Calcium channel blockers

- Like ACE Inhibitors, they are recommended agents when the preferred first-line agents are contraindicated or ineffective.

- They are effective in patient with angina and diabetes.

- They exerts their antihypertensive effect by their vasodilation effect.

Calcium channel blockers

- They divided into three chemical classes:
  a. Diphenylalkylamines, Varapamil.
  b. Benzothiazepines, Diltiazem
  c. Dihydropyridines, Nifedipine

- Mechanism of action

- Calcium enters muscle cell through special voltage sensitive calcium channel. These agents exert their effect by antagonists block for the inward movement of calcium by binding to the L-type channels in the heart and peripheral vasculature.

	NIFEDIPINE*	DILTIAZEM	VERAPAMIL
coronary arteries dill	+ +	+ +	+ +
peripheral arteries dill	+ + + +	+ +	+ + +
negative inotropic	+	+ +	+ + +
slowing AV cond	↔	+ + +	+ + + +
heart rate	↑ ↔	↓ ↔	↓ ↔
↓ blood presure	+ + + +	+ +	+ + +
depression of SA	↔	+ +	+ +
increase in cardiac output	+ +	↔	↔

* and others dihydropyridines

↓ = decrease

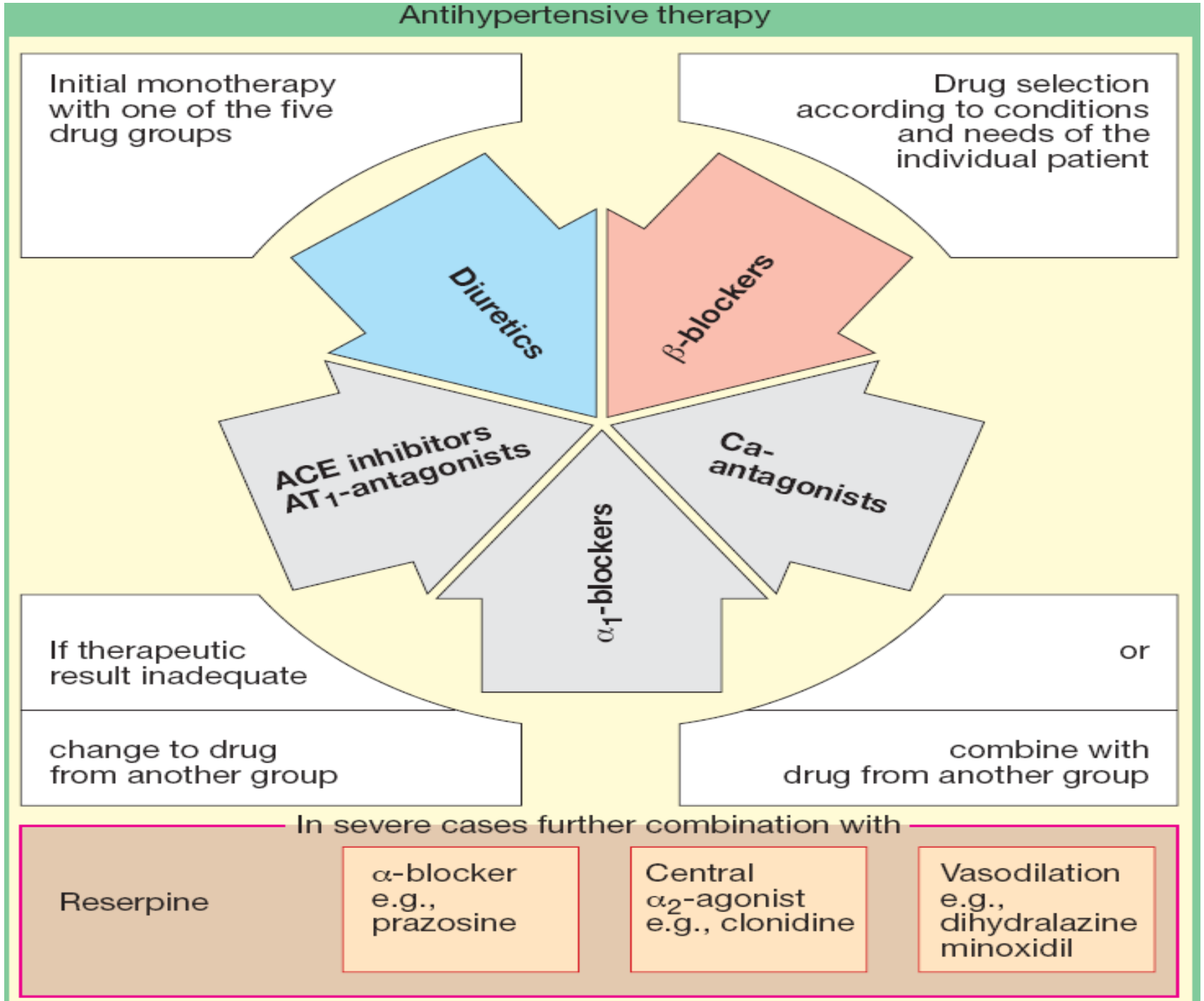
↑ = increase

↔ = without change

Adverse effects of calcium channel-blocking agents

Drug	Effect on heart rate	Adverse effects
Nifedipine	↑	Headache, flushing, ankle swelling
Amlodipine	↑	Ankle swelling
Nimodipine	±	Flushing, headache
Diltiazem	±	Generally mild
Verapamil	↓	Constipation, marked negative inotropic action

Calcium channel blockers **do not affect** concentrations of plasma cholesterol or triglycerides, or extracellular calcium homeostasis.


Antihypertensive therapy
Initial monotherapy with one of the five drug groups
Drug selection according to conditions and needs of the individual patient
Diuretics
β-blockers
ACE inhibitors
AT1-antagonists
Ca-antagonists
α1-blockers
If therapeutic result inadequate
or
change to drug from another group
combine with drug from another group
In severe cases further combination with
Reserpine
α-blocker e.g., prazosine
Central α2-agonist e.g., clonidine
Vasodilation e.g., dihydralazine minoxidil

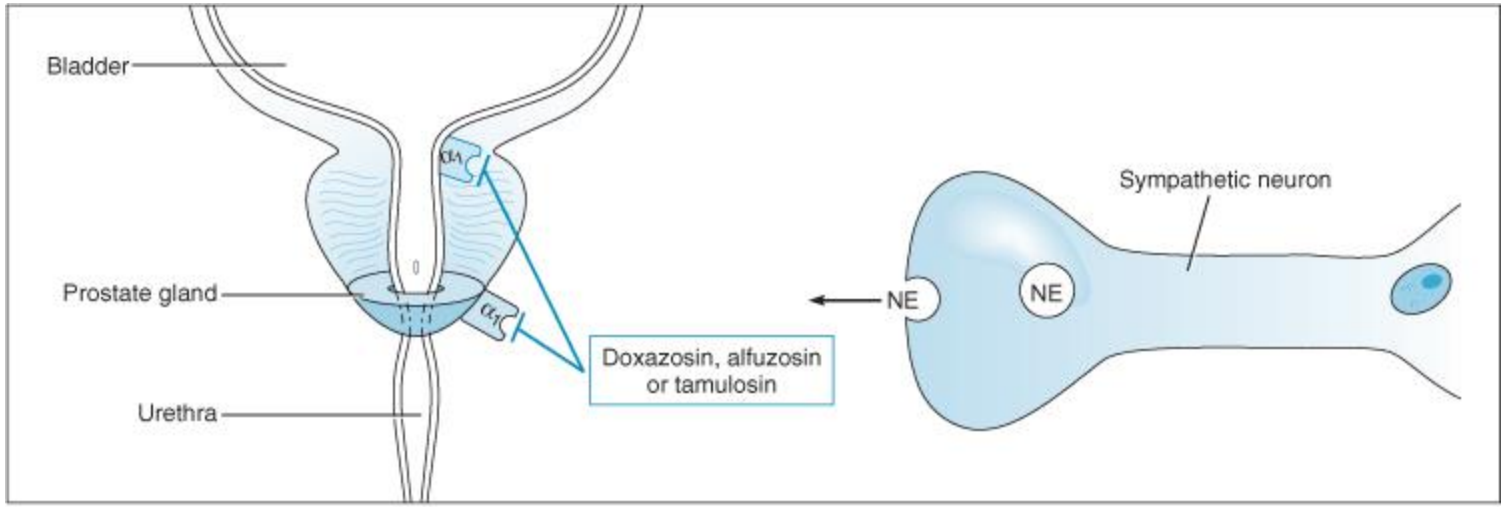
Selective α_1-blockers

- Selectively block α_1 receptors

  Alfuzosin, doxazosin, prazosin, terazosin

- **Silodosin**

- Used in the treatment of chronic hypertension
- Also used to treat urinary retention in men with benign prostatic hyperplasia



Centrally acting adrenergic drugs

- **Clonidine**, an $\alpha 2$ agonist diminishes central adrenergic outflow.

- Used to treat mild to moderate hypertension that has not responded adequately to treatment with diuretics alone.

- Does not decrease renal blood flow, thus it is useful in the treatment of the hypertension complicated with renal disease.

- Nonetheless it does produce sodium and water retention, and so usually administered in combination with a diuretics

Centrally acting

- Methyldopa and clonidine produce slightly different hemodynamic effects: clonidine lowers heart rate and cardiac output more than does methyldopa.

- Withdrawal of clonidine after protracted use, particularly with high dosages (more than 1 mg/d), can result in life-threatening hypertensive crisis mediated by increased sympathetic nervous activity. Patients exhibit nervousness, tachycardia, headache, and sweating after omitting one or two doses of the drug.

- all patients who take clonidine should be warned of the possibility. If the drug must be stopped, it should be done gradually while other antihypertensive agents are being substituted. Treatment of the hypertensive crisis consists of reinstitution of clonidine therapy or administration of - and - adrenoceptor–blocking agents.

Clonidine

- Adverse effects
  - effects include dry mouth, sedation and drying of the nasal mucosa.
  - Rebound hypertension occur following sudden withdrawal, so should withdraw slowly.

Methyldopa

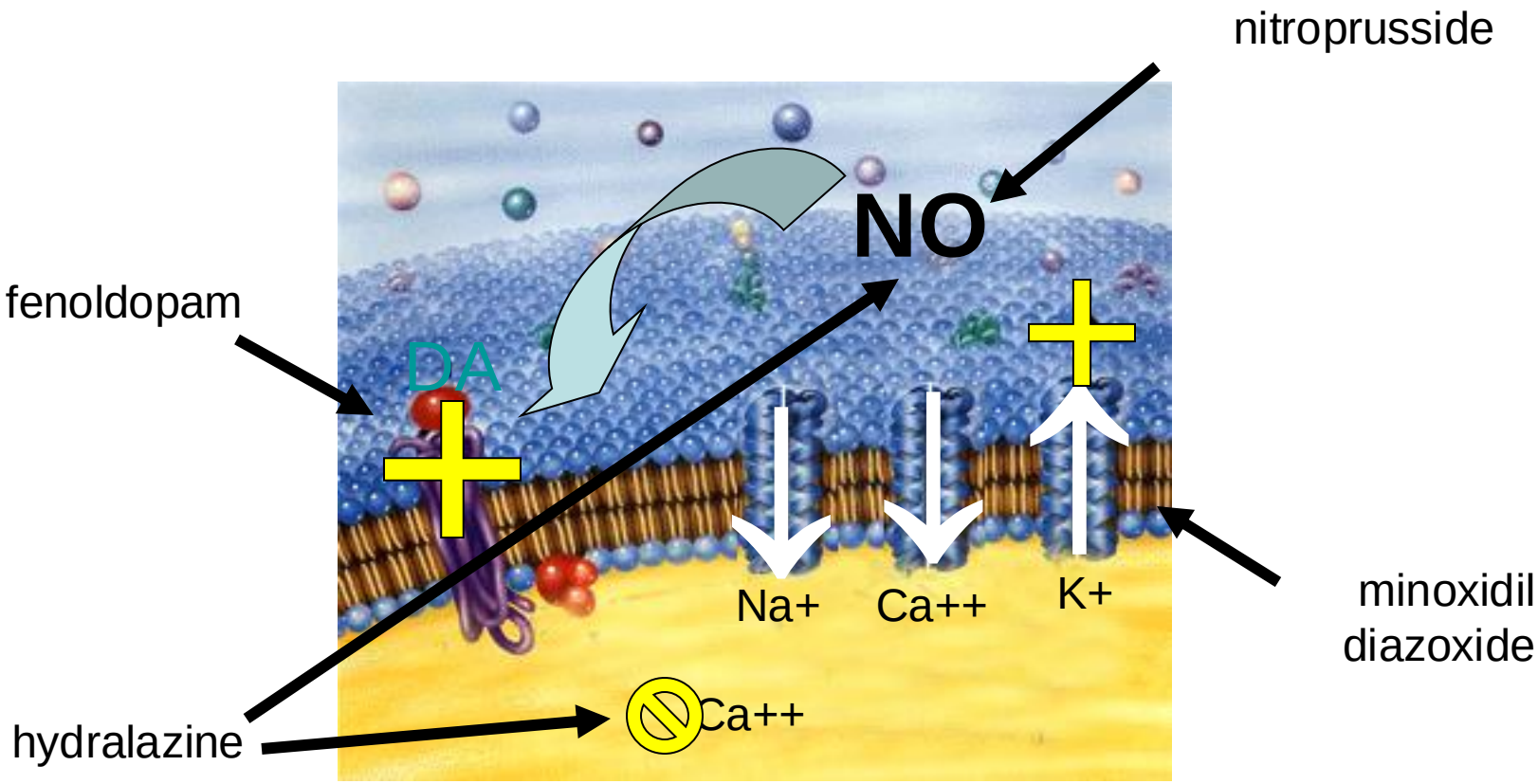
- **α2 agonist that converted to methylnorepinihrine centrally to diminish the adrenergic outflow from the CNS,**
- **Which lead to reduced the peripheral resistance and decreased blood pressure.**
- **Cardiac output is not decreased, and so the blood supply to the vital organs, such as kidney, which make**
- **Methyldopa especially valuable in treating hypertension with renal insufficiency. (cause reduction in renal vascular resistance)**
- **used primarily for hypertension during pregnancy**
- **The Most common side effect are sedation and drowsiness.**

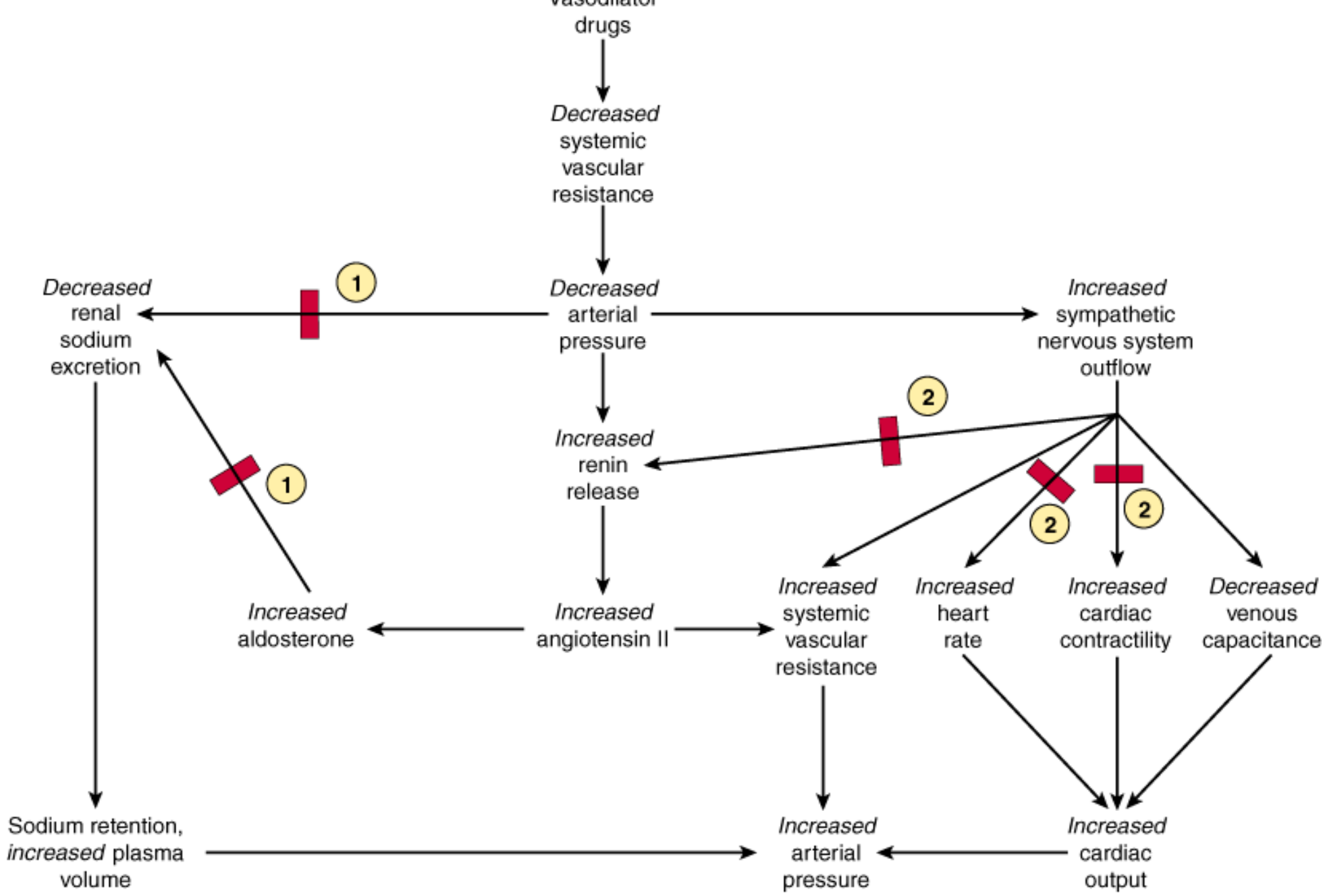
Vasodilator

- These agents are a smooth muscle relaxants, such as Hydralazine and minoxidil.
- They produce reflex stimulation of the heart resulting in increasing the myocardiac contractibility, heart rate, and oxygen consumption, so they may prompt angina, Myocardiac Infarction in predisposed individuals .
- They increase plasma renin concentration, which resulting in sodium and water retention.
- These unwanted effects can be blocked by the combination with a diuretics and a β blocker.

Vasodilators

Hydralazine ; Minoxidil;
Nitroprusside; Diazoxide;
Fenoldopam





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

Hydralazine

- **Used to treat moderately severe hypertension, combine with diuretic (sodium and water retention) and β blocker (reflex tachycardia).**

- **Hydralazine monotherapy is accepted method of controlling blood pressure in pregnancy-induced hypertension.**

- **Main side effects are arrhythmia, precipitation of angina. Lupus-like syndrome can occur with high doses, but it is reversible on stopping the therapy.**

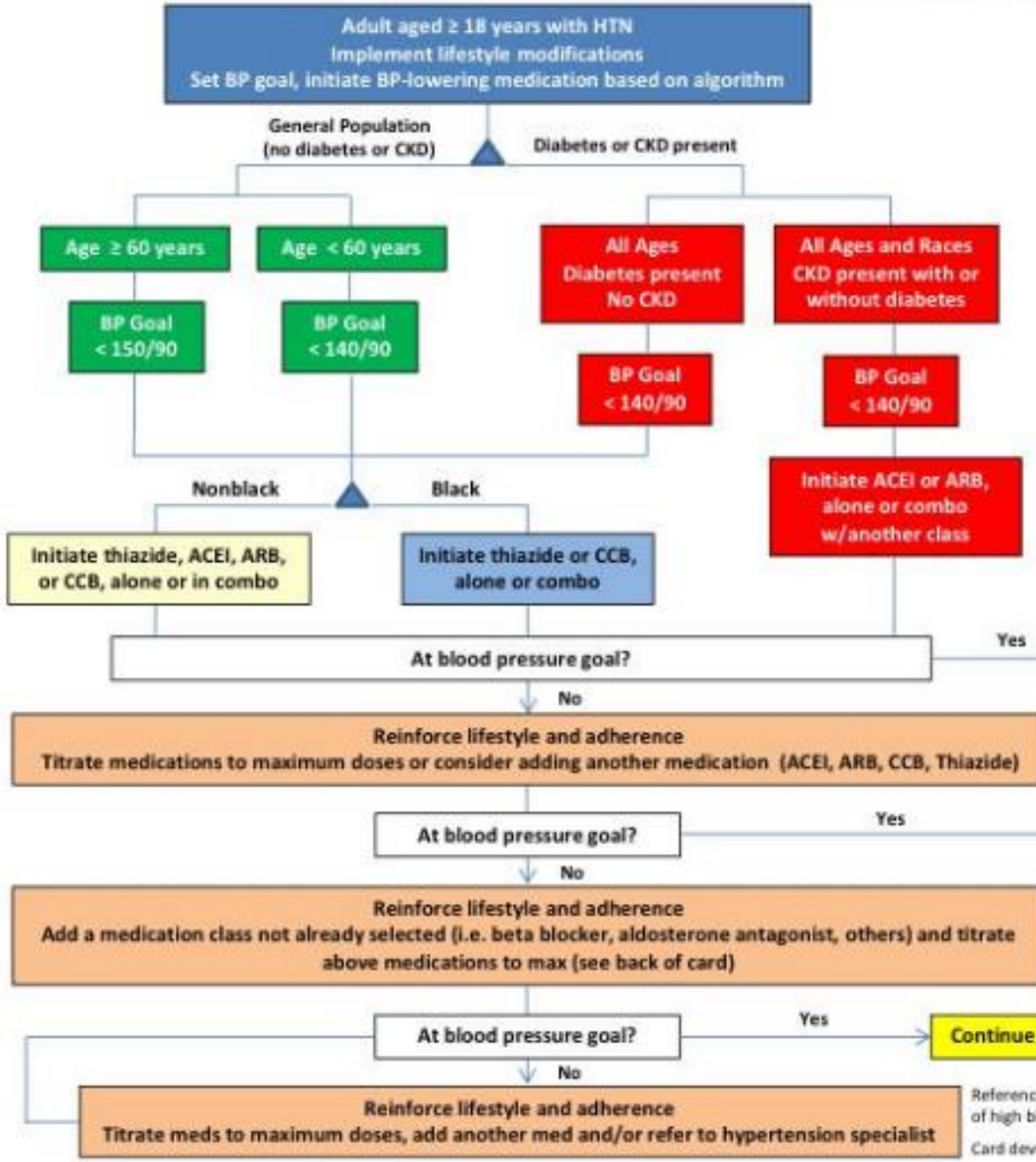
Hypertension emergency

- It is rare but life threatening, in which DBP is > 150 mm Hg with SBP > 210 mm Hg (healthy person), or DBP of > 130 mm Hg in individual with pre-existing complications, such as encephalopathy, cerebral hemorrhage, and left ventricular failure, or aortic stenosis.

- **Sodium nitropresside** (onset 1-2 min), is administered intravenously and causes sudden vasodilation and reflex tachycardia, it is effective in all patients regardless the cause.

  It metabolized rapidly (half life of minutes) and require continuous perfusion. An overdose can cause hypotension.

JNC 8 Hypertension Guideline Algorithm



Initial Drugs of Choice for Hypertension

- ACE inhibitor (ACEI)
- Angiotensin receptor blocker (ARB)
- Thiazide diuretic
- Calcium channel blocker (CCB)

Strategy	Description
A	Start one drug, titrate to maximum dose, and then add a second drug.
B	Start one drug, then add a second drug before achieving max dose of first
C	Begin 2 drugs at same time, as separate pills or combination pill. **Initial combination therapy is recommended if BP is greater than 20/10mm Hg above goal**

Lifestyle changes:

- Smoking Cessation
- Control blood glucose and lipids
- Diet
  - ✓Eat healthy (i.e., DASH diet)
  - ✓Moderate alcohol consumption
  - ✓Reduce sodium intake to no more than 2,400 mg/day
- Physical activity
  - ✓Moderate-to-vigorous activity 3-4 days a week averaging 40 min per session.

Reference: James PA, Ortiz E, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: (JNC8). JAMA. 2014 Feb 5;311(5):507-20

Card developed by Cole Gleen, Pharm.D. & James L Taylor, Pharm.D.

Table 1. Interactions between antihypertensive and other drugs

Drugs (class)	Interaction with	Mechanism	Effect
β-Blockers	verapamil diltiazem	Additive effects	A-V conduction impaired; risk of A-V block
	oral antidiabetics	β_2-receptor blockade	symptoms of hypoglycaemia are suppressed
	broncho-spasmolytic agents	β_2-receptor blockade	suppression of the bronchospasmolytic effect
	dobutamine	β_1-receptor antagonism	the inotropic action of dobutamine is inhibited
Thiazid diuretics	digoxin	Hypokalaemia	digoxin becomes more toxic (arrhythmogenic)
	lithium ions	renal excretion of lithium ions impaired	accumulation of lithium ions
α-Blockers	noradrenaline	α_1-receptor blockade	noradrenaline shows less vasoconstrictor activity
Calcium antagonists			
Verapamil, diltiazem	β-Blocker	additive effect	A-V conduction impaired; risk of A-V block
	digoxin	renal excretion of digoxin	digoxin may accumulate; arrhythmogenic effect
	protease inhibitors (HIV-treatment)	inhibition of hepatic degradation	accumulation of verapamil or diltiazem
	cimetidine	ibid.	ibid.
DihydropyridineCa-antagonists	β-blocker	β-receptor blockade	suppression of reflex tachycardia (favourable)
Felodipine	Grapefruit Juice	Enzymic inhibition (Cyt.L450 system)	accumulation of felodipine
ACE-inhibitors	diuretics (thiazide)	additive effect	strong hypotensive action
	Diuretics (K^+-sparing)	reduced renal excretion of K^+	hyperkalemia
	NSAID´-s including high dose ASA	retention of Na^+ and H_2O	reduced antihypertensive effects
	lithium ions	Reduced excretion of lithium ions	lithium ions accumulate

Table 1. Interactions between antihypertensive and other drugs

Drugs (class)	Interaction with	Mechanism	Effect
AT_1-receptor antagonists	virtually the same as ACE-inhibitors	interactions as ACEi-s (see above)	described before
Centrally acting antihypertensives			
α-methyl-DOPA	Fe^{2+}-ions	enteral absorption of α-methyl-DOPA	reduced antihypertensive action
clonidine	tricyclic antidepressants	antagonism of central α_2-adrenoceptors	Ibid.
	β-blockers	unknown	the clonidine rebound phenomenon is more frequent
both clonidine and α-methyl-DOPA	centrally acting depressant agents (hypnotics, tranquillizers, neuroleptics, anti-epileptics, some anti-depressants, H1-anti-histaminic agents, alcohol)	additive effect, non-specific	sedation,fatigue

Hypertension emergency

- **Labetalol** (α and β blocker), (onset 5-10 min) does not induce reflex tachycardia, given intravenous bolus or infusion.

  Have the same β blockers contraindication (Asthma ….) and major limitation of this agent is the long half-life(3-6 hr), that prevent rapid titration.

- **Fenoldopam** (onset 2-5 min), peripheral dopamine 1 receptor agonist that also given as an intravenous infusion.

  It lowers blood pressure through arteriolar vasodilation and also through specific dopamine receptors along the nephron promoting sodium excretion.

Hypertension emergency

may be particularly beneficial in patients with renal insufficiency (maintains or increases renal perfusion).

Types of angina

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

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

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

This type is rapidly relieved by rest or nitroglycerin.

Types of angina

B. Unstable angina, lies between stable angina and myocardial infarction, Often unrelated to exercise.

The symptoms are not relieved by rest or nitroglycerin.

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

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

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

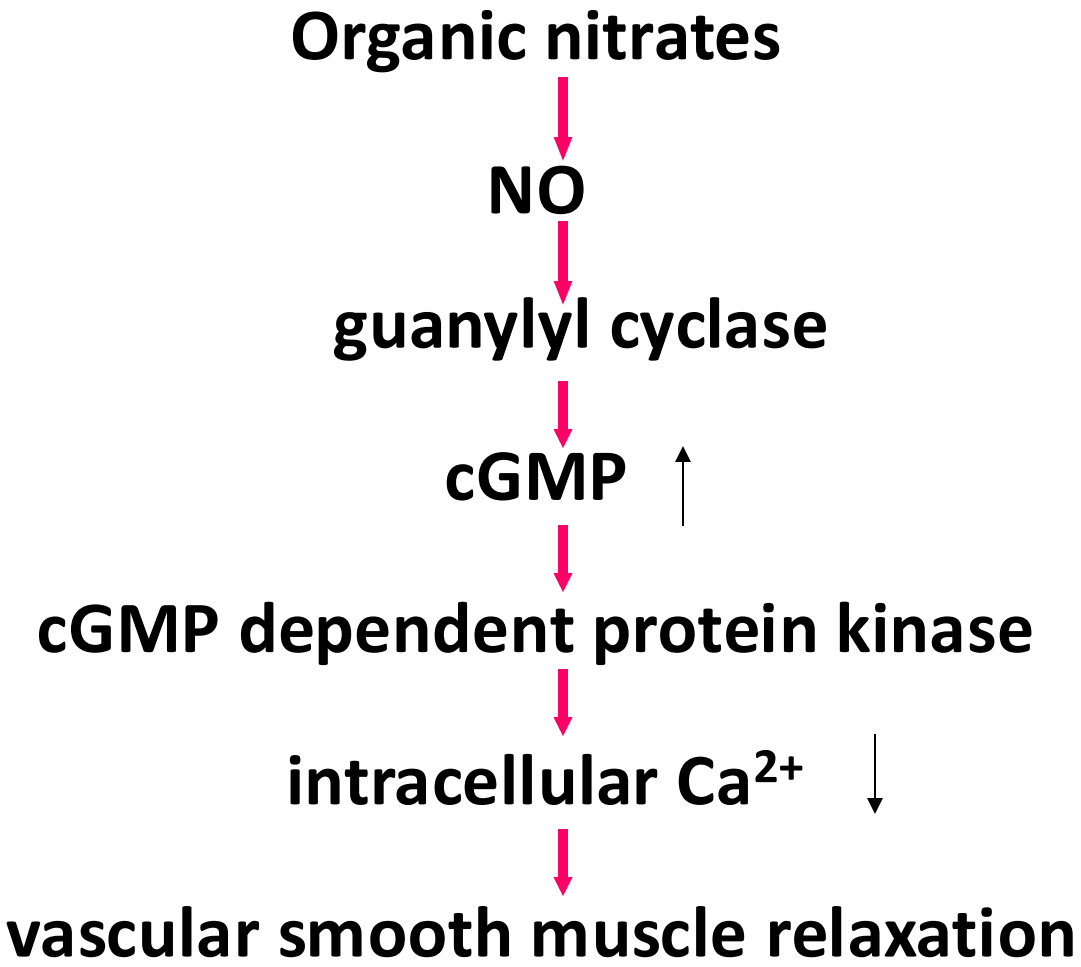
Organic nitrates

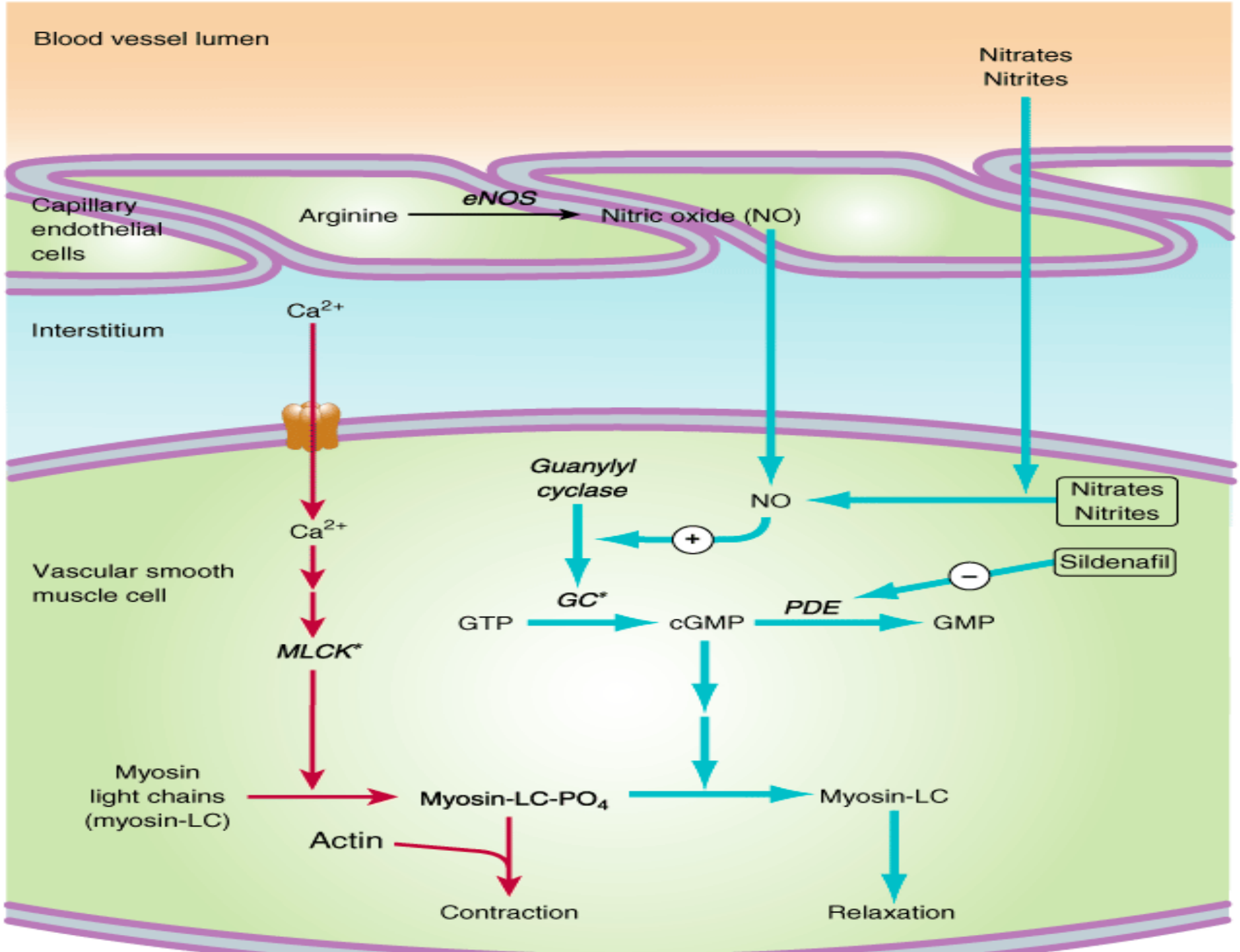
- These compounds cause a rapid reduction in the myocardial oxygen demand, and so provide a rapid relief for the angina symptoms.

- Their mechanism of action summarized in a decrease coronary spasm or vasoconstruction and in an increase perfusion of the myocardial by relaxing the coronary arteries.

- Members of this group include: isosorbide dinitrate, isosorbide mononitrate, and Nitroglycerine.

2.Pharmacological mechanism




Blood vessel lumen
Nitrates
Nitrites
Capillary
endothelial
cells
Arginine
eNOS
Nitric oxide (NO)
Interstitium
Ca2+
Guanylyl
cyclase
NO
Nitrates
Nitrites
Ca2+
+
Vascular smooth
muscle cell
Sildenafil
−
GC*
PDE
GTP
cGMP
GMP
MLCK*
Myosin
light chains
(myosin-LC)
Myosin-LC-PO4
Myosin-LC
Actin
Contraction
Relaxation

Organic nitrates

- All of the three agents are effective but they differ in the onset and duration of action.

- For rapid relief of an ongoing attack that precipitate by exercise and emotional stress, sublingual nitroglycerine is the drug of choice.

- At therapeutics dose nitroglycerine has two major effects:

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

  orthostatic hypotension and syncope.

  b. dilates the coronary arteries.

Beneficial and Deleterious Effects of Nitrates in the Treatment of Angina

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

Organic nitrates

- The time to onset the action varies from 1 min for nitroglycerine to 1 hr for isosorbide mononitrate .
- Significant first pass metabolism of nitroglycerine occurs so it administrated sublingually or transdermally (patch).
- Isosorbide mononitrate has long duration of action due to its ability to avoid first pass effect (so it is administrated orally).

Organic nitrates

- Adverse effect:

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

b. high doses can cause postural hypotension syncope, also can result and tachycardia.

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

Tolerance

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

Important notes to your patient

- The conventional sublingual tablet form of nitroglycerin may lose potency when stored as a result of volatilization and adsorption to plastic surfaces. Therefore, it should be kept in tightly closed glass containers. Nitroglycerin is not sensitive to light.

- spray is equally effective; it has a shelf life of two to three years and does not require refrigeration

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 attack.
- The cardioselective β1 agents, such as acebutolol and atenolol and metoprolol are preferred.
- They combined with nitrates to increase exercise duration and tolerance.

Beta-Blockers

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

Undesirable effects

- **An increase in end-diastolic volume and an increase in ejection time, both of which tend to increase myocardial oxygen requirement.**

- **These deleterious effects of beta -blocking agents can be balanced by the concomitant use of nitrates.**

β-adrenergic blocking agents

2.clinical uses

stable and unstable angina

myocardia infarction

3.contraindication

variant angina,

bronchial asthma,

bradycardia,

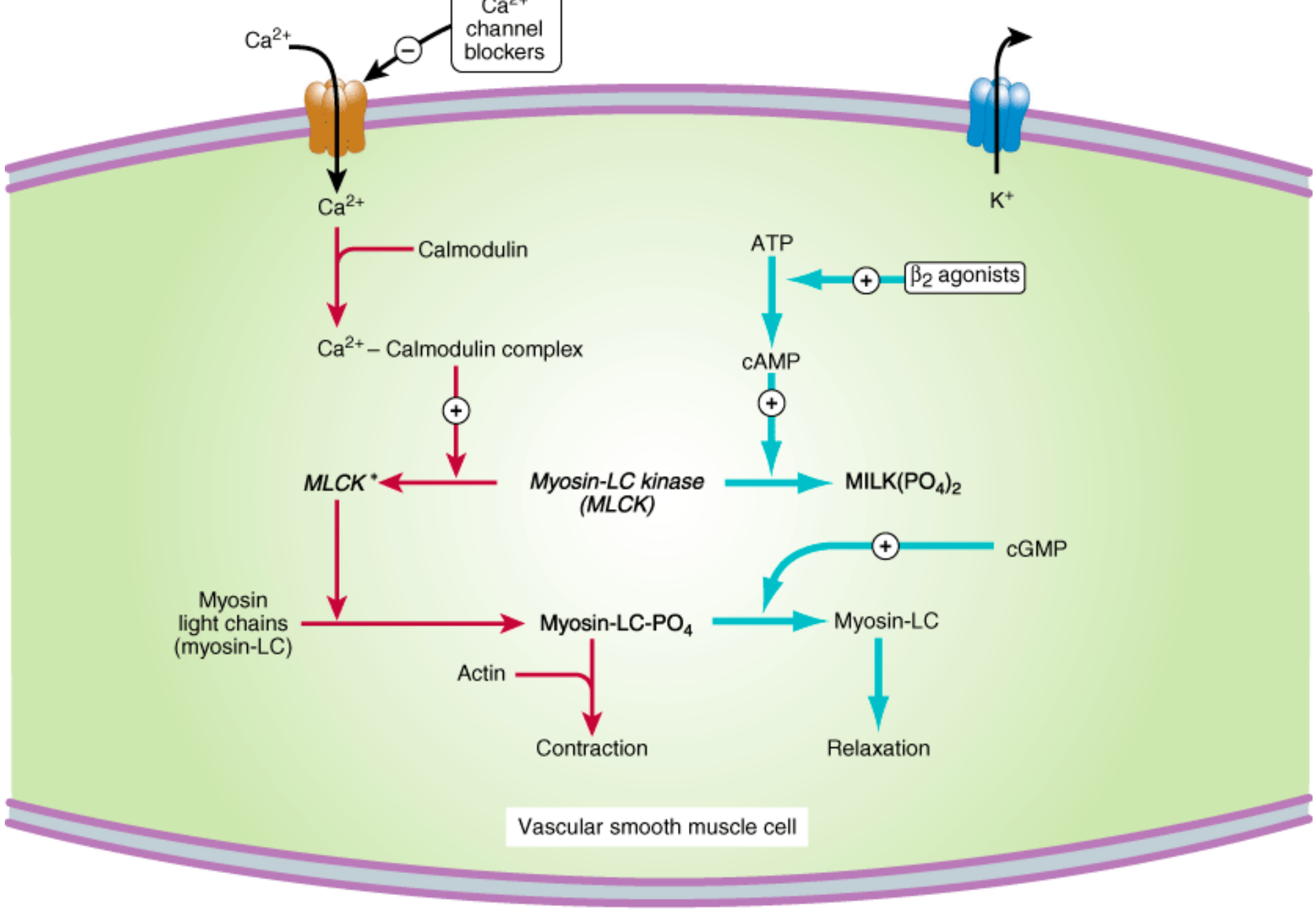
Calcium channel blockers

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

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

B. Verapamil, slow cardiac conduction directly, and thus decrease oxygen demand, so should be avoided with patient with a congestive heart failure due to its negative inotropic effect on the heart.

C. Diltiazem has similar effect on the heart to Verapamil.



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

Calcium Channel Blockers
Mechanisms of Action

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

Calcium channel blockers

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

to minimize fluctuations of plasma concentrations and cardiovascular effects.

- Side-effects are also concentration-dependent, and mainly related to the arterial vasodilator responses

  (headache, flushing and ankle oedema);

  these effects are more pronounced with dihydropyridine CCB's.

Verapamil and Diltiazem

- **In patients with relatively low blood pressure, dihydropyridines can cause further deleterious lowering of pressure.**

Verapamil and diltiazem appear to produce less hypotension and may be better tolerated in these circumstances.

- **In patients with a history of atrial tachycardia, flutter, and fibrillation, verapamil and diltiazem provide a distinct advantage because of their antiarrhythmic effects.**

Comparison

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

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

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

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

Combination Therapy of Angina

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

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

Undesireable effects are shown in italics

Recommendations for pharmacological therapy of vasospastic angina

- Treatment with calcium antagonists and if necessary nitrates in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.

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