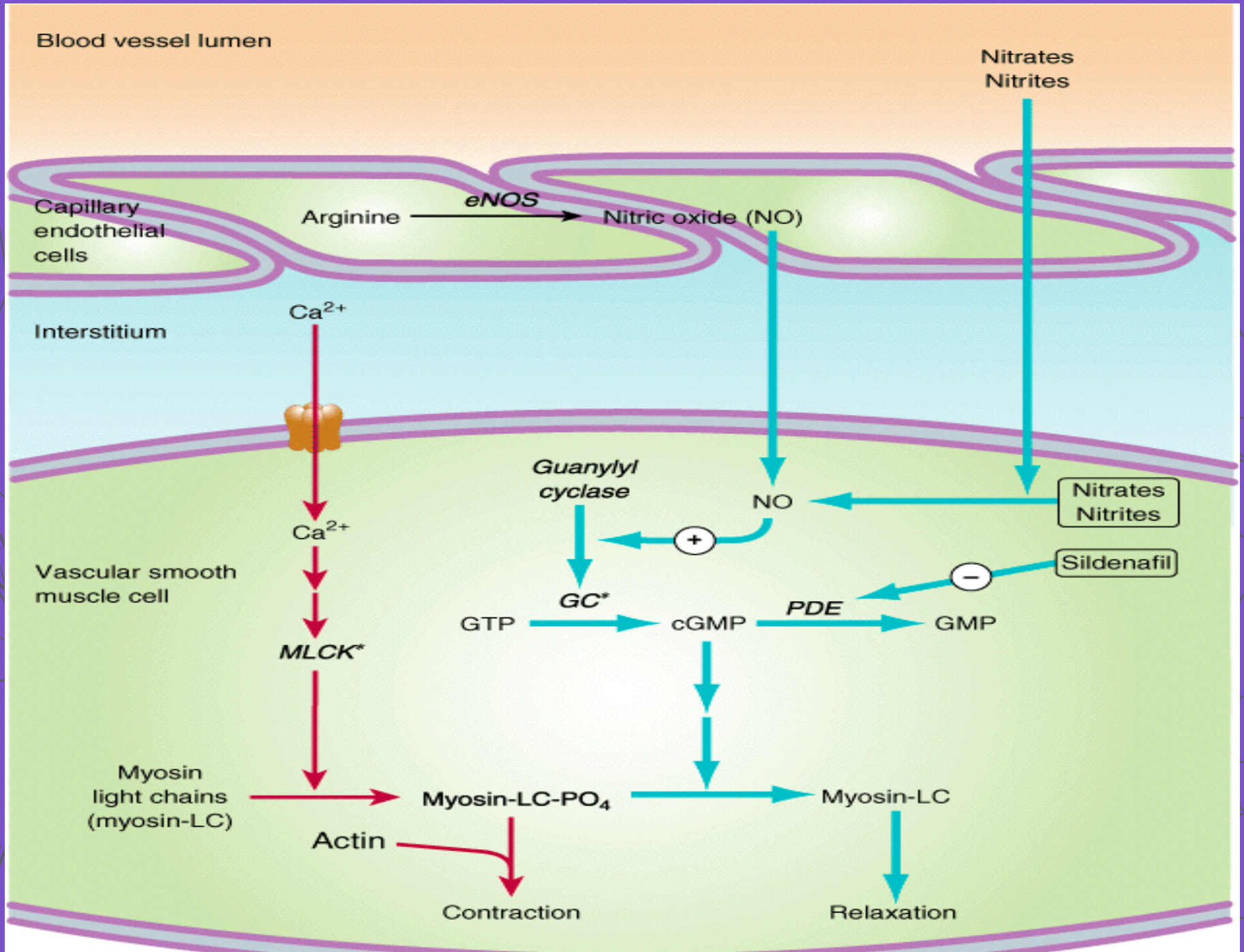

Organic nitrates
Nitric oxide
GTP
Guanylyl cyclase
Epinephrine
Vascular smooth muscle cell
cGMP
β2-adrenoceptor
Phosphatase
Actin
Myosin
Myosin phosphate
Contraction
ATP
Adenylyl cyclase
cAMP
Myosin light-chain kinase
Ca2+-calmodulin complex
Ca2+
L-type calcium channel
α1-adrenoceptor
PIP2
IP3
Ca2+
Phospholipase C
Sarcoplasmic reticulum
Norepinephrine
Ca2+
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.

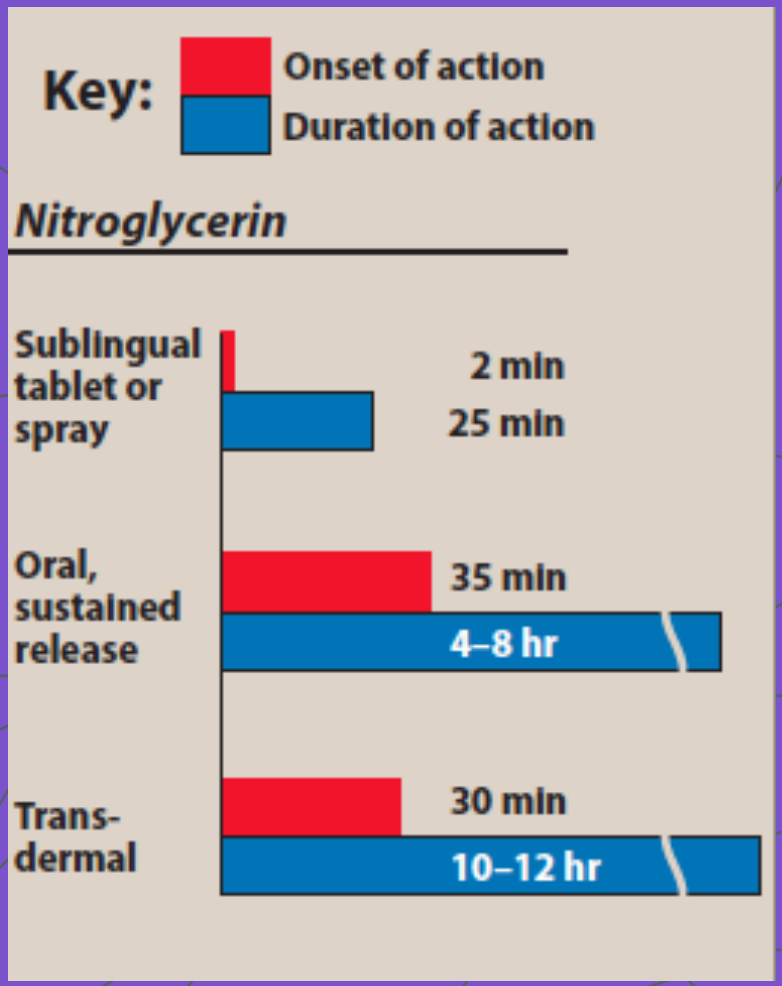

Blood vessel lumen
Nitrates
Nitrites
Capillary endothelial cells
Arginine
eNOS
Nitric oxide (NO)
Interstitium
Ca2+
Guanylyl cyclase
NO
Nitrates
Nitrites
Ca2+
Sildenafil
Vascular smooth muscle cell
GC*
PDE
GTP
cGMP
GMP
MLCK*
Myosin light chains (myosin-LC)
Myosin-LC-PO4
Myosin-LC
Actin
Contraction
Relaxation

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.



Significant first-pass metabolism of *nitroglycerin* occurs in the liver. Administered via the sublingual or transdermal route (patch or ointment),

Nitroglycerine (GTN)

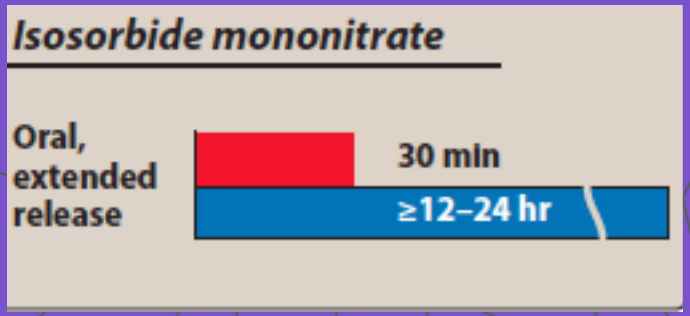
- Causes general vasodilation:
- Arteriolar dilation: short lived (5-10 min)
  - Decreases systemic blood pressure (afterload) and causes reflex tachycardia and increased contractility, ?might increase MVO2.
- Venous dilation: more intense, even with low doses, lasts for 30 minutes.
  - Decreases venous return (preload) and decreases MVO2.

Nitroglycerine (GTN)

- Uses:For prompt relief of an angina attack precipitated by exercise or emotional stress, sublingual (or spray form) nitroglycerin is the drug of choice.
- **Side Effects:**
- **Headache.**
- **Hypotension and tachycardia.**
- **Increased intraocular and intracranial pressures.**
- **Methemoglobinemia.**
- **Tolerance: only for the arteriolar effects.**
- **Withdrawal: in workers in ammunition industry.**

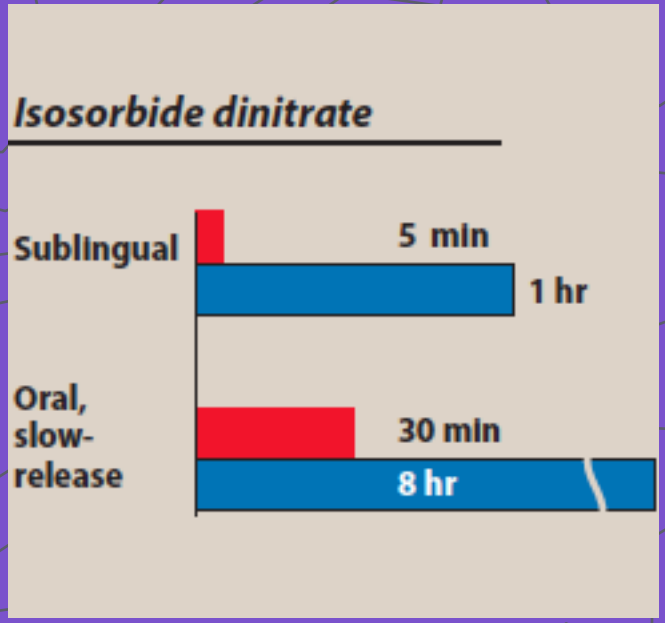
Isosorbide mononitrate

Better bioavailability and long duration
Not subjected to hepatic breakdown.



Isosorbide dinonitrate

Oral isosorbide dinitrate undergoes denitration to two mononitrates, both of which possess antianginal activity.



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	3–6 hours
Nitroglycerin, slow-release, buccal	3–6 hours
Nitroglycerin, slow-release patch, transdermal	8–10 hours
Isosorbide dinitrate, sublingual	1.5–2 hours
Isosorbide dinitrate, oral	4–6 hours
Isosorbide dinitrate, chewable oral	2–3 hours
Isosorbide mononitrate, oral	6–10 hours

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:

in which β-blockers are ineffective and may actually worsen symptoms.

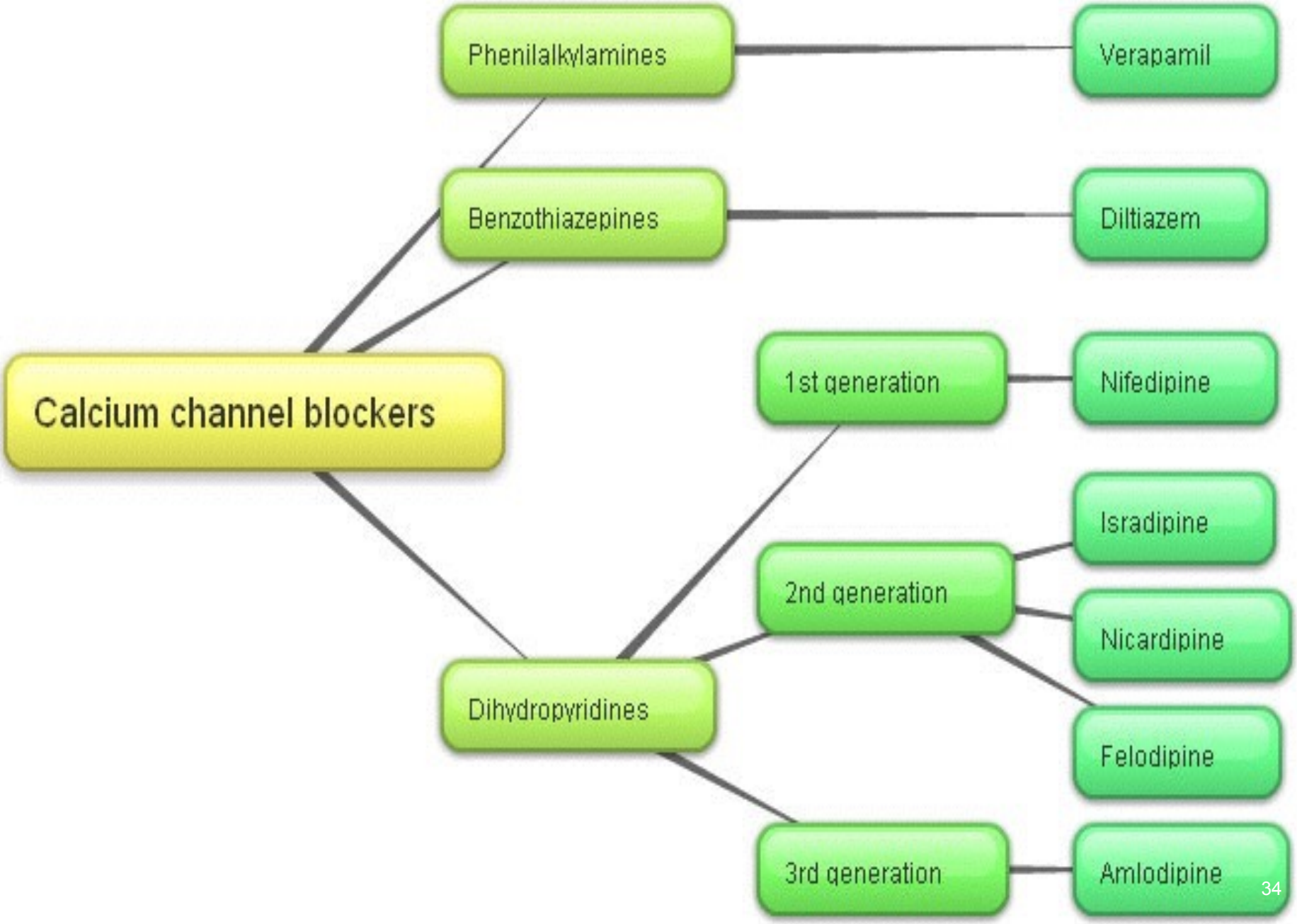
Bronchial asthma

Bradycardia

Pindolol XXX

β-adrenergic blocking agents

- β-Blockers are recommended as initial antianginal therapy in all patients unless contraindicated.
- β-Blockers reduce the risk of death and MI in patients who have had a prior MI
- They improve mortality in patient with hypertension and heart failure with reduced ejection fraction


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

Calcium channel blockers

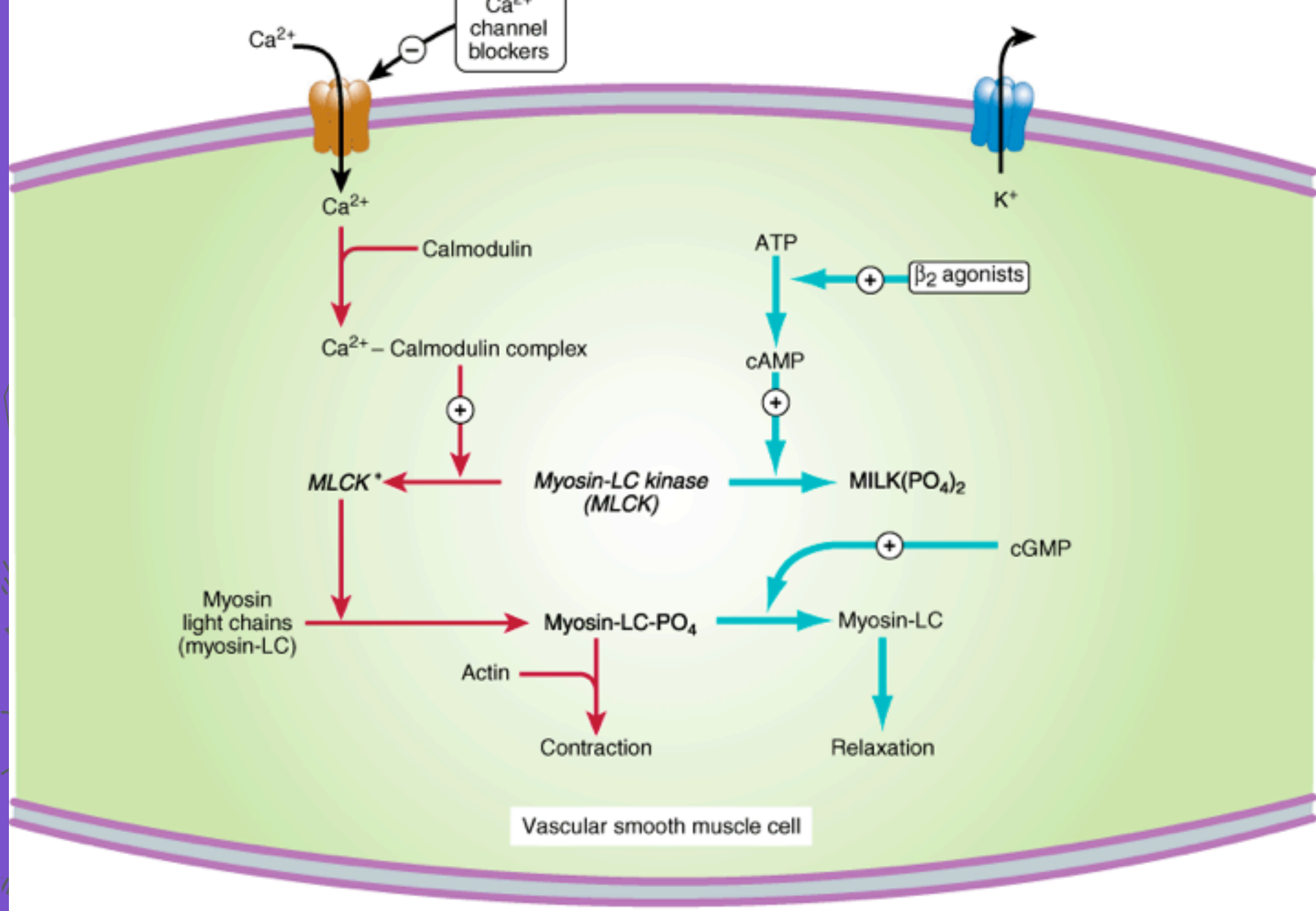
- Inhibiting the entrance of calcium into cardiac and smooth muscles cells of the coronary arteries

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.

Calcium Channel Blockers

- All calcium channel blockers are, therefore, arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance.
- In the treatment of effort-induced angina, calcium channel blockers reduce myocardial oxygen consumption.
- Their efficacy in vasospastic angina is due to relaxation of the coronary arteries.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

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.**

Calcium Channel Blockers

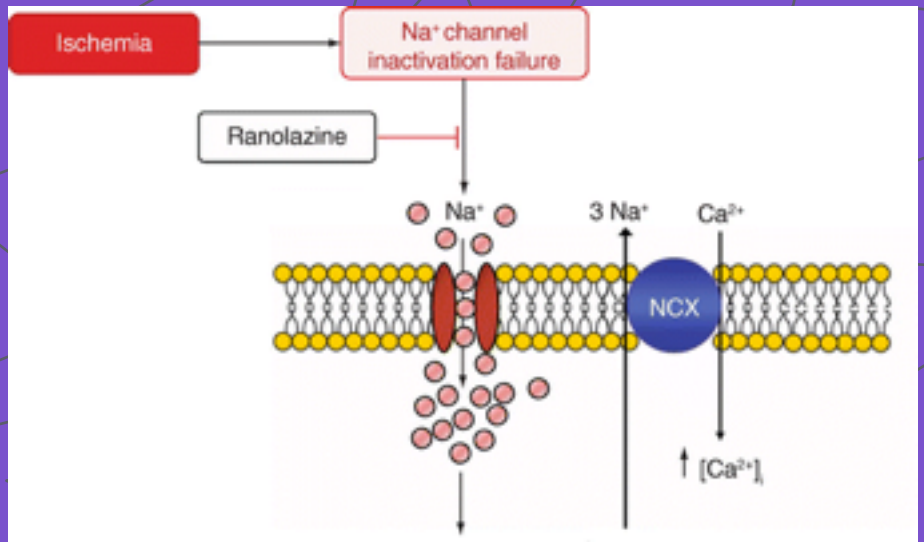
- **Side Effects:**
- Hypotension.
- Headache, dizziness.
- Flushing.
- Peripheral edema.

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

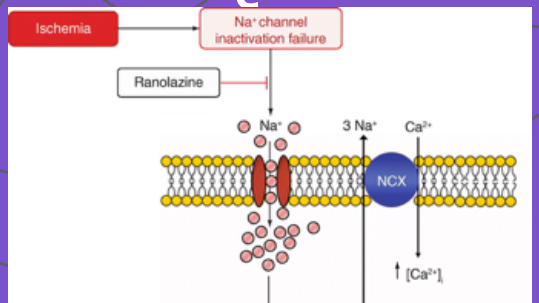
Ranolazine

- Ranolazine is a newer antianginal drug 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
- Inhibition of late INa reduces intracellular sodium and calcium overload, thereby improving diastolic function.



Ranolazine

- Ranolazine has antianginal as well as antiarrhythmic properties.
- **USES:** patients who have failed other antianginal therapies.
- **Drug interactions:** Extensively metabolized in the liver by the CYP3A family and also by CYP2D6. It is also a substrate of P-glycoprotein.
- In addition, ranolazine can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.



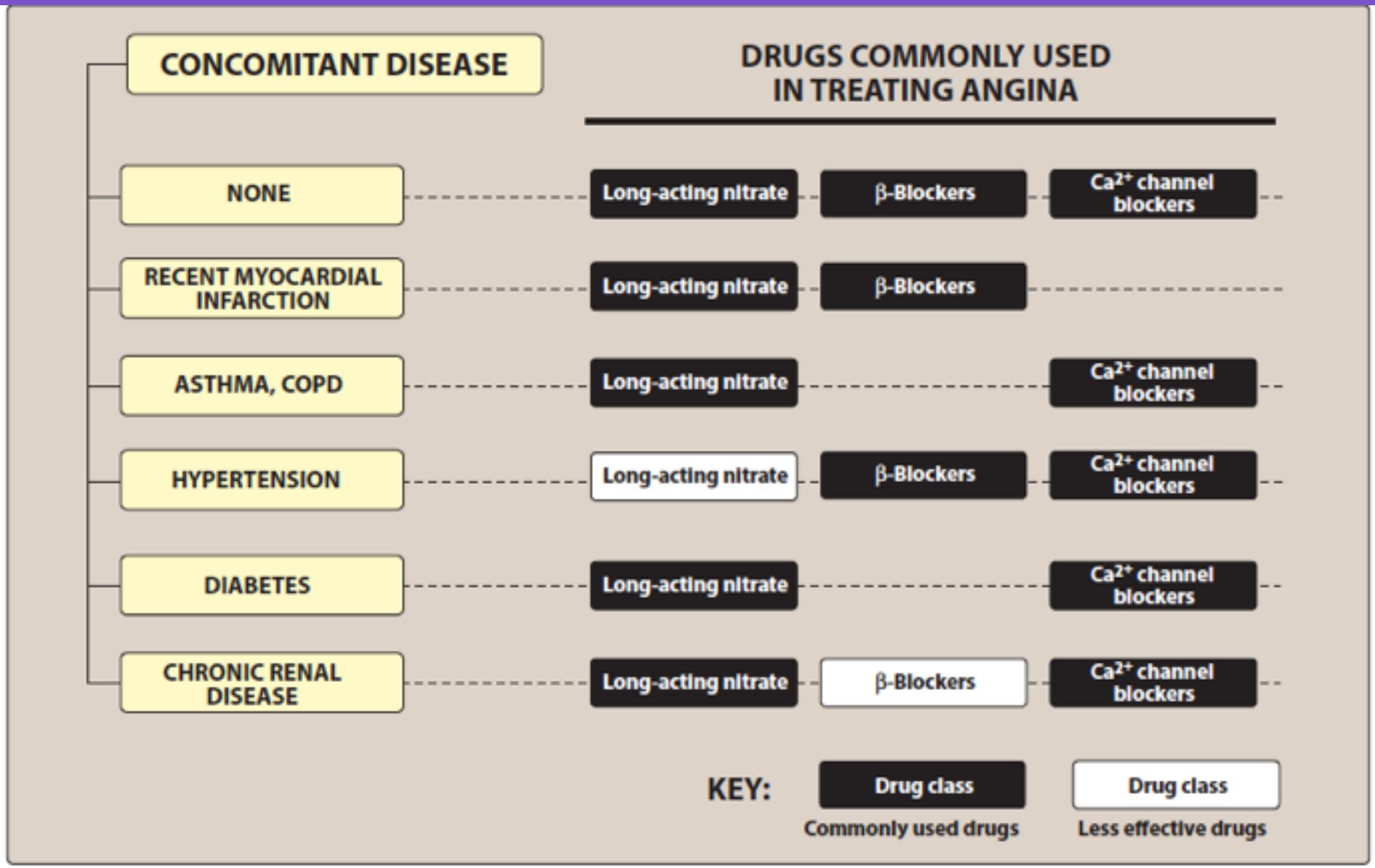
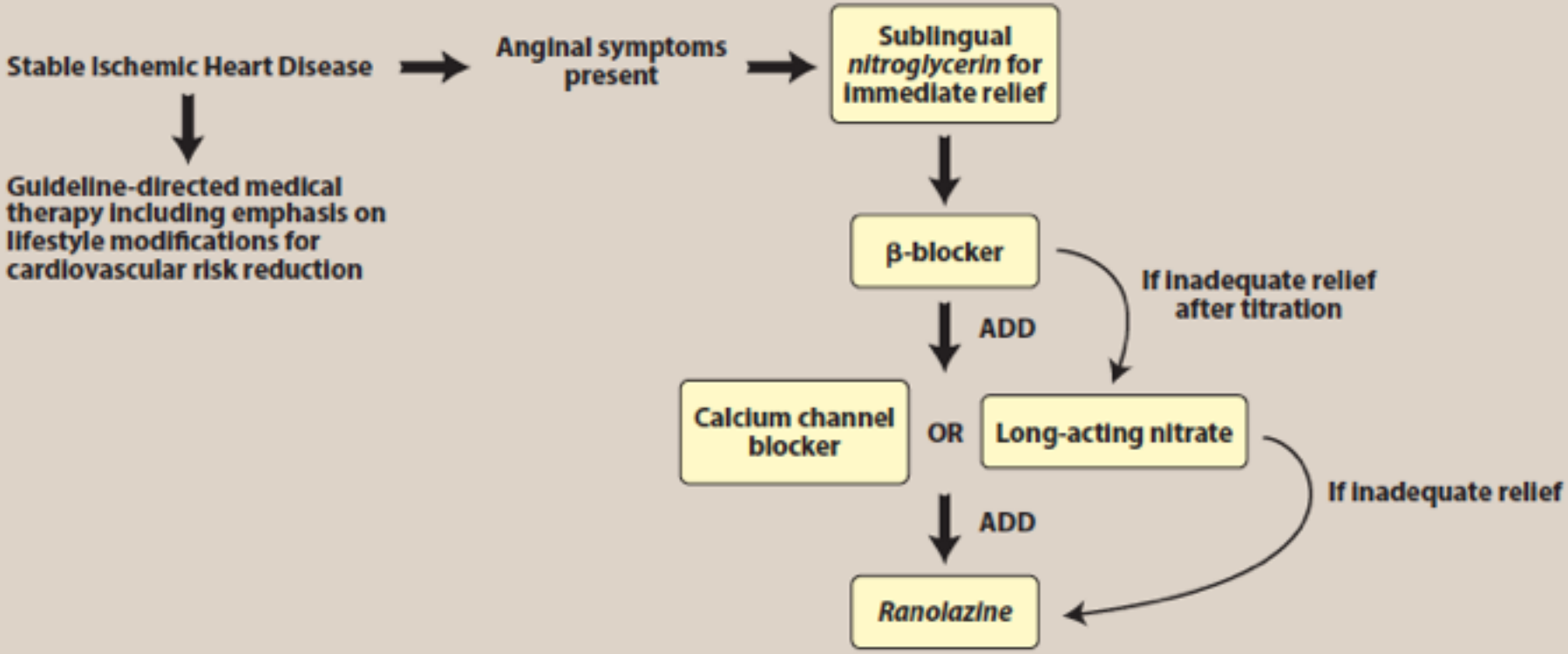

CONCOMITANT DISEASE
DRUGS COMMONLY USED IN TREATING ANGINA
NONE
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
RECENT MYOCARDIAL INFARCTION
Long-acting nitrate
β-Blockers
ASTHMA, COPD
Long-acting nitrate
Ca2+ channel blockers
HYPERTENSION
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
DIABETES
Long-acting nitrate
Ca2+ channel blockers
CHRONIC RENAL DISEASE
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
KEY:
Drug class
Commonly used drugs
Drug class
Less effective drugs

Figure 21.3


Stable Ischemic Heart Disease
Anginal symptoms present
Sublingual *nitroglycerin* for immediate relief
Guideline-directed medical therapy including emphasis on lifestyle modifications for cardiovascular risk reduction
β-blocker
If inadequate relief after titration
ADD
Calcium channel blocker
OR
Long-acting nitrate
If inadequate relief
ADD
Ranolazine

Trimetazidine:

- First cytoprotective anti-ischemic agent .
- metabolic modulators are known as pFOX inhibitors because they partially inhibit the fatty acid beta-oxidation pathway in myocardium.
- Preserves energy metabolism in cells exposed to hypoxia…. prevents the decrease in intracellular ATP levels

Ivabradine

- **Bradycardic** drugs, relatively selective If $_f$ sodium channel :reduce cardiac rate by inhibiting the sodium channel in the SA node (**inhibition of pace maker current**).
- No other significant hemodynamic effects have been reported.
- USES: heart-related chest pain and heart failure
- The lack of effect on gastrointestinal and bronchial smooth muscle is an advantage of ivabradine.

Ivabradine

- Ivabradine appears to reduce anginal attacks with an efficacy similar to that of calcium channel blockers and β blockers.
- It may be as effective as the beta blocker atenolol[4] and comparable with amlodipine in the management of chronic stable angina.
- It is used in combination with beta blockers in people with heart failure with LVEF lower than 35 percent
- Side effects: luminous phenomena, bradycardia 2% and 5% of.[4] 2.6–4.8% reported headaches. first-degree AV block, ventricular extrasystoles, dizziness and/or blurred vision.

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.

Allopurinol

- 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.

Dipyridamole

- Inhibits the uptake of adenosine and PDE3 inhibitor .
- 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.
- Dipyridamole enhances exercise-induced myocardial ischemia even the usual oral dosage and hence it not used as an anti-platelet agent in patients with stable angina

Others

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