Cardiovascular Drugs

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Cardiovascular Drugs

- **Antianginal drugs**
  Nitroglycerin; β antagonists; Ca^{2+}blockers
- **Drugs used to treat heart failure**
  Classification; ACEIs, β blockers, cardiac glycoside, diuretics
- **Antihypertensive drugs**
  Classification; Properties of main drug classes
- **Antiarrhythmic drugs**
  Classification; Typical drugs and their properties
- **Antiatheroscleotic drugs**
  HMG CoA reductase inhibitors (e.g. statins)

Antianginal Drugs

Overview

- angina pectoris is a characteristic sudden, severe, pressing chest pain starting substernal and radiate to left arm
- may be associated with nausea, vomiting, or diaphoresis.
- due to imbalance between myocardium oxygen requirement and oxygen supply

Types of Angina

1) stable or typical angina

2) unstable angina

3) Prinzmetal's or variant angina

Stable angina

- the most common form of angina
- it is characterized by a burning, heavy, or squeezing feeling in the chest
- it is caused by the reduction of coronary perfusion due to a fixed obstruction produced by coronary atherosclerosis
- typical AP is promptly relieved by rest or nitroglycerin

Stable angina

- discomfort is precipitated by activity
- minimal or no symptoms at rest
- symptoms disappear after rest/cessation of activity

Stable angina

- **Therapeutic goals:** Decrease cardiac load (preload and afterload), decrease heart rate (*decrease oxygen demand*)
- increase myocardial blood flow by dilating coronary arteries and arterioles (*increase oxygen delivery*),

Unstable angina

- unstable angina lies between stable angina on the one hand and myocardial infarction on the other
- in unstable angina, chest pains occur with increased frequency
- the symptoms are not relieved by rest or nitroglycerin
- it requires hospital admission and more aggressive therapy to prevent death and progression to myocardial infarction

Unstable angina

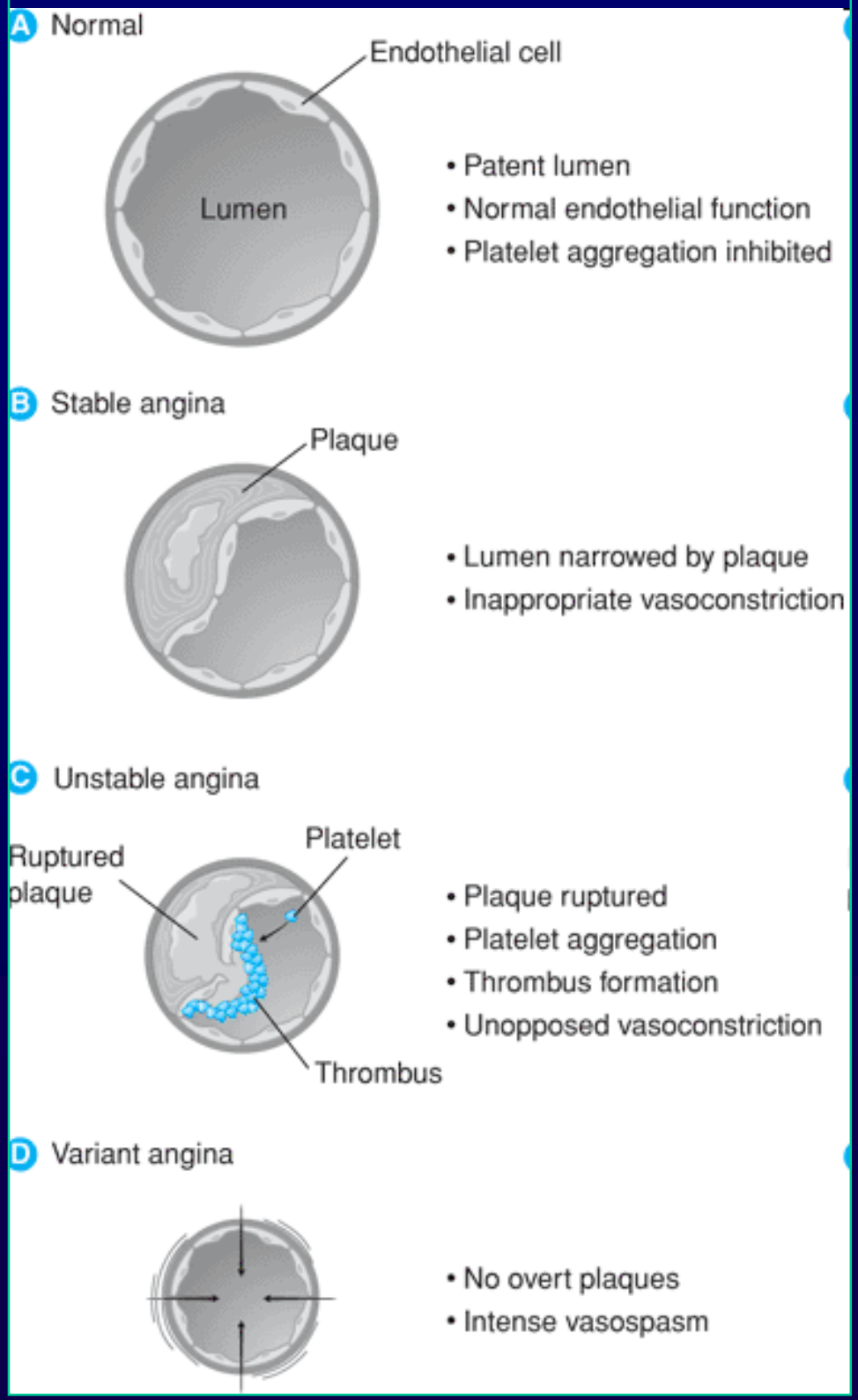
- **Therapeutic rationale:** **Inhibit platelet aggregation and thrombus formation (*increase oxygen delivery*), decrease cardiac load (*decrease oxygen demand*), and vasodilate coronary arteries (*increase oxygen delivery*)**

Prinzmetal's or variant or vasospastic angina

- it is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm
- symptoms are caused by decreased blood flow to the heart muscle due to spasm of the coronary artery
- the angina attacks are unrelated to physical activity, heart rate, or blood pressure
- Prinzmetal's angina generally responds promptly to coronary vasodilators, such as nitroglycerin and calcium-channel blockers

Vasospastic angina

- **Therapeutic rationale:** **Decrease vasospasm of coronary vessels (calcium channel blockers are efficacious in >70% of patients; *increase oxygen delivery*)**



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Treatment Goals

Feel better

Live longer

Risk Factors

We can control

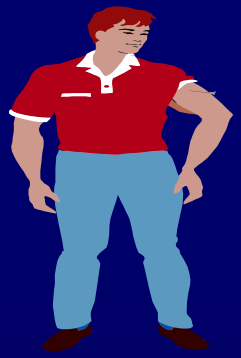
- Hypertension
- Smoking
- Dyslipidemia
- Diabetes Mellitus
- Obesity
- Stress

We cannot control

- Age
- Sex
- Genetic predisposition

General principles

Stop smoking



Reduce weight

Treat Hypertension, Hypercholestrolemia and Diabetes

AVOID

Severe exertion

Heavy meal

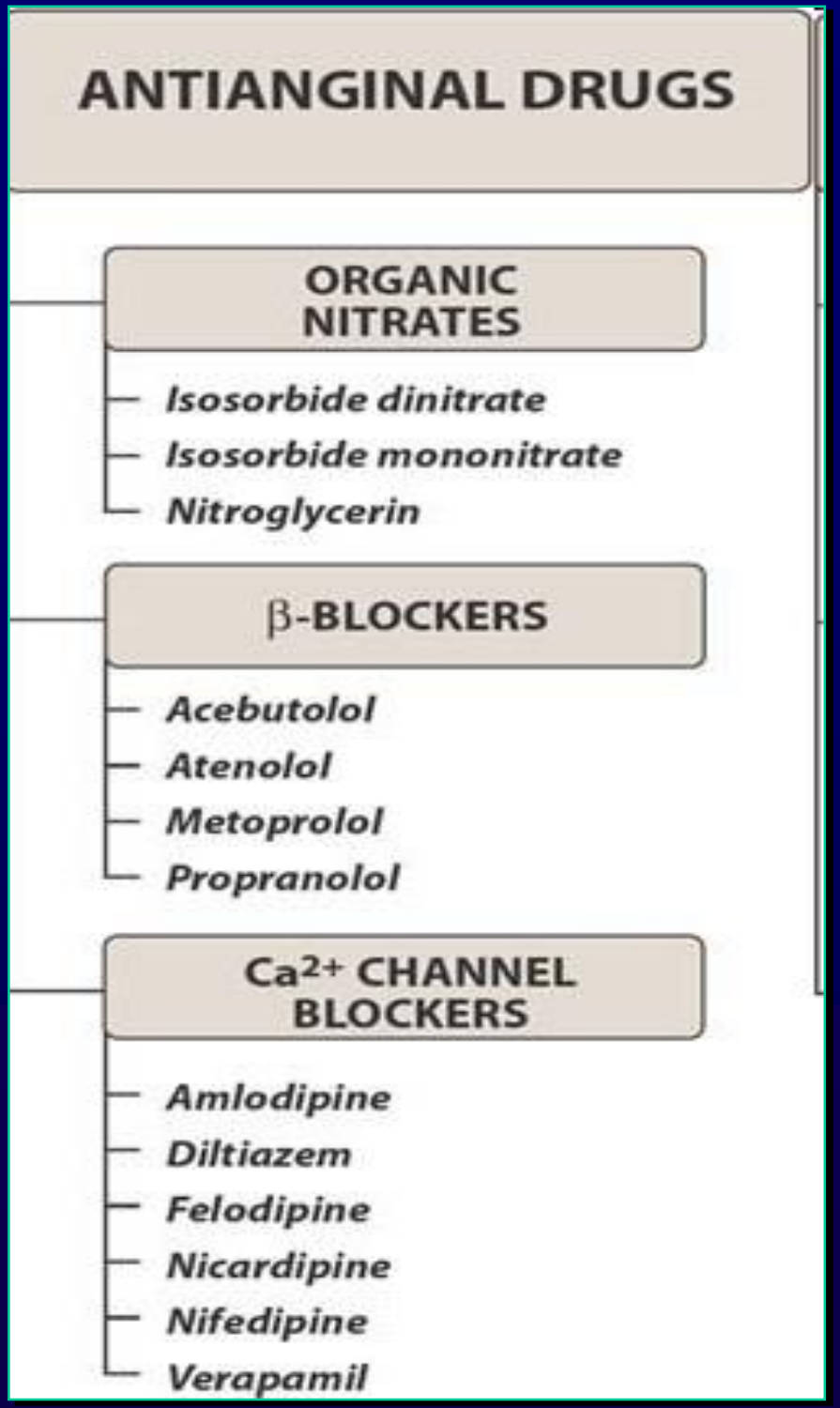
Emotions

Cold Weather

- **Graduated exercise may open new collaterals**

History of Antianginal Drugs

- Amyl nitrate and nitroglycerin were found to provide transient relief of angina in the mid-to late 1800s
- Subsequently many other vasodilators were introduced for the treatment of angina, but double-blinded clinical trials showed many were no better than placebo
- β-adrenergic blockers and CCB were developed during the early 1960's and are now also widely used in the prophylactic therapy of angina



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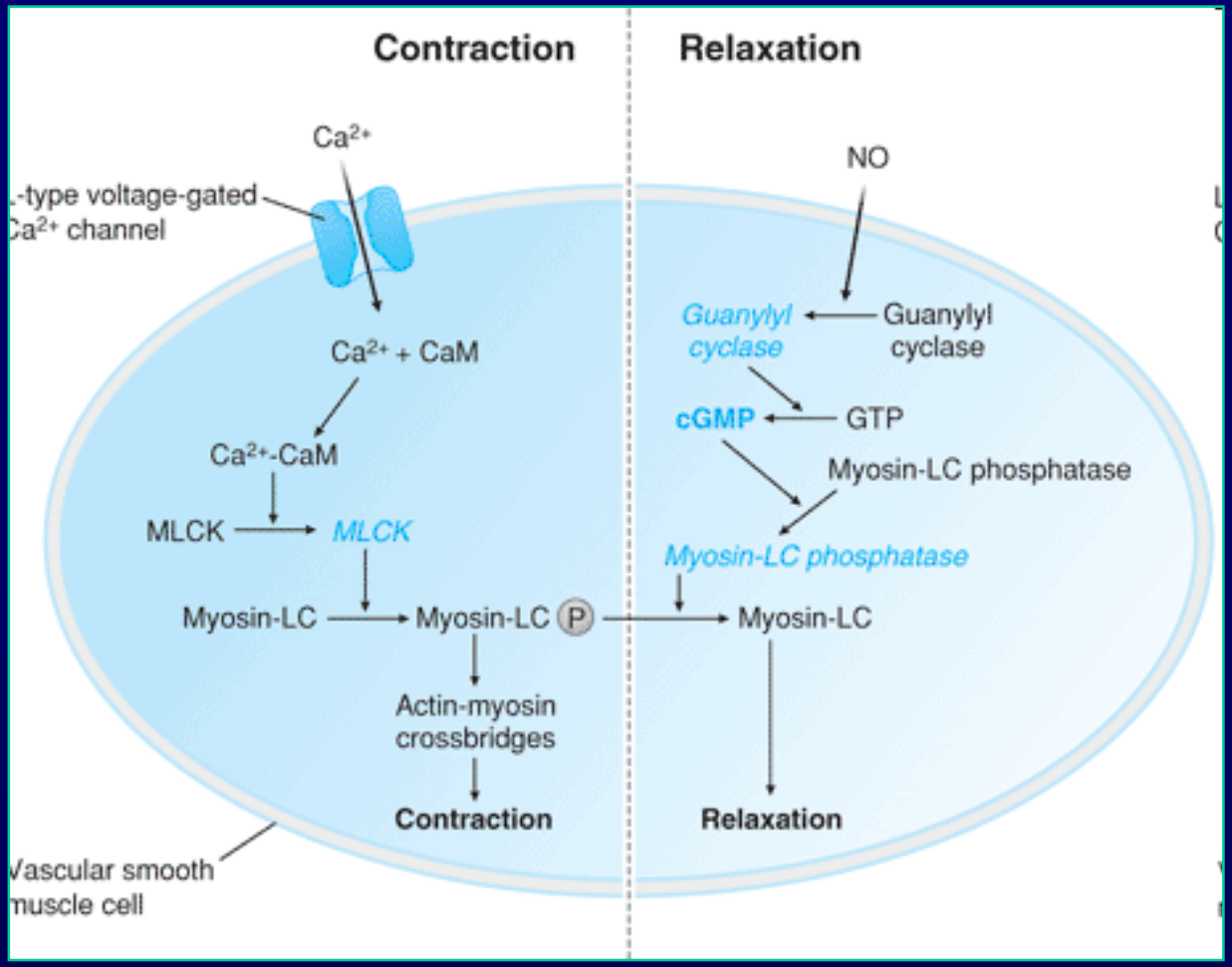
Organic Nitrates

- organic nitrates used in the treatment of AP are simple nitric and nitrous acid esters of glycerol
- these compounds cause a rapid reduction in myocardial oxygen demand, followed by rapid relief of symptoms
- they are effective in stable and unstable angina as well as in variant angina pectoris

Mechanism of action

- nitrates decrease coronary vasoconstriction or spasm and increase perfusion of the myocardium by relaxing coronary arteries
- in addition, they relax veins, decreasing preload and myocardial oxygen consumption
- nitrates - relax vascular smooth muscle by their intracellular conversion to nitrite ions, and then to nitric oxide, which in turn activates GC and increases cGMP
- elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation



NO diffuses into the cell and activates GC. The activated GC catalyzes the conversion of GTP to cGMP. cGMP activates myosin-LC phosphatase, which dephosphorylates myosin light chain, preventing actin–myosin cross-bridge formation. As a result, the vascular smooth muscle cell relaxes.

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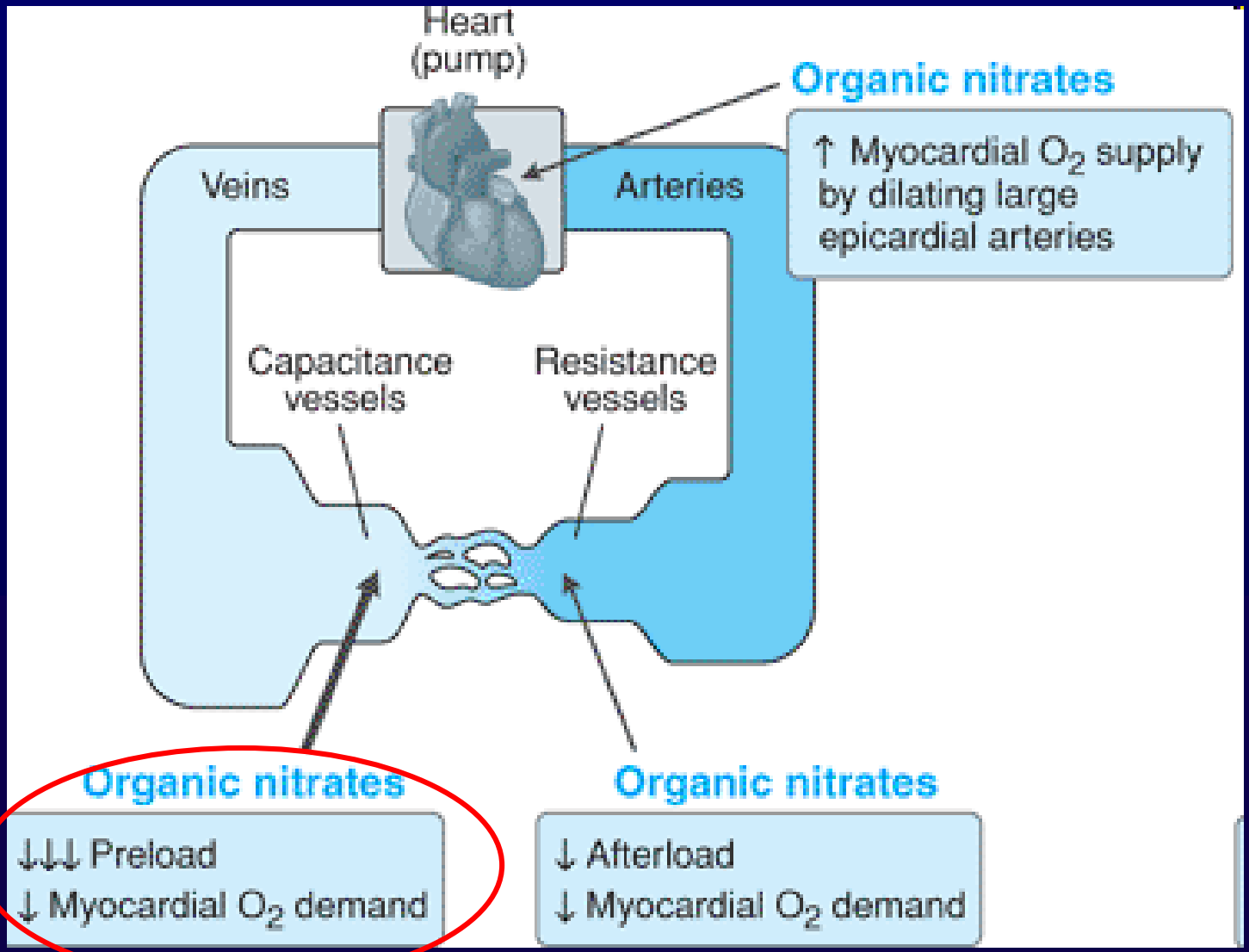
Effects on the cardiovascular system

- nitroglycerin (glyceryl trinitrate) has two major effects
  - first, it causes dilation of the large veins, resulting in pooling of blood in the veins; this diminishes preload and reduces the work of the heart
  - second, nitroglycerin dilates the coronary vasculature, providing an increased blood supply to the heart muscle
- nitroglycerin decreases myocardial oxygen consumption because of decreased cardiac work

Sites of action of organic nitrates



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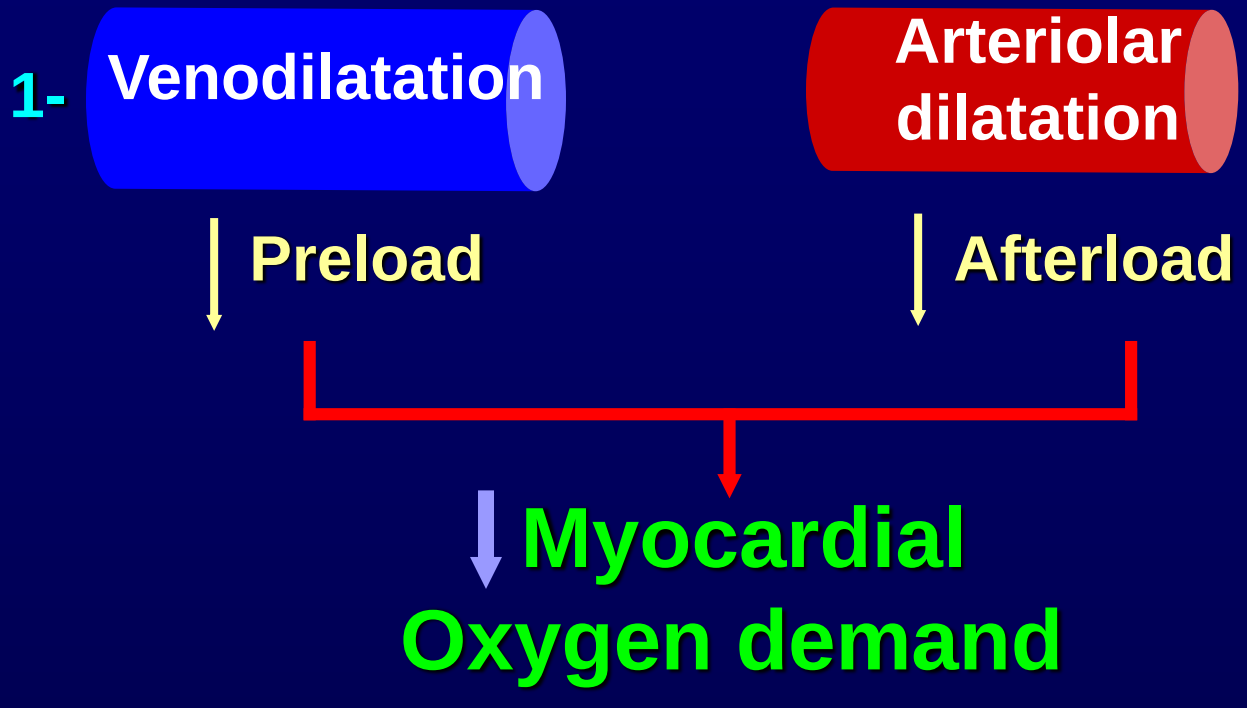
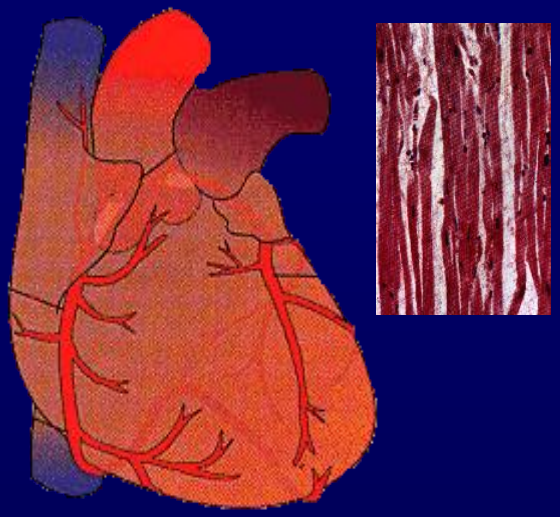
Stable Angina



2- Redistribution of coronary flow towards subendocardium

3- Dilatation of coronary collateral vessels.

Variant Angina



Relax smooth muscles of the epicardial coronaries → relieve coronary artery spasm

Unstable Angina

Dilatation of epicardial coronary arteries + reducing O_2 demands

Pharmacokinetics

- the time to onset of action varies from 1 minute for nitroglycerin to more than 1 hour for isosorbide mononitrate
- significant first-pass metabolism of nitroglycerin occurs in the liver; therefore, it is common to take the drug either sublingually or via a transdermal patch, thereby avoiding this route of elimination
- IMN - improved bioavailability and long duration of action to its stability against hepatic breakdown
- oral IDN undergoes denitration to two mononitrates, both of which possess antianginal activity

Routes of Administration

- GTN and ISDN have a rapid onset of action (1-3 min) when administered sublingually, but the short duration of action (20-30 min) is not suitable for maintenance therapy
- IV nitrogylcerin can be used to treat severe recurrent unstable angina
- Slowly absorbed preparations of nitrovasodilators (oral, transdermal) can be used to provide prolonged prophylaxis against angina (3-10 hrs), but can lead to tolerance

Short acting

- start within few minutes and total duration of action 15-30 minutes

- a) nitroglycerine (Glyceryl trinitrate) used as sublingual tablets

- b) isosorbide dinitrate as sublingual spray

Long acting

- **nitroglycerine, isosorbide dinitrate, isosorbide mononitrate**
  - **action of all start within hour and continue for hours**
- **the most common application: orally, transdermal patch**

Adverse effects

- the most common adverse effect – headache (30-60 % of patients receiving long-acting agents)
- high doses of organic nitrates can also cause postural hypotension, facial flushing, and tachycardia (contraindicated with sildenafil)
- Organic nitrates are contraindicated in patients with elevated intracranial pressure

Tolerance

- it develops rapidly
- tolerance can be overcome by providing a daily “nitrate-free interval” to restore sensitivity to the drug
- this interval is typically 10 to 12 hours, usually at night
- !!! variant angina worsens early in the morning - therefore, the nitrate-free interval in these patients should occur in the late afternoon

Effects of Nitrates in Addition to Vasodilation

- NO from organic nitrates can cause relaxation of other types of smooth muscle - such as esophageal, bronchial, biliary, intestinal, and genitourinary
- the ability of NTG to relieve the angina-like chest pain of esophageal spasm can occasionally result in a misdiagnosis of coronary artery disease
- actions of nitrates on nonvascular smooth muscle are usually of limited clinical significance, however
- NO generated from organic nitrates functions as an antiplatelet agent NO-mediated increases in platelet cGMP inhibit platelet aggregation
- nitrate-induced inhibition of platelet aggregation may be especially important in the treatment of unstable angina

Table 12–3. Nitrate and Nitrite Drugs 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

β adrenoreceptor blockers

The main uses of β-blockers in patients with ischemic heart disease are in *prophylaxis of angina*, and in *reducing the risk of sudden death or reinfarction* following myocardial infarction ("secondary prevention").

In addition, β -blockers are used in treating hypertension, cardiac arrhythmias, in patients with essential tremor and to suppress symptoms of hyperthyroidism before more specific therapy has time to work (risk factors for CAD).

β adrenoreceptor blockers

β-blockers are effective in **STABLE** and **UNSTABLE** angina

- In contrast they are **not** useful for **vasospastic angina** (may worsen the condition)

- This deleterious effect is likely due to an increase in coronary resistance caused by the unopposed effects of catecholamines acting at α-adrenoceptors.

Mechanism of action

- β -adrenoceptors are linked via stimulatory G-proteins to AC and so noradrenaline or adrenaline - ⇧ cytoplasmic cAMP

- *In cardiac tissue cAMP:*
  - ↑ force of contraction and heart rate
  - is arrhythmogenic
  - in arteriolar vascular smooth muscle - vasodilatation
  - in the juxta-glomerular cells ⇨ renin release
  - in airways smooth muscle causes relaxation.

- β -Blocking drugs *work by competing* with endogenous noradrenaline and adrenaline and thereby reduce their β-receptor-mediated effects.

Mechanism of antianginal action

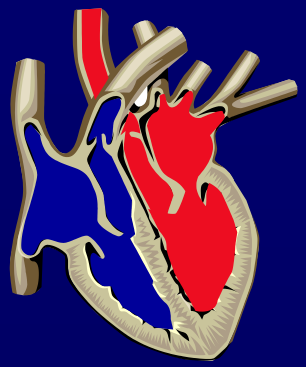
The effectiveness of β-adrenoceptor blockers in the treatment of exertional angina is attributable to a fall in myocardial O_2 requirement at rest & during exertion due to:

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

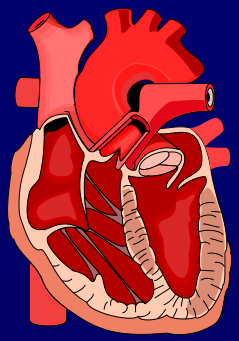
Dosage and Route of Administration

Drug	Route	Dosage
Propranolol	Oral	30-360 mg/day in 2-4 divided doses
Nadolol	Oral	40-80 mg ONCE daily
Atenolol	Oral	50-100 mg ONCE daily
Metoprolol	Oral	50-100 mg TWICE daily

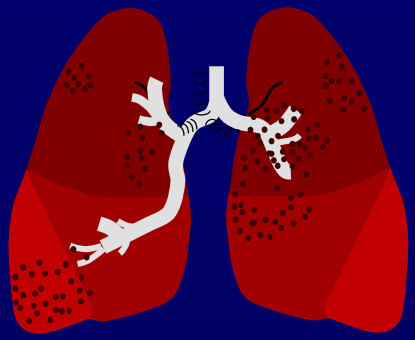
Adverse Reactions :



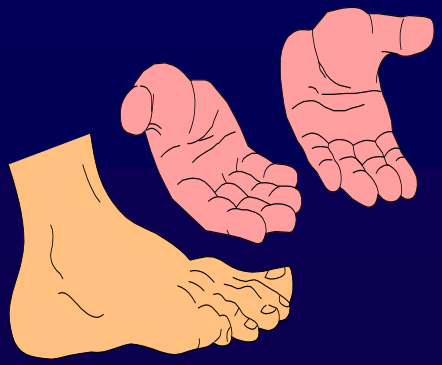
CHF



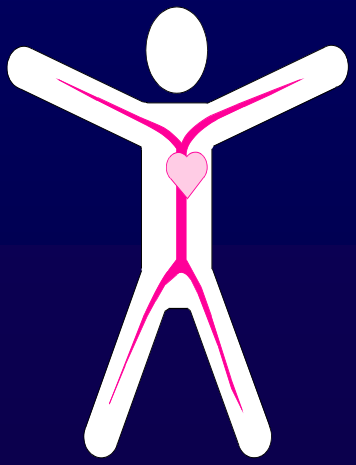
A-V block



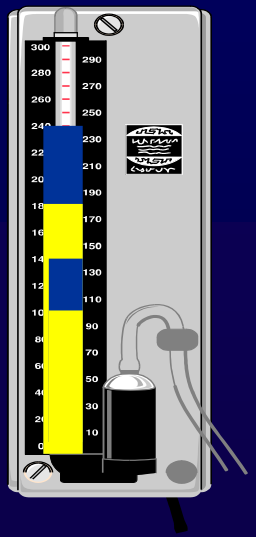
Bronchospasm



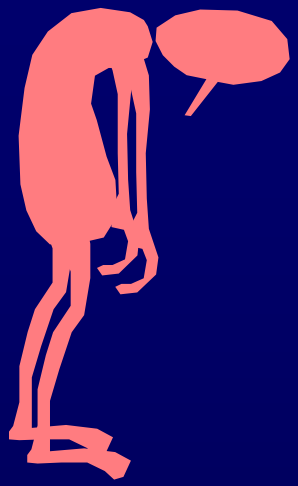
Cold extremities



Worsening symptoms of PVD



Hypotension

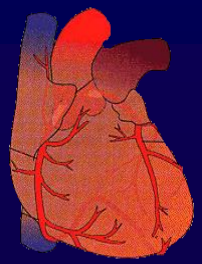


Fatigue & weakness

Mask signs of hypoglycemia

Nightmares, hallucinations, depression

↑ Plasma TAG, ↓HDL Cholesterol



Discontinuation after long th. exacerbates angina

Calcium channel blockers

- several different subtypes of voltage-gated Ca^{2+} channels have been identified (termed L, T, N, and P channels)
- Ca^{2+} influx through the L-type channel is an important determinant of vascular tone and cardiac contractility
- the CCB in current use all act by inhibiting Ca^{2+} entry through the L-type channel, although different members of this drug class have markedly different pharmacodynamic and pharmacokinetic properties

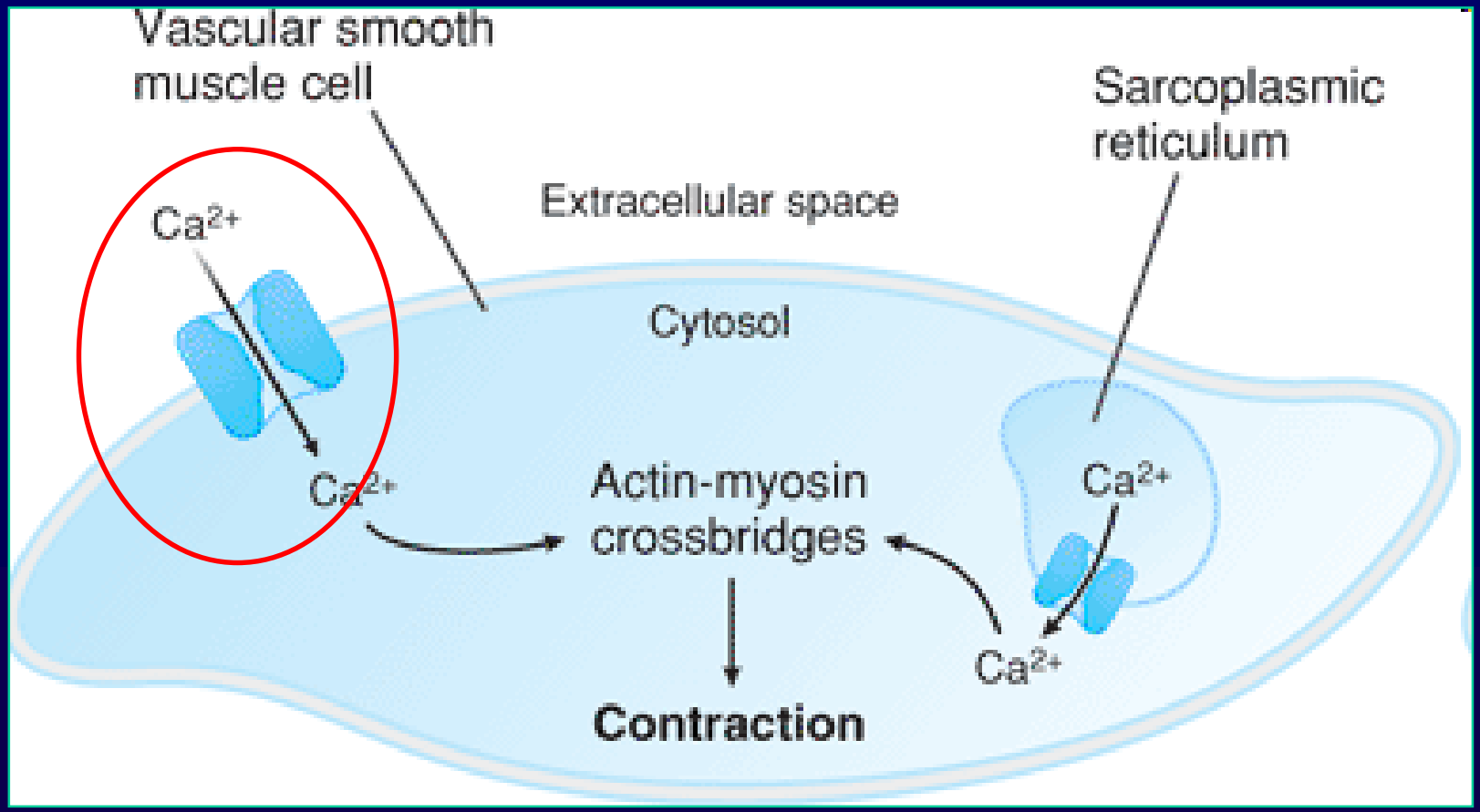
CCB block calcium entry in myocardium causing:

- **a) decrease myocardium contractility and myocardium oxygen requirement**
- **b) decrease heart rate causing decrease in myocardium oxygen requirement**

Block calcium entry in vascular smooth muscles (arterioles) causing:

- **a) decrease in peripheral resistance (⇩ after load) ⇨ decrease in oxygen requirement**
- **b) relief of coronary spasm**

Sources of Ca^{2+} for contraction of vascular smooth muscle cells



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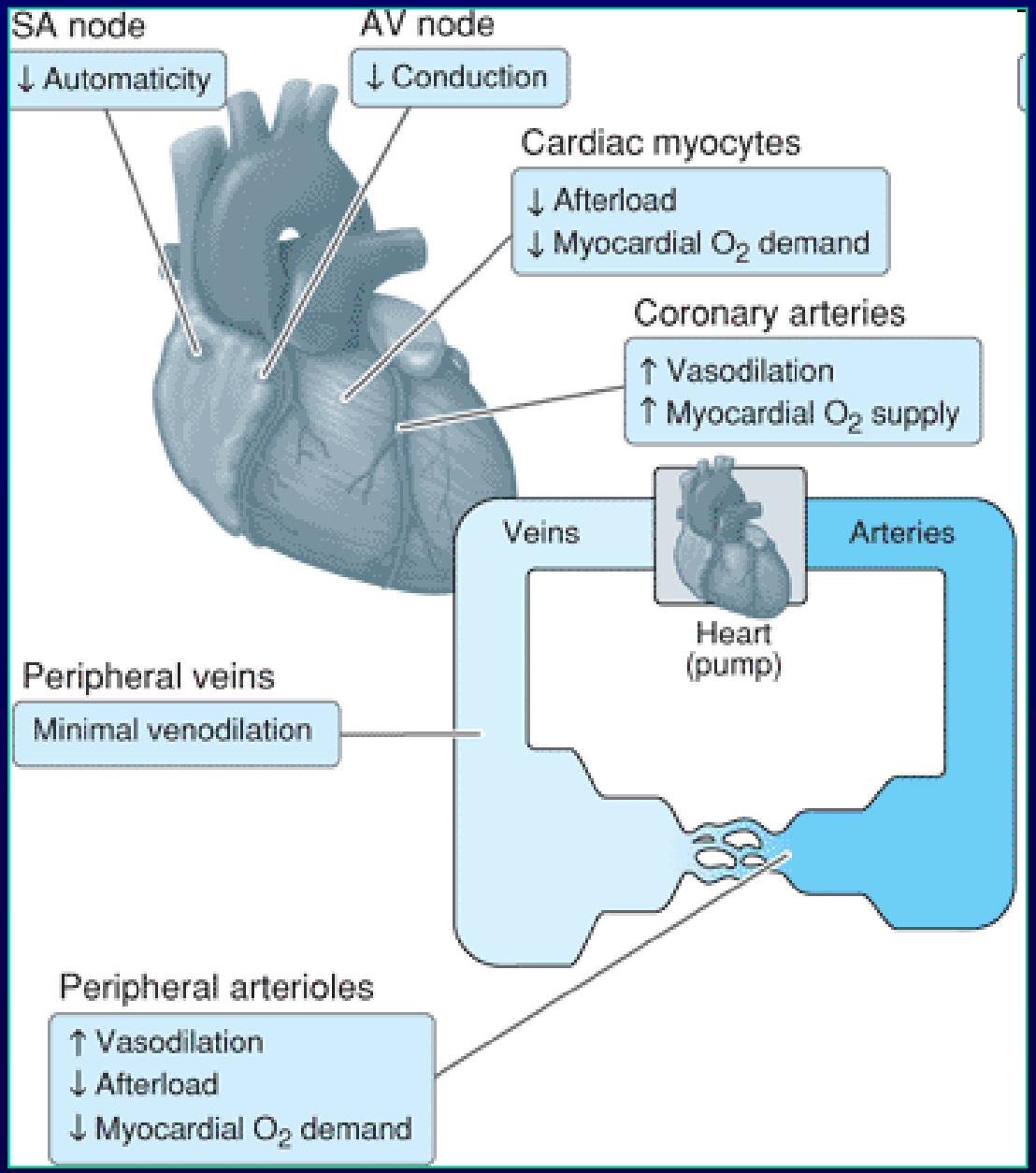
- all calcium-channel blockers (CCB) are arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance
- at clinical doses, these agents affect primarily the resistance of vascular smooth muscle and the myocardium
- all CCB lower blood pressure; they may worsen heart failure due to their negative inotropic effect

Chemical Classes

- dihydropyridines (nifedipine, amlodipine and felodipine)
- benzothiazepines (diltiazem)
- phenylalkylamines (verapamil)
- diarylaminopropylamine ethers (bepridil)
- benzimidazole-substituted tetralines (mibefradil)

Sites of action of Ca^{2+} channel blockers



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Nifedipine

- a dihydropyridine derivative, functions mainly as an arteriolar vasodilator
- minimal effect on cardiac conduction or heart rate; amlodipine, nicardipine, and felodipine - similar cardiovascular characteristics
- Nifedipin can activate severe reflex tachycardia, which can worsen myocardial ischemia by ⇧ myocardial O_2 demand and ⇩ myocardial O_2 supply
- The general consensus is that short-acting dihydropyridines should be avoided in coronary artery disease

Verapamil

- it slows cardiac AV conduction directly, and decreases heart rate, contractility, blood pressure, and oxygen demand
- verapamil causes greater negative inotropic effects than nifedipine, but it is a weaker vasodilator
- it is extensively metabolized by the liver (care must be taken to adjust the dose in patients with liver dysfunction)
- it is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities

Diltiazem

- it has cardiovascular effects that are similar to those of verapamil; both drugs slow AV conduction and decrease the rate of firing of the sinus node pacemaker
- it reduces the heart rate, although to a lesser extent than verapamil, and also decreases blood pressure
- diltiazem can relieve coronary artery spasm and, therefore, is particularly useful in patients with variant angina
- It is extensively metabolized by the liver

Effects on vascular smooth muscle

- CCB inhibit mainly L-type voltage-dependent Ca^{2+} channels

- little or no effect on receptor-operated channels or on release of Ca^{2+} from SR

- "Vascular selectivity" is seen with the CCB:
- ⇩ iCa^{2+} in arterial smooth muscle ⇨ vasodilatation ⇨ decreased cardiac afterload
  - little or no effect of CCB on venous beds ⇨ no effect on cardiac preload
  - specific dihydropyridines may exhibit greater potencies in some vascular beds (e.g.- nimodipine more selective for cerebral blood vessels, nicardipine for coronary vessels)
  - little or no effect on nonvascular smooth muscle

Effects on cardiac cells

- **It depends on the class of CCB:**
  - **Negative inotropic effect (myocardial L-type channels)**
    - Reduced inward movement of Ca^{2+} during action potential plateau phase
    - Dihydropyridines have very modest negative inotropic effect
    - Mibefradil (T-type) has no negative inotropic effect
  - **Negative chronotropic/dromotropic effects (L- and T-type channels)**
    - Verapamil, diltiazem, and mibefradil depress SA node and AV conduction
    - Dihydropyridines have minimal direct effects on SA node and AV conduction (but they can cause reflex tachycardia)

Effects of CCBs on the heart

	Nif.	Dil.	Ver.
Coronary dilatation	+ +	+ +	+ +
Peripheral dilatation	+ + + +	+ +	+ + +
Negative inotropic	+	+ +	+ + +
↓ AV conduction	↔	+ + +	+ + + +
Heart rate	↑ ↔	↓ ↔	↓ ↔
↓ blood pressure	+ + + +	+ +	+ + +
Sinus node depression	↔	+ +	+ +
Cardiac output	+ +	↔	↔

Desired therapeutic effects of calcium channel blockers for angina

- **Improve oxygen delivery to ischemic myocardium**
  - Vasodilate coronary arteries
  - May inhibit platelet aggregation
  - Particularly useful in treating vasospastic a.

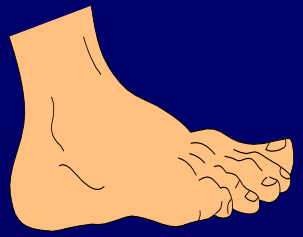
- **Reduce myocardial oxygen consumption**
  - Decrease afterload (no effect on preload)
  - Non-dihydropyridines also lower heart rate and decrease contractility
  - Dihydropyridines may aggravate angina in some patients due to reflex increases in heart rate and contractility

Pharmacokinetics

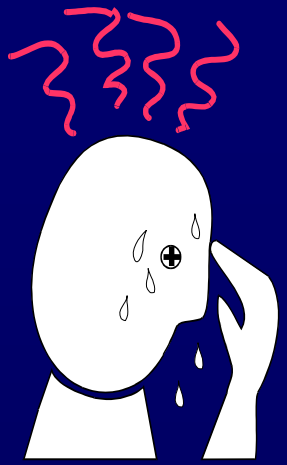
- CCB are typically used in oral dosage forms, although intravenous formulations of diltiazem and verapamil are also available
- nifedipine and verapamil are excreted by the kidney; diltiazem is excreted by the liver
- several pharmacokinetic properties of these drugs are sub-optimal;
  - the bioavailability of oral formulations of nifedipine, diltiazem, and verapamil is lowered by significant first-pass metabolism in the gut and liver
  - oral nifedipine has a rapid onset of action (less than 20 min) and can cause a significant fall in BP

Adverse reactions

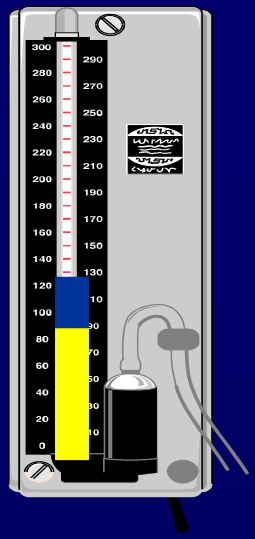
Dizziness



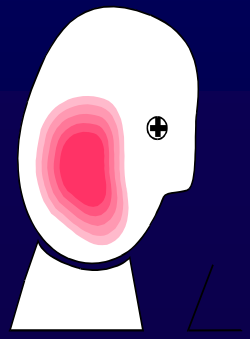
Ankle edema



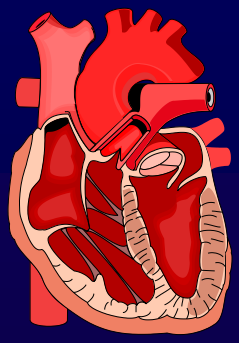
Headache



Hypotension



Flushing



A-V block & HF only with Verapamil & Diltiazem

Reflex Tachycardia with Nifedipine

Antianginal combination therapies

Good Ones

- A dihydropyridine CCB and a β-blocker (coronary vasodilation, decreased afterload, lower heart rate, suppression of reflex tachycardia)

- A nitrovasodilator and a β -blocker (coronary vasodilation, decreased preload, lower heart rate, suppression of reflex tachycardia)

- A nitrovasodilator and a non-dihydropyridine CCB (coronary vasodilation, decreased preload and afterload, lower heart rate, suppression of reflex tachycardia)

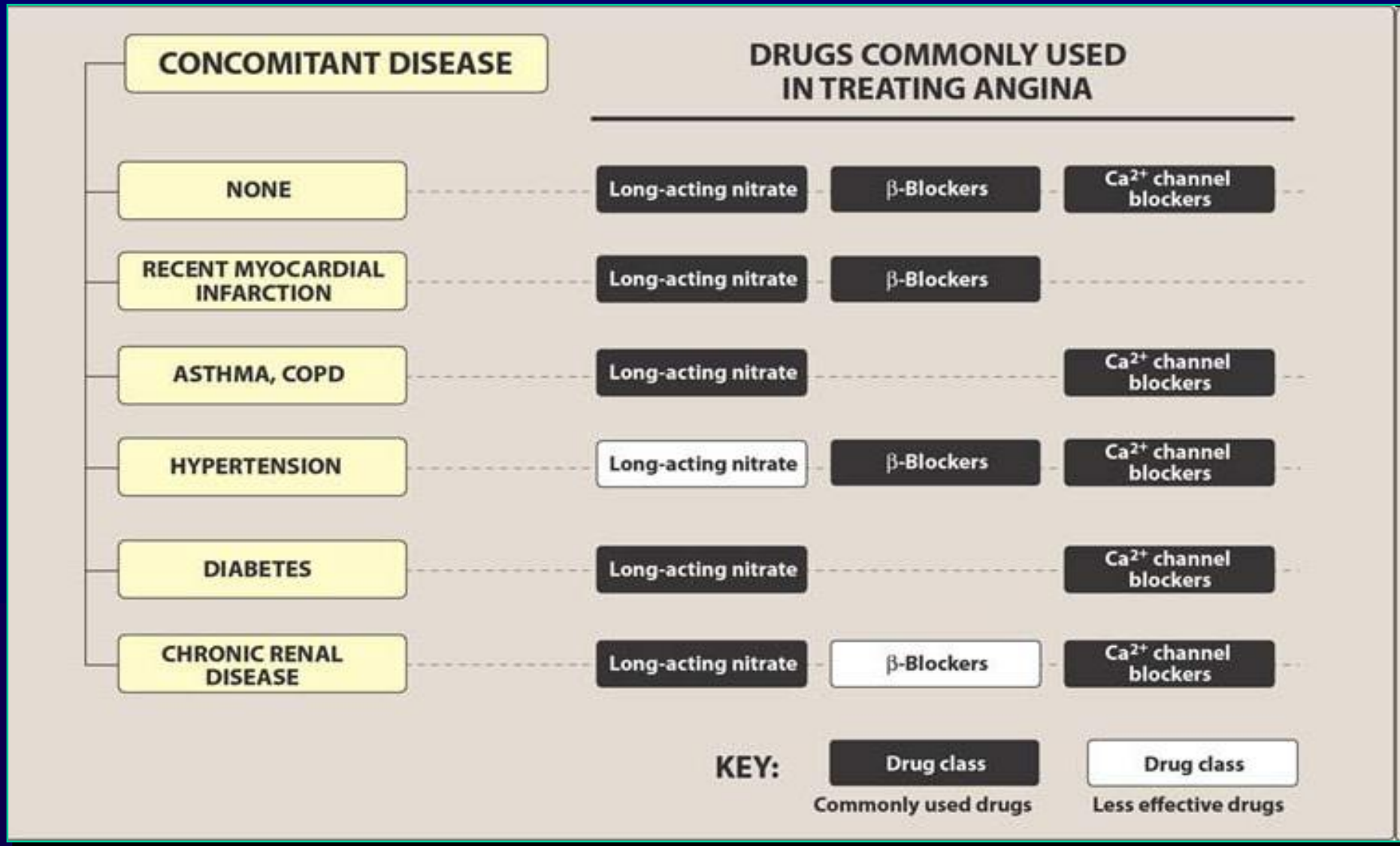
Antianginal combination therapies

Good Ones – *cont.*

- A nitrovasodilator, a dihydropyridine CCB and a β-blocker (coronary vasodilation, decreased preload and afterload, lower heart rate, suppression of reflex tachycardia)

Bad Ones:

- A β-blocker and non-dihydropyridine CCB (bradycardia, AV block, depressed LV function)



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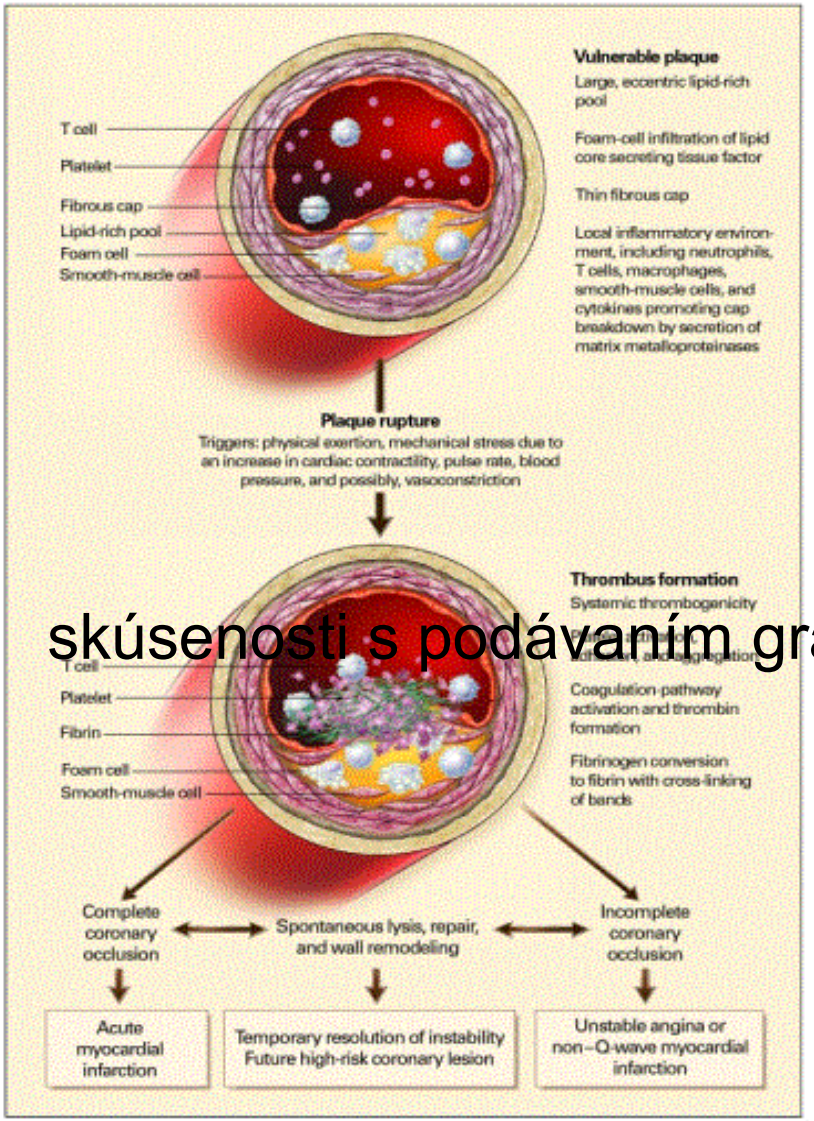
Aspirin

- clinical data have demonstrated a significant treatment benefit for aspirin in patients with unstable angina (~50% reduction in death and nonfatal MI)
- aspirin is contraindicated in patients with a known allergy to the drug; in this setting, clopidogrel is indicated as an alternative
- aspirin and other antiplatelet agents should be used cautiously in patients with compromised liver function (decreased circulating levels of hepatically-synthesized coagulation factors)
- aspirin - gastritis and peptic ulcer disease



skúsenosti s podávaním grantov

Figure 1: Pathophysiologic Events Culminating in the Clinical Syndrome of Unstable Angina.
Numerous physiologic triggers probably initiate the rupture of a vulnerable plaque. Rupture leads to the activation, adhesion, and aggregation of platelets and the activation of the clotting cascade, resulting in the formation of an occlusive thrombus. If this process leads to complete occlusion of the artery, then acute myocardial infarction with ST-segment elevation occurs. Alternatively, if the process leads to severe stenosis but the artery nonetheless remains patent, then unstable angina occurs.

Ranolazine:

- Reserve agent for treatment of chronic, resistant angina
- Inhibits cardiac late Na^+ current
- Effects the Na^+ dependent Ca^{2+} channels and prevents Ca^{2+} overload that causes cardiac ischemia
- Decreases cardiac contractility
- No change in HR, BP

Nicorandil

- Vasodilatory drug used to treat angina pectoris
- It has dual properties of a nitrate and ATP sensitive K^+ channel opener
- Nitrate action dilates the large coronary arteries at low plasma concentrations
- At high concentrations it reduces coronary artery resistance which is associated with opening of ATP sensitive K^+ channels
- Nicorandil has cardioprotective effect which appears to be due to activation of ATP sensitive K^+ channels
- ADRs: Flushing, palpitation, headache, mouth ulcers, nausea and vomiting