

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 be 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.

The symptoms are not relieved by rest or nitroglycerin.

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

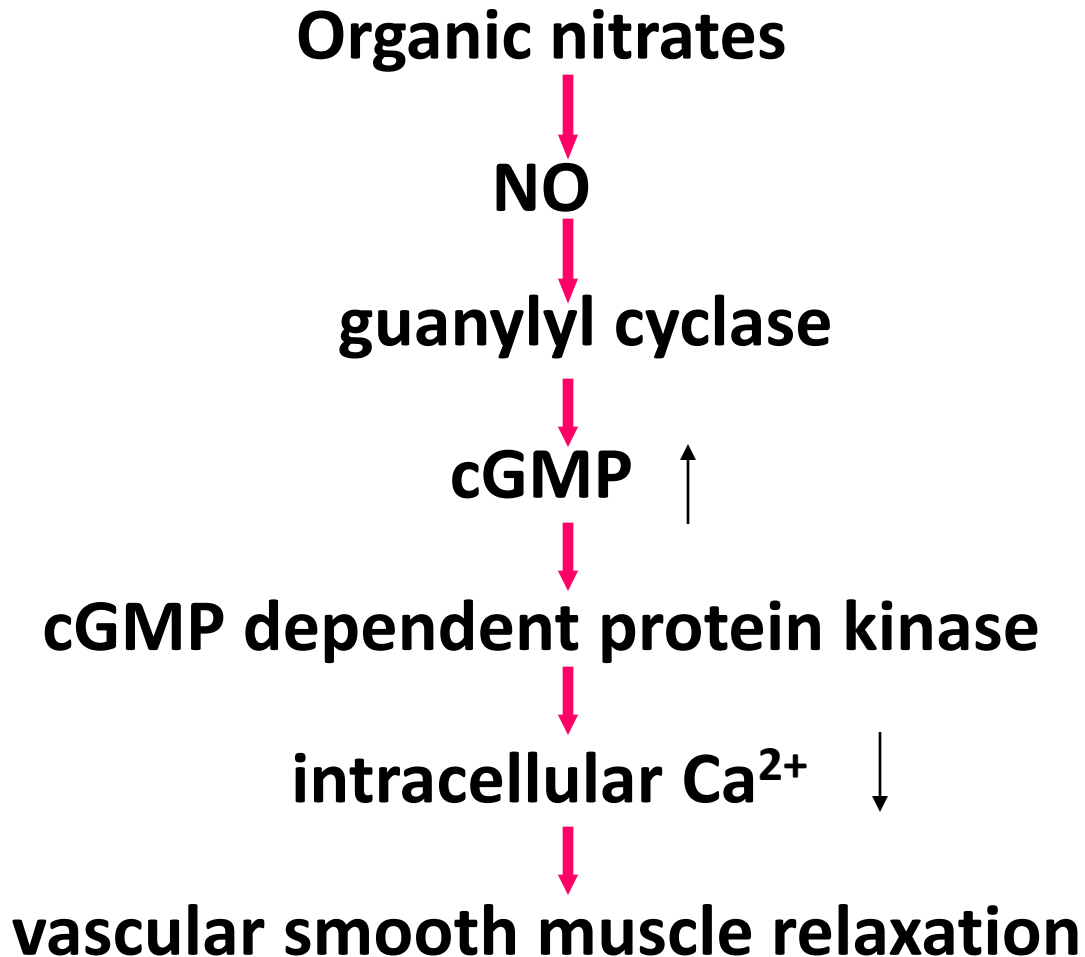
- C. Variant angina, occurs at rest and caused by coronary artery spasm (i.e. caused by contraction of the smooth muscle tissue in the vessel walls rather than directly by atherosclerosis)

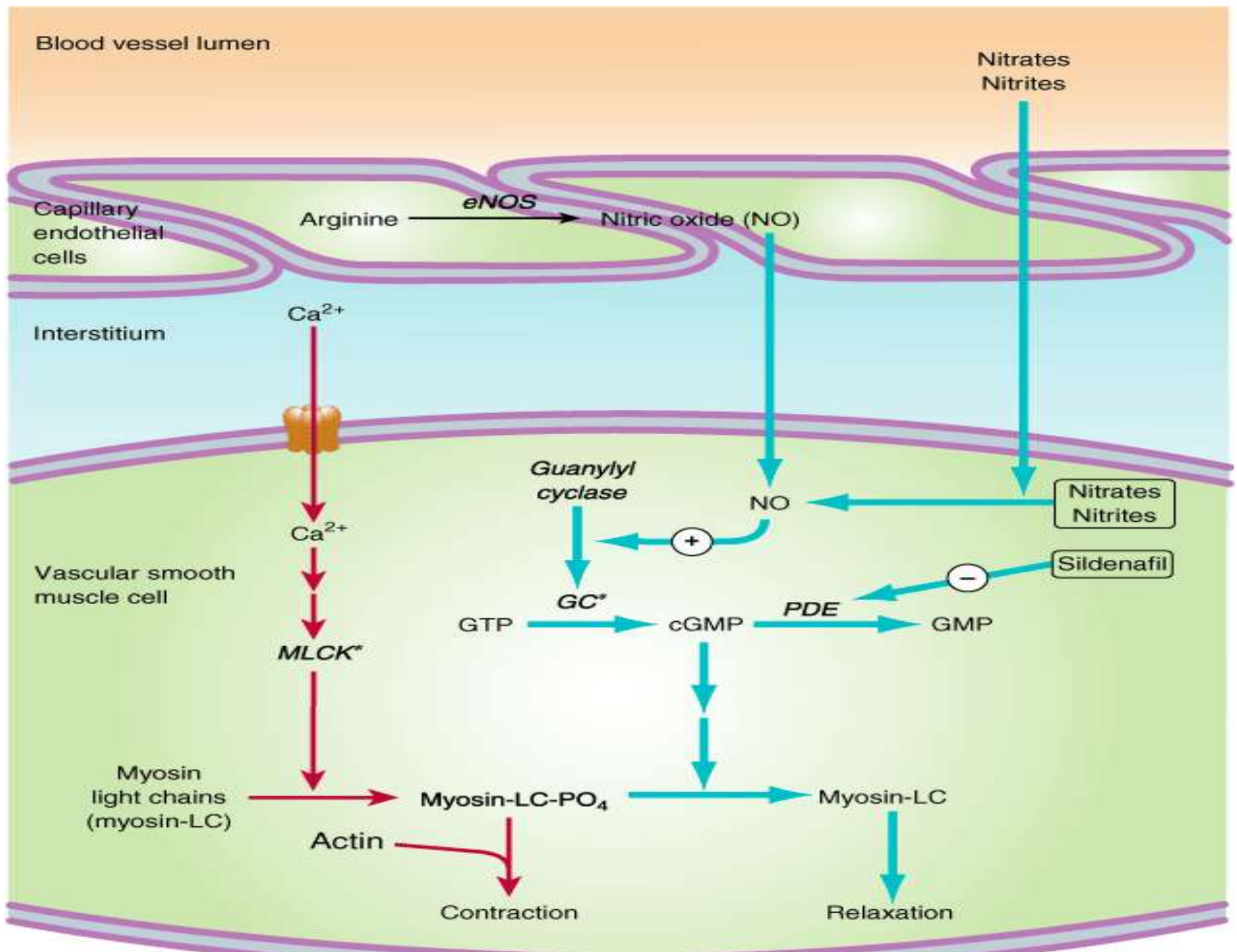
Generally, this type rapidly responds to nitroglycerin and calcium channel blockers.

Organic nitrates

- These compounds cause a rapid reduction in the myocardial oxygen demand, and so provide a rapid relief for the angina symptoms.
- They are effective in the three types of angina pectoris.
- Their mechanism of action summarized in a decrease coronary spasm or vasoconstriction and in an increase perfusion of the myocardial by relaxing the coronary arteries.
- Members of this group include: isosorbide dinitrate, isosorbide mononitrate, and Nitroglycerine.

2. Pharmacological mechanism





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).
orthostatic hypotension and syncope.
 - b. dilates the coronary arteries.

Beneficial and Deleterious Effects of Nitrates in the Treatment of Angina

	Result
1. Potential beneficial effects	
Decreased ventricular volume	Decreased myocardial oxygen requirement
Decreased arterial pressure	
Decreased ejection time	
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
2. Potential deleterious effects	
Reflex tachycardia	Increased myocardial oxygen requirement
Reflex increase in contractility	
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

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).

Organic nitrates

- Adverse effect:
 - a. headache (throbbing headach) is a common early side effect of nitrates, which is usually decrease after the first few days (patient develop tolerance).

Contraindicated in if intracranial pressure elevated.

- b. high doses can cause postural hypotension syncope, also can result in tachycardia.
- Sildenafil (Viagra) potentiates the action of nitrates, and to avoid the dangerous hypotension, an interval of six hour between the two agents is recommended.

Tolerance

- Tolerance to the action of the nitrates develops rapidly, the blood vessels become desensitized to the vasodilation.
- Why????? diminished release of nitric oxide resulting from depletion of tissue thiol compounds may be partly responsible for tolerance to nitroglycerin.
- The tolerance can be overcome by providing a daily “nitrate free intervals” to restore sensitivity to the drug (this interval are usually 10 – 12 hr at night)

Important notes to your patient

- The conventional sublingual tablet form of nitroglycerin may lose potency when stored as a result of volatilization and adsorption to plastic surfaces. Therefore, it should be kept in tightly closed glass containers. Nitroglycerin is not sensitive to light.
- spray is equally effective; it has a shelf life of two to three years and does not require refrigeration

General Guideline

- One or fewer — People who have one or fewer angina episodes per week are usually advised to take sublingual (under the tongue) nitroglycerin when an episode of angina occurs and immediately before activities that could cause angina.
- Two or more — People who have two or more angina episodes per week are usually advised to take longer-acting antianginal medicines. This may include a long-acting nitrate or a beta blocker.
- Treatment with added medicines — If angina persists while taking one medicine, a second medicine may be added. Combined treatment may relieve angina more effectively than a single medicine.

β -adrenergic blocking agents

- They suppress the heart by blocking β_1 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_1 agents, such as acebutolol and atenolol and metoprolol are preferred.
- They combined with nitrates to increase exercise duration and tolerance.

Beta-Blockers

- Decrease myocardial oxygen consumption
- Blunt exercise response
- Try to avoid drugs with intrinsic sympathomimetic activity
- First line therapy in all patients with stable angina

Undesirable effects

- **An increase in end-diastolic volume and an increase in ejection time, both of which tend to increase myocardial oxygen requirement.**
- **These deleterious effects of beta -blocking agents can be balanced by the concomitant use of nitrates.**

β -adrenergic blocking agents

2. clinical uses

stable and unstable angina

myocardial infarction

3. contraindication

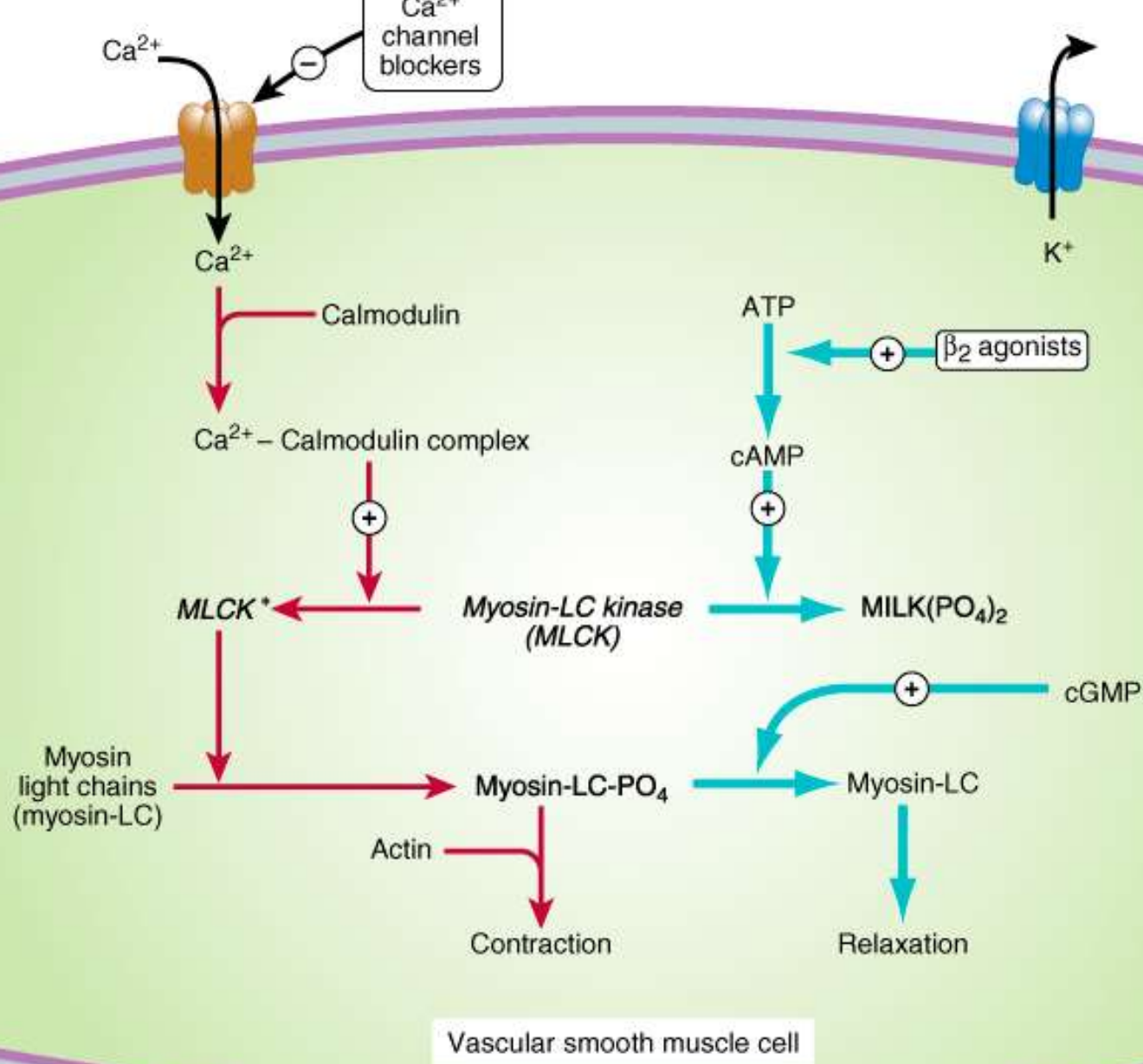
variant angina,

bronchial asthma,

bradycardia,

Calcium channel blockers

- Inhibiting the entrance of calcium into cardiac and smooth muscles cells of the coronary arteries and so they lower blood pressure.
 - A. Nifedipine, 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

Mechanisms of Action

- Arterial dilation/after-load reduction
- Coronary arterial vasodilation
- Prevention of coronary vasoconstriction
- Enhancement of coronary collateral flow
- Improved subendocardial perfusion
- Slowing of heart rate with **diltiazem, verapamil**

Calcium channel blockers

- Long-acting CCB's (e.g. amlodipine) or sustained release formulations of short-acting CCB's (e.g. nifedipine, felodipine, verapamil and diltiazem) are preferred,

to minimize fluctuations of plasma concentrations and cardiovascular effects.

- Side-effects are also concentration-dependent, and mainly related to the arterial vasodilator responses
(headache, flushing and ankle oedema);

these effects are more pronounced with dihydropyridine CCB's.

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.

Comparison

- Meta-analyses comparing effects of beta-blockers and CCB's in stable angina pectoris indicate that:

beta-blockers are more effective than CCB's in reducing anginal episodes,

but that effects on exercise tolerance and ischemia of the two drug classes are similar

- However, CCB's are especially effective in patients with vasospastic (Prinzmetal) angina

Combination Therapy of Angina

- Use of more than one class of antianginal agent can reduce specific undesirable effects of single agent therapy

Effect	Nitrates Alone	Beta-Blockers or Channel Blockers Alone	Nitrates Plus Beta-Blockers or Channel Blockers
Heart Rate	<i>Reflex Increase</i>	Decrease*	Decrease
Afterload	Decrease	Decrease	Decrease
Preload	Decrease	<i>Increase</i>	None or decrease
Contractility	<i>Reflex increase</i>	Decrease*	None
Ejection time	Decrease	<i>Increase</i>	None

Undesireable effects are shown in italics

Stable angina for medical management

Immediate short-term relief

Short acting sublingual or buccal nitrate, prn

Treatment aimed at improving prognosis

Aspirin 75-150mg od

Statin
+/-Titrate dose ↑ to get target cholesterol

ACE-inhibitor in proven CVD

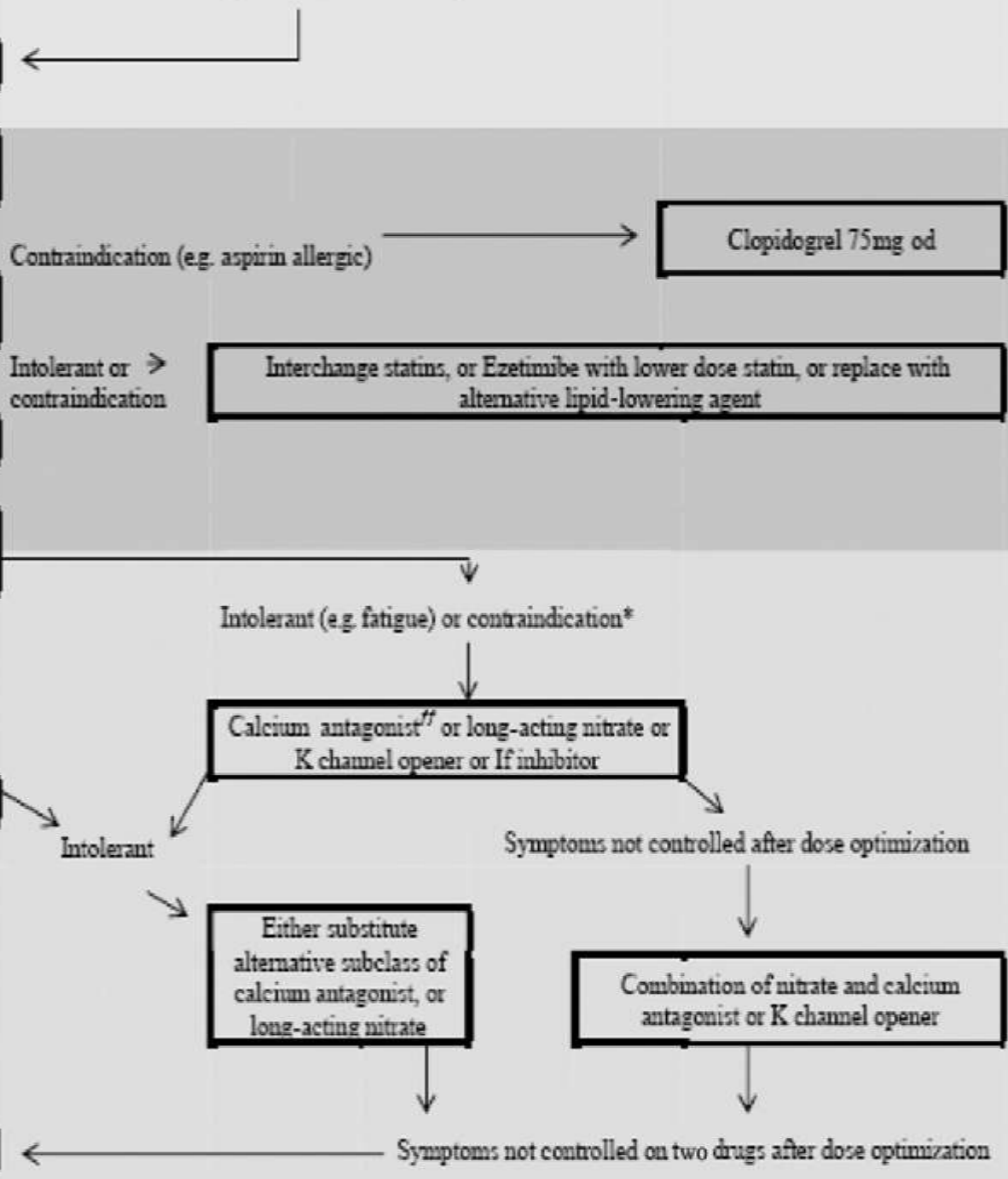
Beta blocker post MI
Beta blocker- no prior MI

Treatment aimed at relief of symptoms

Add calcium antagonist or long acting nitrate

Symptoms not controlled after dose optimization

Consider suitability for revascularization



Recommendations for pharmacological therapy of vasospastic angina

- Treatment with calcium antagonists and if necessary nitrates in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.
- Decrease vasospasm of coronary vessels (calcium channel blockers are efficacious in >70% of patients; *increase oxygen delivery*)