Drug treatment of myocardial ischemia

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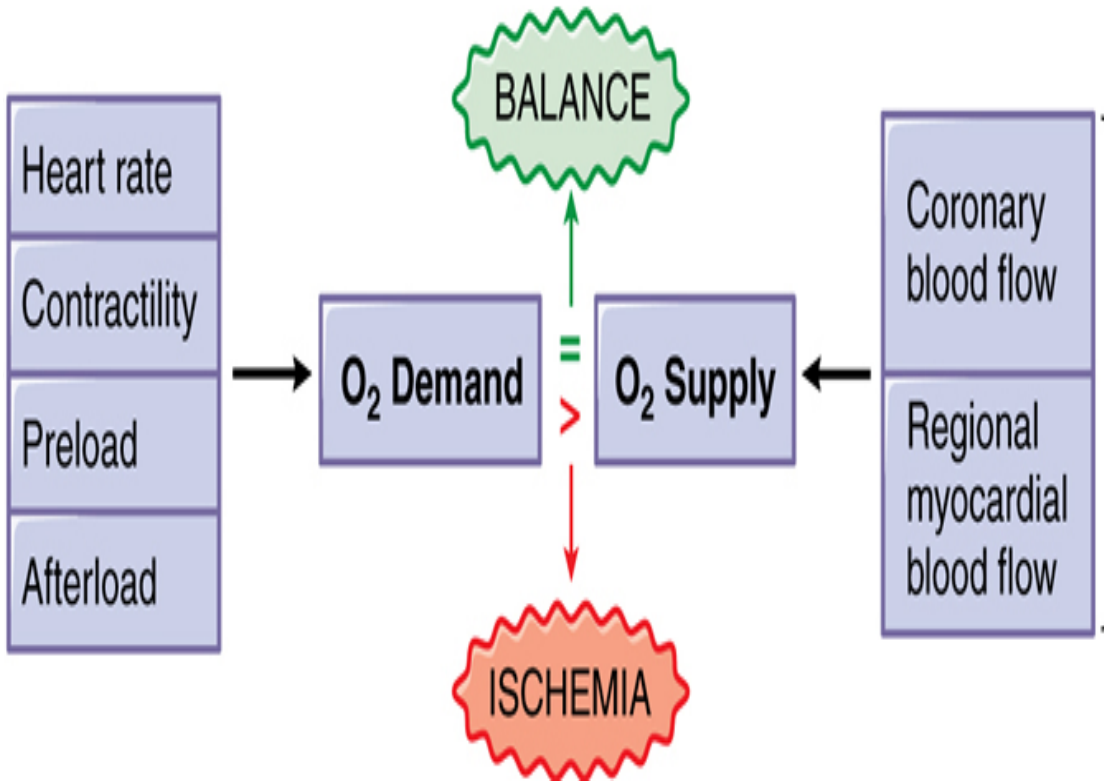
LEARNING OBJECTIVES

- Know the names, classifications and mechanisms of action of drugs used to treat myocardial ischemia.
- Know the side effects of individual drugs and also in combination therapy.
- Know which drugs can be used in combination to treat ischemic heart diseases.

Myocardial O_2 balance



The imbalance may be caused by an increase in myocardial oxygen demand or by a decrease in myocardial oxygen supply or sometimes by both.

1. Determinants of myocardial oxygen demand

Heart rate

Contractility

Wall stress

- Intraventricular pressure
- Ventricular radius (volume)
- Wall thickness

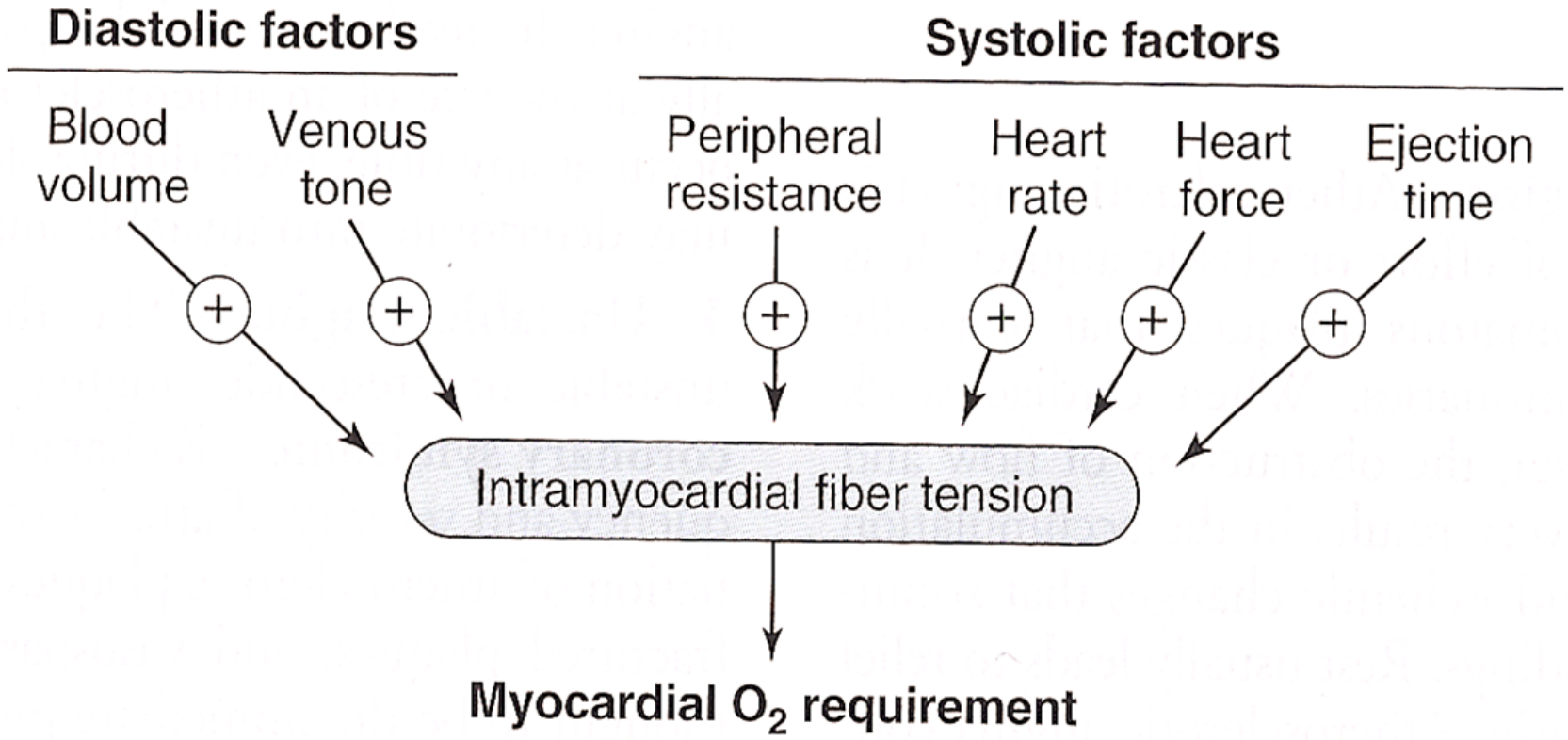
Vascular tone: peripheral arteriolar (systolic wall stress) and venous tone (diastolic wall stress)

2. Determinants of coronary blood flow and myocardial oxygen supply

Coronary blood flow is regulated by duration of diastole, perfusion pressure and is inversely proportional to coronary vascular resistance

Other factors: endothelial function, metabolic products, autonomic activity.

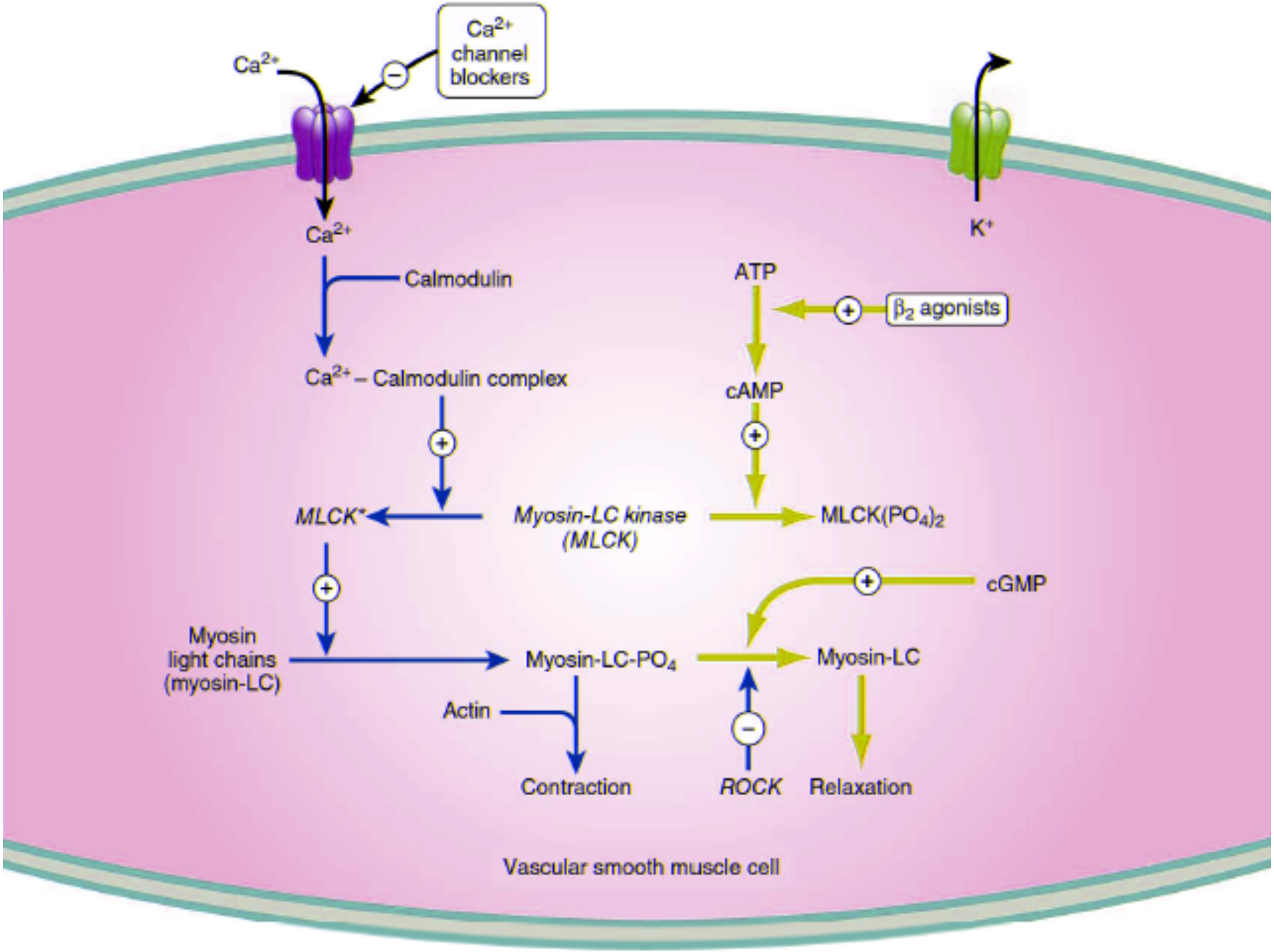
Determinants of myocardial O_2 requirement



Determinant of myocardial O_2 supply

- **The primary determinant of myocardial O_2 supply is the coronary blood flow.**
- **The progressive decrease in vessel radius that characterizes coronary atherosclerosis can impair coronary blood flow.**

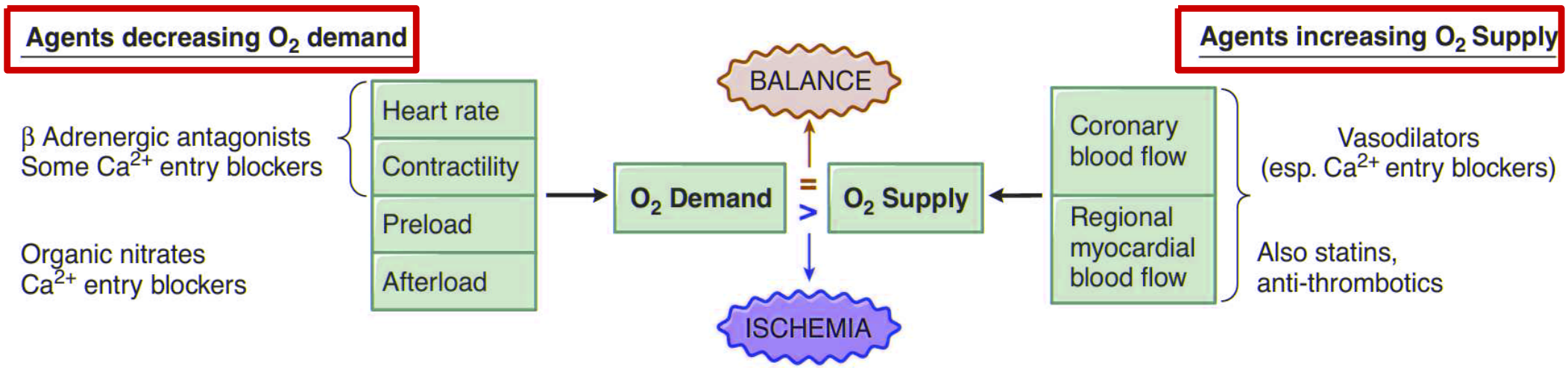
Mechanism of vascular smooth muscle contraction & the site of action of vasorelaxing drugs



Determinants of Vasorelaxation

- Increased cGMP
- Increased cAMP
- Decreased intracellular Ca^{+2}
- Stabilization of vascular smooth muscle cell membrane (i.e., K^{+} channel openers)

The imbalance between oxygen delivery and myocardial oxygen demand can be corrected by decreasing oxygen demand or by increasing O_2 supply via increasing coronary flow.



Drugs used in mycocardial ischemia

1) Vasodilators (Nitrates/nitrites, Ca^{2+} channel blockers)

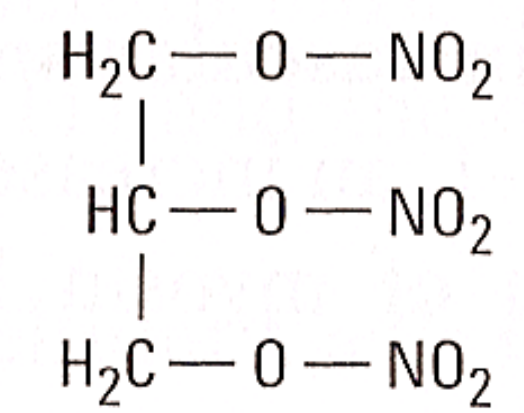
2) Cardiac depressants (Ca^{2+} channel blockers, □-adrenoceptor blockers)

3) Antiplatelets & Antitrombotic Agents (aspirin, clopidogrel, heparin)

4) Others (metabolism modifiers, rate inhibitors)

Vasodilators: Nitrate/nitrites

- **Nitroglycerine (prototype)**
- **Sodium nitroprusside**
- **Isosorbite dinitrate**
- **Amyl nitrite** (not used anymore)



Nitroglycerin (glyceryl trinitrate)

PK: Nitrate/nitrites

- Short half lives.
- Due to low oral bioavalibility, nitroglycerin and isosorbide dinitrate is sublingually used.
- Reach therapeutic blood levels within a few minutes.
- For longer duration of action, oral preparations are available (Pentaerythritol).
- Transdermal and buccal route from slow-release preparations are also available.
- Once absorbed, unchanged nitrates have half lives only 2-8 min. Partially denitrated metabolites have longer half-lives (up to 3 hours).
- Isosorbide mononitrate is an active metabolite of isosorbide dinitrate and it can be used orally (100% bioavailability).

Nitrates and nitrites used in the treatment of angina

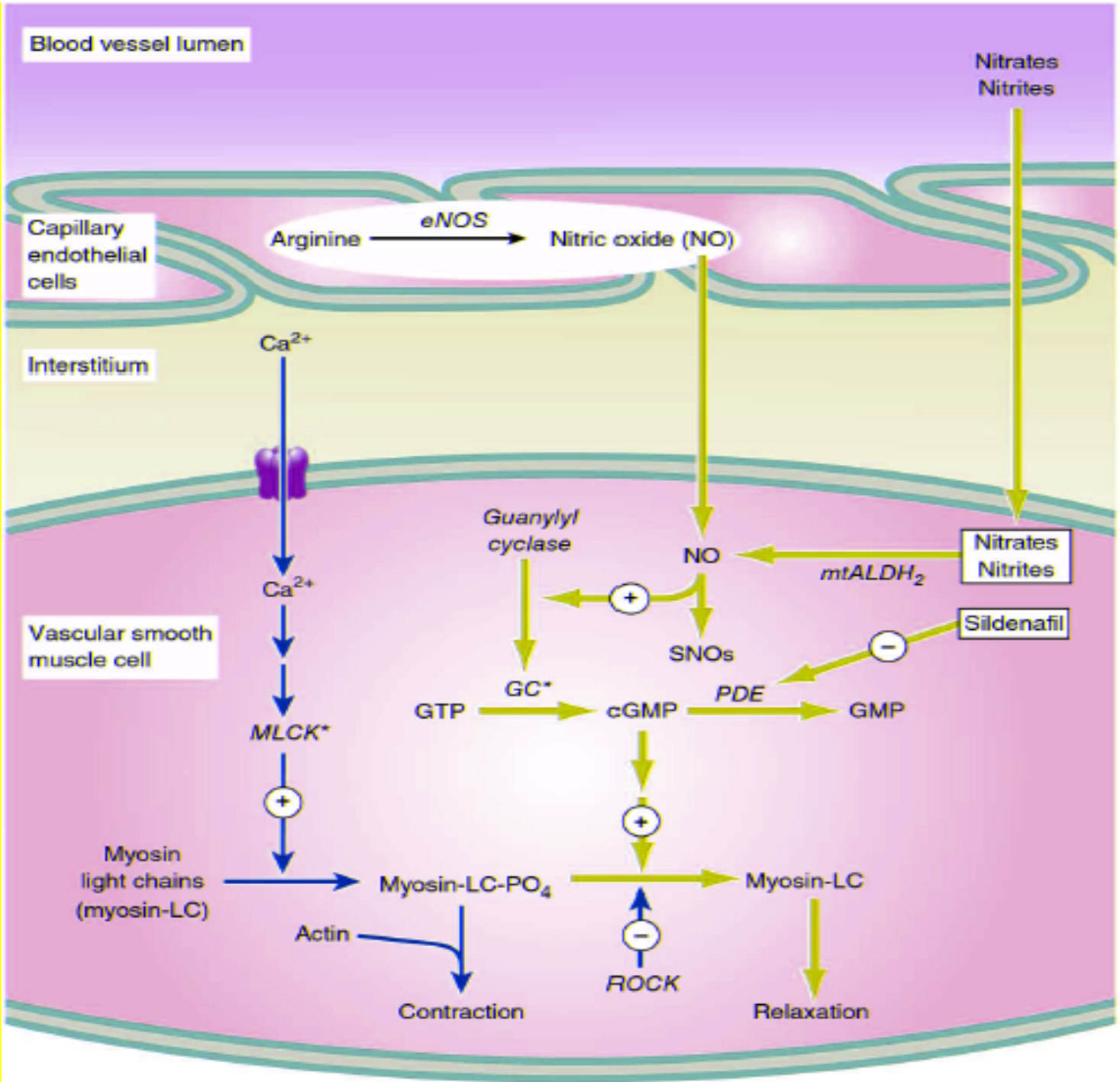
Drug	Dose	Duration of Action
Short-acting		
Nitroglycerin, sublingual	0.15–1.2 mg	10–30 minutes
Isosorbide dinitrate, sublingual	2.5–5 mg	10–60 minutes
Amyl nitrite, inhalant	0.18–0.3 mL	3–5 minutes
Long-acting		
Nitroglycerin, oral sustained-action	6.5–13 mg per 6–8 hours	6–8 hours
Nitroglycerin, 2% ointment, transdermal	1 1.5 inches per 4 hours	3 6 hours
Nitroglycerin, slow-release, buccal	1–2 mg per 4 hours	3–6 hours
Nitroglycerin, slow-release patch, transdermal	10–25 mg per 24 hours (one patch per day)	8–10 hours
Isosorbide dinitrate, sublingual	2.5–10 mg per 2 hours	1.5–2 hours
Isosorbide dinitrate, oral	10–60 mg per 4–6 hours	4–6 hours
Isosorbide dinitrate, chewable oral	5–10 mg per 2–4 hours	2–3 hours
Isosorbide mononitrate, oral	20 mg per 12 hours	6–10 hours
Pentaerythritol tetranitrate (PETN)	50 mg per 12 hours	10–12 hours

Amyl nitrite is not used anymore.

MAO:Nitrate/nitrites

- Nitrovasodilators are prodrugs, they need enzymatic activation.
- Nitroglycerin is denitrated (by glutathione S transferase) in smooth muscle and other cells and free nitrite ion is released, it is then converted to nitric oxide (NO).
- NO can be also be released directly from drug molecule by unknown enzymatic mechanism.
- NO (probably complexed with cysteine) combines with the heme group of soluble guanylyl cyclase (sGC), activates the enzyme and increases cGMP.
- Formation of cGMP represents a first step toward smooth muscle relaxation.

Mechanism of action of nitrates, nitrites, and other substances



MAO:Nitrate/nitrites

- Increased intracellular cGMP → dephosphorylation of the myosin light chain, ↓ cystolic (Ca^{2+}) and leads to the relaxation of smooth muscle cells in a broad range of tissues.
- NO-dependent relaxation of vascular smooth muscle leads to vasodilation.

- NO-mediated guanylyl cyclase activation also inhibits platelet aggregation.
- NO may also increase PGE and/or prostacylin (PGI_2); therefore, membrane hyperpolarization could contribute to vasodilation.

Nitrate/nitrites

Hemodynamic Effects

- Nitroglycerin relaxes all types of smooth muscle regardless of the cause of the preexisting muscle tone.
- It has no direct effect on cardiac or skeletal muscle.
- All segments of the vascular system from large arteries through large veins relax in response to nitroglycerin depending on the dose:
- Low concentrations of nitroglycerin preferentially dilate the veins more than the arterioles (for arterioles slightly higher concentration required).
- The primary result of nitroglycerin treatment increases venous capacitance and decreases ventricular preload.

Nitrate/nitrites

- Systemic arterial pressure may fall slightly, and heart rate is unchanged or may increase slightly in response to a decrease in blood pressure.

- Pulmonary VR and cardiac output slightly ↓

- Higher doses of organic nitrates cause:

  venous pooling → systolic blood pressure ↓

  arteriolar resistance ↓ → diastolic blood pressure ↓

  cardiac output ↓

  Due to these effects pallor, weakness, dizziness, activation of compensatory sympathetic reflexes, orthostatic hypotension and syncope may occur.

- Temporal artery pulsations and a throbbing headache associated with meningeal artery pulsations are common effects of nitroglycerin.

Nitrate/nitrites

Vasodilation and Coronary Blood Flow

- Coronary artery blood flow increases in normal subjects.
- Due to atherosclerotic obstructive coronary artery disease the increase in coronary blood flow may be minimal.
- Redistribution of blood flow in cardiac vessels may help to reduce ischemic events.

By their effects on the systemic circulation, organic nitrates also can reduce myocardial oxygen demand:

- **by increasing venous capacitance, venous return to the heart ↓, ventricular end-diastolic volume ↓, thereby oxygen consumption ↓**
- **by reducing preload, pressure gradient for perfusion across the ventricular wall ↑; subendocardial perfusion improves.**
- **by decreasing peripheral arteriolar resistance, afterload ↓; myocardial work and oxygen consumption ↓**

Nitrate/nitrites

Indirect effects:

- Tachycardia
- Increased contractility
- Orthostatic hypotension and syncope
- Throbbing headache associated with meningial artery pulsation
- Retention of salt and water

Nitrate/nitrites

Tolerance

- Frequently repeated (oral or transdermal) or continuous IV infusions to high doses of organic nitrates leads to a marked attenuation in the magnitude of most of their pharmacological effects.
- Increasing doses are required to achieve the same therapeutic effects.
- Tolerance may result from a reduced capacity of the vascular smooth muscles to convert nitroglycerin to NO.

* dose response curve shift to R.

Tolerance

- Systemic compensation mechanisms also plays a role in tolerance:

  Significant sympathetic discharge occurs, and after one or more days with long-acting nitrates, retention of salt and water may partially reverse hemodynamic changes normally caused by nitroglycerin.

- Sublingual organic nitrates should be taken at the time of an anginal attack or in anticipation of exercise or stress.

Nitrate/nitrites

- An effective approach against tolerance is to interrupt therapy for 8-12 h each day, which allows the return of efficacy.
- Most convenient way is to omit dosing at night in patients with effort angina either by adjusting dosing intervals of oral or buccal preparations or by removing cutaneous nitroglycerin.
- While these approaches appear to be effective, some patients develop an increased frequency of nocturnal angina.
- Tolerance is not universal, and some patients develop only partial tolerance.

Nitrate/nitrites

- A special form of nitroglycerin tolerance is observed in people exposed to nitroglycerin in the manufacture of explosives:
- If protection is inadequate, workers may experience severe headaches, dizziness, and postural weakness during the first several days of employment.
- Tolerance then develops, but headache and other symptoms may reappear after a few days away from the job, the "Monday disease."

Nitrate Dependence

- It is the most serious effect of chronic exposure.
- Workers without demonstrable organic vascular disease have been reported to have an increase in the incidence of acute coronary syndromes during the 24- 72 hour periods away from the work environment.
- Coronary and digital arteriospasm occurs during withdrawal and it relaxes by nitroglycerin.
- Because of the potential problem of nitrate dependence, nitrates should not be abruptly withdrawn if patient has received long therapy.

Adverse Effects:Nitrate/nitrites

Almost all side effects are secondary to actions on the CVS.

- **Headache** is common and can be severe. It usually decreases over a few days if treatment is continued and often can be controlled by decreasing the dose.

- **Transient episodes of dizziness, weakness,** and **other manifestations associated with postural hypotension** may develop, particularly if the patient is standing immobile, and may progress occasionally to loss of consciousness, a reaction that appears to be accentuated by alcohol.

- **Drug rash** (all organic nitrates occasionally can produce).

- The combination of sildenafil and other PDE5 → sildenafil inhibitors with organic nitrates can cause **extreme hypotension (important to question the male patients).**

Chronic Toxicity: Nitrate/nitrites

- Nitrosamines are small molecules formed from the combination of nitrates and nitrites with amines.
- Some nitrosamines are powerful carcinogens in animals, through conversion to reactive derivatives.
- Although no direct proof that they cause cancer in humans, a strong epidemiologic correlation between the incidence of esophageal and gastric carcinoma and the nitrate content of food in certain cultures.
- They are also found in tobacco and in cigarette smoke.
- There is no evidence that the small doses of nitrates used in the treatment of angina result in significant body levels of nitrosamines.

Beneficial and deleterious effects of nitrates in the treatment of angina

Effect	Mechanism and Result
Potential beneficial effects	
Decreased ventricular volume Decreased arterial pressure Decreased ejection time	Decreased work and myocardia oxygen requirement
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion of ischemi myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
Potential deleterious effects	
Reflex tachycardia	Increased myocardial oxygen requirement; decreased diastol perfusion time and coronary perfusion
Reflex increase in contractility	Increased myocardial oxygen requirement

increase O_2 saturation in the heart tissue

Drugs used in mycocardial ischemia

1) Vasodilators (Nitrates/nitrites, **Ca^{2+} entry blockers)**

2) Cardiac depressants (**Ca^{2+} entry blockers,**

?-adrenoceptor blockers)

3) Antiplatelets & Antitrombotic Agents (aspirin, clopidogrel, heparin)

4) Others (metabolism modifiers, rate inhibitors)

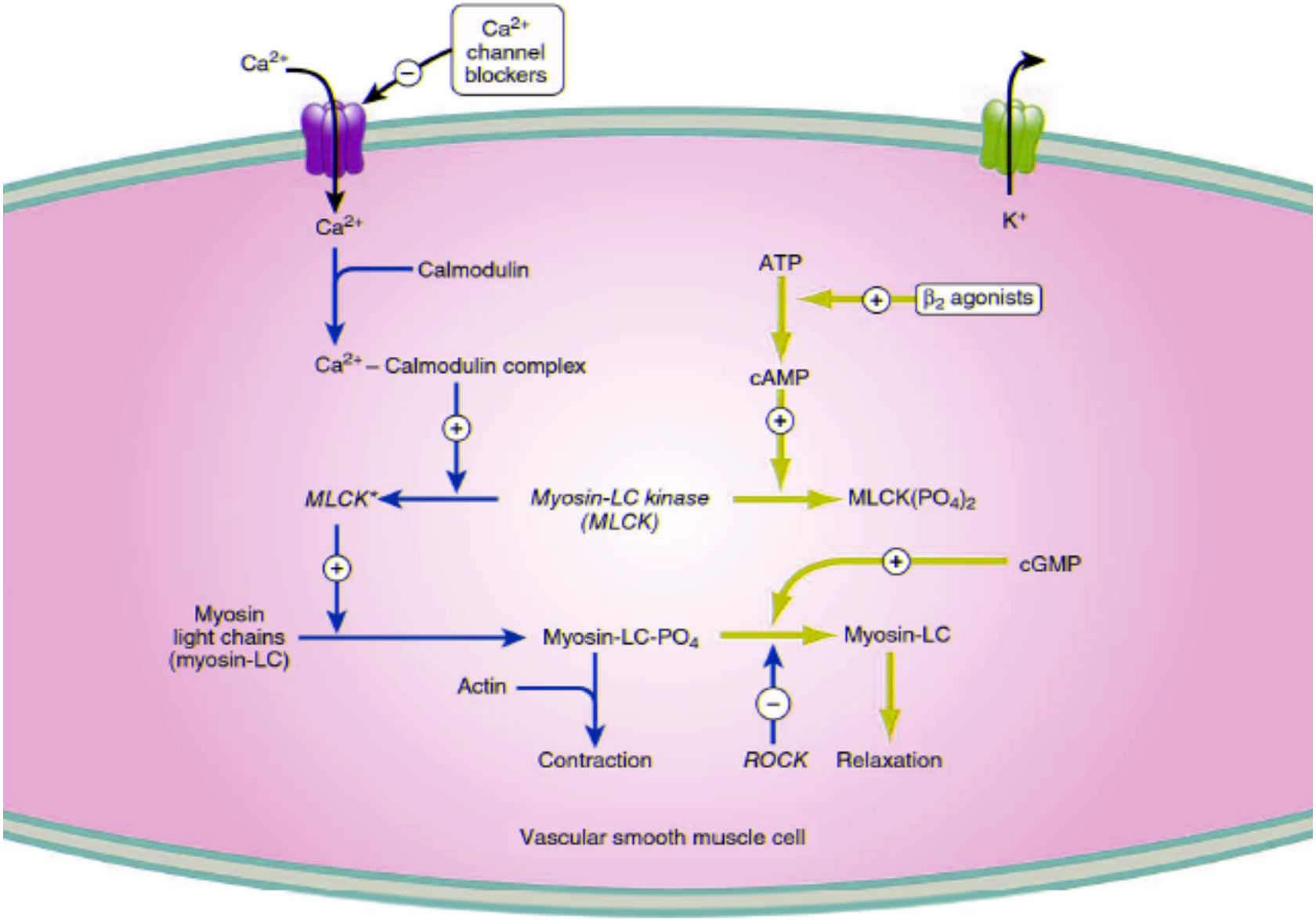
Calcium channel-blockers

- There are different calcium channels (L-type, T-type, N-type, P/Q-type and R-type).
- L-type channel is the dominant type in cardiac and smooth muscle.
- L-type channels consist α_1, α_2, δ and γ units.
- For cardiovascular indications L-type channel blockers are used in clinical practice.

Calcium channel-blockers

- Voltage-sensitive Ca^{2+} channels (L-type or slow channels) mediate the entry of extracellular Ca^{2+} into smooth muscle, cardiac myocytes, sinoatrial and atrioventricular nodal cells in response to electrical depolarization.
- In both smooth muscle and cardiac myocytes, Ca^{2+} is a trigger for contraction.

Mechanism of smooth muscle contraction and the site of action of Calcium channel blocking drugs



Calcium channel-blockers

Mechanism of action

- **Ca^{2+} channel blockers, also called *Ca^{2+} entry blockers,* inhibit Ca^{2+} channel function.**

- **They block Ca^{+2} entry though L-type channel in cardiac and vascular smooth muscle.**

- **Ca^{2+} channel blockers produce negative inotropic and chronotropic effects in the heart.**

- **Ca^{2+} channel blockers cause relaxation in vascular smooth muscle, especially in arterial beds.**

Clinical pharmacology of some calcium channel-blocking drugs

Drug	Oral Bioavailability (%)	Half-life (hours)	Indication	Dosage
Dihydropyridines				
Amlodipine	65–90	30–50	Angina, hypertension	5–10 mg orally once daily
Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon	5–10 mg orally once daily
Isradipine	15–25	8	Hypertension	2.5–10 mg orally twice daily
Nicardipine	35	2–4	Angina, hypertension	20–40 mg orally every 8 hours
Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon	3–10 mcg/kg IV; 20–40 mg orally every 8 hours
Nisoldipine	< 10	6–12	Hypertension	20–40 mg orally once daily
Nitrendipine	10–30	5–12	Investigational	20 mg orally once or twice daily
Miscellaneous				
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon	75–150 mcg/kg IV; 30–80 mg orally every 6 hours
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine	75–150 mcg/kg IV; 80–160 mg orally every 8 hours

Fenilalkilamine: diltiazem
Benzotiazepin: Verapamil

Calcium channel-blockers

- **All Ca^{2+} channel blockers decrease coronary vascular resistance and can increase coronary blood flow.**
- **The dihydropyridines are more potent vasodilators than verapamil.**
- **They cause selective dilatation in arterial vascular beds.**
- **Their effects on venous pooling is much lesser than the arterial vessels.**

Calcium channel-blockers

Effects on smooth muscle

- With all Ca^{2+} channel blockers blood pressure is reduced.
- PVR ↓, coronary vascular resistance ↓ and coronary blood flow ↑, patients with effort angina/variant angina benefit from these drugs.
- Dihydropyridines have a greater ratio of vascular smooth muscle effects relative to cardiac effects than do diltiazem and verapamil.
- Bronchiolar, GI, and uterine smooth muscles also relax.

Calcium channel-blockers

Effects on cardiac muscle

Impuls generation and conduction in SA and AV nodes ↓

Action Potential ↓

Cardiac contractility ↓

Cardiac output ↓

- Decrease in the oxygen requirement in patients with angina

Dihydropyridines block smooth muscle calcium channels at concentrations below those required for significant cardiac effects; they are therefore less depressant on the heart than verapamil or diltiazem.

Calcium channel-blockers

Adverse effects:

- Slow-release and long-acting dihydropyridine calcium channel blockers are usually well tolerated.
- Relatively short-acting calcium channel blockers such as immediate-release nifedipine potentially enhance the risk of adverse cardiac events and should be avoided.
- Patients receiving β-blocking drugs are more sensitive to the cardiodepressant effects of calcium channel blockers.

Minor:

Reflex tachycardia (most frequently with nifedipine, less with verapamil and diltiazem), flushing, dizziness, nausea, constipation (more w verapamil), peripheral edema (more w diltiazem)

Calcium channel-blockers

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 advantage because of their antiarrhythmic effects.

In patients with unstable angina, immediate-release short-acting calcium channel blockers can increase the risk of adverse cardiac events and therefore are contraindicated.

Drugs used in mycocardial ischemia

1) Vasodilators (Nitrates/nitrites, Ca^{2+} entry blockers)

2) Cardiac depressants (Ca^{2+} entry blockers,

-adrenoceptor blockers)

3) Antiplatelets & Antitrombotic Agents (aspirin, clopidogrel, heparin)

4) Others (metabolism modifiers, rate inhibitors)

-AR antagonists

Although they are not vasodilators (except carvedilol and nebivolol), β-blocking drugs are very useful in the treatment of effort angina.

The beneficial effects of β-blocking agents are:

- hemodynamic effects
- heart rate ↓
- blood pressure ↓
- contractility ↓

} **myocardial oxygen requirements at rest and during exercise ↓**

Decreased heart rate => diastolic perfusion time ↑ => coronary perfusion ↑
Beta blockers decrease mortality of patients with recent MI, improve survival and prevent stroke in patients with hypertension.

-AR antagonists

The effectiveness of AR antagonists in the treatment of effort angina is attributed to fall in myocardial O_2 consumption at rest and during exercise.

The decrease in myocardial oxygen consumption is due to:

- negative chronotropic effect (particularly during exercise)
- negative inotropic effect
- reduction in arterial blood pressure (particularly systolic pressure) during exercise

-antagonists may also increase blood flow toward ischemic regions.

-AR antagonists

- Not all actions of -AR antagonists are beneficial in all patients:

- The decreases in heart rate and contractility =>
  - ↑ systolic ejection period
  - ↑ left ventricular end-diastolic volume

- These alterations may tend to increase O_2 consumption.

?-AR antagonists

Adverse Effects:

- **Increase in end-diastolic volume**
- **Increase in ejection time**

} **tend to increase myocardial oxygen requirement**

These deleterious effects of β-blockers can be balanced by the concomitant use of nitrates.

Others:
Fatigue, impaired exercise tolerance, insomnia, unpleasant dreams, worsening of claudication, erectile dysfunction.

Contraindications:

Asthma, severe bradycardia, atrioventricular blockade,
bradycardia-tachycardia syndrome,
severe unstable left ventricular failure.

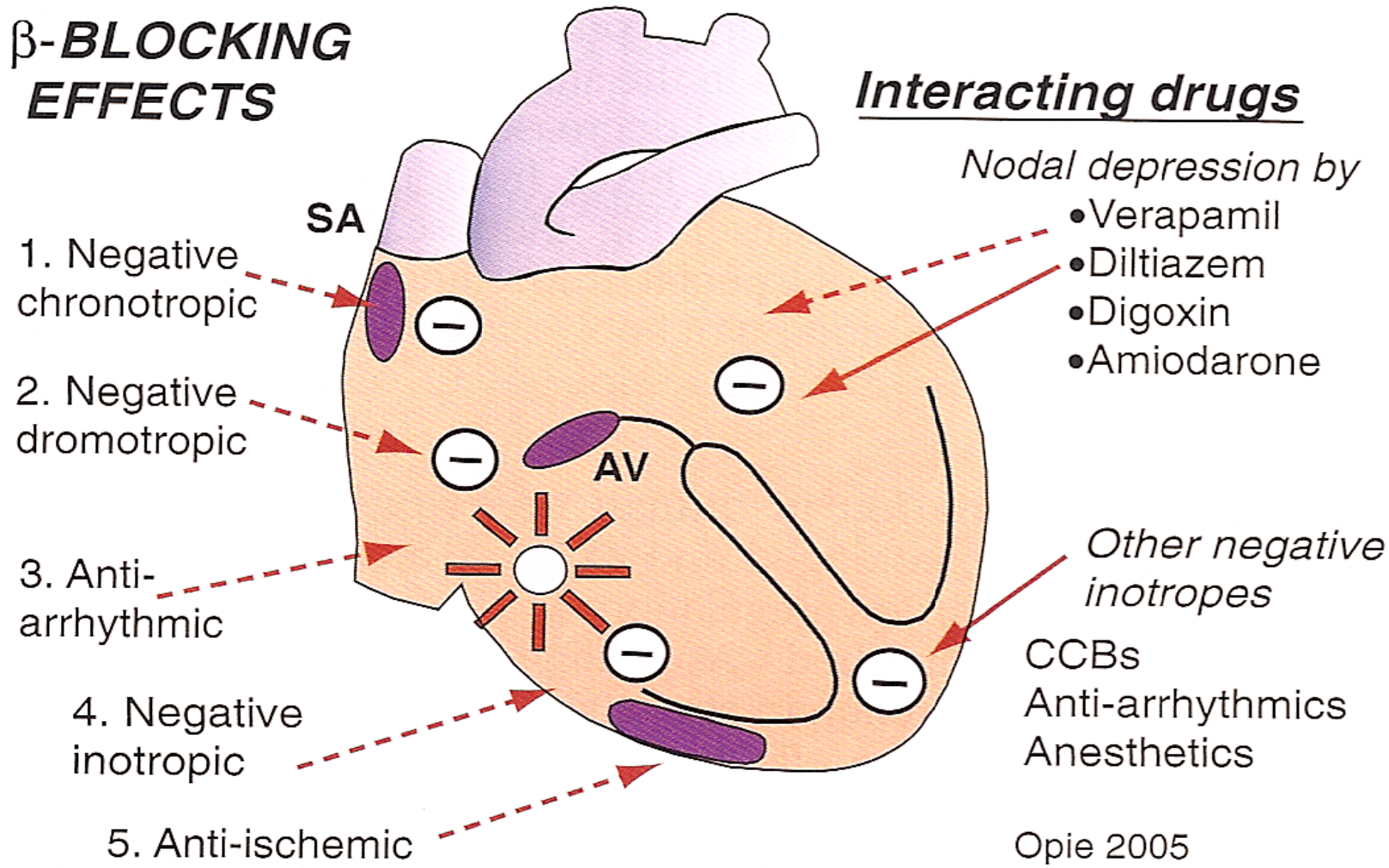
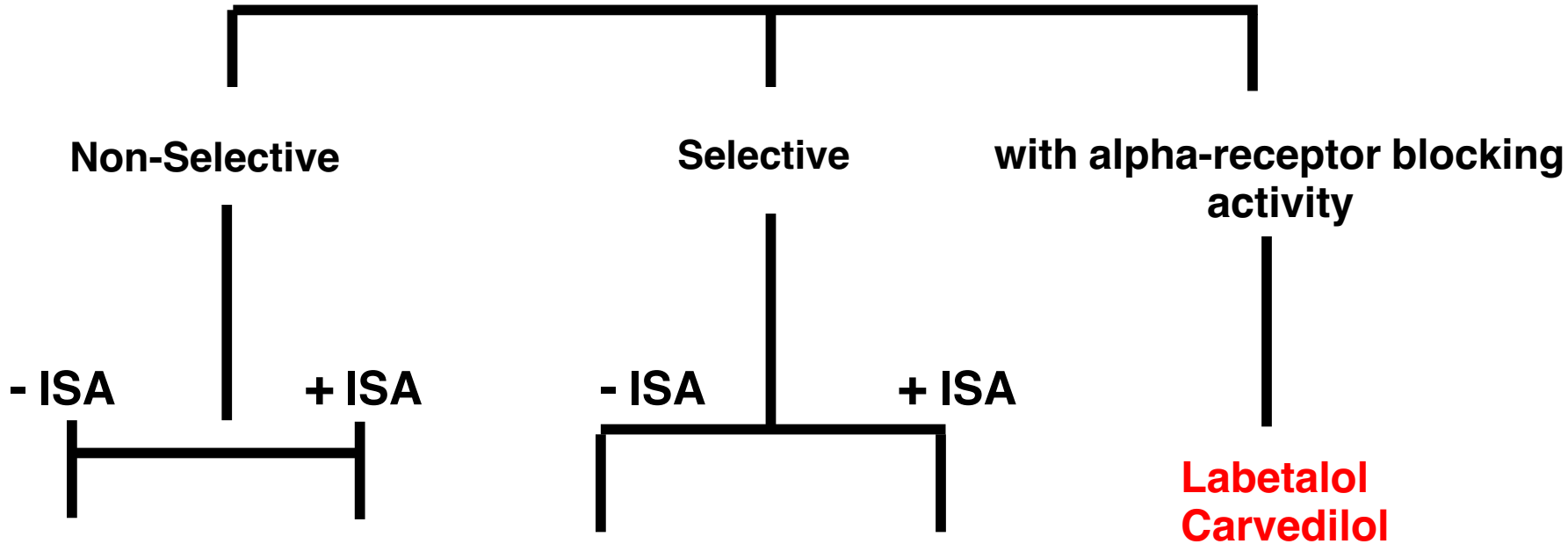


Figure 1-3 **Cardiac effects of β-adrenergic blocking drugs** at the levels of the SA node, AV node, conduction system, and myocardium. Major pharmacodynamic drug interactions are shown on the right. (SA, sinoatrial; AV, atrioventricular.) (Figure © L.H. Opie, 2008.)

BETA RECEPTOR BLOCKERS



ISA=intrinsic sympathomimetic activity (partial agonists): inhibits the activation of βAR in presence of high catecholamine concentrations but moderately activate receptors in absence of endogenous agonists.

Timolol, metoprolol, atenolol, and propranolol have been shown to exert cardioprotective effects.

TABLE 12–7 Effects of nitrates alone and with β 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*	None or decrease
Contractility	*Reflex[1] increase*	Decrease	None
Ejection time	Decrease[1]	*Increase*	None

[1]Baroreceptor reflex.

Note: Undesirable effects are shown in italics.

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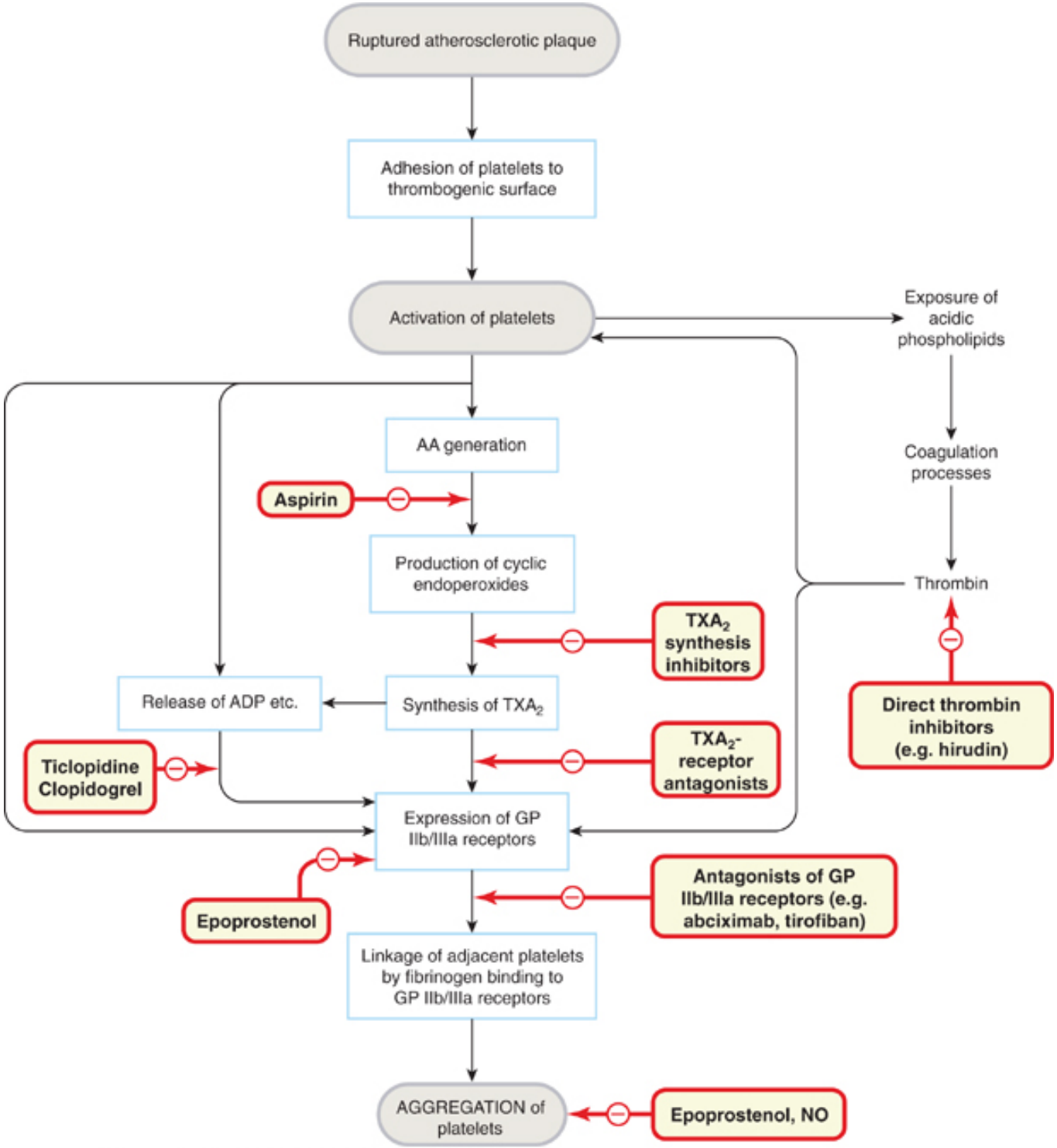

ANTIPLATELET & ANTITHROMBOTIC AGENTS

- **Aspirin reduces the incidence of MI and death in patients with unstable angina.**
- **In addition, low doses of aspirin appear to reduce the incidence of MI in patients with chronic stable angina.**
- **Aspirin, given in doses of 160 - 325 mg at the onset of treatment of MI, reduces mortality in patients presenting with unstable angina.**
- **The addition of clopidogrel to aspirin therapy reduces mortality in patients with acute coronary syndromes.**

ANTIPLATELET & ANTITHROMBOTIC AGENTS

- **Aspirin inhibits COX-1 irreversibly.**
- **Low doses of aspirin (80-300 mg) very effectively**

(> 95%) inhibit platelet thromboxane (TX)A_2 synthesis and reduce the risk of thrombosis.

- **Clopidogrel is a prodrug. It irreversibly inhibits**

P2Y12 receptors and thereby inhibits platelet responses to ADP.

- **Clopidogrel`s clinical effect is additive with aspirin.**
- **Prasugrel is similar to Clopidogrel.**
- **Dipyridamole inhibits PDE and adenosine uptake. It**

is used in addition to aspirin in some patients with stroke or transient ischemic attack.

ANTIPLATELET & ANTITHROMBOTIC AGENTS

- **Antagonists of GPIIb/IIIa receptors include a monoclonal antibody (abciximab) and several synthetic molecules (e.g. tirofiban).**
- **They are administered intravenously for short-term treatment.**
- **Intravenous administration of the platelet GPIIb/IIIa receptor inhibitors are effective in preventing the complications (ie., myocardial injury) of percutaneous coronary interventions (PCIs) and in the treatment of patients with acute coronary syndromes .**

ANTIPLATELET & ANTITHROMBOTIC AGENTS

- **Epoprostenol is synthetic PGI_2.**
- **Given as an intravenous infusion, it acts on prostanoid (IP) receptors on vascular smooth muscle and platelets → adenylyl cyclase activation; → vasodilatation and inhibiting platelet aggregation caused by any pathway (e.g. ADP or TXA_2).**

ANTIPLATELET & ANTITHROMBOTIC AGENTS

- **Heparin also reduces symptoms and prevents infarction in unstable angina.**
- **Heparin activates antithrombin III.**
- **Thrombin inhibitors, such as hirudin or bivalirudin, are being investigated; they directly inhibit even clot-bound thrombin.**
- **Thrombolytic agents, on the other hand, are of no benefit in unstable angina.**

Drugs used in mycocardial ischemia

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4) Others (metabolism modifiers, rate inhibitors)

New drugs or drug groups under investigation for use in angina

Drugs
Amiloride
Capsaicin
Direct bradycardic agents, eg, ivabradine
Inhibitors of slowly inactivating sodium current, eg, ranolazine
Metabolic modulators, eg, trimetazidine
Nitric oxide donors, eg, L-arginine
Potassium channel activators, eg, nicorandil
Protein kinase G facilitators, eg, detanonoate
Rho-kinase inhibitors, eg, fasudil
Sulfonylureas, eg, glibenclamide
Thiazolidinediones
Vasopeptidase inhibitors
Xanthine oxidase inhibitors, eg, allopurinol

Effort angina

This is predictable chest pain on exertion.

Produced by an increased demand on the heart and is caused by a fixed narrowing of the coronary vessels, almost always by atheroma. The reduction in oxygen demand is the major mechanism for the relief of effort angina.

Symptomatic therapy is directed at reducing cardiac work with organic nitrates, β-adrenoceptor antagonists and/or calcium antagonists, together with treatment of the underlying atheromatous disease, usually including a statin, and prophylaxis against thrombosis with an antiplatelet drug, usually aspirin.

Unstable angina

Characterised by pain that occurs with less exertion, culminating in pain at rest.

The pathology is similar to that involved in myocardial infarction: platelet-fibrin thrombus associated with a ruptured atheromatous plaque, but without complete occlusion of the vessel.

Nitrates may exert their beneficial effects both by dilating the epicardial coronary arteries and by simultaneously reducing myocardial oxygen demand.

Antiplatelet drugs (aspirin and/or an ADP antagonist such as clopidogrel/prasugrel) reduce the risk of myocardial infarction, and heparin and platelet glycoprotein receptor antagonists add benefit.

Variant angina

This is uncommon.

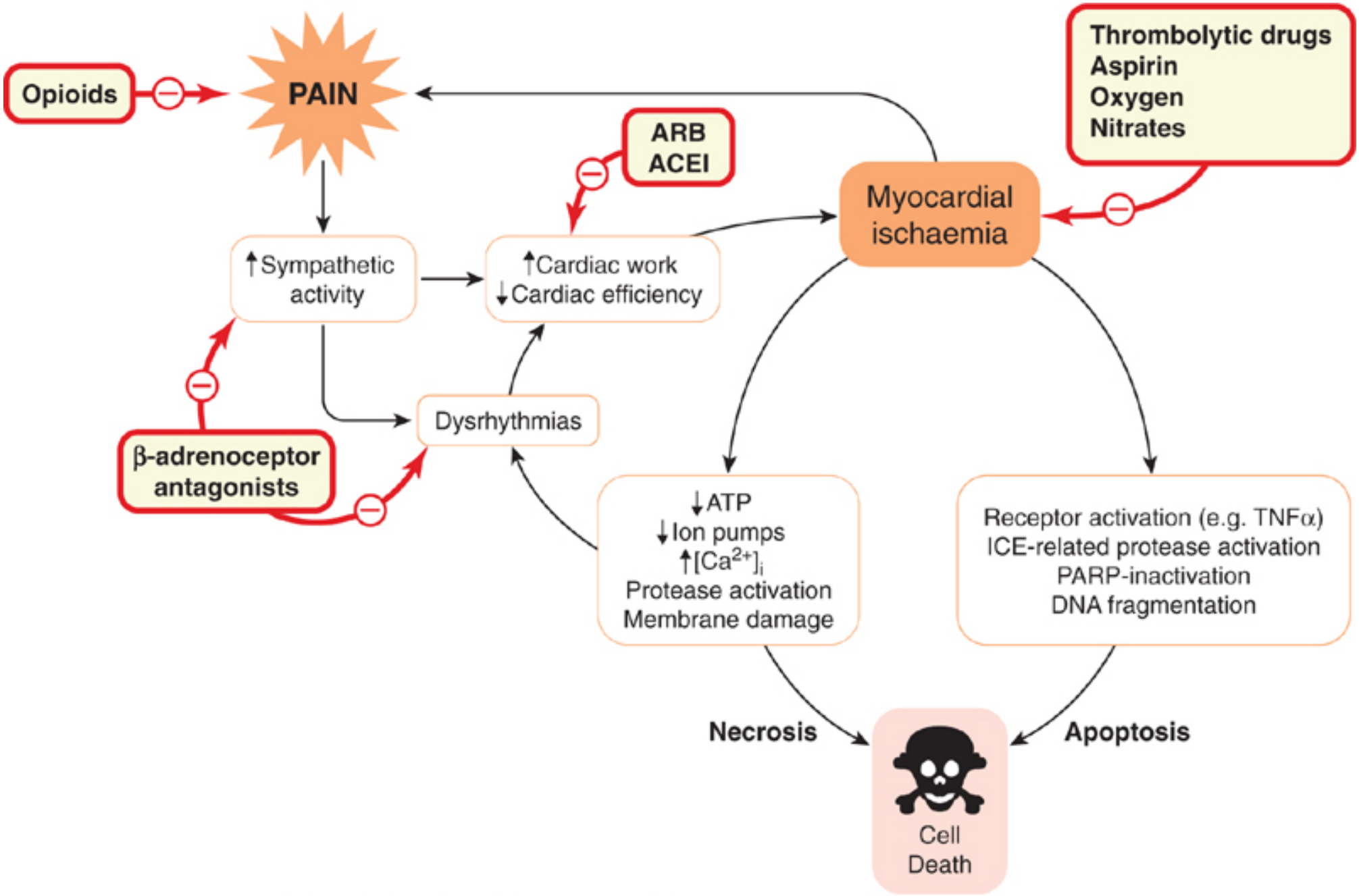
Caused by coronary artery spasm, again usually in association with atheromatous disease.

Therapy is with coronary artery vasodilators (e.g. organic nitrates, calcium antagonists).

Nitrates benefit patients with variant angina by relaxing the smooth muscle of the epicardial coronary arteries and relieving coronary artery spasm.

MYOCARDIAL INFARCTION

- **MI occurs when a coronary artery has been blocked by thrombus.**
- **MI may be fatal and is a common cause of death, usually as a result of mechanical failure of the ventricle or from dysrhythmia.**
- **Cardiac myocytes rely on aerobic metabolism. If the supply of oxygen remains below a critical value, a sequence of events lead to cell death (by necrosis or apoptosis). This is detected clinically by an elevation of circulating troponin (the gold-standard biochemical marker of myocardial injury).**



MYOCARDIAL INFARCTION

- **Prevention of irreversible ischemic damage** following an episode of coronary thrombosis is an important therapeutic aim.
- **Opening the occluded artery** is key, and it is important that this is achieved promptly, irrespective of the means by which it is done.
- If possible, **angioplasty with a glycoprotein IIb/IIIa antagonist** (more effective than thrombolytic drugs).
- **The main therapeutic drugs are to improve cardiac function by maintaining oxygenation, reducing cardiac work, treating pain and preventing further thrombosis.**

MYOCARDIAL INFARCTION

Drugs are used in combination:

- Combinations of antiplatelet (aspirin and clopidogrel) and antithrombotic (a heparin preparation) drugs to open the blocked artery and prevent re-occlusion.
- Oxygen against arterial hypoxia.
- Opioids (given with an antiemetic) to prevent pain and reduce excessive sympathetic activity.
- Organic nitrates.
- β-AR blockers to reduce cardiac work and metabolic needs of the heart and are used as soon as the patient is stable.
- Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin AT1 receptor antagonists also reduce cardiac work and improve survival as does opening the coronary artery and antiplatelet treatment.

MECHANOPHARMACOLOGICAL THERAPY: DRUG-ELUTING ENDOVASCULAR STENTS

- Intracoronary stents can ameliorate angina and reduce adverse events in patients with acute coronary syndromes.
- The long-term efficacy of intracoronary stents is limited by subacute luminal restenosis within the stent, which occurs in some of patients.
- The pathways that lead to "in-stent restenosis" are complex, but smooth muscle proliferation within the lumen of the stented artery is a common pathological finding.
- Local antiproliferative therapies at the time of stenting have been explored over many years, and the development of drug-eluting stents has had an important impact on clinical.

MECHANOPHARMACOLOGICAL THERAPY: DRUG-ELUTING ENDOVASCULAR STENTS

- Two drugs are currently being used in intravascular stents: paclitaxel and sirolimus.
- Paclitaxel inhibits cellular proliferation by binding to and stabilizing polymerized microtubules.
- Sirolimus (a hydrophobic macrolide) binds to the cytosolic immunophilin FKBP12.
- The rate of restenosis with drug-eluting stents is reduced markedly compared with "bare metal" stents, and the ongoing development of mechanopharmacological approaches likely will lead to novel approaches in intravascular therapeutics.