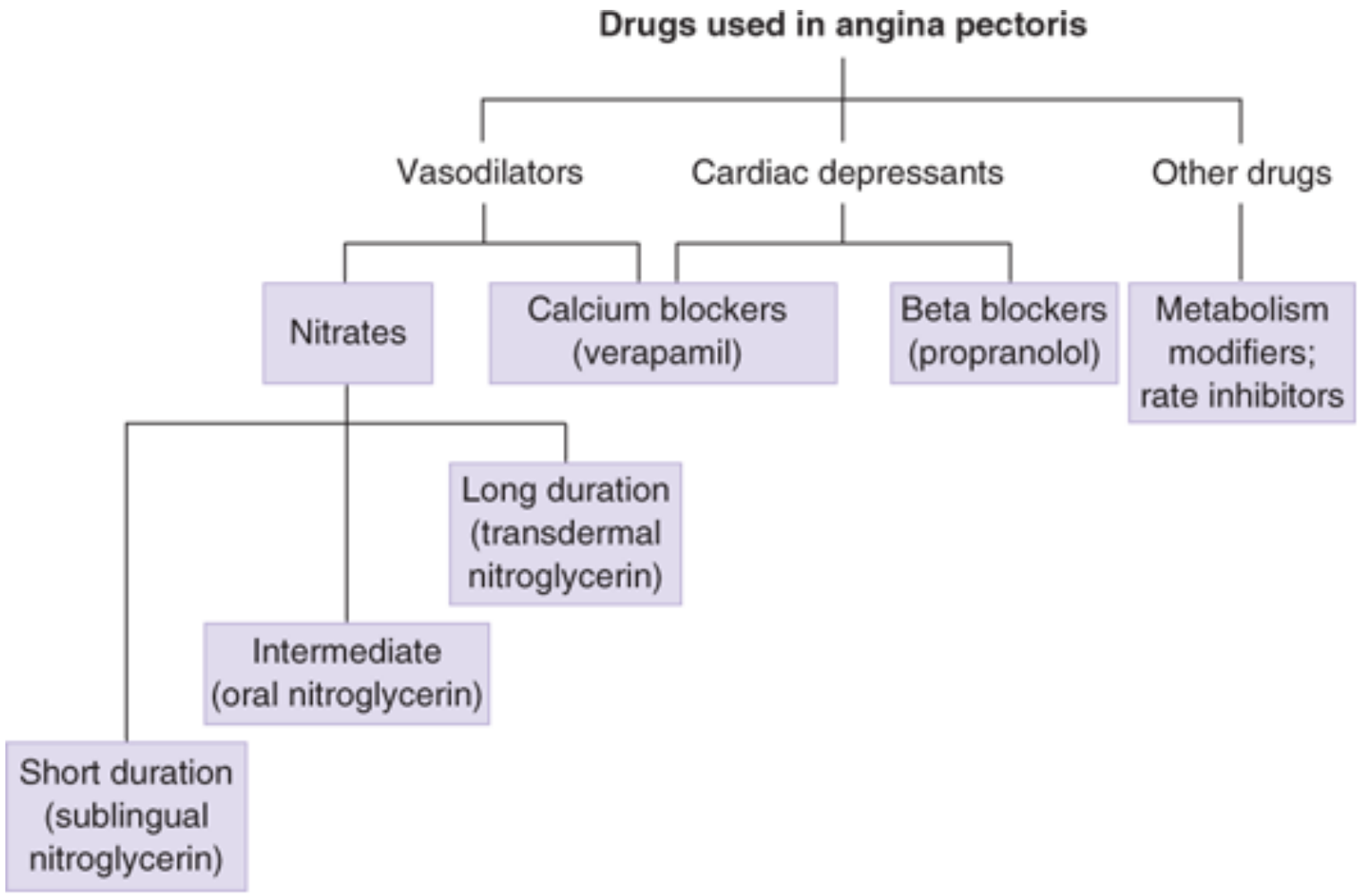
Drugs Used in the Treatment of Angina Pectoris



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
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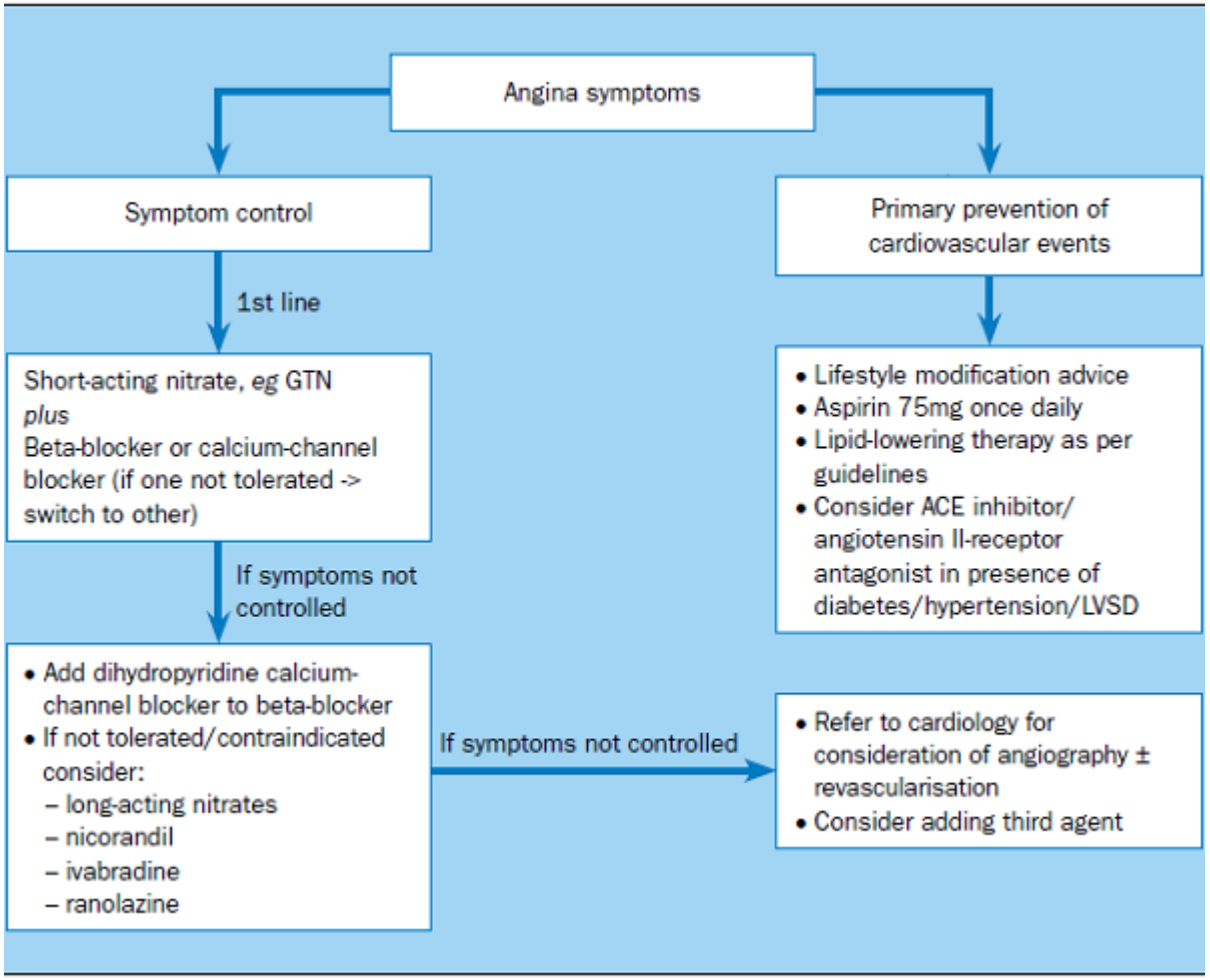
Overview of drugs used in the treatment of angina



Drugs used in angina pectoris

- **Nitrates and nitrites**: decrease vasoconstriction and coronary spasm; increase myocardial perfusion by relaxing coronary arteries.

- **Ca^{++} channel antagonists**: cause relaxation of the arterial smooth muscle but have little effect on veins.

- **β-blockers**: improve the survival rate in ischemic heart disease because they are effective in increasing endurance during physical exercise.

- **Other drugs** (second and third line therapies).

Table 1: Chronic Stable Angina Pharmacotherapy: Comparison of Guideline Recommendations

Antianginal Drug	European Society of Cardiology	National Institute for Health and Care Excellence
First-line therapy		
Sublingual nitroglycerin	IB	
Short-acting nitrates	IB	First-line treatment
Long-acting nitrates	IIaB	Second-line treatment
Beta-blockers	Uncomplicated patient: IA Previous MI: IB Reduced LVEF (<40%): IB	First-line treatment*
Calcium channel blockers:	Non-dihydropyridines: IA Dihydropyridines: IA	First-line treatment* Avoid non-dihydropyridines with BB or ivabradine
Second- and third-line therapy		
Ranolazine	IIaB	Second-line treatment[t,‡,§]
Ivabridine	IIaB Use when beta-blockers are contraindicated	Second-line treatment[t,‡,§]
Nicorandil	IIaB Preferred to nitrates	Second-line treatment[t,‡,§]
Trimetazidine	IIbB	NA
Allopurinol	Second- or third-line agent for symptom control	NA
Interventions for secondary prevention of cardiovascular disease		
Abstain from smoking	I	Assess the need for lifestyle advice, including smoking cessation
Aspirin	I 75–150 mg daily (consider clopidogrel if aspirin intolerance)	75 mg. Take into account the risk of bleeding
Statin	I Target dose to achieve LDL level <1.8 mmol/l or >50% reduction	Offer statin in line with lipid modification guidelines (atorvastatin 80 mg to achieve non-HDL cholesterol reduction >40%)
ACE inhibitor or ARB	II: normal LVEF I: with hypertension and/or diabetes	Consider ACE inhibitor for patients with diabetes

Interchangeable. If symptoms not controlled switch to other option or use both. Avoid the combination of BB and non-dihydropyridine CCB. †Use as monotherapy if first-line agents (BB and/or CCB) are not tolerated or contraindicated. Use as addition to BB or CCB if one of these is not tolerated or contraindicated. Do not routinely combine these antianginals in addition to dual therapy with BB and CCB except in patients awaiting revascularisation consideration or when revascularisation is inappropriate. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = beta-blocker; CCB = calcium channel blocker; LVEF = left ventricular ejection fraction; NA = not applicable.

Rousan TA, Thadani U. Stable Angina Medical Therapy Management Guidelines: A Critical Review of Guidelines from the European Society of Cardiology and National Institute for Health and Care Excellence. Eur Cardiol. 2019 Apr;14(1):18-22. doi: 10.15420/ecr.2018.26.1.

Overview of drugs used in the treatment of angina

DRUG CLASS	COMMON ADVERSE EFFECTS	DRUG INTERACTIONS	NOTES
β-blockers *atenolol* *metoprolol* *propranolol*	Bradycardia, worsening peripheral vascular disease, fatigue, sleep disturbance, depression, blunt hypoglycemia awareness, inhibit β_2-mediated bronchodilation in asthmatics	β_2 agonists (blunted effect); non-dihydropyridine calcium-channel blockers (additive effects)	β_1-selective agents preferred (*atenolol, metoprolol*). Avoid agents with ISA for angina therapy (*pindolol*).
Dihydropyridine calcium-channel blockers *amlodipine* *felodipine* *nifedipine*	Peripheral edema, headache, flushing, rebound tachycardia (immediate release formulations), hypotension	CYP 3A4 substrates (will increase drug concentrations)	Avoid short-acting agents as they can worsen angina (may use extended-release formulations)
Non-dihydropyridine calcium-channel blockers *diltiazem* *verapamil*	Bradycardia, constipation, heart failure exacerbations, gingival hyperplasia (*verapamil*), edema (*diltiazem*)	CYP 3A4 substrates (will increase drug concentrations); increase *digoxin* levels; β-blockers and other drugs affecting AV node conduction (additive effects)	Avoid in patients with heart failure Adjust dose of both agents in patients with hepatic dysfunction
Organic nitrates *isosorbide dinitrate* *isosorbide mononitrate* *nitroglycerin*	Headache, hypotension, flushing, tachycardia	Contraindicated with PDE5 inhibitors (*sildenafil* and others)	Ensure nitrate-free interval to prevent tolerance
Sodium-channel inhibitor *ranolazine*	Constipation, headache, edema, dizziness, QT interval prolongation	Avoid use with CYP 3A4 inducers (*phenytoin, carbamazepine, St. John's wort*) and strong inhibitors (*clarithromycin*, azole antifungals) and agents that prolong QT interval (*citalopram, quetiapine*, others)	No effect on hemodynamic parameters

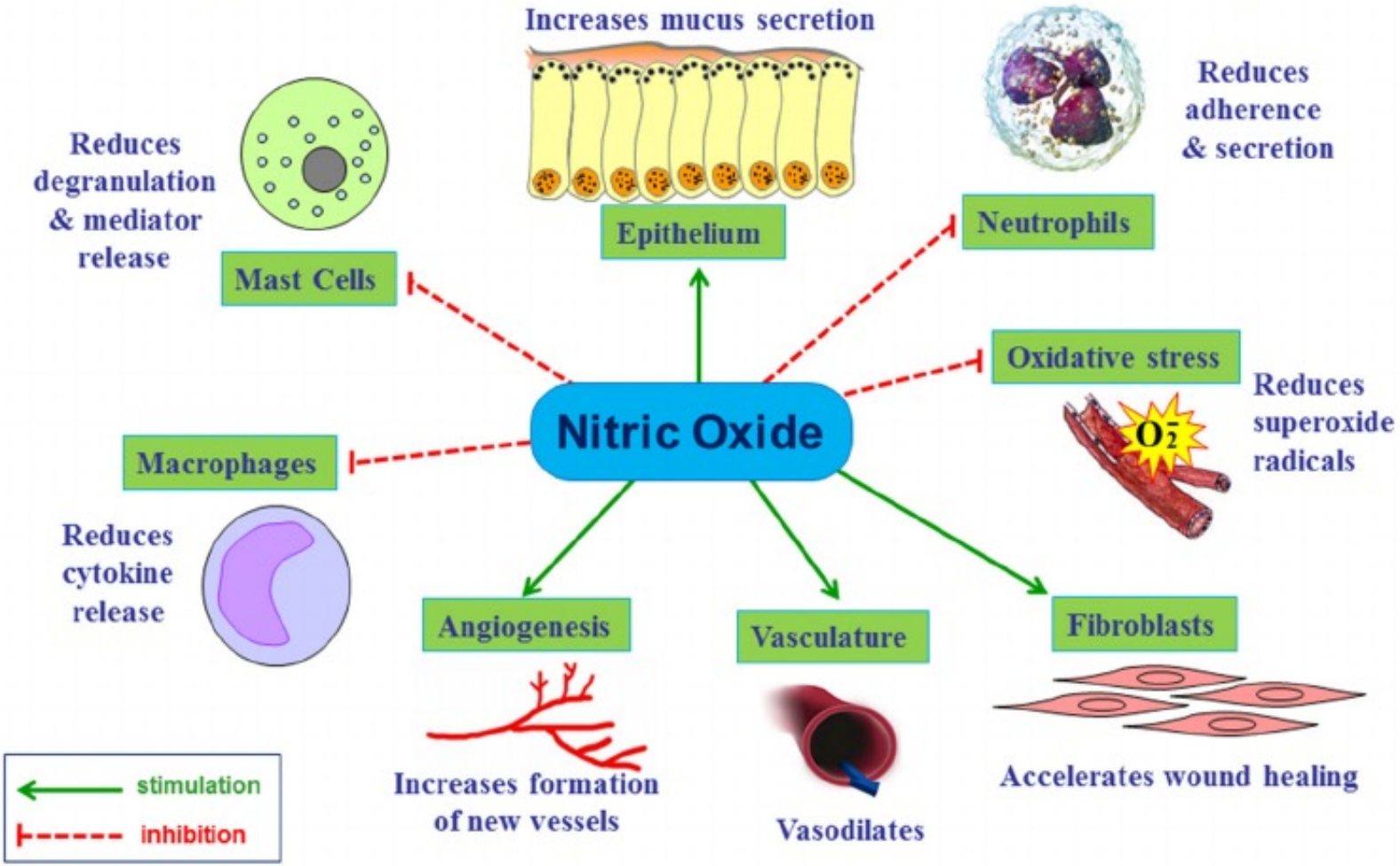
CYP = cytochrome P450; ISA = intrinsic sympathomimetic activity; PDE5 = phosphodiesterase type 5

The discovery of Nitrates

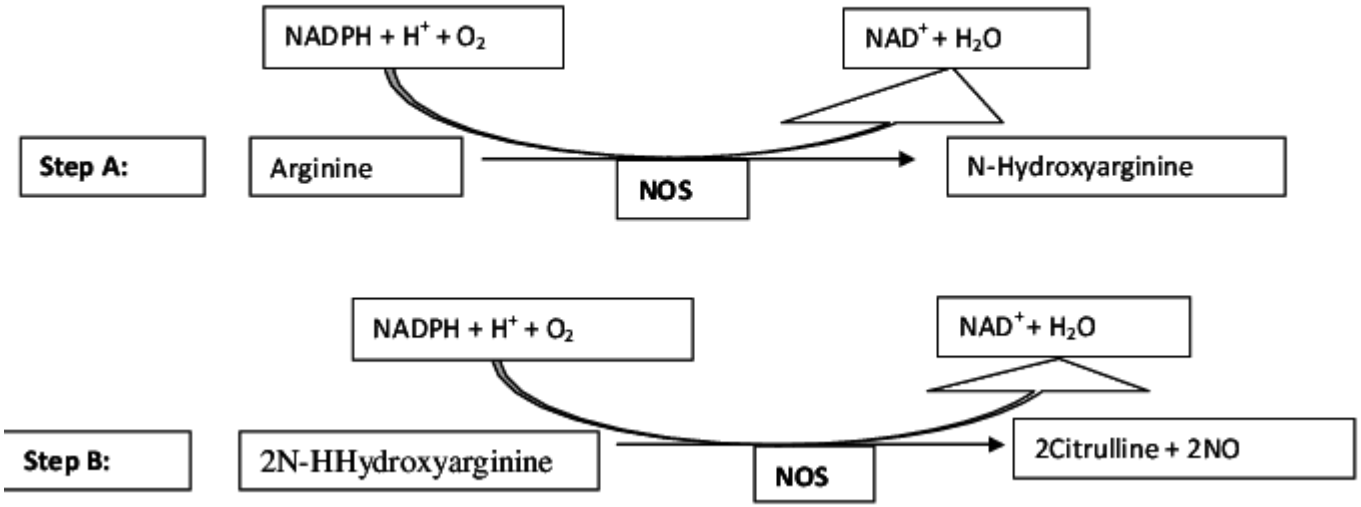
Uses of NO derivatives

Substance	Utilization
Aniline dyes	Laundry inks, markers
Benzocaine, lidocaine	Local anesthetics
Chlorates	Matches
Isobutyl nitrite	Roomdeodorizers
Naphtalene	Moth balls
Nitrate/nitrite	Drinking water, fruits, vegetables, cured meats
Nitric oxide	Inhalant used to treat pulmonary hypertension in newborns
Nitrobenzene	Metal cleaners
Nitroethane	Nail care products
Nitrogen oxides	Auto emissions, wood smoke, gas-burning appliances
Nitroglycerine	Angina drug, explosives
Resorcinol	Antipruritic, over-the-counter medications
Sodium nitrite	Pickling salts, boiler conditioners, cleaning solutions
Sulfonamides	Antibiotics

Effects of NO in the body



Synthesis of NO



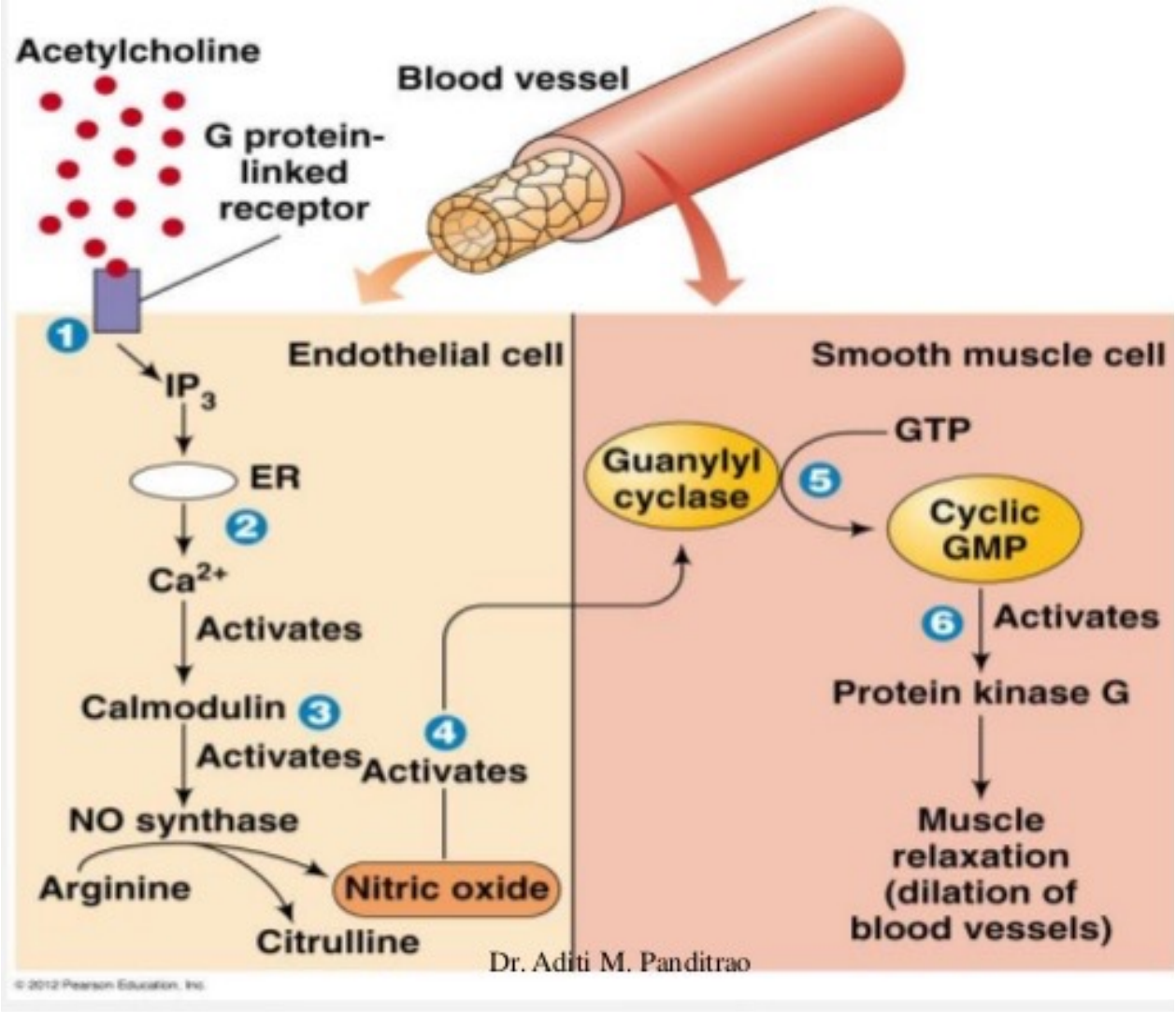
Nitric oxide synthase isoforms

Property	*Isoform I*	*Isoform II*	*Isoform III*
Name	bNOS, cNOS, nNOS	iNOS, mNOS	eNOS
Tissue	Neuronal, epithelial, skeletal, cardiac muscle cells	Macrophages, smooth muscle cells	Endothelial, smooth muscle cells
Expression	Constitutive	Transcriptional induction	Constitutive
Calcium requirement	Yes	No	Yes
Chromosome	12	17	7
Approximate mass of protein	150–160 kDa	125–135 kDa	133 kDa

bNOS = brain NOS, cNOS = constitutive or Ca^{+} regulated NOS, nNOS = neuronal NOS, iNOS = inducible NOS, mNOS = macrophage NOS, eNOS = endothelial NOS.

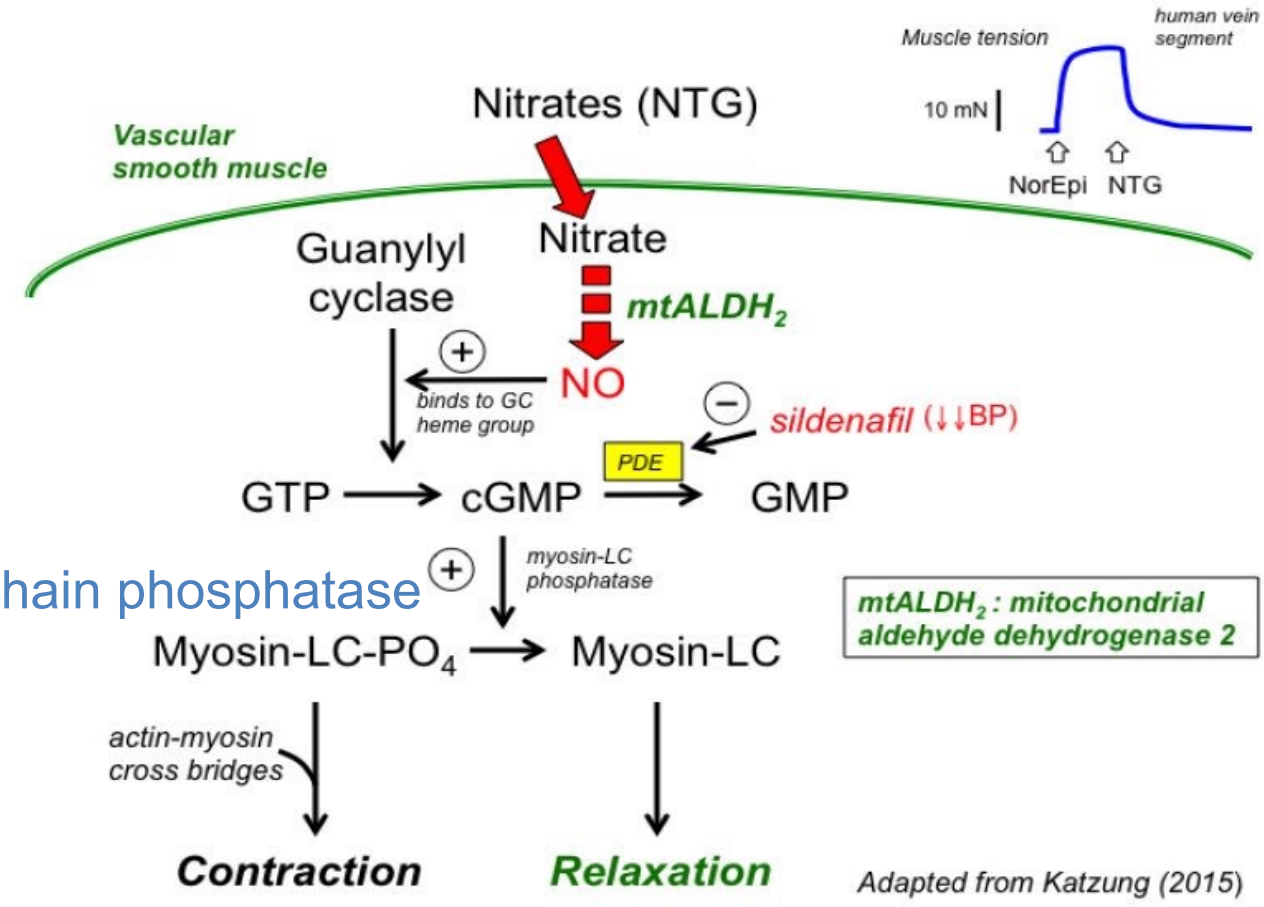
Synthesis of NO and mechanism of vasodilation

Dr. Robert Furchgott
(Nobel prize in 1998)



Mechanism of action of Nitrates

Nitrates produce dilatation of veins, arteries, and coronary arteries by relaxing vascular smooth muscle.



Myosin light chain phosphatase

Pharmacological feature of Nitrates

❑ Nitrates are available in different formulations and both **short and long-acting organic nitrates** have been shown to be effective in treating angina.

❑ Nitrates are **as effective as β-blockers and Ca++ channel antagonists**. Sublingual nitroglycerin tablets and oral nitroglycerin spray are rapidly absorbed and when taken prophylactically can improve exercise tolerance and reduce the incidence of myocardial ischemia.

❑ Nitrates **increase the blood perfusion** by relaxing the coronaries. The powerful dilation of the veins decreases the venous return to the heart and therefore the work and the oxygen demand of the heart.

❑ One of the major side-effects of nitrate use is **headache**. Administered at high doses, nitrates can induce flushing, tachycardia and postural hypotension.

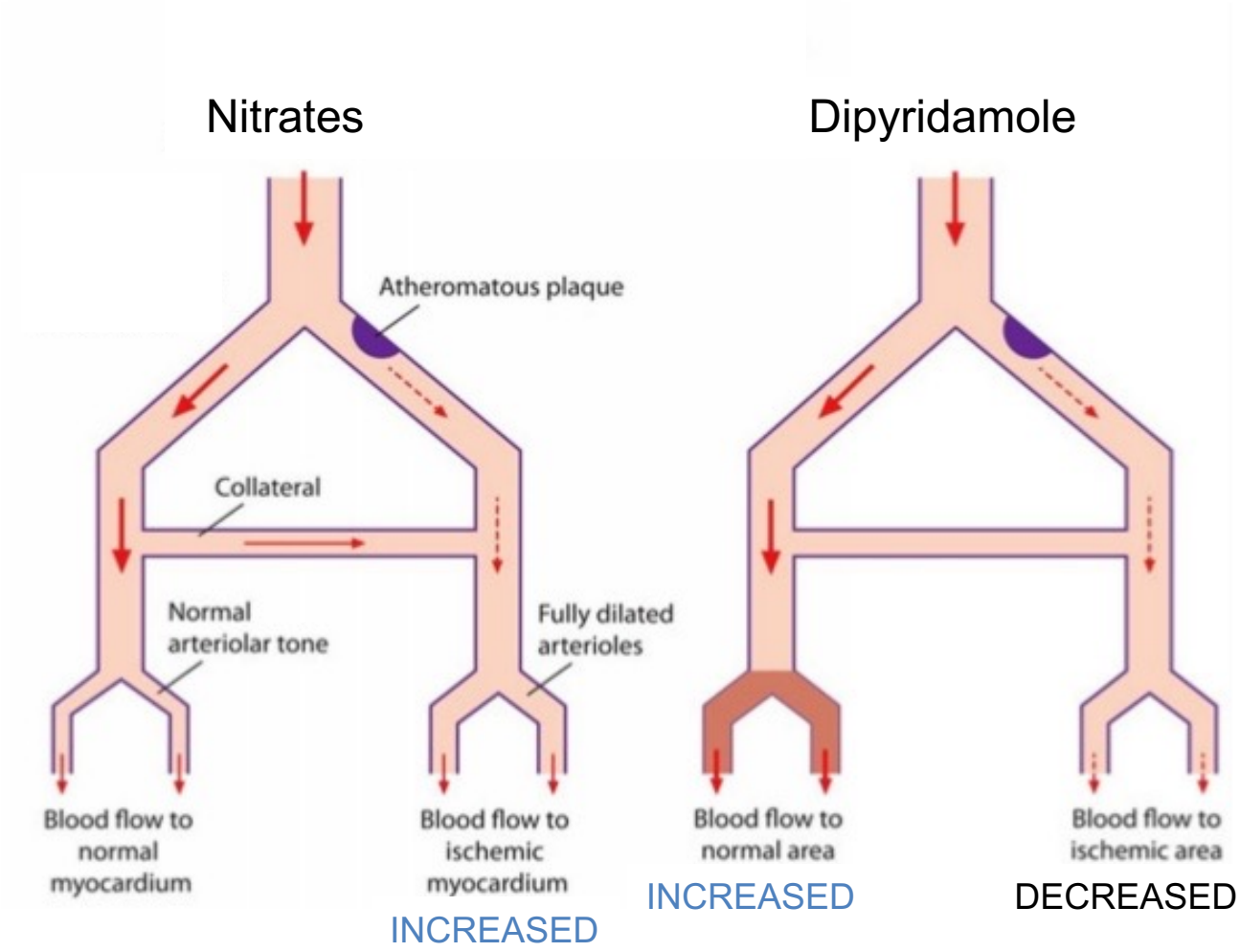
❑ When nitrates are administered concomitantly with **sildefanil, tadalafil or vardenafil** a potential dangerous postural hypotension can appear. For this reason, concomitant therapy of nitrates and sildenafil requires a six-hour-interval between the administration of the two drugs.

Route of administration and doses of nitro derivatives

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

All these agents are effective, but they differ in their onset of action and rate of elimination.

Importance of vasodilation action of nitrates on collateral vessels



Nitroglycerin

❑ The half-life of nitroglycerin is very short (1-4 min) and the systemic clearance usually exceeds the cardiac output. Therefore, common routes of administration for nitroglycerin are sublingual or via transdermal patch.

❑ FDA approved nitroglycerin use for the acute relief from an angina attack or acute prophylaxis of angina pectoris secondary to coronary artery disease.

❑ Nitroglycerin has adverse effects resulting from the vasodilatory effects of the medication. These include: headaches, dizziness, weakness, palpitations, vertigo, nausea, vomiting, diaphoresis, syncope. Many of these adverse effects are secondary to the hypotensive effects of nitroglycerin. Tolerance.

Sildenafil Citrate and Blood-Pressure–Lowering Drugs: Results of Drug Interaction Studies with an Organic Nitrate and a Calcium Antagonist

David J. Webb, MD, Stephen Freestone, MD, Michael J. Allen, MD, and Gary J. Muirhead, BSc

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EXPRESS PUBLICATION

Time Course of the Interaction Between Tadalafil and Nitrates

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Isosorbide dinitrate

- Isosorbide dinitrate is bioavailable to the systemic circulation after oral administration.

- Isosorbide dinitrate is used for angina, in addition to other medications for congestive heart failure, and for esophageal spasms.

- Isosorbide dinitrate can cause severe headaches, necessitating analgesic (very rarely up to morphine) administration for relief of pain, as well as severe hypotension, and, in certain cases, bradycardia. This makes some physicians nervous and should prompt caution when starting nitrate administration. Tolerance.

Tolerance as a side effect of nitrates

❑ Long-term therapy with nitrates is frequently associated with **tolerance**.

❑ Tolerance is a progressive reduction of hemodynamic and antiaggregatory effects.

❑ Tolerance imposes a major limitation to the efficacy of nitrate therapy for stable angina pectoris, congestive heart failure, and acute myocardial infarction.

❑ The mechanism responsible for tolerance remains controversial. Multiple theories have been proposed, but the major categories are:

(1) impaired nitrate bioconversion resulting in diminished NO release;

(2) increased NO clearance mediated by the incremental generation of superoxide (O_2^-).

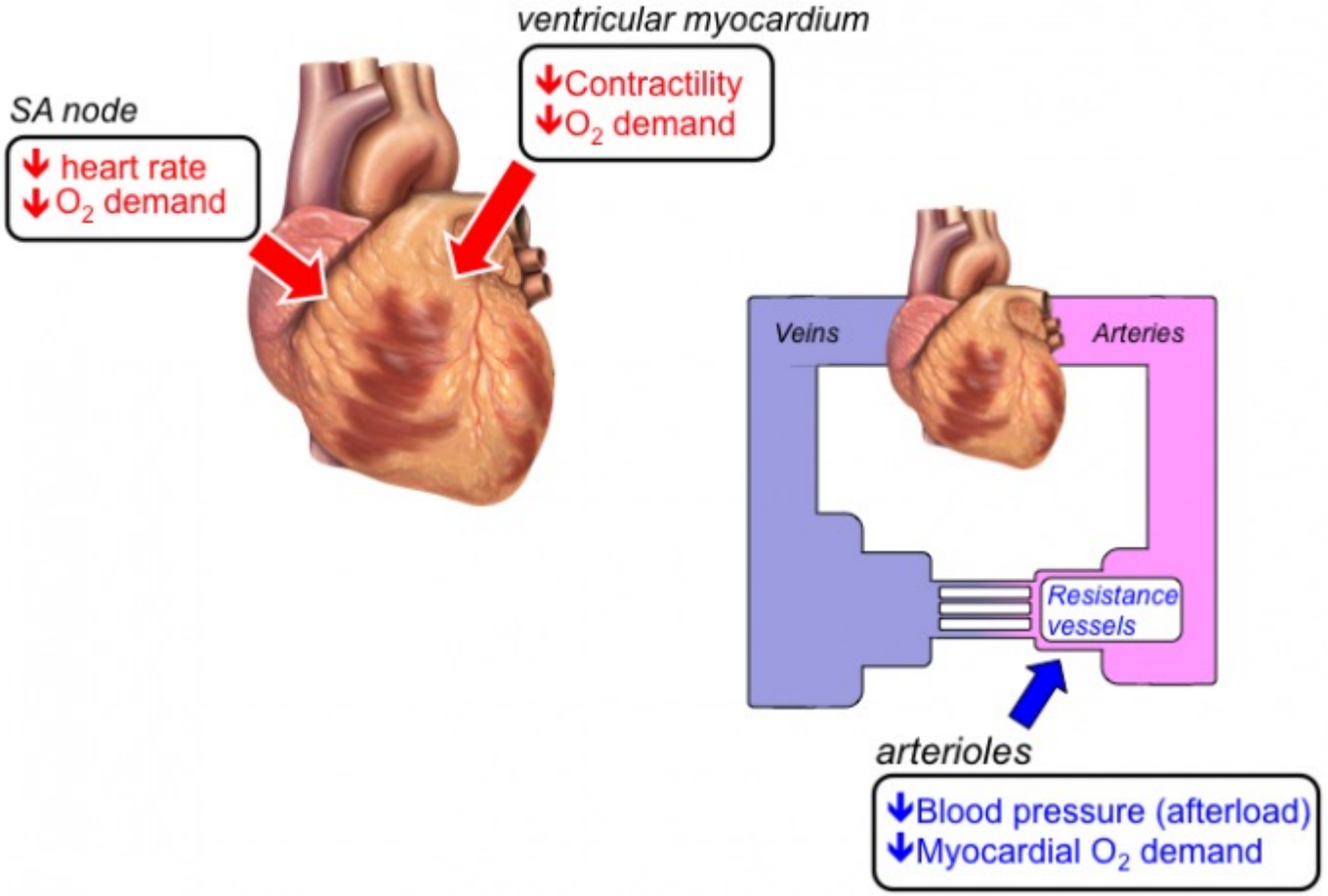
The supporting evidence for these mechanisms has been derived almost entirely from animal studies; definitive evidence from studies in human subjects is lacking.

❑ Interval dosing with eccentric doses providing a nitrate-free interval of 10-12 hours should be observed **to reduce or prevent tolerance**. Other (less consistent) ways to reduce the incidence of tolerance are the co-therapy with ACE inhibitors, carvedilol, hydralazine, vitamin C .

β-blockers

❑ Their effects in the treatment of angina have been attributed to the following actions:

1) **blockade of β1 receptors in the SA node** decreases the heart rate, resulting in decreased myocardial oxygen demand and increased oxygen delivery to the heart.
2) **blockade of β1 receptors in the ventricular myocardium** decreases myocardial contractility, helping to preserve energy or to decrease the demand.



β–blockers used in the treatment of angina

Drug	Receptor Selectivity	Onset of Action	Usual Dose
Atenolol	β_1	2–4 h	50–200 mg/d
Bisoprolol	β_1	2–4 h	10 mg/d
Esmolol (IV)	β_1	9 min	50–300 μg/kg/min
Metoprolol	β_1	1–2 h	50–200 mg twice daily (extended release once daily preparation available)
Propranolol	None	1–2 h	80–120 mg twice daily
Nadolol	None	3–4 h	40–80 mg/d
Timolol	None	1–2 h	10 mg twice daily
Carvedilol	Nonselective β and selective α_1	1.0–1.5 h	3.125–25 mg twice daily
Labetalol	Nonselective β and selective α_1	2–4 h	200–600 mg twice daily

Side effects and drug-drug interactions of β–blockers used in the treatment of angina

- β-blockers may induce **diarrhea, stomach cramps, nausea, vomiting, rash, blurred vision, disorientation, insomnia, hair loss, weakness, muscle cramps, fatigue**.

- β-blockers, especially the non-cardioselective blockers, **should not be used in patients with pathologies** such as asthma, diabetes and severe bradycardia (block of the effect of adrenaline).

- β-blockers **should not be withdrawn suddenly** because sudden withdrawal may worsen angina and cause heart attacks, serious abnormal heart rhythms, or sudden death.

- β-blockers **can interact with certain other cardiac drugs**, including Ca^{++} channel antagonists and some drugs used to treat arrhythmias.

Ca^{++} channel antagonists used in the treatment of angina

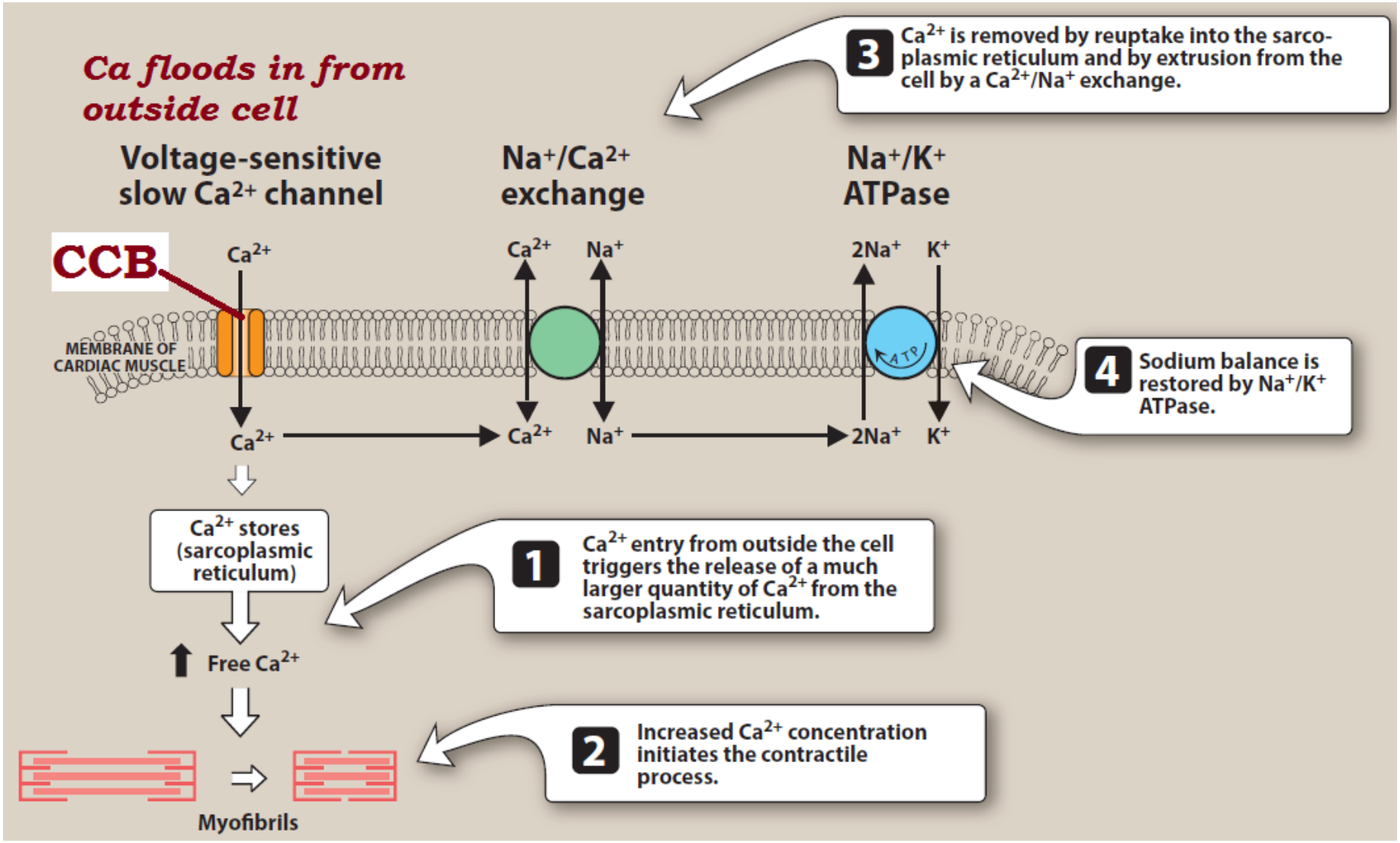
❑ All the Ca^{++} channel antagonists have been used for the treatment of angina (especially longer-acting forms of diltiazem and verapamil).

❑ In general, while Ca^{++} channel antagonists are useful for relieving angina, they are considered to be **inferior to β-blockers**. Current recommendations for using Ca^{++} channel blockers for the treatment of angina are:

1) Ca^{++} channel blockers should be tried in **patients who cannot tolerate β-blockers**.

2) Ca^{++} channel blockers should be **added to β-blockers** in patients who have insufficient relief of symptoms with β-blockers.

Role of Ca^{++} in the cardiac muscle contraction



Mechanism of Ca^{++} channel antagonists in the treatment of angina

❑ Similar to nitrates, Ca^{++} channel antagonists can **dilate the coronary vessels**, improving the blood supply to the ischemic area.

❑ Ca^{++} channel antagonists **slow the conduction** of the cardiac action potential in tissues dependent on Ca^{++} currents, such as the AV node.

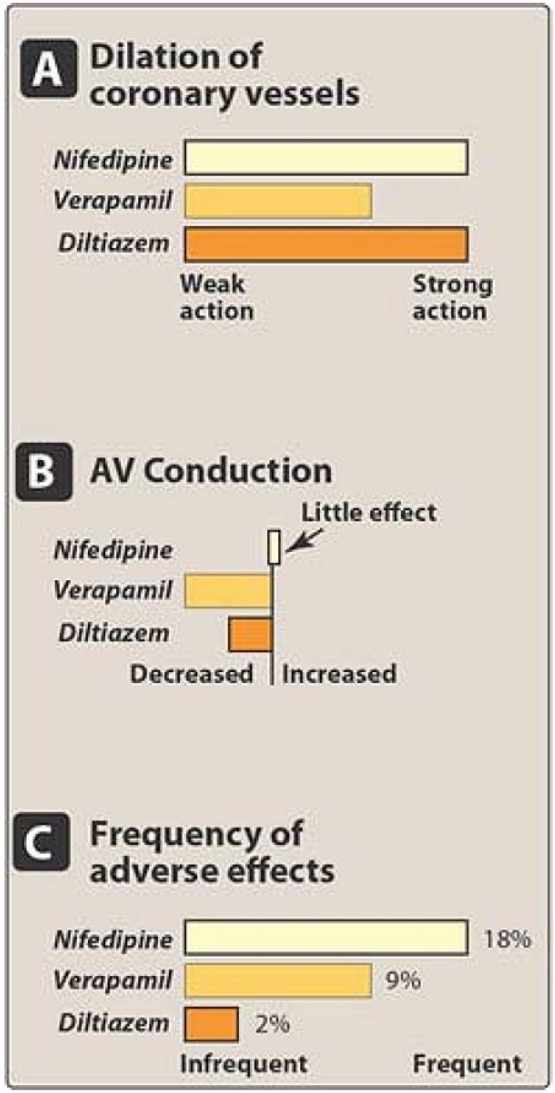
❑ Similar to β-blockers, Ca^{++} channel antagonists **reduce the amount of oxygen required by the heart muscle**. Reducing cardiac oxygen demand helps to prevent cardiac ischemia, even when blood flow through the coronary arteries is partially blocked by an atherosclerotic plaque.

❑ In people who have stable angina, Ca^{++} channel antagonists usually **increase the amount of physical exercise** they can perform before they experience angina.

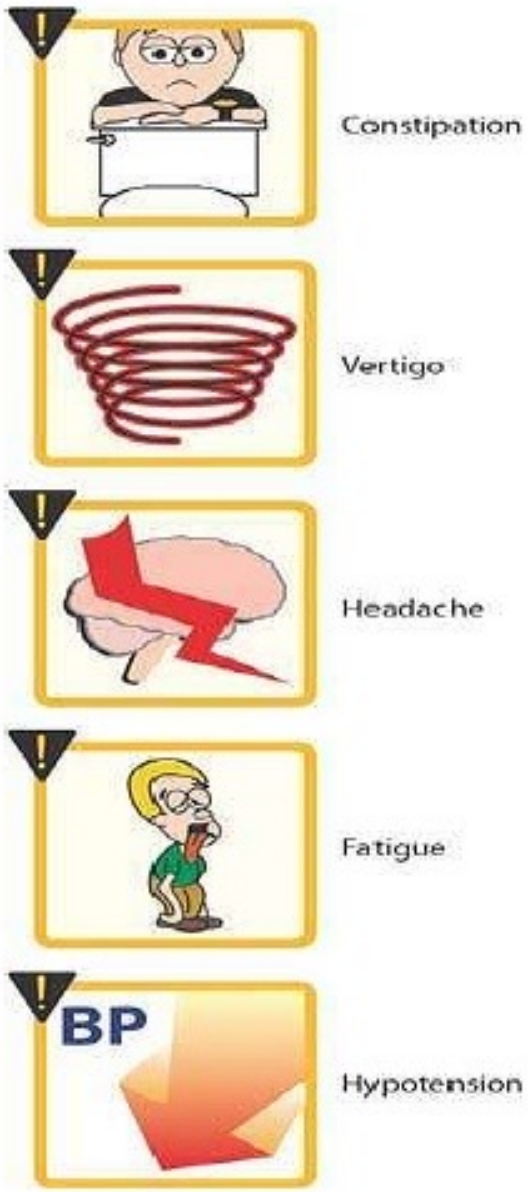
❑ Ca^{++} channel antagonists can be especially useful in people with **Prinzmetal's angina** since they can directly reduce spasm of the coronary arteries.

❑ Ca^{++} channel antagonists are thought to possess **antiplatelet effects**, which may be beneficial in angina. The antiplatelet effect of verapamil is evident both at rest and after exercise-induced platelet activation in vivo.

Ca^{++} channel blockers used in the treatment of angina



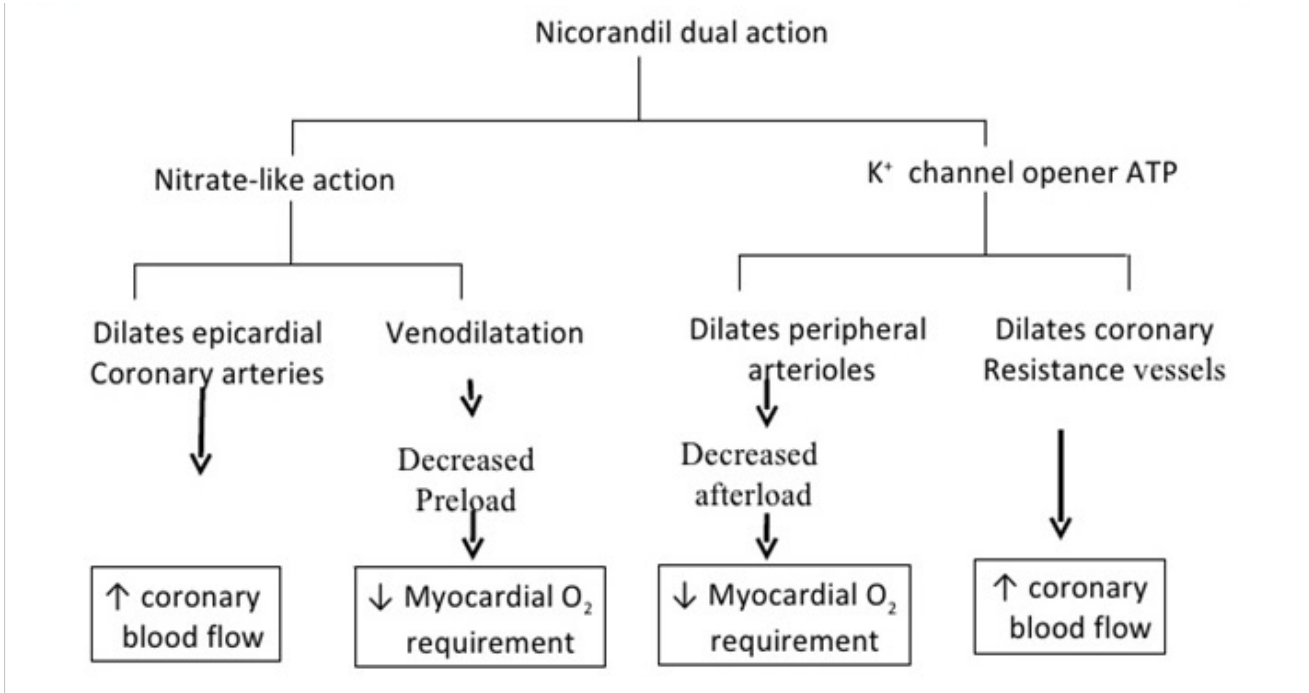
Side effects of Ca^{++} channel antagonists



Other drugs used for the treatment of angina: Nicorandil

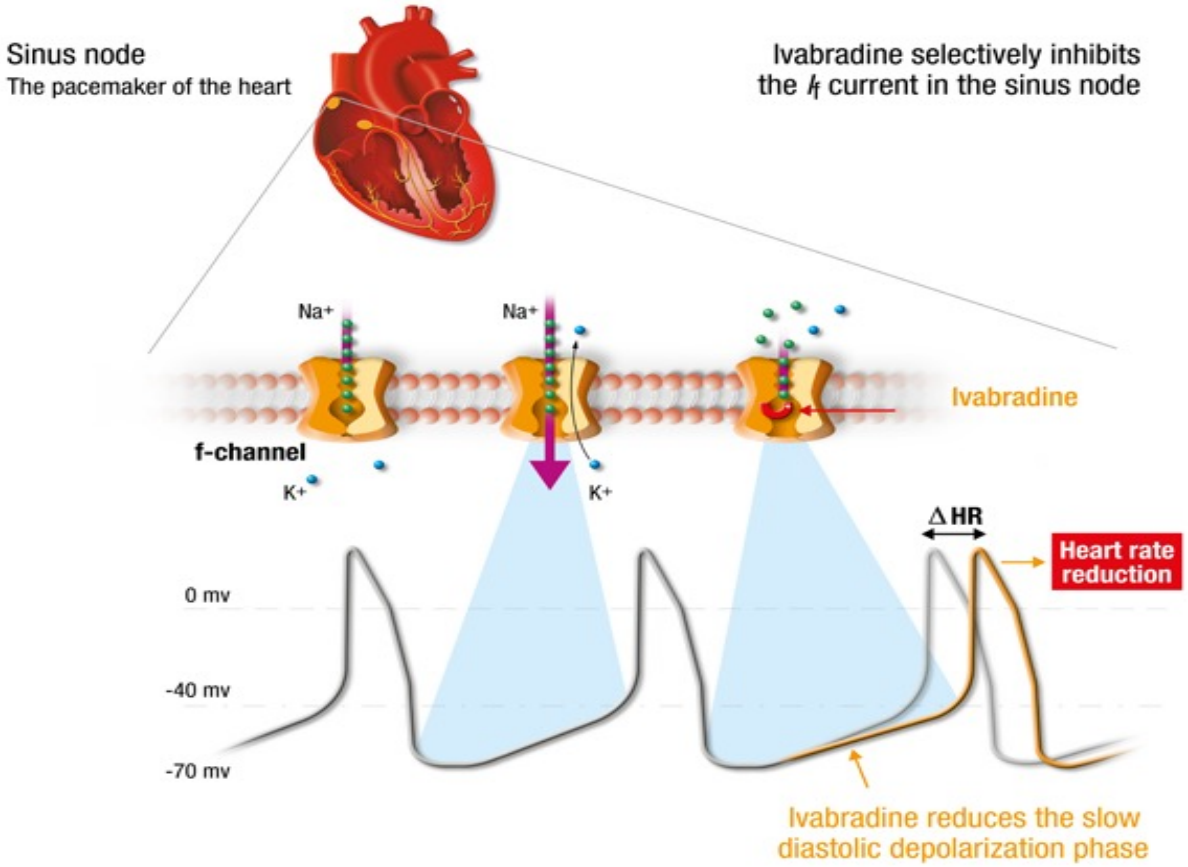
❑ At low plasma concentrations, nicorandil, similar to nitrates, **dilates the coronary arteries**. At high plasma concentrations, nicorandil **reduces coronary vascular resistance**, which is associated with increased ATP-sensitive K^+ channel opening (unknown mechanisms).

❑ Nicorandil is usually administered when nitrates, such as nitroglycerine, are not effective.



Other drugs used for the treatment of angina: Ivabradine

❑ Ivabradine selectively inhibits the inward-depolarizing Na^+-K^+ current in the SA node, decreasing the rate of diastolic depolarization and, consequently, the heart rate. Thus, ivabradine is used in select patients with **systolic heart failure** and **chronic stable angina** without clinically significant adverse effects.



Other drugs used for the treatment of angina: HMG-CoA reductase inhibitors (statins)

❑ Lipid-lowering drugs as statins **reduce the incidence and severity of ischemia** during physical exercise and the incidence of fatal cardiac events.

❑ The **pleiotropic effects** of statins may be primarily responsible for their anti-ischemic and anti-anginal properties.

❑ These pleiotropic effects include **improvement of endothelial function, enhancement of the ischemic vasodilatory response, modulation of inflammation, and protection from ischemia-reperfusion injury**.

Treatment of angina with comorbidities