PHARMACOLOGY

بسم الله الرحمن الرحيم

MID | Lecture 5

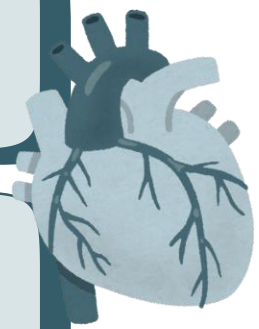
Ischemic Heart Disease Drugs

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا

Written by: Roaa Maakoseh, Sarah Mahasneh

Reviewed by: Sarah Mahasneh



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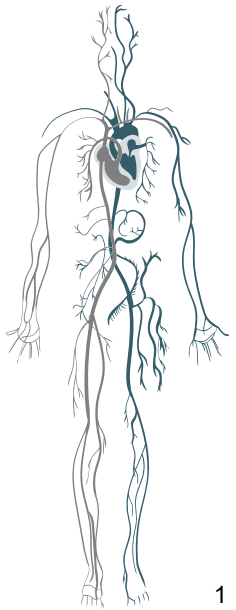


Drug Treatment of Ischemic Heart Disease

Don’t stress about the number of slides.
The lecture is easy to follow ☺

1

Angina pectoris

- Sudden, severe symptom, pressing chest pain and radiating to the neck, jaw, back, and arms. The episodes are transient, lasting between 15 sec and 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. spasm of the vascular smooth muscles, due to stress or emotional distress
    b. obstruction of blood vessels caused by atherosclerosis.

Types of angina

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

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

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

This type is rapidly relieved by rest or **nitroglycerin**.

A potent vasodilator that releases nitric oxide (NO), leading to dilation of different blood vessels including coronary arteries

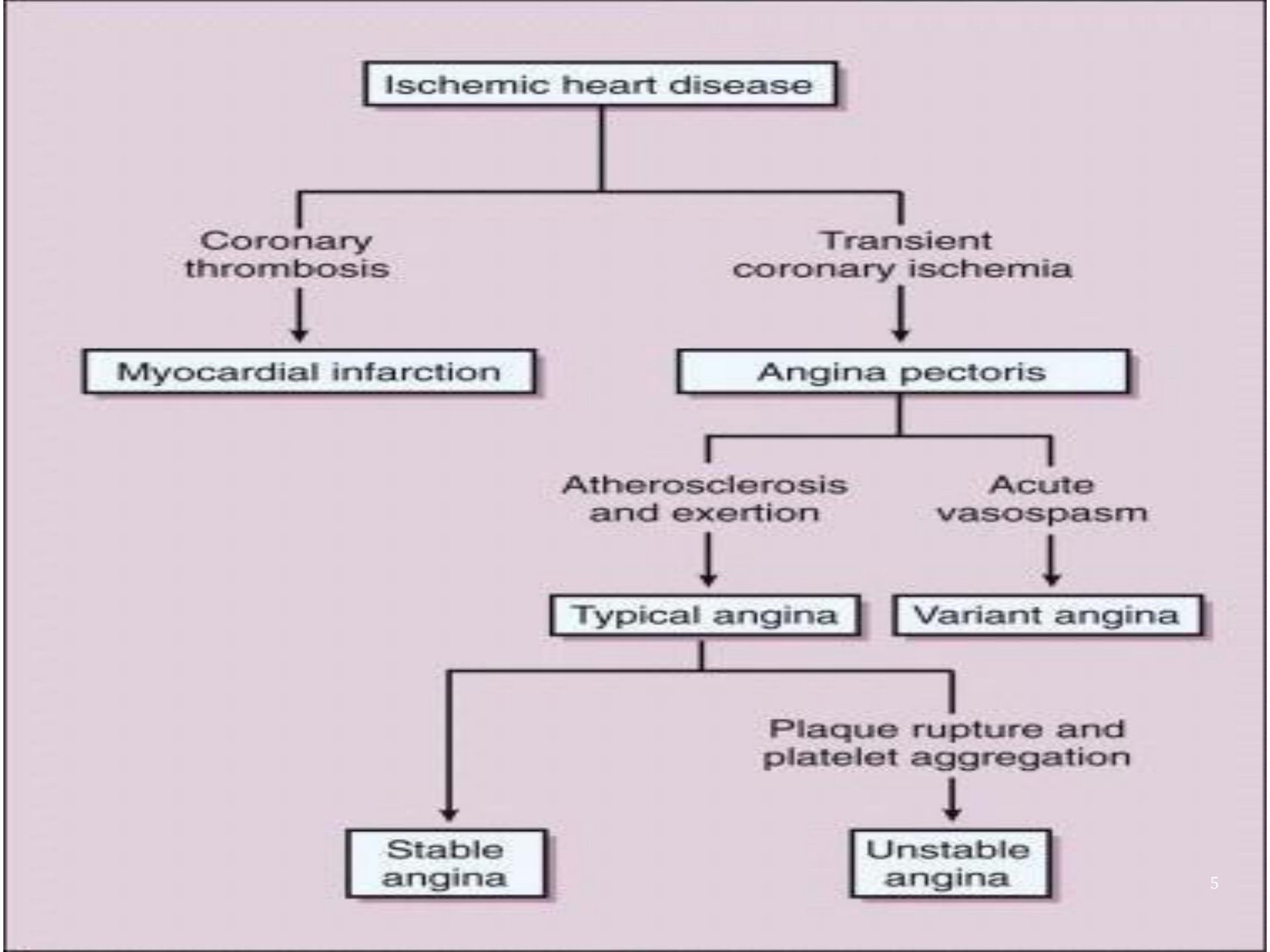
Types of angina

B. Unstable angina lies between stable angina and myocardial infarction (one of the ischemic heart disease forms), often unrelated to exercise. unstable angina requires more aggressive therapy, for example, treatments of dyslipidemias and hypertension.

- We need to treat elevated cholesterol levels, to prevent the patient from reaching that stage of myocardial infarction.

C. Variant angina occurs at rest and is 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

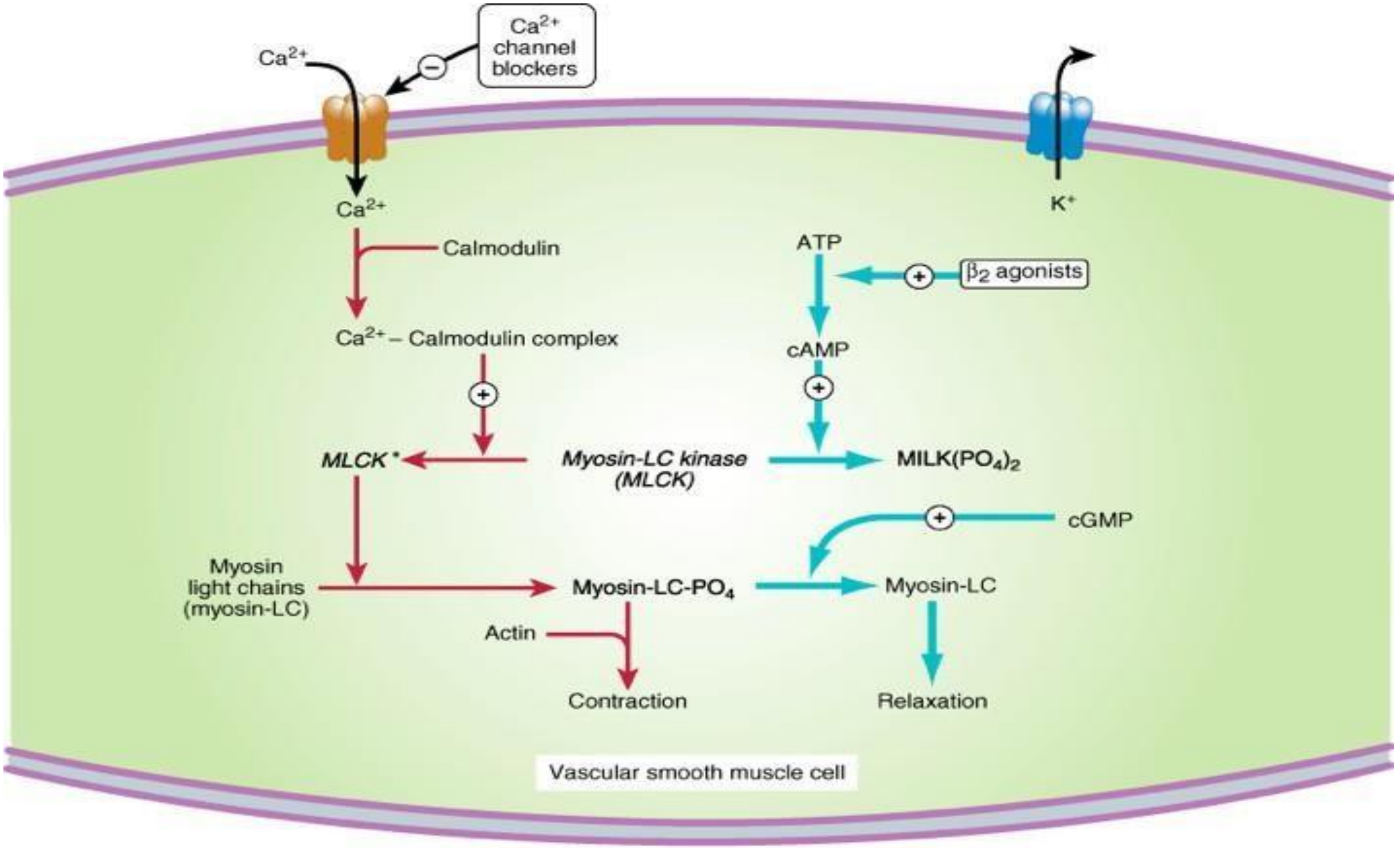
Mechanism of IHD

Due to an imbalance of the ratio:

O_2 Supply (Coronary Blood Flow)

O_2 Demand Work of the Heart

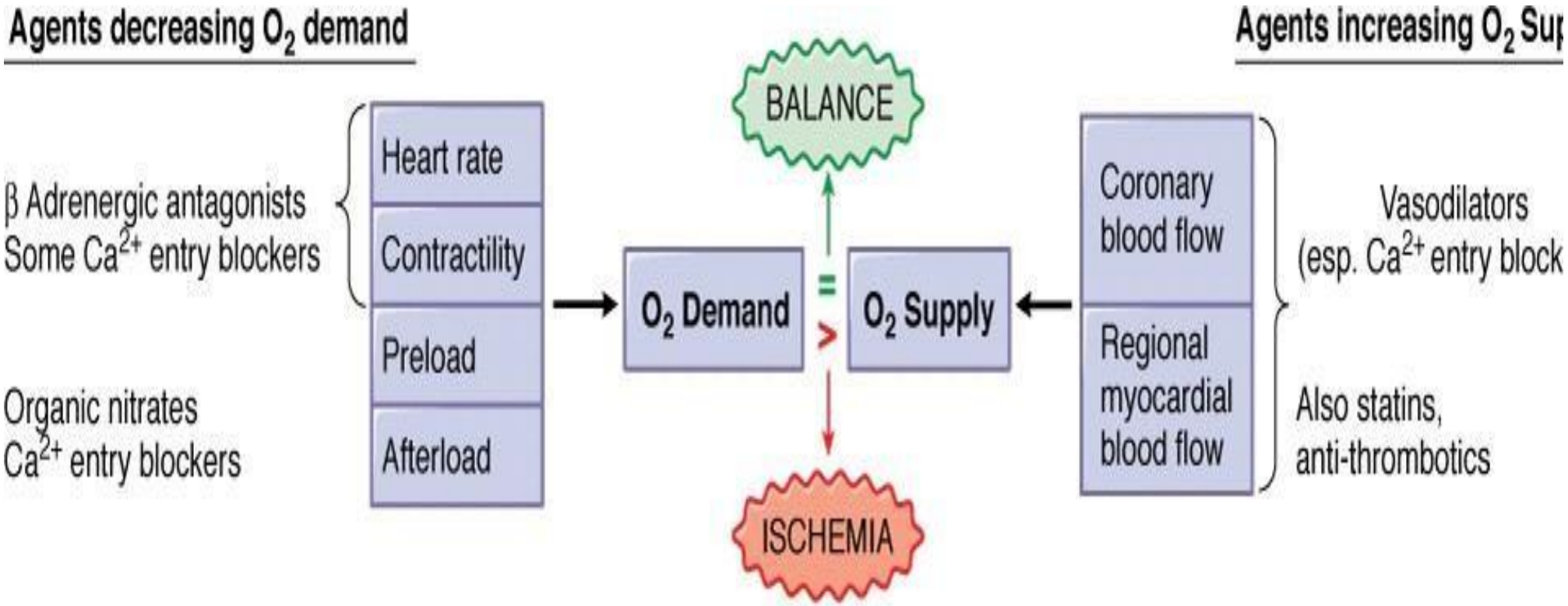
Control of vascular smooth muscle contraction



For any muscle to contract, calcium must enter the muscle cell.
The calcium ions bind to calmodulin, forming a **calcium-calmodulin complex**, which activates myosin light chain kinase (MLCK).
MLCK phosphorylates the myosin light chain, allowing actin-myosin interaction and resulting in vascular smooth muscle **contraction**.

The contraction of vascular smooth muscle is also regulated by receptors, such as **β_2-adrenergic receptors**.
Activation of these receptors increases cAMP levels, which activate protein kinase A (PKA). PKA inhibits MLCK activity, leading to relaxation of the smooth muscle.
By targeting these pathways, we can modulate vascular tone and control whether blood vessels contract or **relax**.

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

Pharmacological Control of Myocardial O_2 Balance

We can also reduce myocardial oxygen demand by decreasing the workload of the heart, primarily by lowering heart rate and contractility.

- **β-Adrenergic antagonists (β-blockers)** reduce heart rate and contractility by blocking β_1-adrenergic receptors in the heart, thereby decreasing oxygen demand.

- **Calcium channel blockers** can also reduce contractility and heart rate and cause vasodilation, which improves oxygen supply.

- **Organic nitrates** are simple nitric oxide esters of glycerol. They release nitric oxide (NO), leading to vasodilation of coronary vessels, thereby increasing coronary blood flow and reducing myocardial oxygen demand.

- Additionally, treating the underlying causes of atherosclerosis is essential.
Lipid-lowering drugs (such as statins) help reduce cholesterol levels and slow plaque formation.

- **Antithrombotic agents** help prevent or dissolve blood clots, improving overall coronary perfusion.

Drug effects on vascular smooth muscle contraction.

- Calcium influx is inhibited by **CCBs,** leading to muscle relaxation.

L-type calcium channels in vascular smooth muscle cells open in response to specific stimuli, allowing calcium influx from the extracellular space. This influx can stimulate additional calcium release from the sarcoplasmic reticulum through a process known as calcium-induced calcium release (CICR), leading to an increase in intracellular calcium concentration and promoting smooth muscle contraction.

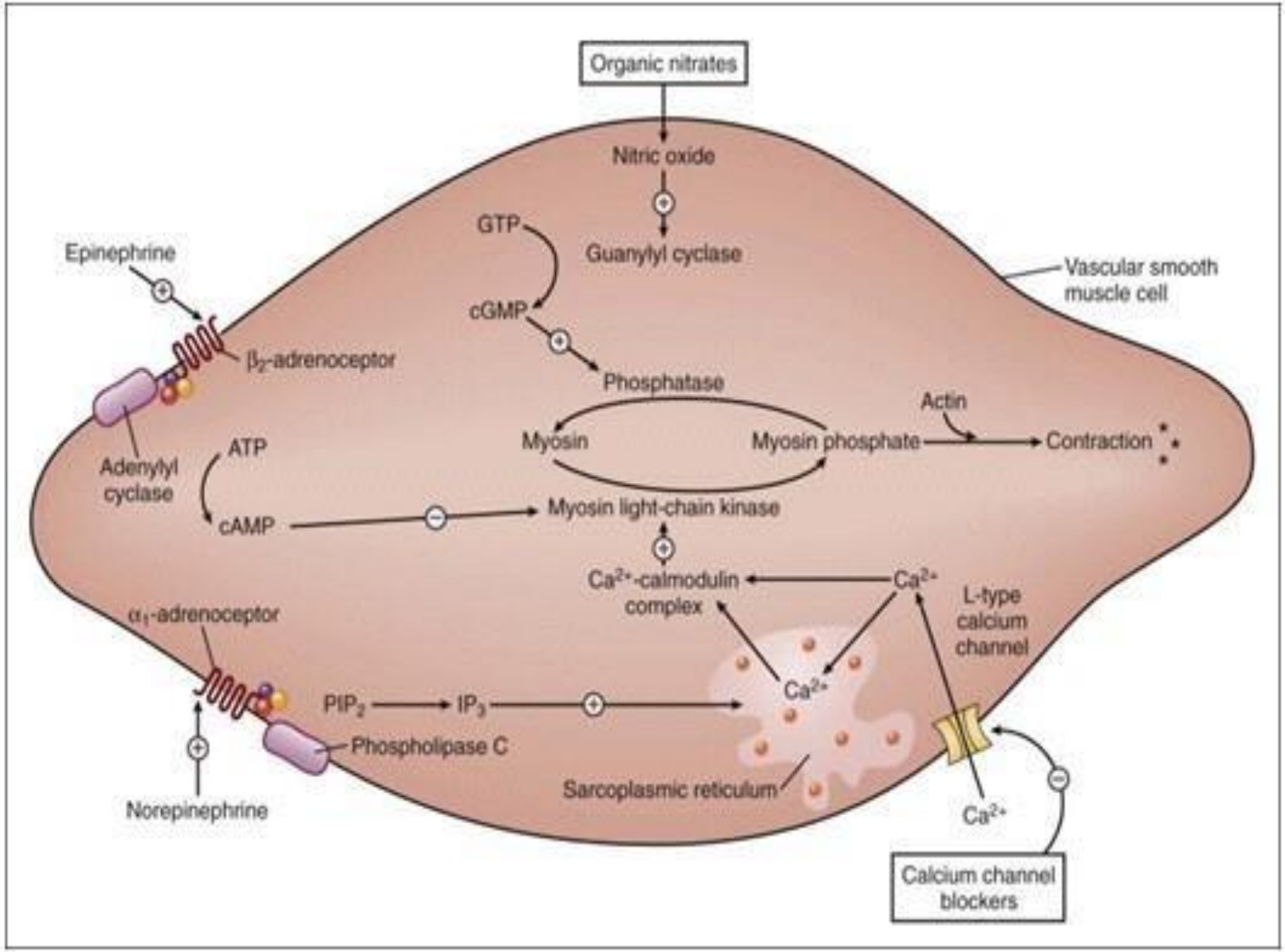
- **Organic nitrates** release nitric oxide, which activates guanylyl cyclase and increases formation of cyclic guanosine monophosphate.
  - cGMP causes smooth muscle relaxation by activating kinases that increase myosin phosphatase activity and decrease myosin phosphate levels.

light chain phosphatase (MLCP). MLCP dephosphorylates the myosin light chains, resulting in smooth muscle relaxation and vasodilation.

- **α 1-Adrenoceptor agonists** activate phospholipase C (PLC), which increases the 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.

CCBs: Calcium Channel Blockers


Organic nitrates
Nitric oxide
GTP
Guanylyl cyclase
Epinephrine
Vascular smooth muscle cell
cGMP
β_2-adrenoceptor
Phosphatase
Actin
Myosin
Myosin phosphate
Contraction
ATP
Adenylyl cyclase
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
Ca^{2+}
Norepinephrine
Calcium channel blockers

Organic nitrates

- They are effective in the three types of angina pectoris.

- **Members of this group include:**

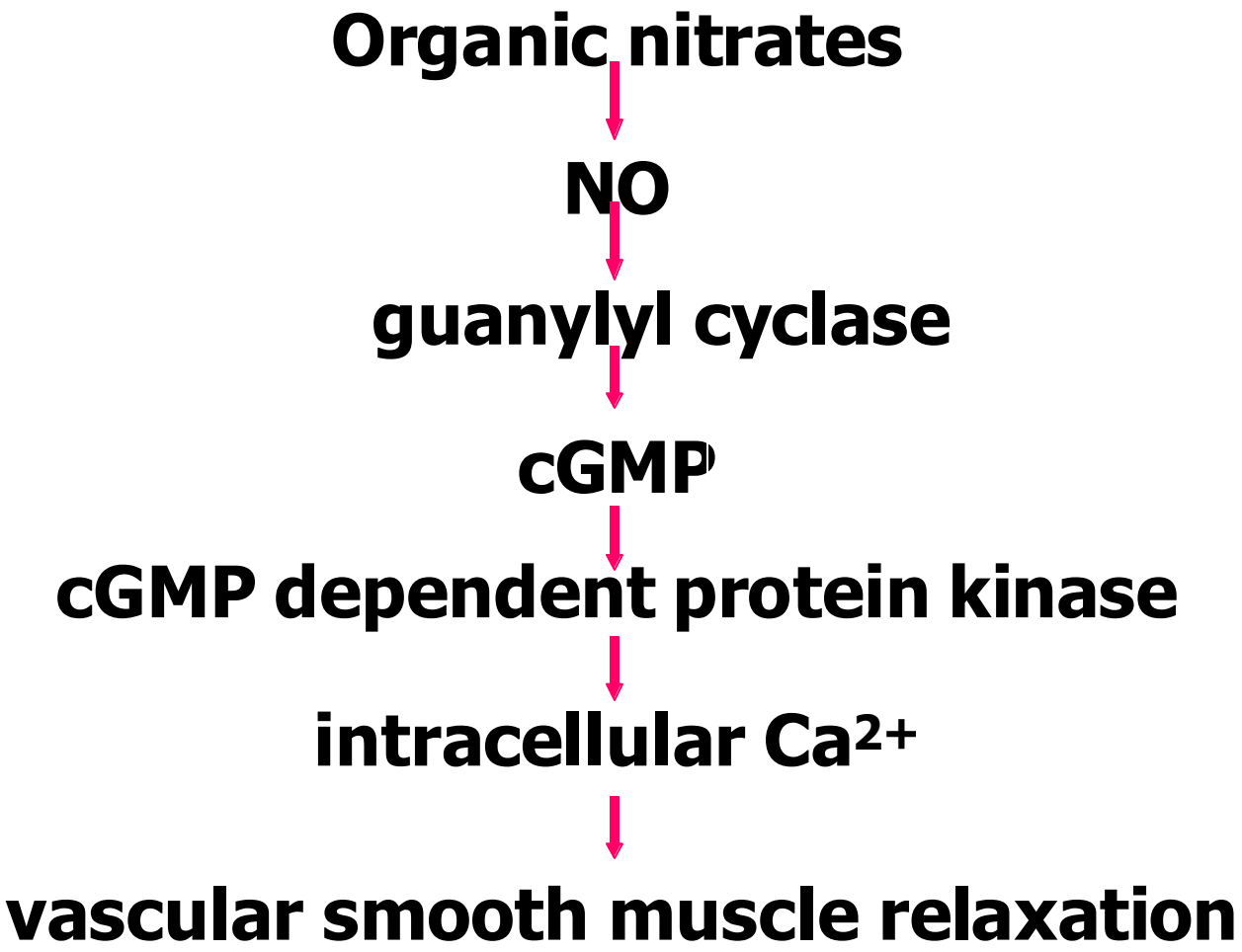
Isosorbide dinitrate, isosorbide mononitrate, Pentaerythritol tetranitrate and Nitroglycerine.

Nitroglycerin is a moderately volatile compound, but more importantly, it undergoes extensive first-pass metabolism in the liver, making oral administration ineffective. Therefore, it is commonly administered sublingually, allowing rapid absorption into the systemic circulation while bypassing hepatic metabolism.

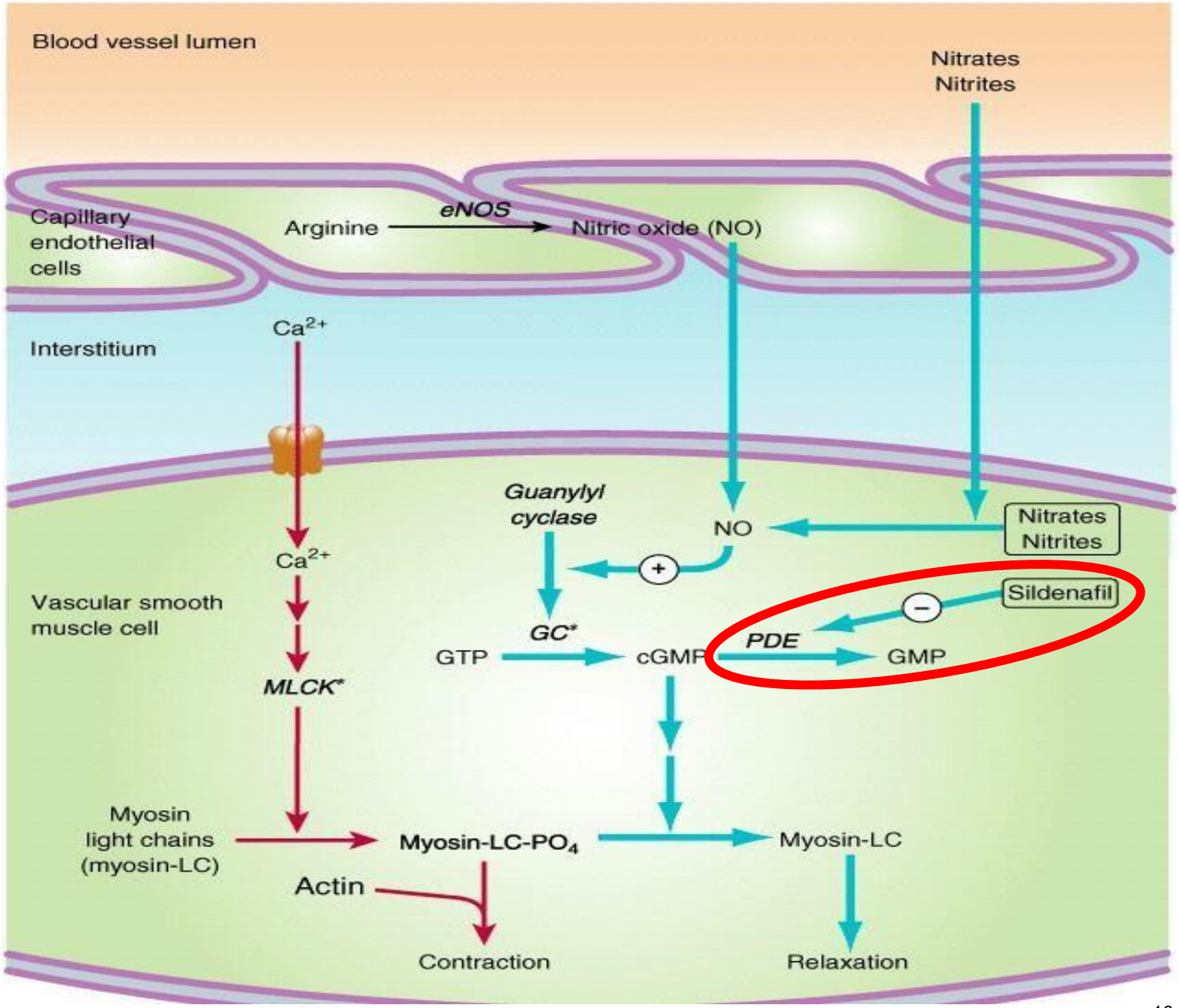
- Their mechanism of action is summarised in a decrease in coronary spasm or vasoconstriction and in an increase in perfusion of the myocardium by relaxing the coronary arteries.

These compounds collectively cause a rapid decrease in myocardial oxygen demand by dilating both arteries and veins. Due to their potent venodilator effect, they reduce venous return to the heart, leading to a decrease in preload, which in turn lowers the workload and oxygen requirement of the myocardium.

2.Pharmacological mechanism



- **Sildenafil** is a phosphodiesterase (PDE) inhibitor, an enzyme responsible for the breakdown of cyclic GMP (cGMP) in vascular smooth muscle.
- Inhibiting PDE increases cGMP levels, leading to more dephosphorylation of myosin light chains and resulting in smooth **muscle relaxation and vasodilation.**



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.

We have also **nitroglycerine patches** that is put for 12 hours then removed for other 12 hours

- Can be administered by various routes.
- Fast onset of action, can be used in emergencies (1-3 minutes, Peaks at 10 minutes).
- Short duration (15-30minutes).
- Reductase enzyme in the liver will break down 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, which might increase MVO_2

- **Venous dilation:**

more intense, even with low doses, lasts for 30 minutes.

  - Decreases venous return (preload) and decreases MVO_2

MVO2: Myocardial Oxygen Demand.

Nitroglycerine (GTN)

Side Effects:

- Headache.
- Hypotension and tachycardia.
- Increased intraocular and intracranial pressures.
- Methemoglobinemia, Methemoglobinemia occurs when nitrites oxidize hemoglobin's iron from Fe^{2+} to Fe^{3+}, forming methemoglobin, which cannot carry oxygen. This leads to tissue hypoxia and cyanosis.
- Tolerance: only for the arteriolar effects. **Most important**

Tolerance can be prevented by introducing a daily nitrate-free interval, which helps restore the drug's sensitivity. This interval is typically 10–12 hours long, usually scheduled overnight, when myocardial oxygen demand is lower.

- Withdrawal: among workers in the ammunition industry.

Withdrawal syndrome can occur when nitrate therapy is abruptly discontinued, so it is important to taper the drug gradually. This phenomenon is also observed in workers in ammunition factories who are chronically exposed to nitroglycerin vapors. Continuous exposure leads to tolerance, and when exposure suddenly stops, these individuals may experience rebound vasoconstriction, angina, or hypertension due to increased vascular sensitivity to catecholamines. Therefore, nitrate withdrawal should always be managed carefully to avoid such adverse reactions.

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 is precipitated by exercise and emotional stress, sublingual nitroglycerine is the drug of choice.

- At therapeutic doses, nitroglycerine has two major effects:

  a. dilation of the large veins, resulting in pooling of blood in the veins (diminishes preload and reduces the work of the heart).

  b. dilates the coronary arteries.

Organic nitrates

- The time to onset the action varies from nitroglycerine to 1 hr for isosorbide mononitrate.

- Significant first pass metabolism of nitroglycerine occurs, so it is administered sublingually or transdermally (patch).

- Isosorbide mononitrate has a long duration of action due to its ability to avoid the first-pass effect (so it is administered orally).
- **Adverse effect:**
  a. Headache is a common early side effect of nitrates, which usually decreases after the first few days (the patient develops tolerance).
  b. High doses can cause postural hypotension, syncope can result and tachycardia.

Organic nitrates

- **Sildinafil** (Viagra) potentiates the action of nitrates, and to avoid the dangerous hypotension, an interval of six hours between the two agents is recommended.

- Tolerance to the action of the nitrates develops rapidly, and the blood vessels become desensitised to the vasodilation.
- The tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug (these intervals are usually 10 – 12 hr at night)

  - Co-administration of organic nitrates and sildenafil can be dangerous.
  - In an elderly patient with erectile dysfunction taking sildenafil (Viagra) who is also on organic nitrates, the combination should be strictly **avoided or separated by at least 24 hours.**

  - Sildenafil inhibits phosphodiesterase type (PDE), an enzyme responsible for the breakdown of cyclic GMP (cGMP). Organic nitrates also increase cGMP levels by stimulating guanylyl cyclase through nitric oxide release.
  - When both drugs are taken together, excessive accumulation of cGMP occurs, leading to marked vasodilation, severe hypotension, reflex tachycardia, and in some cases myocardial ischemia or infarction.

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

Beta Adrenergic Blockers

- Prevent actions of catecholamines, so more effective during exercise, where we actually have more norepinephrine-epinephrine release in the body.
- Do not dilate coronary arteries.
- Do not increase collateral blood flow.
- Rather, they decrease the work of the heart. And their effect is 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 attacks.

- It's preferable to use cardio-selective blockers, and by cardio-selective, we mean the beta-1 selective antagonist, such as acebutolol, atenolol and metoprolol.

β-adrenergic blocking agents

Clinical uses

- They reduce the frequency and severity of angina attacks in patients with stable or unstable angina.
- very useful in the treatment of patients with Myocardial Infarction and has been shown to prolong survival.

Contraindication

- β-blockers may worsen variant angina by blocking β_2-mediated vasodilation, leaving α_1 vasoconstriction unopposed.
- In Asthma, cause bronchoconstriction via β_2 blockade.
- Bradycardia: further decrease HR, possibly leading to cardiac arrest.

- β-blockers should never be stopped abruptly. Their dose must be gradually tapered over 5–10 days to prevent rebound angina or hypertension caused by β-receptor upregulation and hypersensitivity. This rule applies to all cardiovascular conditions such as hypertension, angina, and heart failure.

Calcium channel blockers

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

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

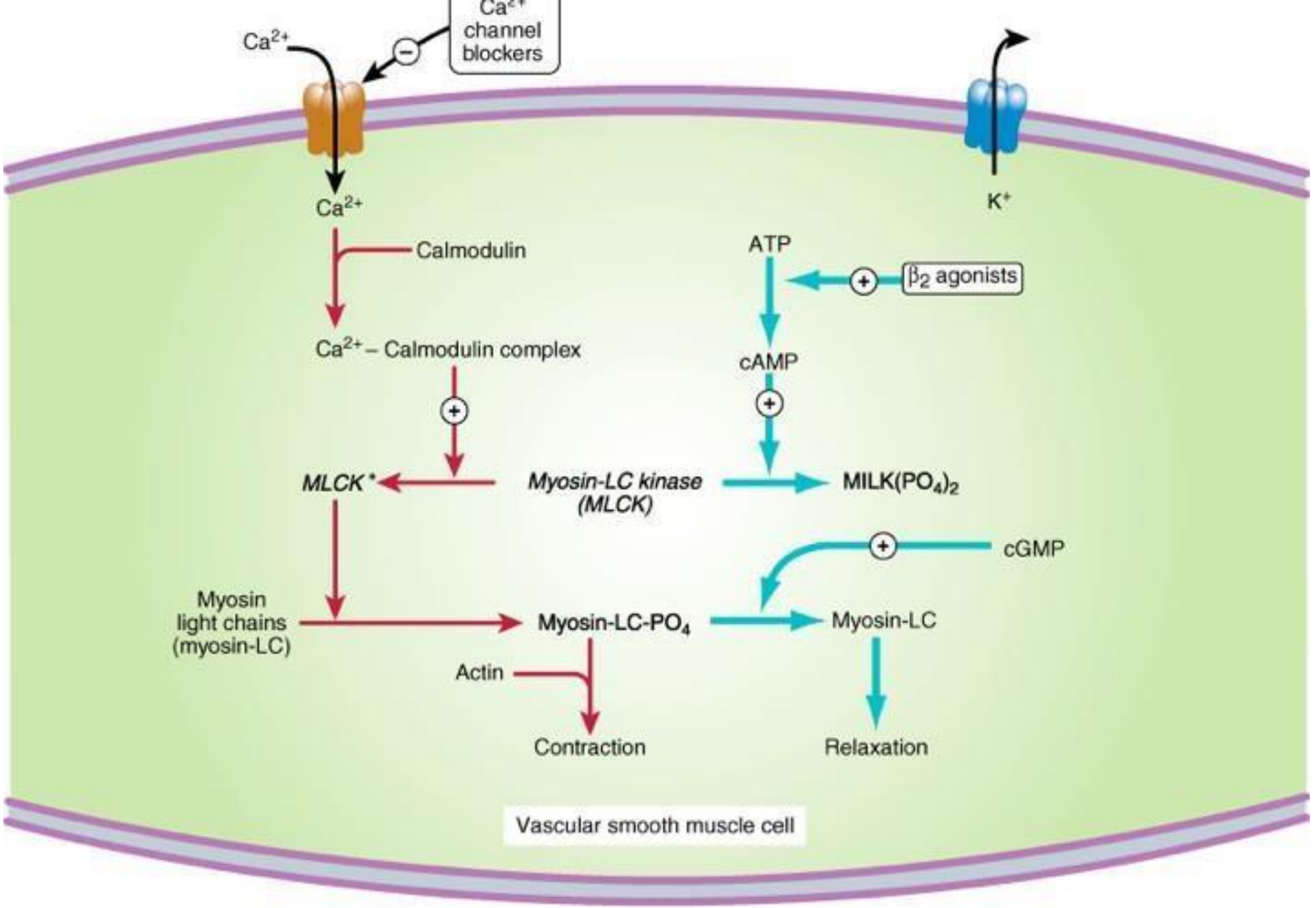
Another name for variant angina is **Prinzmetal's angina.**

A. Verapamil slows cardiac conduction directly, and thus decreases oxygen demand, so it should be avoided in patients with congestive heart failure due to its negative inotropic effect on the heart.

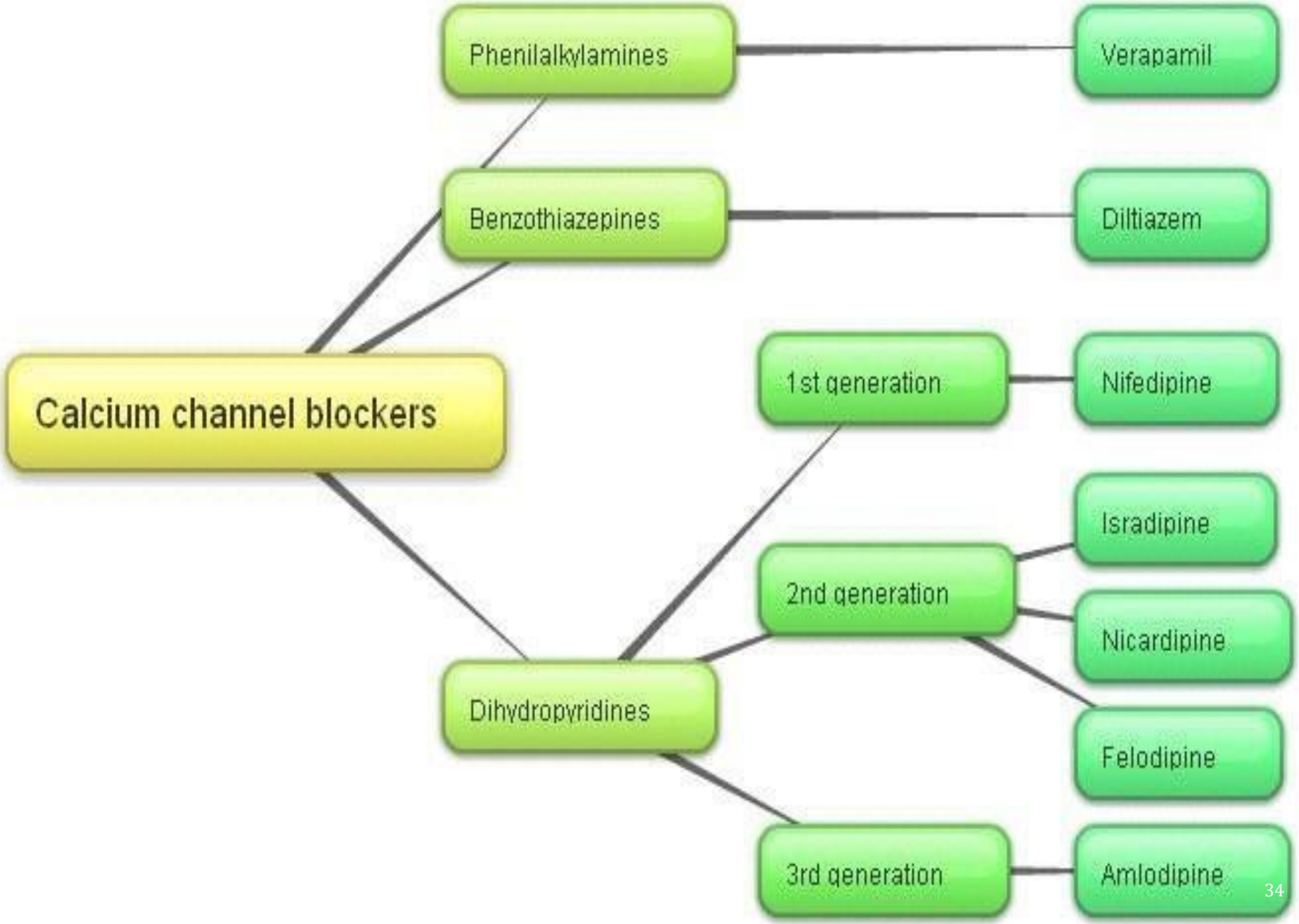
B. Diltiazem has a similar effect on the heart to Verapamil.

Calcium Channel Blockers

- Particularly beneficial in vasospasm.
- Can affect platelet aggregation.
- May be dangerous in heart failure and in patients susceptible to hypotension.



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


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 than the dihydropyridines such as nifedipine 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

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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.

- Nifedipine may cause gingival hyperplasia, and calcium channel blockers in general (especially verapamil) can also cause constipation.

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

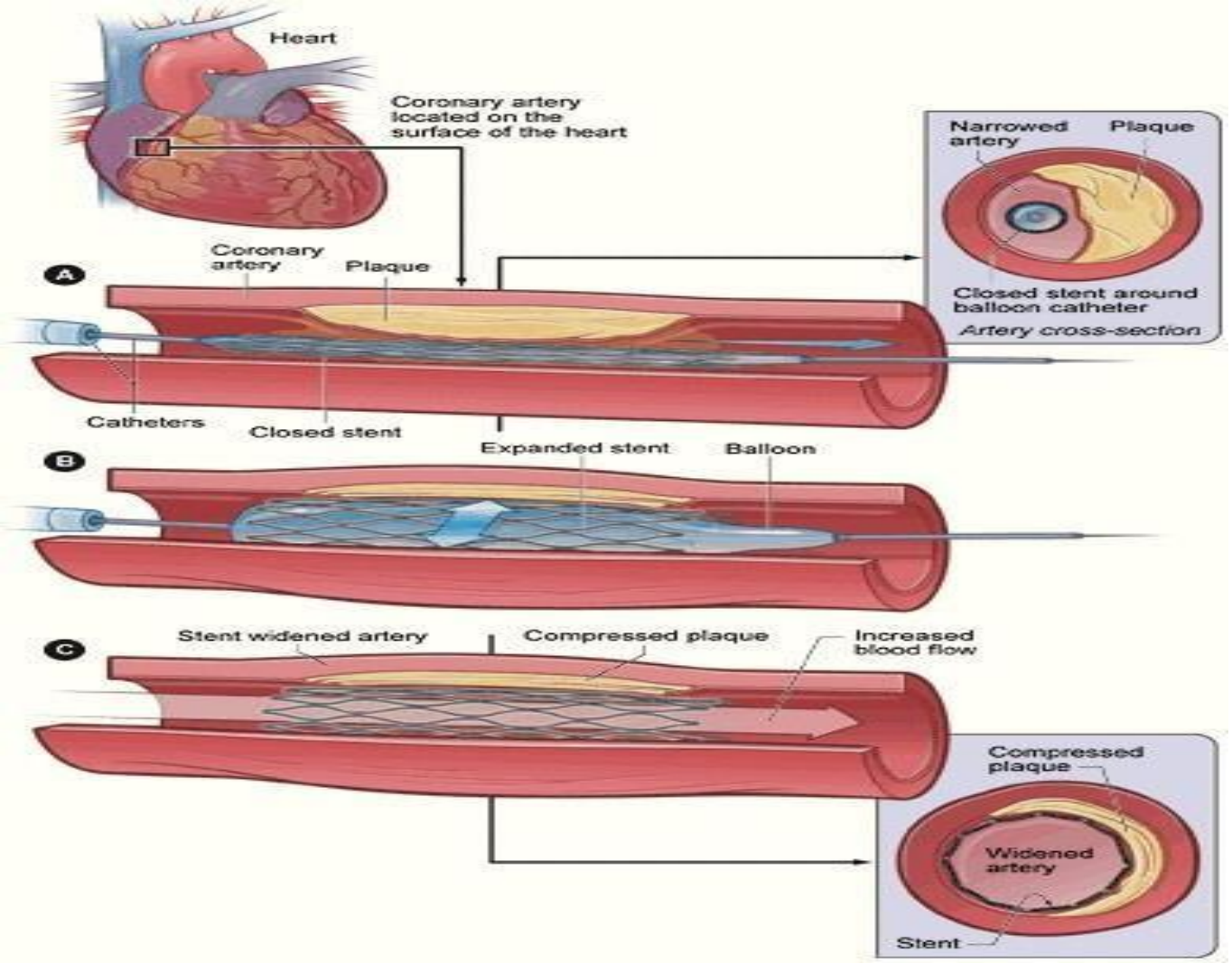
37

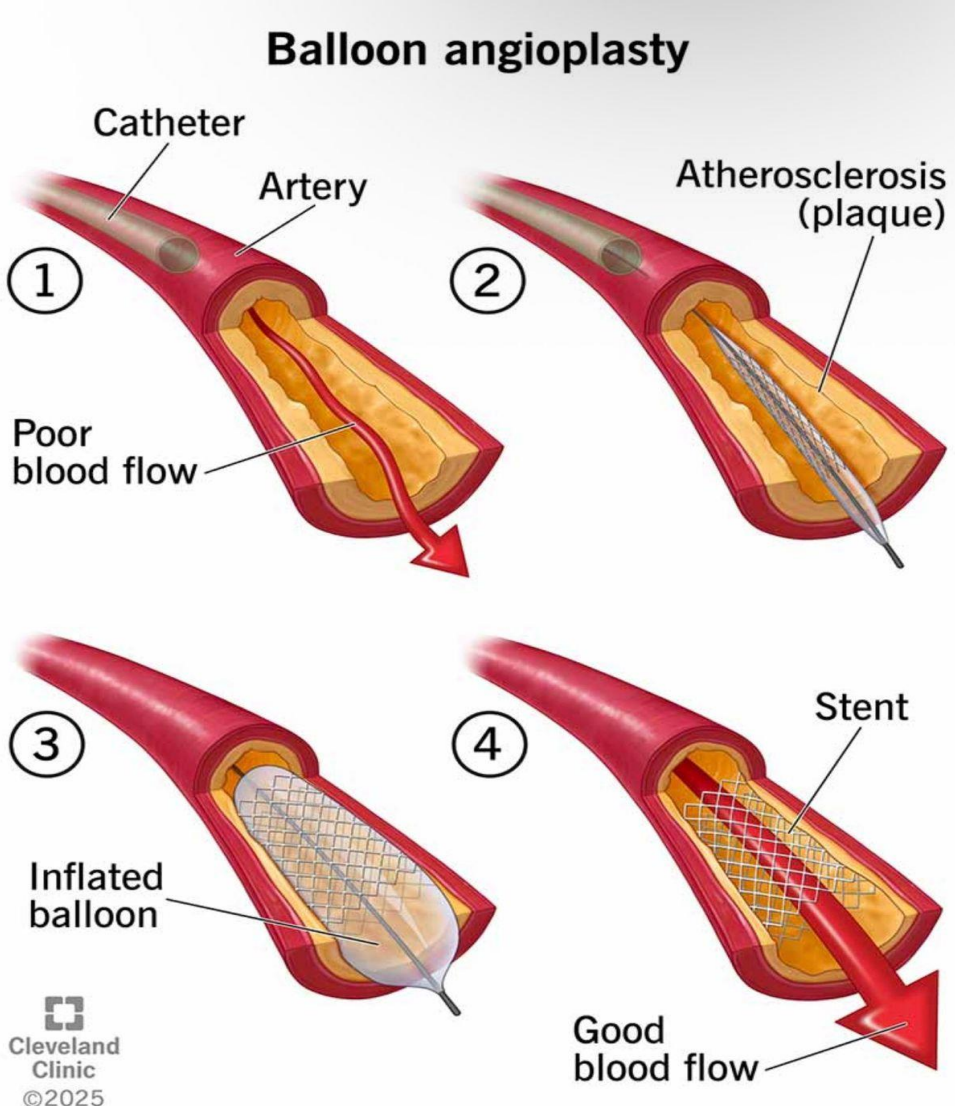
Dipyridamole

- It was previously used for the treatment of angina, works by inhibiting the uptake of adenosine and adenosine deaminase enzyme.
- Thought to be a good coronary dilator.
- It increases blood flow to normal coronary areas rather than dilating vessels in ischemic or spastic regions. Therefore, it is no longer used for angina treatment because it can cause the "coronary steal phenomenon."
- Still used as an antiplatelet drug (in TIAs), but not better than aspirin.

Others

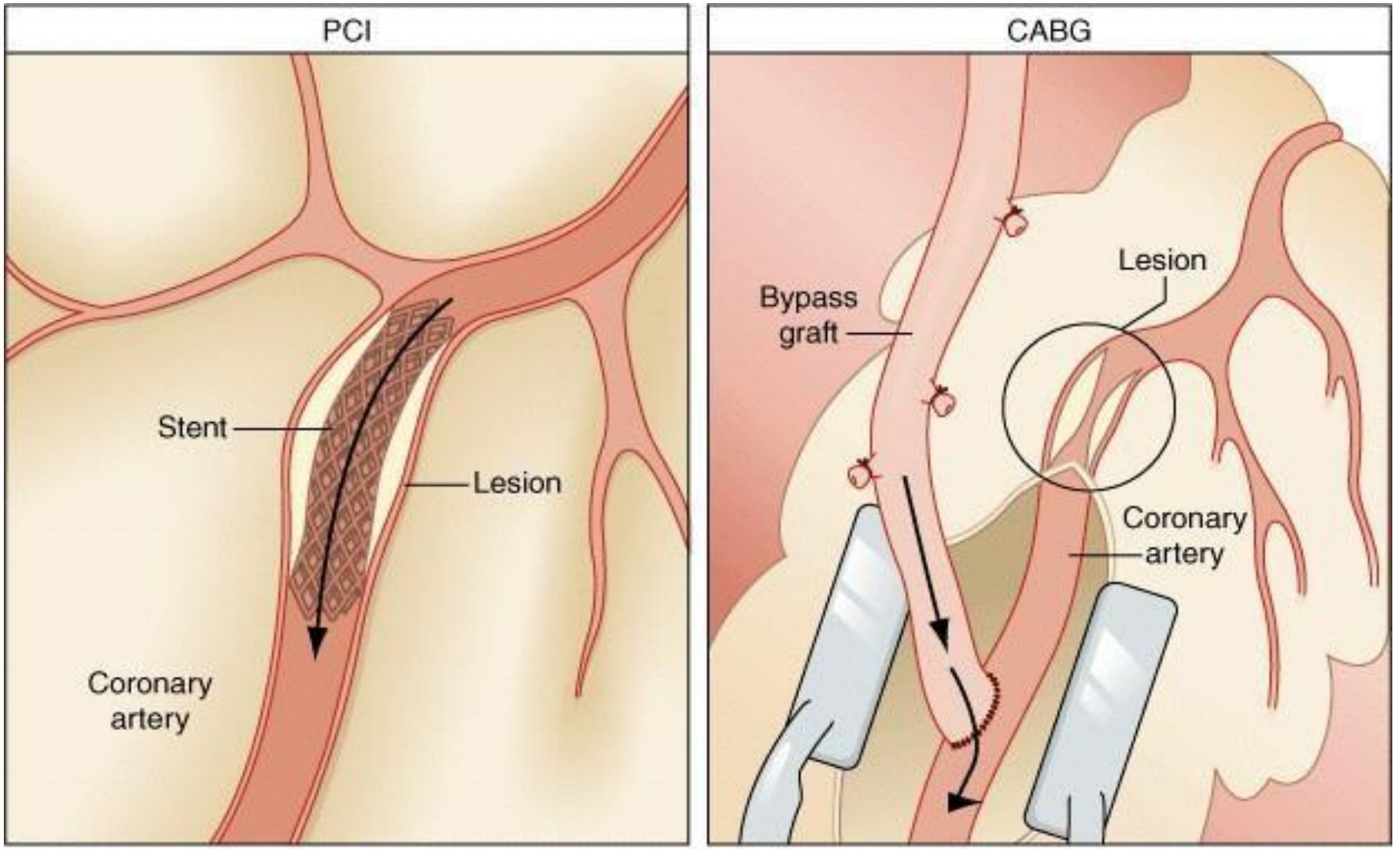
- **ACEI.**
- **Anticoagulants and/or Thrombolytic Therapy.**
- **Cholesterol Lowering Agents.**
- **Angioplasty**
- **Surgery.**





Extra figure

The figure shows how a stent is inserted into a blood vessel, and this represents a form of angioplasty.



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 – are used for the treatment of Angina

- 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 inward sodium current (INa,late) 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 the myocardium.

- Because metabolism Shifts to oxidation of fatty acids in ischemic myocardium, the oxygen requirement per unit of ATP produced increases.

- During ischemia, myocardial metabolism normally shifts toward fatty acid oxidation, which increases oxygen demand per unit of ATP produced. By inhibiting this pathway, trimetazidine shifts energy production toward glucose oxidation, a more oxygen-efficient process.
- This metabolic shift optimises ATP generation, preserves intracellular energy levels, and supports the function of ionic pumps and transmembrane Na^+/K^+ balance, thereby maintaining cellular homeostasis in hypoxic or ischemic conditions.

pFOX inhibitor: (partial fatty acid oxidation inhibitor)

Newer Antianginal Drugs

- Ivabradine is a relatively selective inhibitor of the If channel(funny current), a hyperpolarization-activated mixed Na^+/K^+ current in the sinoatrial node that generates the pacemaker potential.
- By inhibiting this current, ivabradine slows the heart rate and reduces the frequency of anginal attacks, with an efficacy comparable 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**, Ivabradine has improved performance in stress tests.

Newer Antianginal Drugs

- Allopurinol (used in the treatment of gout) represents another type of metabolic modifier. Allopurinol inhibits xanthine oxidase, an enzyme that contributes to oxidative stress and endothelial dysfunction.
  - Endothelial dysfunction means that the ability of the endothelial cells to produce a vasodilator such as nitric oxide is impaired.
- A recent study suggests that high-dose allopurinol prolongs exercise time in patients with atherosclerotic angina.

PHARMACOLOGY QUIZ

LECTURE 5

External Resources

رسالة من الفريق العلمي

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	29 33	"and may be better tolerated than the **non-dihydropyridines** such as nifedipine in these circumstances."	The spelling of Prinzmetal's angina (the other name for variant angina) has been corrected. "and may be better tolerated than the **dihydropyridines** such as nifedipine in these circumstances."
V1 → V2			