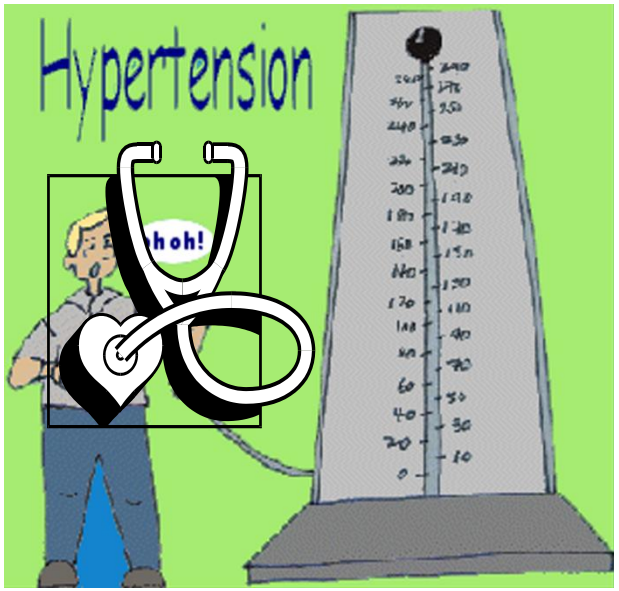
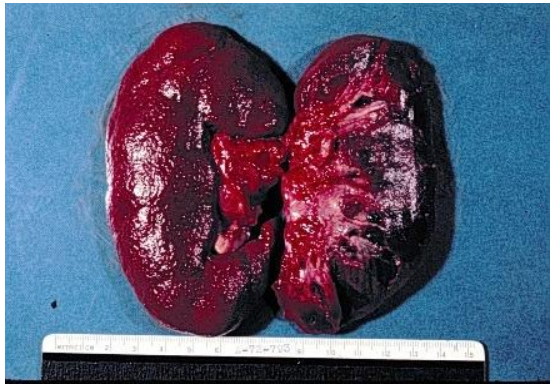
دراسة صحية تظهر ان 39% من عينتها يعانون من ضغط الدم

- الراي - اظهرت دراسة نفذتها وزارة الصحة بالتعاون مع شركة أسترا زينكا الدوائية ضمن حملة (سلامة قلبك للوقاية من الامراض القلبية والوعائية) ان معدل أنتشار ضغط الدم 39 بالمئة لجميع المشاركين في الحملة.
وبينت الدراسة التي اعلنت نتائجها اليوم الاثنين في مؤتمر صحافي خصص لهذه الغاية، ان5ر34 بالمئة من المشاركين فيها لديهم أحد أفراد الأسرة مصاب بمرض في القلب و3ر52 بالمئة عندهم اقارب يعانون من السكري.
وكشفت الدراسة التي اجريت في محافظات عمان واربد والزرقاء على مواطنين ضمن الفئة العمرية25 عاما فما فوق، أن أكثر من90 بالمئة من المواطنين يعرفون بخطورة إرتفاع ضغط الدم والسكري والكوليستيرول بالتسبب بالأصابة بأمراض القلب ولكن هذا لا ينطبق على ممارساتهم للوقاية من هذة الأمراض اذ أن نسبة كبيرة منهم8ر41 بالمئة لم يقوموا بقياس ضغط الدم خلال السنة الماضية. وبينت الدراسة كذلك ان7ر52 بالمئة من المشاركين لم يقوموا بفحص سكر الدم وان4ر70 بالمئة لم يجروا فحص الكوليستيرول ايضا خلال العام الماضي

Hypertension: The Silent Killer





CRITICAL POINT!

Hypertension- asymptomatic

Morbidity and mortality due to end organ damage

congestive heart failure, myocardiac infarction, renal damage, cerebrovascular accidents.

Hypertension as a disease

- **Most of the international committees classified hypertension in four categories:**

JNC 6 Category	SBP/DBP	JNC 7 Category
Optimal	< 120/80	→ **Normal**
Normal	120–129/80–84	→ **Prehypertension**
Borderline	130–139/85–89	
Hypertension	≥ 140/90	→ **Hypertension**
Stage 1	140–159/90–99	→ Stage 1
Stage 2	160–179/100–109	→ Stage 2
Stage 3	≥ 180/110	

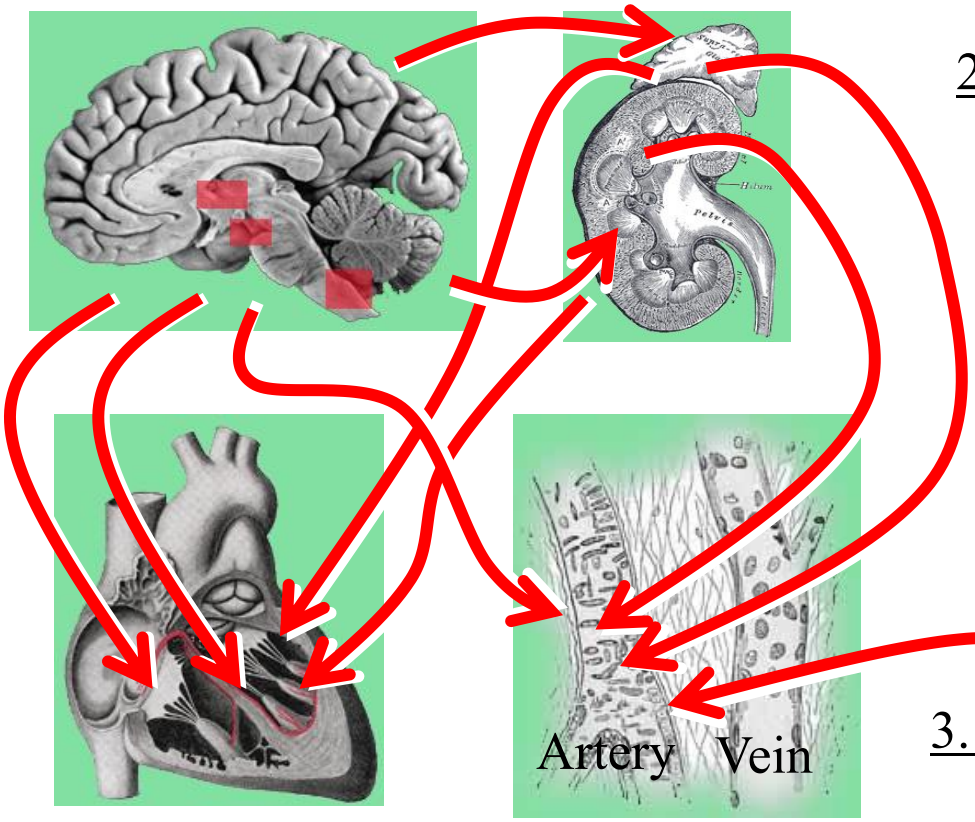
Lifestyle Modification

Modification	Approximate SBP Reduction (range)
Weight reduction	5-20 mmHg/ 10 kg weight loss
Adopt DASH eating plan	8-14 mmHg
Dietary sodium reduction	2-8 mmHg
Physical activity	4-9 mmHg
Moderation of alcohol consumption.	2-4 mmHg

JNC 7 Express. JAMA. 2003 Sep 10; 290(10):1314

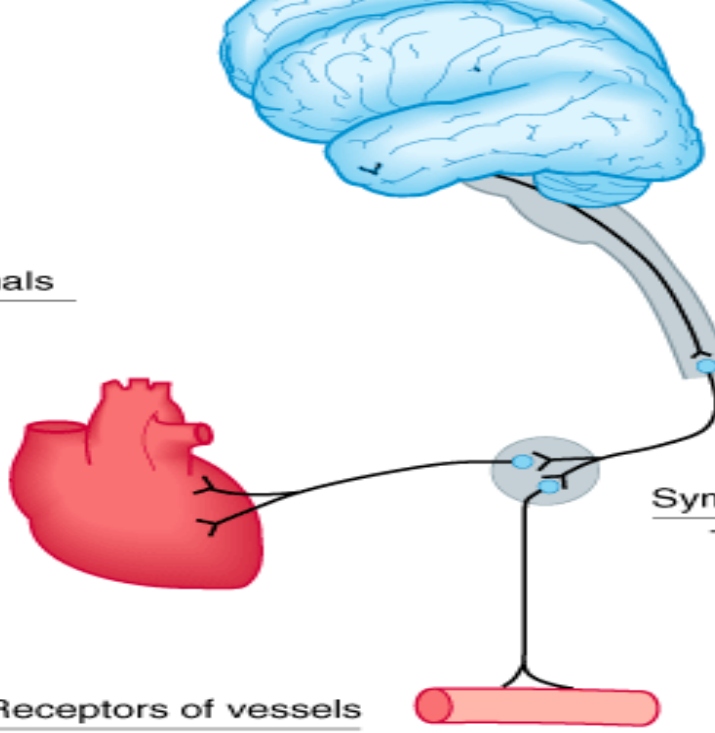
Mechanisms Controlling CO and TPR

1. Neural
   SymNS
   PSNS



2. Hormonal
   Renal
      Ang II
   Adrenal
      Catecholamines
      Aldosterone

3. Local Factors



Vasomotor center

Methyldopa
Clonidine
Guanabenz
Guanfacine

Sympathetic nerve terminals

Guanethidine
Guanadrel
Reserpine

Sympathetic ganglia

Trimethaphan

β-Receptors of heart

Propranolol and other β-blockers

Angiotensin receptors of vessels

Losartan and other angiotensin receptor blockers

α-Receptors of vessels

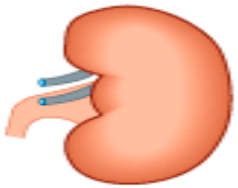
Prazosin and other α_1-blockers

Vascular smooth muscle

Hydralazine
Minoxidil
Nitroprusside
Diazoxide
Verapamil and other calcium channel blockers
Fenoldopam

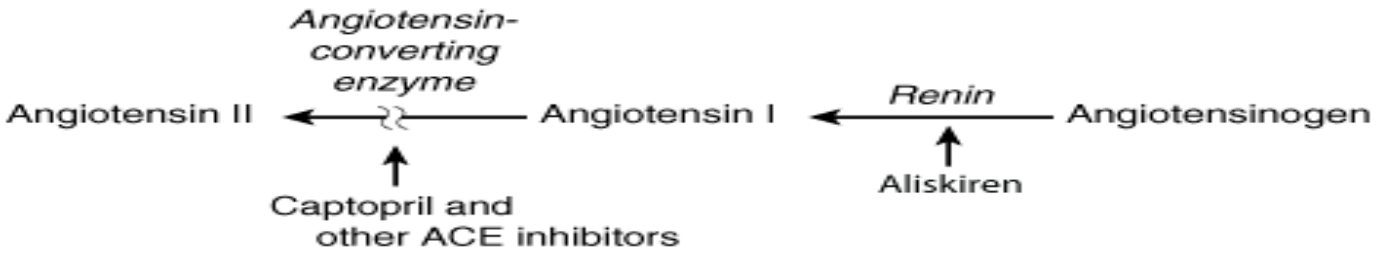
Kidney tubules

Thiazides, etc

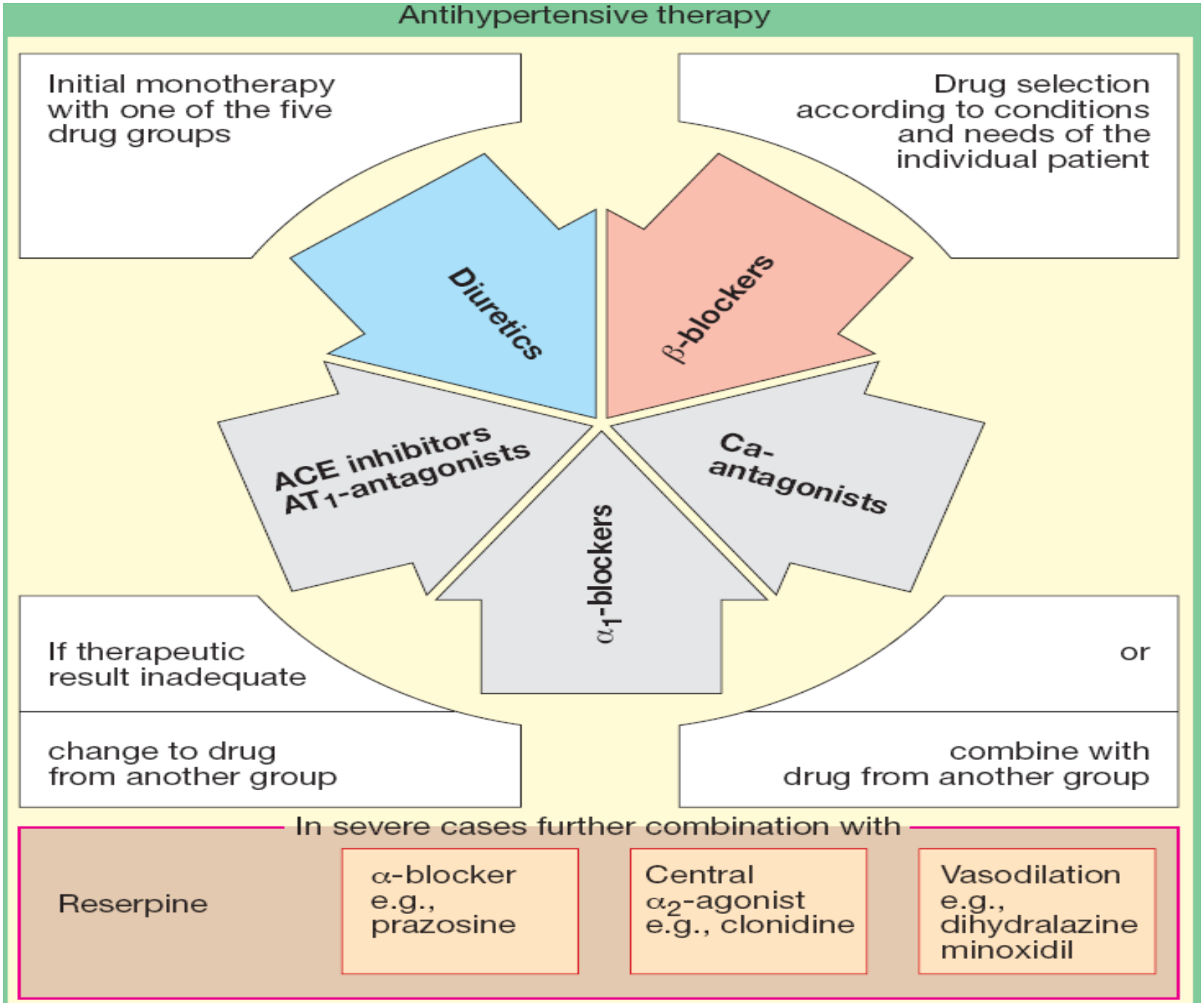


β-Receptors of juxtaglomerular cells that release renin

Propranolol and other β-blockers



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


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

Monotherapy or combination

- Monotherapy of hypertension (treatment with a single drug) is desirable because compliance is likely to be better and cost is lower, and because in some cases adverse effects are fewer.

- However, most patients with hypertension require two or more drugs, preferably acting by different mechanisms (polypharmacy).

What to choose first?

- Initial antihypertensive therapy without compelling indications
  - JNC 6: Diuretic or a beta-blocker
  - JNC 7: Thiazide-type diuretics
- Most outcome trials base antihypertensive therapy on thiazides

JNC 7 Express. JAMA. 2003 Sep 10; 290(10):1314

Diuretics

- Diuretics are effective in lowering blood pressure by 10–15 mm Hg in most patients, and diuretics alone often provide adequate treatment for mild or moderate essential hypertension.

- In more severe hypertension, diuretics are used in combination with sympathoplegic and vasodilator drugs to control the tendency toward sodium retention caused by these agents.

Thiazide Diuretics

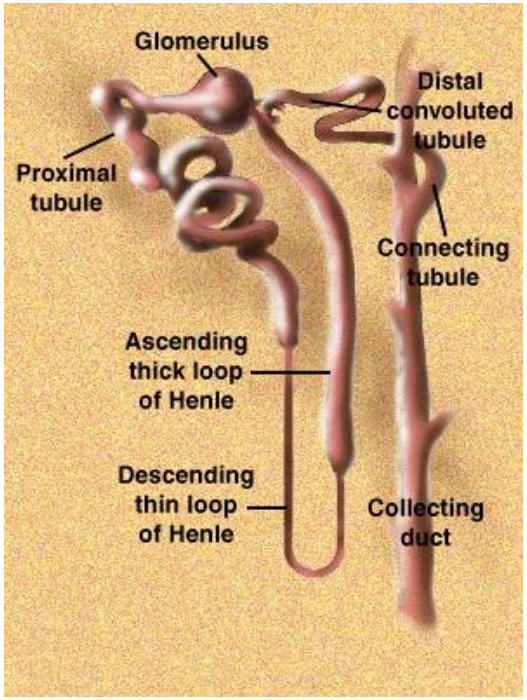
- Diuretics lower blood pressure primarily by depleting body sodium stores.
- Initially, diuretics reduce blood pressure by reducing blood volume and cardiac output; peripheral vascular resistance may increase.
- After 6–8 weeks, cardiac output returns toward normal while peripheral vascular resistance declines.
- Sodium is believed to contribute to vascular resistance by increasing vessel stiffness and neural reactivity, possibly related to altered

Diuretics (cont)

2. Mechanism of Action

↑ Urinary Na+ excretion
↑ Urinary water excretion

↓ Extracellular Fluid
↓ and/or Plasma Volume



3. Effect on Cardiovascular System

↓ Acute decrease in CO

↓ Chronic decrease in TPR, normal CO
Mechanism(s) unknown

Thiazide diuretics

- lower doses (25–50 mg) exert as much antihypertensive effect as do higher doses.

- In contrast to thiazides, the blood pressure response to loop diuretics continues to increase at doses many times greater than the usual therapeutic dose.

Thiazide diuretics

- **Decrease blood pressure in supine and standing position, and postal hypotension is rarely observed except in elderly.**

- **There are many analogs, but the most important prototypes are:**

  - **Chlorothiazide, given orally 1-2 times a day.**

  - **Hydrochlorothiazide, 1-2 times a day.**

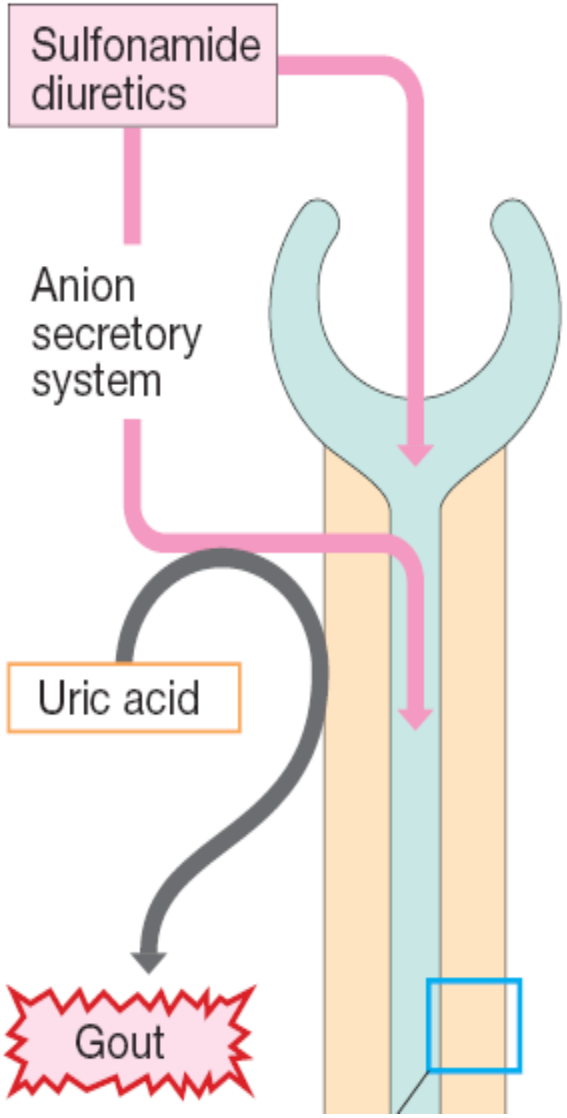
Thiazide diuretics

Adverse effect includes:

- **hypokalermia (70% of patients), thus a potassium supplementation is recommended.**

- **hyperuricemia (70% of patients), result from the inhibition of renal tubular secretion of uric acid.**

- **hyperglycemia (10% of patients), may interfere with the conversion of pro-insulin to insulin.**



Side effect

- mild degrees of hypokalemia are tolerated well by many patients, hypokalemia may be hazardous in persons taking digitalis, those who have chronic arrhythmias.

- Potassium loss is coupled to reabsorption of sodium, and restriction of dietary sodium intake therefore minimizes potassium loss.

Loop diuretics

- Furosemide, ethacrynic acid, and bumetanide, produce greater diureses than thiazides, but they have weaker anti-hypertensive effect and cause severe electrolyte imbalance.

- Typically only beneficial in patients with

    1. resistant HTN and evidence of fluid;

    2. effective if CrCl <30 ml/min

- MUST be dosed at least twice daily (Lasix = Lasts six hours)
- Administer AM and lunch time to avoid nocturia

- **Adverse effects of the loop diuretics summarized in**

  -Ototoxicity, specially when used with aminoglycosides.

  -hyperurecemia.

Hypocalcemia	**loop**
hypercalcemia	**thiazide**

β-adrenergic blocking agents

- **The various β blockers all appear to be equally effective for the treatments of hypertension.**

- **Propranolol, Timolol, Nadolol, Pindolol, Penbutolol, carvedilol, are nonselective,**

- **while Metoprolol, Acebutolol, and Atenolol, Esmolol are Cardioselective, sotalol.**

- **Adverse effects,**

Dizziness, sudden weight gain , irregular heart beat.

congestive heart failure, asthma (non-selective), hypoglycemia (non-selective) in patient with diabetes mellitus.

Beta blockers

- Metoprolol and atenolol, which are cardioselective, are the most widely used blockers in the treatment of hypertension.

- Pindolol, acebutolol, and penbutolol are partial agonists, ie, blockers with some intrinsic sympathomimetic activity. They lower blood pressure by decreasing vascular resistance and appear to depress cardiac output or heart rate less than other blockers. this may be particularly beneficial for patients with bradyarrhythmias or peripheral vascular disease.

- Labetalol, Carvedilol cause of its combined - and -blocking activity, labetalol is useful in treating the hypertension of pheochromocytoma and hypertensive emergencies.

Esmolol

- Esmolol has a short half-life (9–10 minutes) and is administered by constant intravenous infusion.

- Esmolol is used for management of intraoperative and postoperative hypertension,

- and sometimes for hypertensive emergencies, particularly when hypertension is associated with tachycardia.

Indications for beta blockers include

- Angina pectoris
- Atrial fibrillation
- Cardiac arrhythmia
- Congestive heart failure
- Essential tremor
- Glaucoma
- Hypertension
- Migraine prophylaxis
- Mitral valve prolapse
- Phaeochromocytoma, in conjunction with α-blocker
- Symptomatic control (tachycardia, tremor) in anxiety and hyperthyroidism

β-adrenergic blocking agents

- **sudden withdrawal may cause rebound hypertension,**
- **The withdrawal syndrome may involve up-regulation or supersensitivity of beta receptor adrenoceptors.**
- **So the removal should therefore be gradual to avoid precipitation of arrhythmia**

ACE Inhibitors

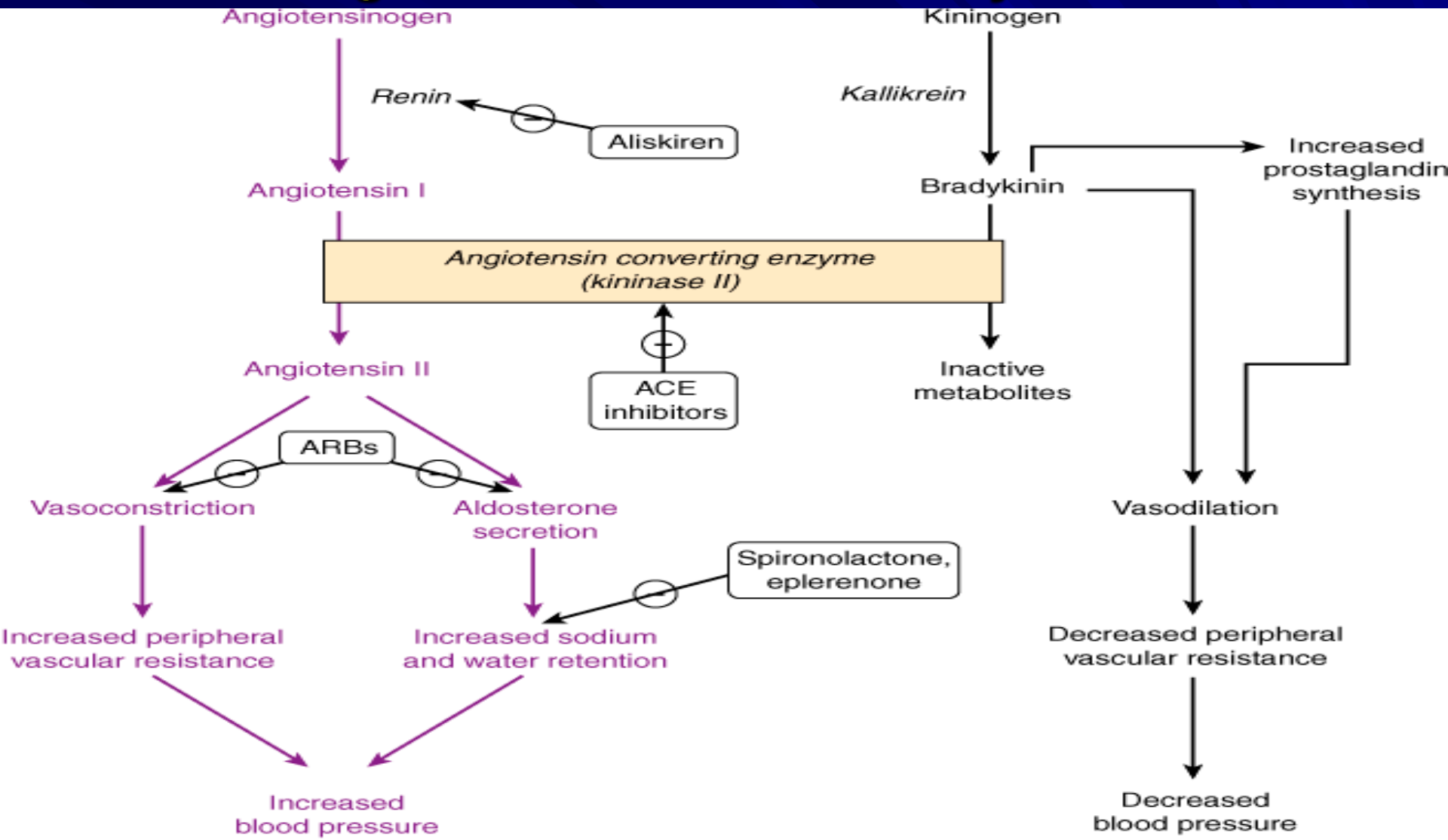
- **ACE Inhibitors, such as Enalapril, Lisinopril, and Captopril are recommended when the preferred first line agents (diuretics or β blockers) are contraindicated or ineffective.**

- **They lower the blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output.**

- **The block the ACE that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. Moreover, ACE is also responsible for the breakdown bradykinin (endogenous vasodilator).**

- **Benazepril, fosinopril, moexipril, perindopril, quinapril, ramipril,** and **trandolapril**

Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system.



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

ACE Inhibitors

-Dry cough occurs in 10% of patients and thought to be due to increase level of bradykinin in the pulmonary tree.

-Potassium level should be monitored and spironolactone (Prevent potassium secretion) is contraindicated.

-Angioedema is rare but a potential life-threading reaction (may be caused by bradykinin).

-Because of the risk of first-dose syncope, and the angioedema ACE inhibitors are first administrated under the doctor observation.

- Contraindications pregnancy

- **ACE inhibitors have a particularly useful role in treating patients with chronic kidney disease because they diminish proteinuria and stabilize renal function (even in the absence of lowering of blood pressure).**

- **This effect is particularly valuable in diabetes, and these drugs are now recommended in diabetes even in the absence of hypertension.**

ACEI

- These benefits probably result from improved intrarenal hemodynamics, with decreased glomerular efferent arteriolar resistance and a resulting reduction of intraglomerular capillary pressure.

- ACE inhibitors have also proved to be extremely useful in the treatment of heart failure, and after myocardial infarction.

Angiotensin II-receptors antagonists

- These agents are alternatives to the ACE Inhibitors, and can be used in patient who cannot tolerate ACE Inhibitors. **Losartan** being the prototype.

- Their pharmacologic effects are Similar to ACE Inhibitors (vasodilation, block aldesterone secretion), however they do not increase the bardykinin levels.

- Their adverse effect are similar to ACE Inhibitor, although the risks of cough and angioedema are significantly decreased.

- **Candesartan, eprosartan, irbesartan,telmisartan, and olmesartan**

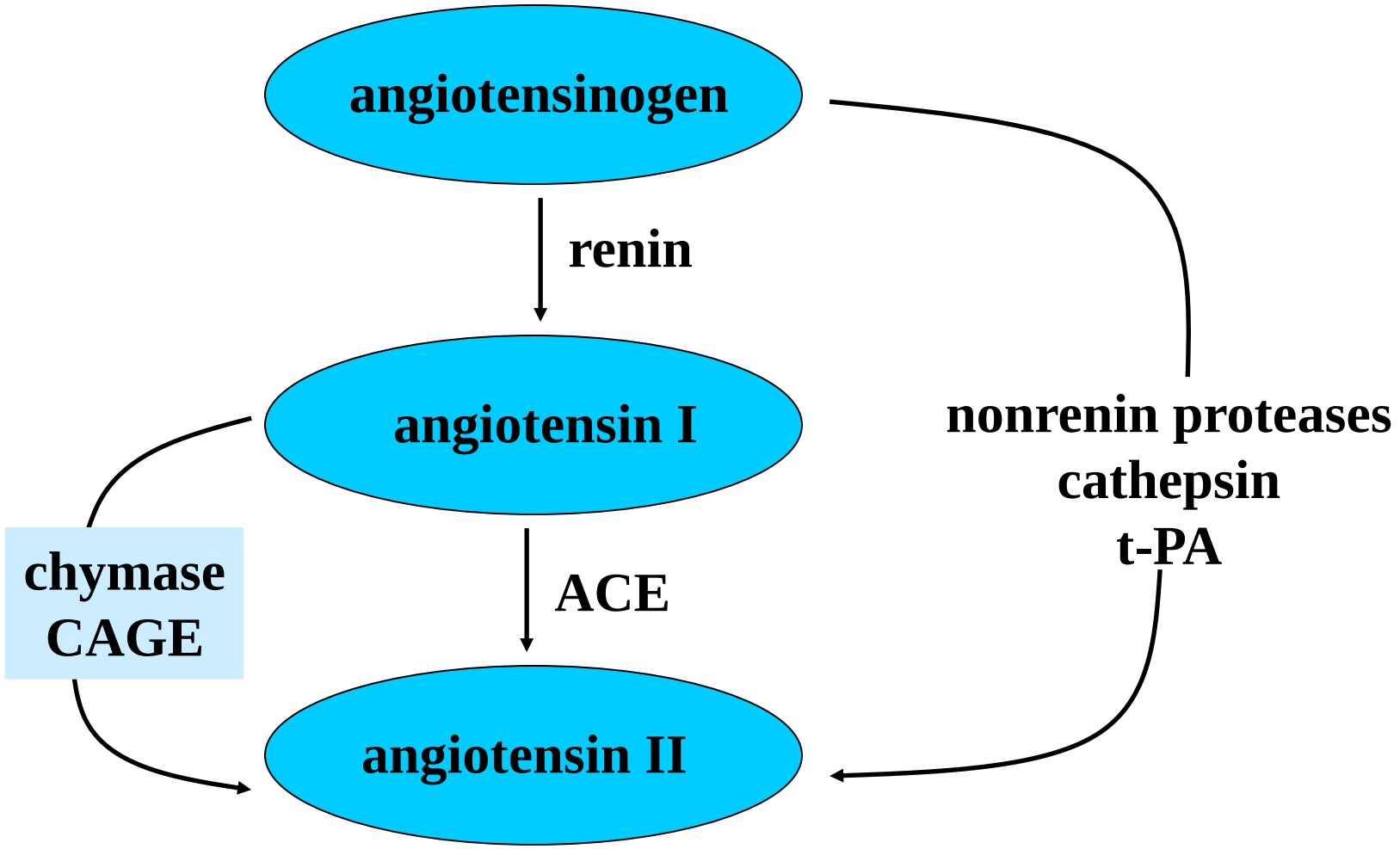
- these drugs lower blood pressure as the ACE inhibitors and have the

advantage of much lower incidence of adverse effects resulting from

accumulation of bradykinin (cough, angioneurotic oedema)

- they **cause fetal** renal toxicity (like that of the ACE inhibitors)

- these drugs reduce aldosterone levels and cause **potassium accumulation** (attainment of toxic levels - hazardous in patients with renal impairment).


angiotensinogen
renin
angiotensin I
ACE
angiotensin II
chymase
CAGE
nonrenin proteases
cathepsin
t-PA

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

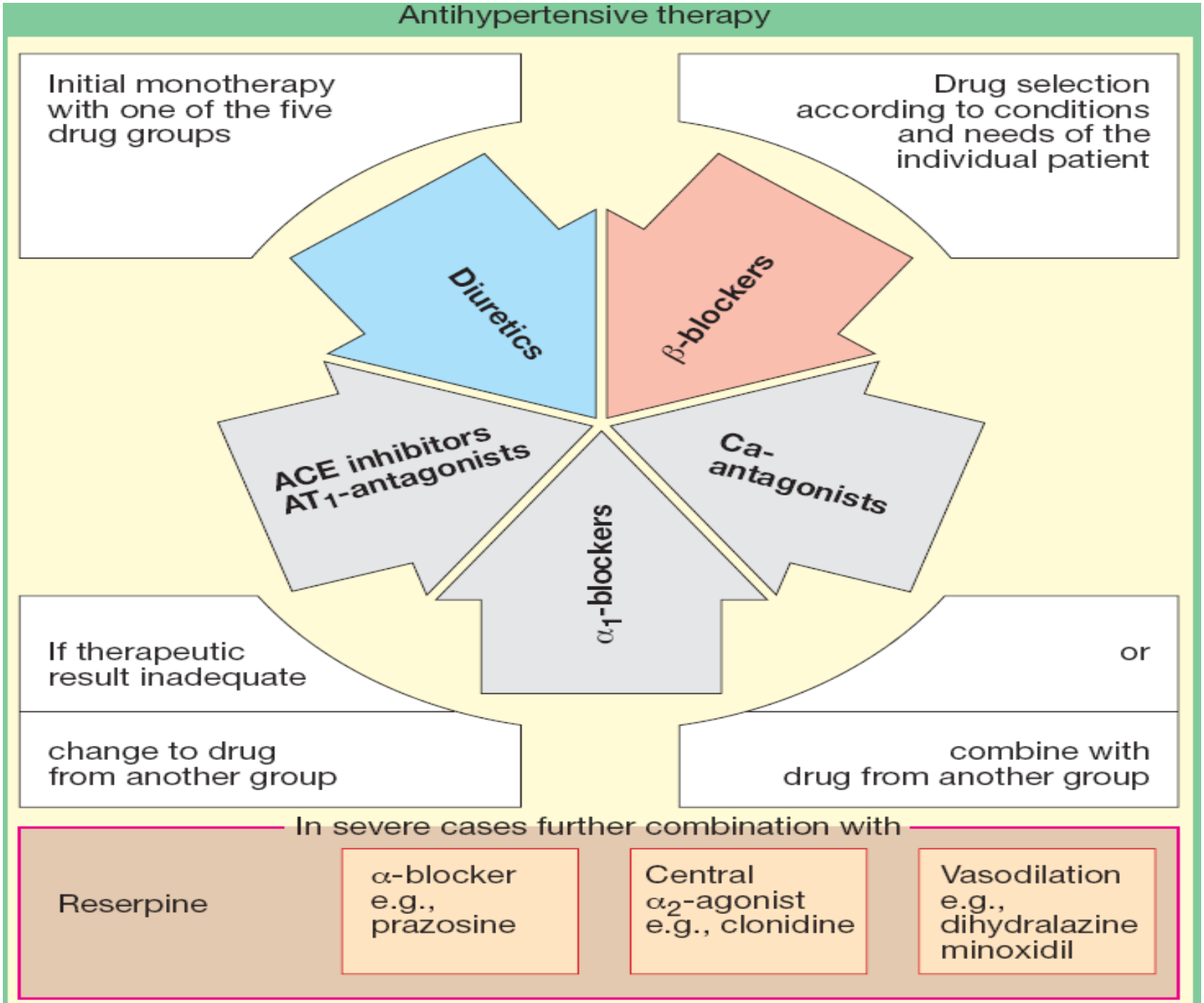
↑ = increase

↔ = 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.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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

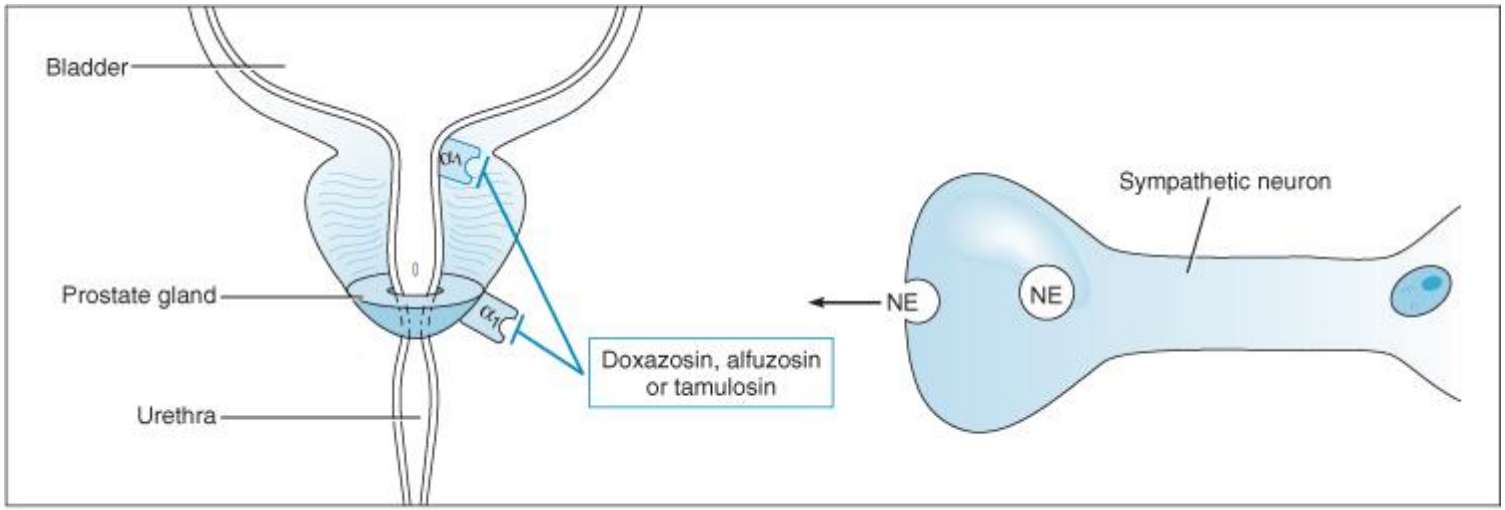
Selective α_1-blockers

- 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

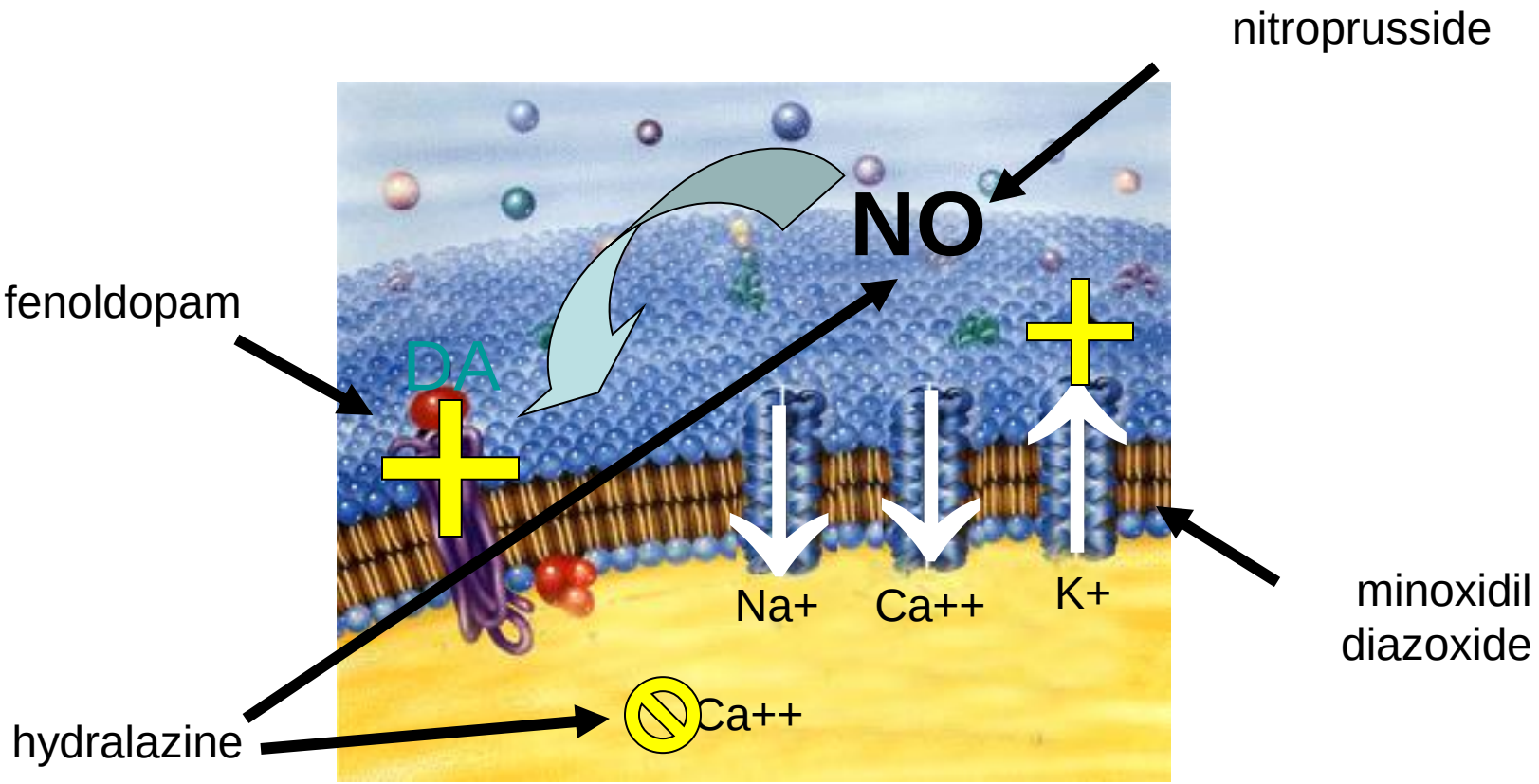
- **α2 agonist that converted to methylnorepinihrine centrally to diminish the adrenergic outflow from the CNS,**
- **Which lead to reduced the peripheral resistance and decreased blood pressure.**
- **Cardiac output is not decreased, and so the blood supply to the vital organs, such as kidney, which 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.**

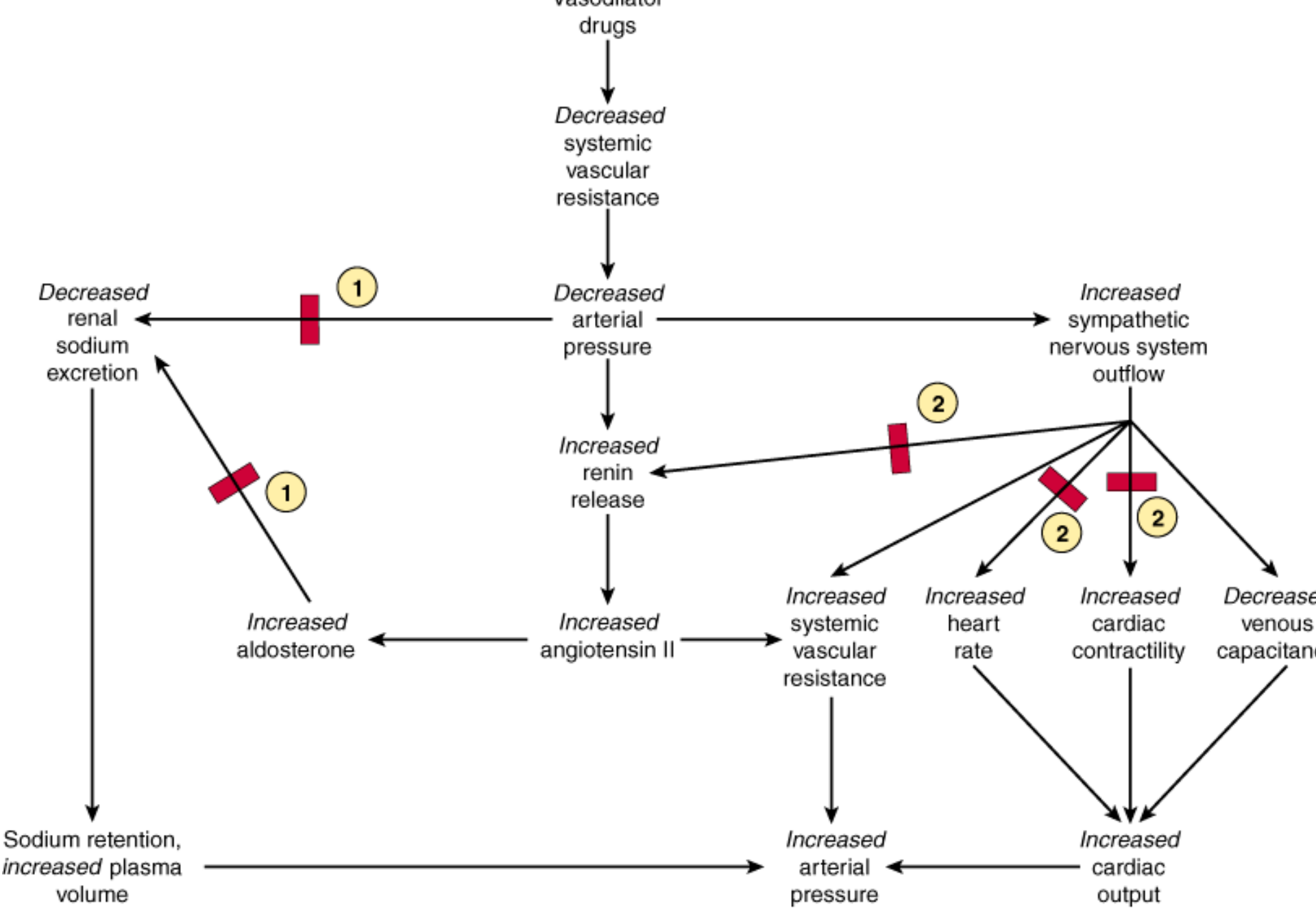
Vasodilator

- 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.**

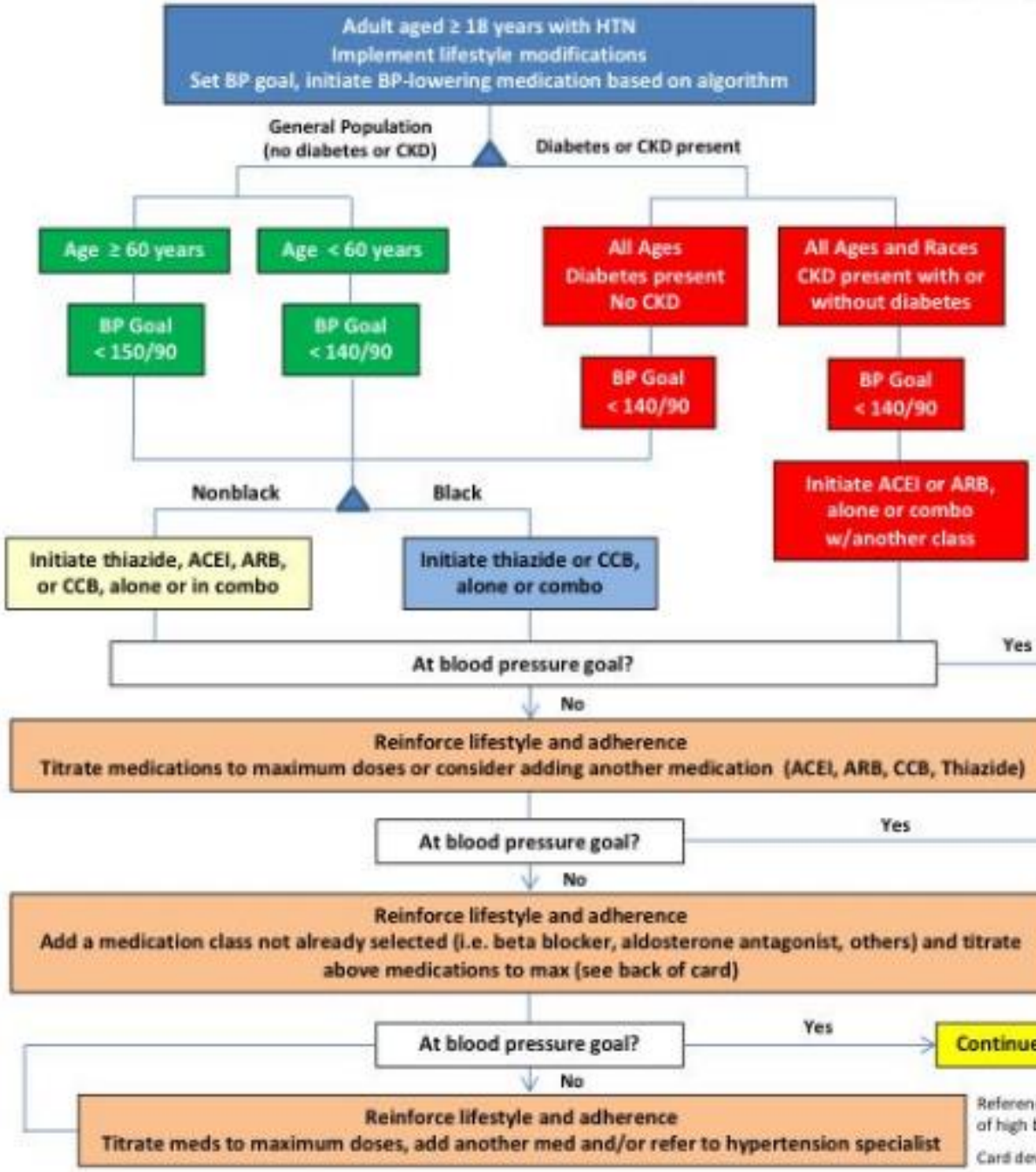
Hypertension emergency

- 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.

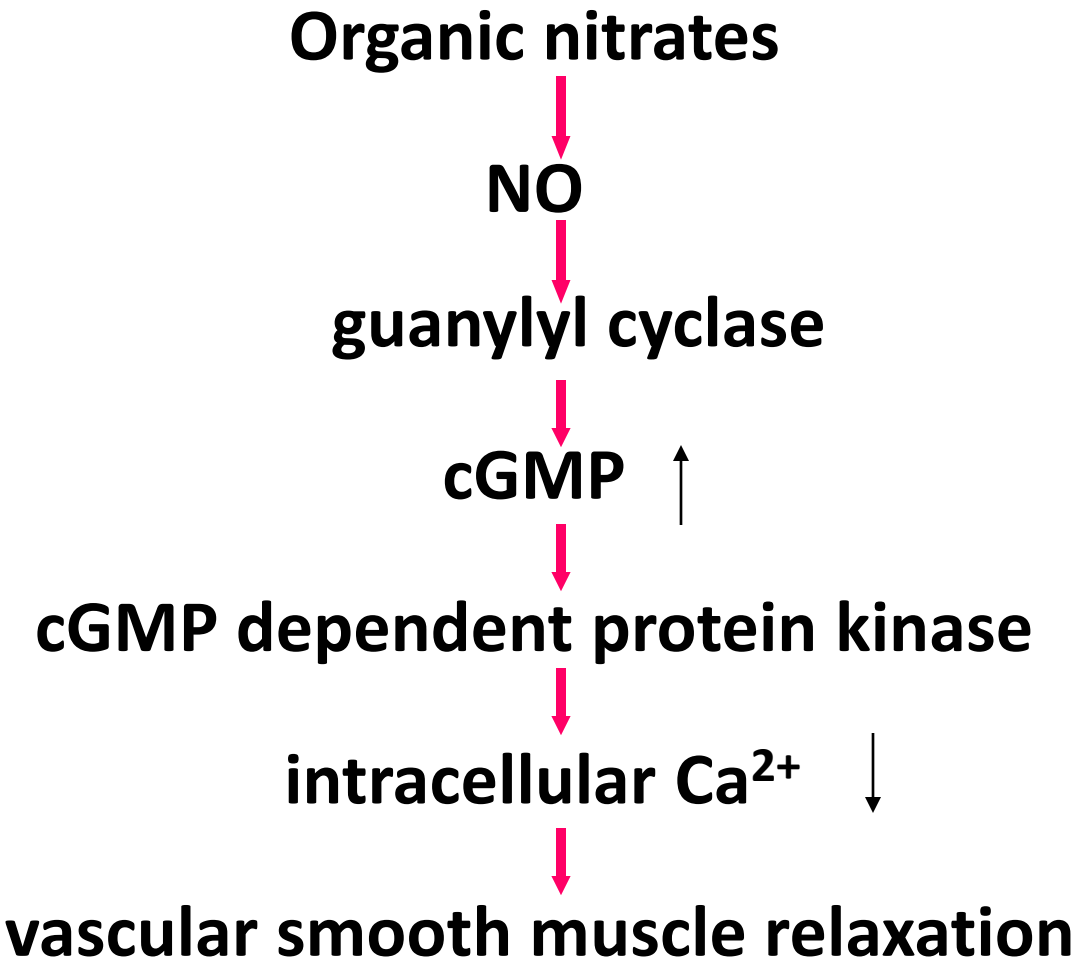
Organic nitrates

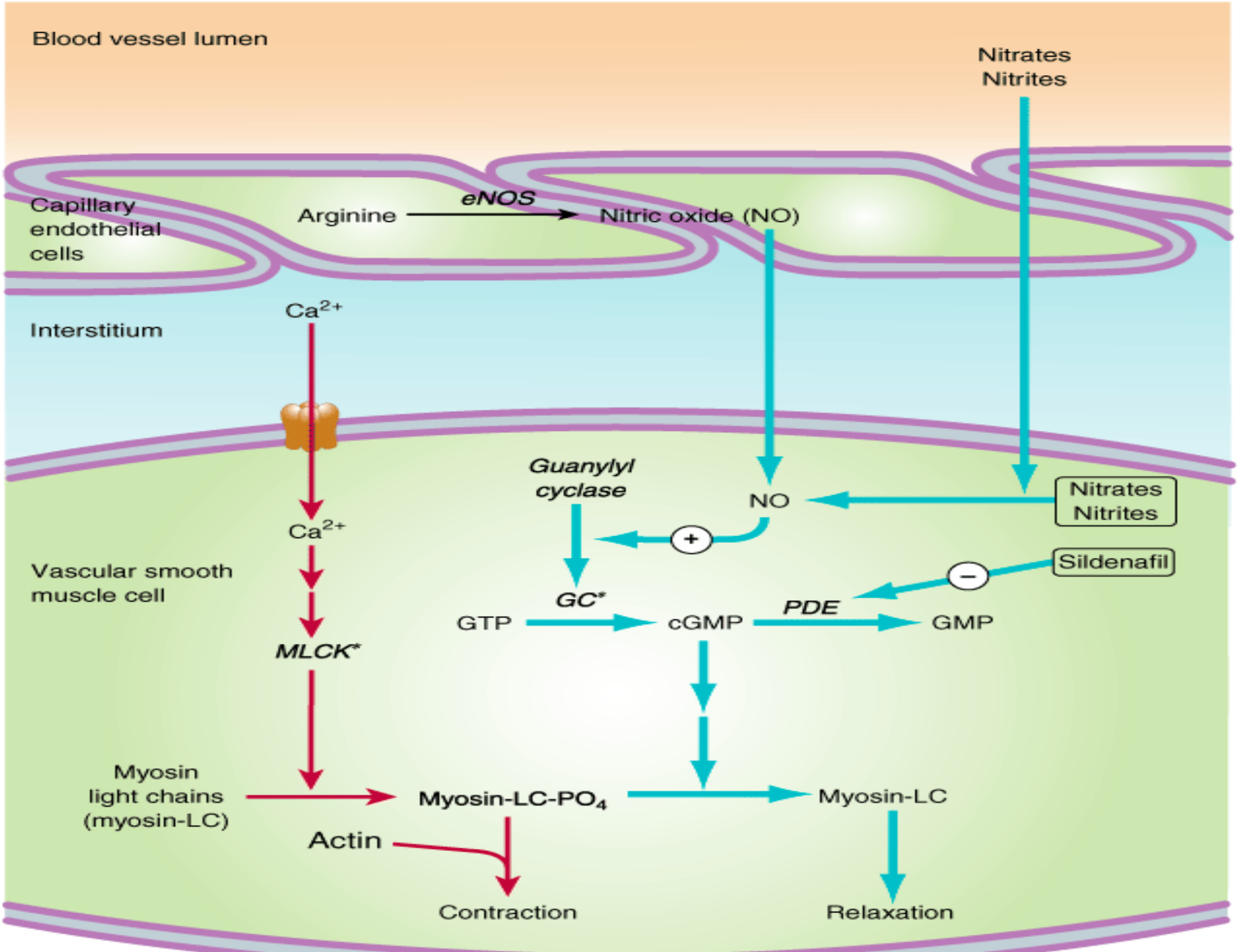
- These compounds cause a rapid reduction in the myocardial oxygen demand, and so provide a rapid relief for the angina symptoms.

- 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+
Sildenafil
Vascular smooth muscle cell
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,

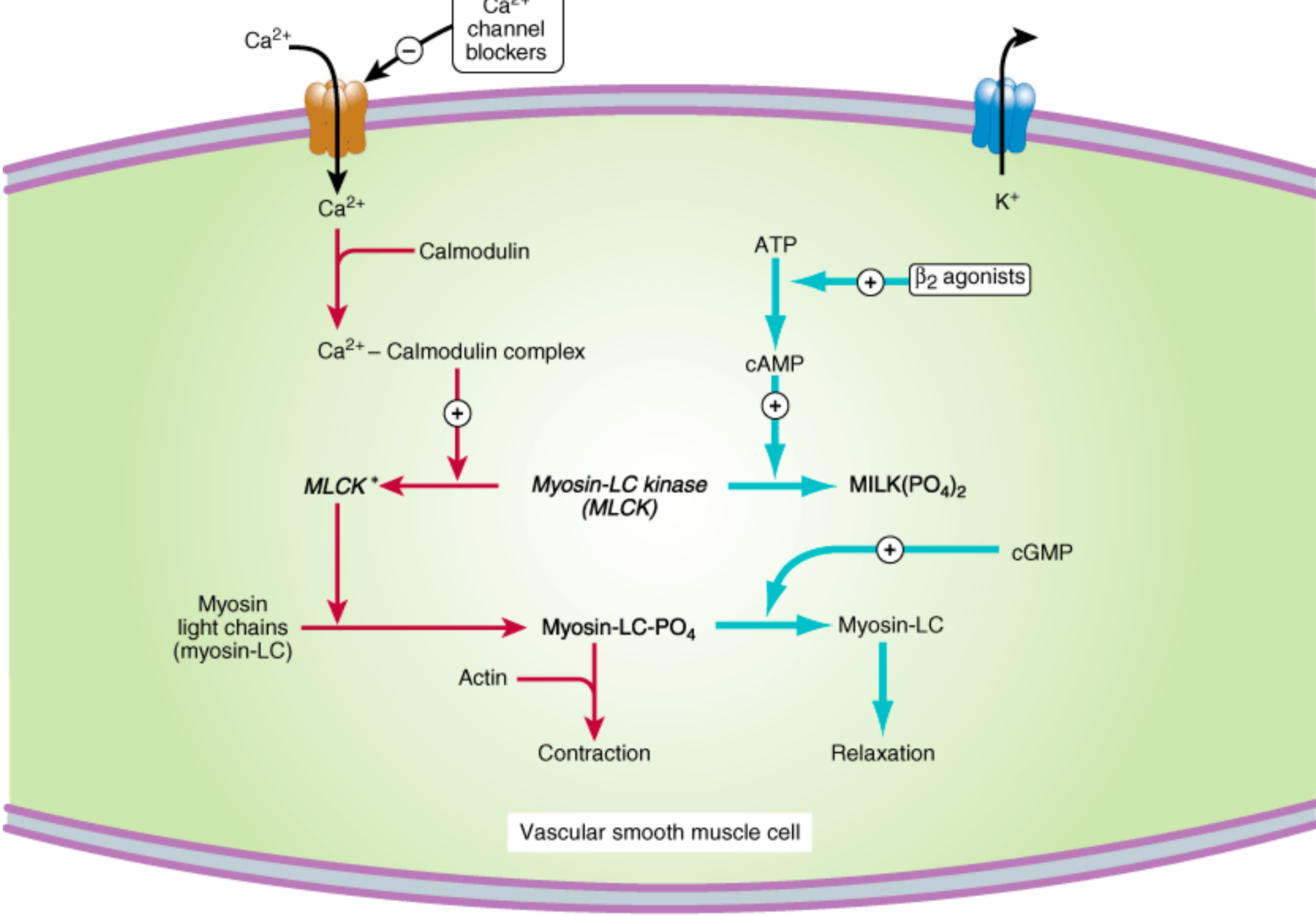
Calcium channel blockers

- 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.



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*)

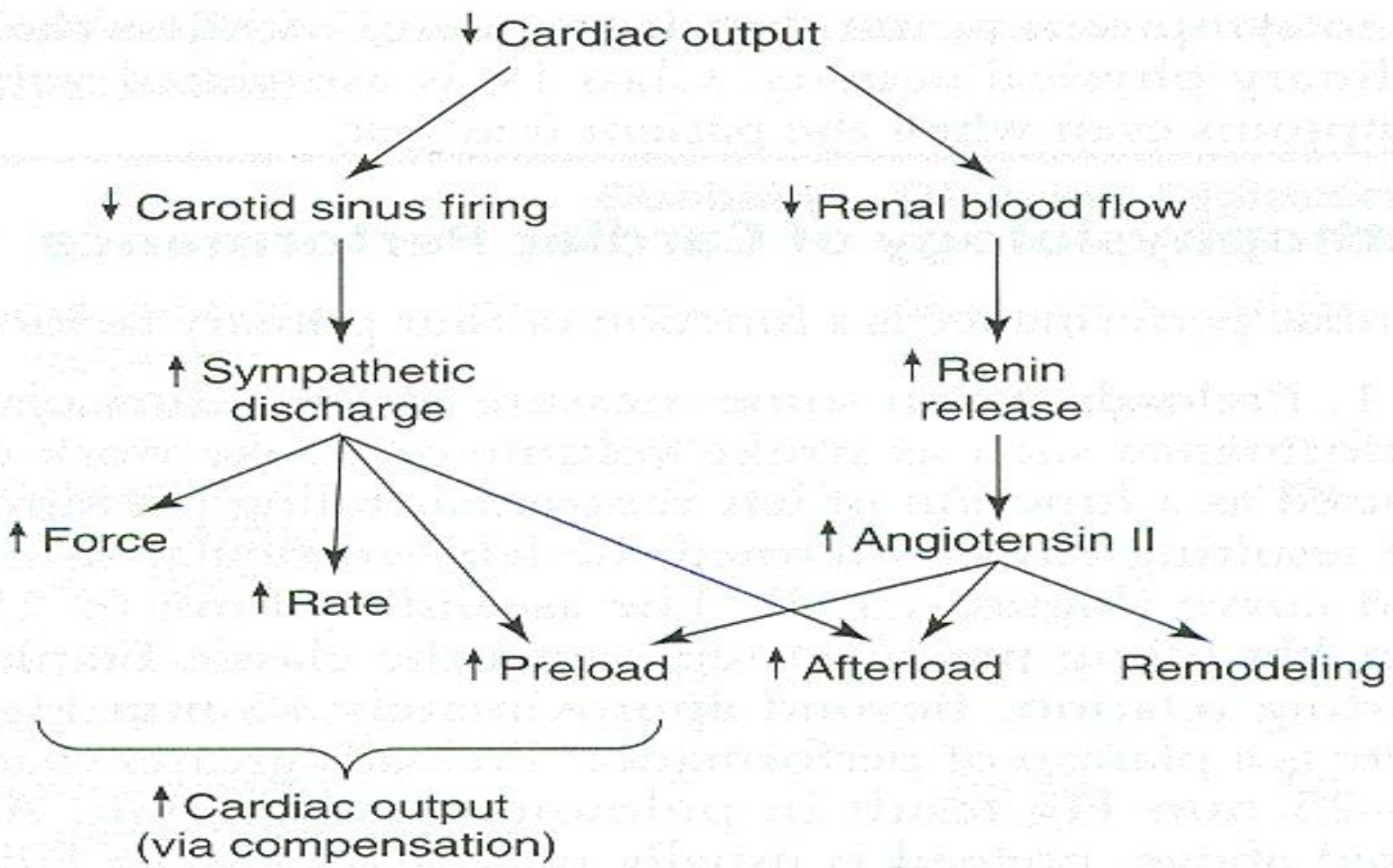


Figure 13–2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

Physiological responses in HF

- **Myocardial hypertrophy, here the heart increases in size and its chamber dilate, initially this will lead to a stronger contraction.**

  However, excessive elongation of fibers will result in weaker contraction, and the ejection of the blood will be diminished, producing systolic failure.

Treating HF

- **The main aims being**
- **(1) decrease the symptoms.**
- **(2) slow disease progression,**
- **(3) improve survival.**

Six Classes of drugs have been shown to be effective

(1) ACE inhibitors,

(2) β-adrenergic blocking agents,

(3)diuretics,

(4) inotropic agents,

(5) direct vasodilators, and

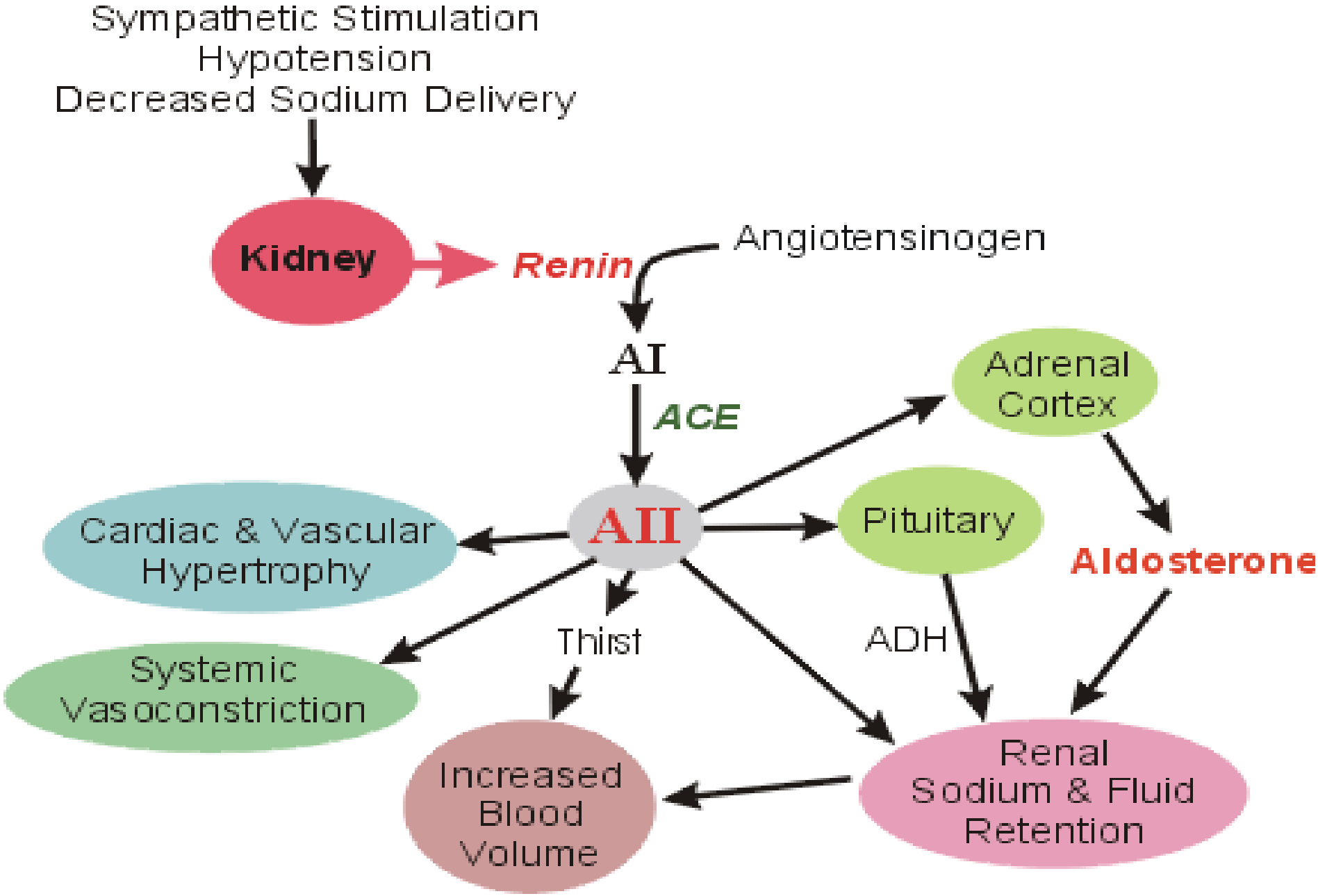
(6) aldesterone antagonist.

- **Depending on the severity of HF and individual patient factors, one or more of these classes of drugs are administrated.**

ACE Inhibitors

- **Decreases vascular resistance and so blood pressure, resulting in an increase in the cardiac output.**
- **They also blunt the usual angiogensin II-mediated increase in adrenaline and aldesterone seen in HF.**
- **These agents show a significant decrease in the mortality and morbidity.**
- **May be considered as a single-agent therapy in patients who have mild dyspnea on excursion, and do not have signs of volume overload.**
- **Early use of these ACE Inhibitors Indicated in patient with all stages of left ventricular failure, with or without symptoms.**

ACE Inhibitors for CCF



ACE Inhibitors

Adverse effects :

- Dry irritating persistent cough
- Hyperkalemia
- Angioedema
- Fetal toxicity

- Patients with heart failure due to left ventricular systolic dysfunction who are still symptomatic despite therapy with an angiotensin converting enzyme inhibitor and a beta blocker may benefit from the addition of candesartan, following specialist advice.

β-adrenergic blocking agents

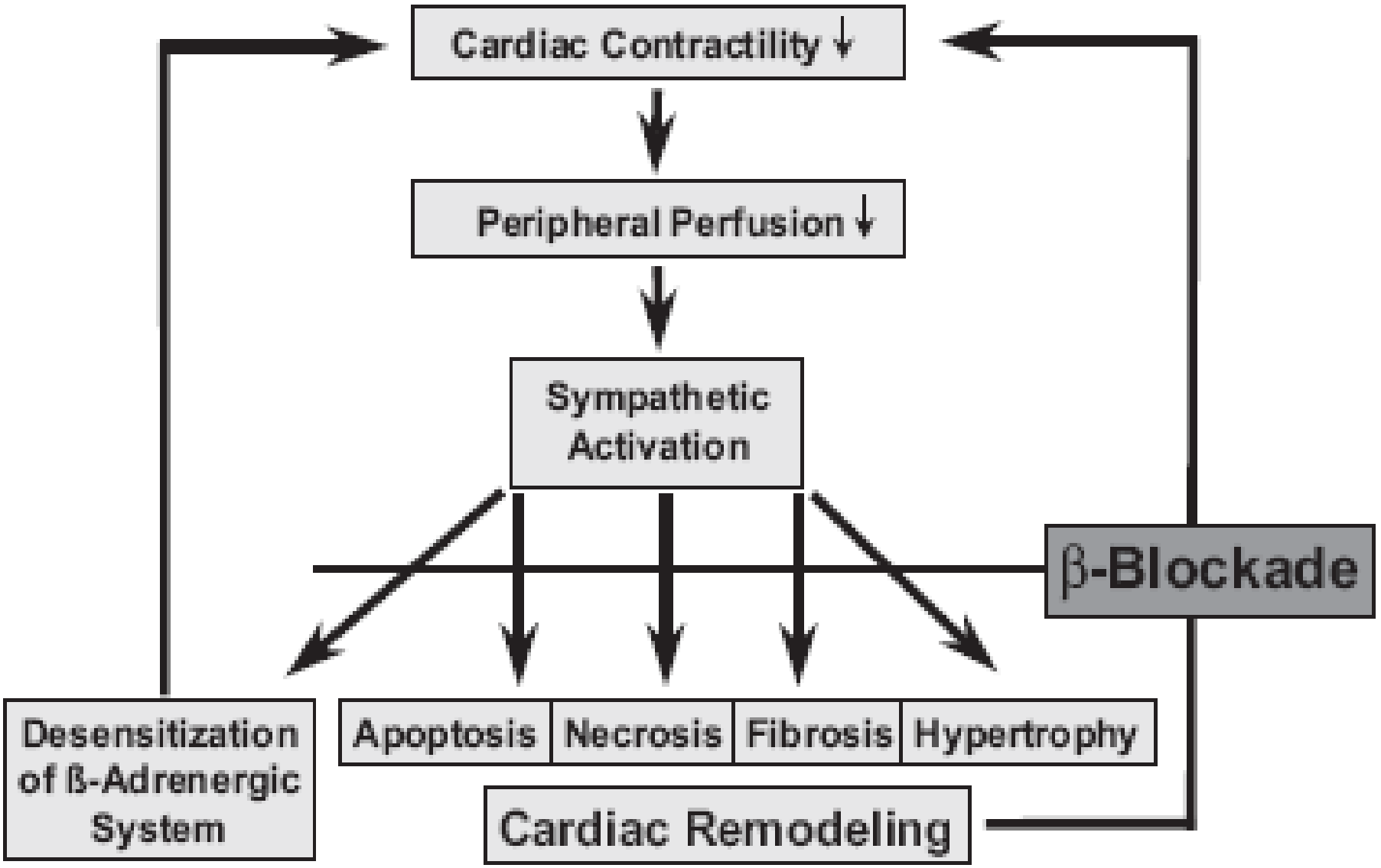
- Although it may seem in logical to administer drugs with negative inotropic activity to patient with HF.

- Several clinical studies have clearly demonstrated improve systolic functioning and reverse cardiac remodeling in patients receiving β blocker

- The benefit is attributed in part to their ability to prevent changes of the sympathetic system, include decreasing the heart rate and inhibiting renin secretion.

- Bisoprolol, carvedilol or nebivolol should be the beta blocker of first choice for the treatment of patients with chronic heart failure due to left ventricular systolic dysfunction.

Beta blockers in CCF



β-adrenergic blocking agents

- produce benefit in the medium to long term.
- In the short term they can produce decompensation with worsening of heart failure and hypotension.
- They should be initiated at low dose and only gradually increased with monitoring up to the target dose.
- contraindicated in patients with asthma, second or third degree atrioventricular heart block or symptomatic hypotension and should be used with caution in those with low initial blood pressure (ie systolic BP <90 mm Hg).

Diuretics

These are useful in reducing the symptoms of volume overload by

- **decreasing the extra cellular volume**
- **decreasing the venous return**

- **Diuretic therapy should be considered for heart failure patients with dyspnoea or Oedema**

- **Loop diuretics like furosemide and bumetanide are the most effective and commonly used.**

- **Thiazides are effective in mild cases only.**

Diuretics

- The dose of diuretic should be individualised to reduce fluid retention without overtreating, which may produce dehydration or renal dysfunction.

- Loop diuretics and thiazides cause hypokalemia.

- Potassium sparing diuretics help in reducing the hypokalemia due to these diuretics.

Spironolactone

- Generally Patient with advanced heart disease have elevated levels of aldosterone due to angiotension II stimulation and decrease hepatic clearance of this hormone.

- Spironolactone is a direct antagonist of aldesterone, and so prevent sodium retention, myocardial hypertrophy, and hypokalemia.

- Spironolactone should be preserved for the most advanced cases of HF.

Spironolactone

- The dose of spironolactone should be no more than 25-50 mg/day and it is only recommended in those with moderate to severe heart failure due to LVSD.

- Main side effects include CNS effects, such as confusion, endocrine abnormalities, and gastric disturbances like peptic ulcer.

- Eplerenone can be substituted for spironolactone in patients who develop gynaecomastia

Stage C Therapy
(Reduced LVEF with Symptoms)

Aldosterone Antagonists

Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.

Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF.

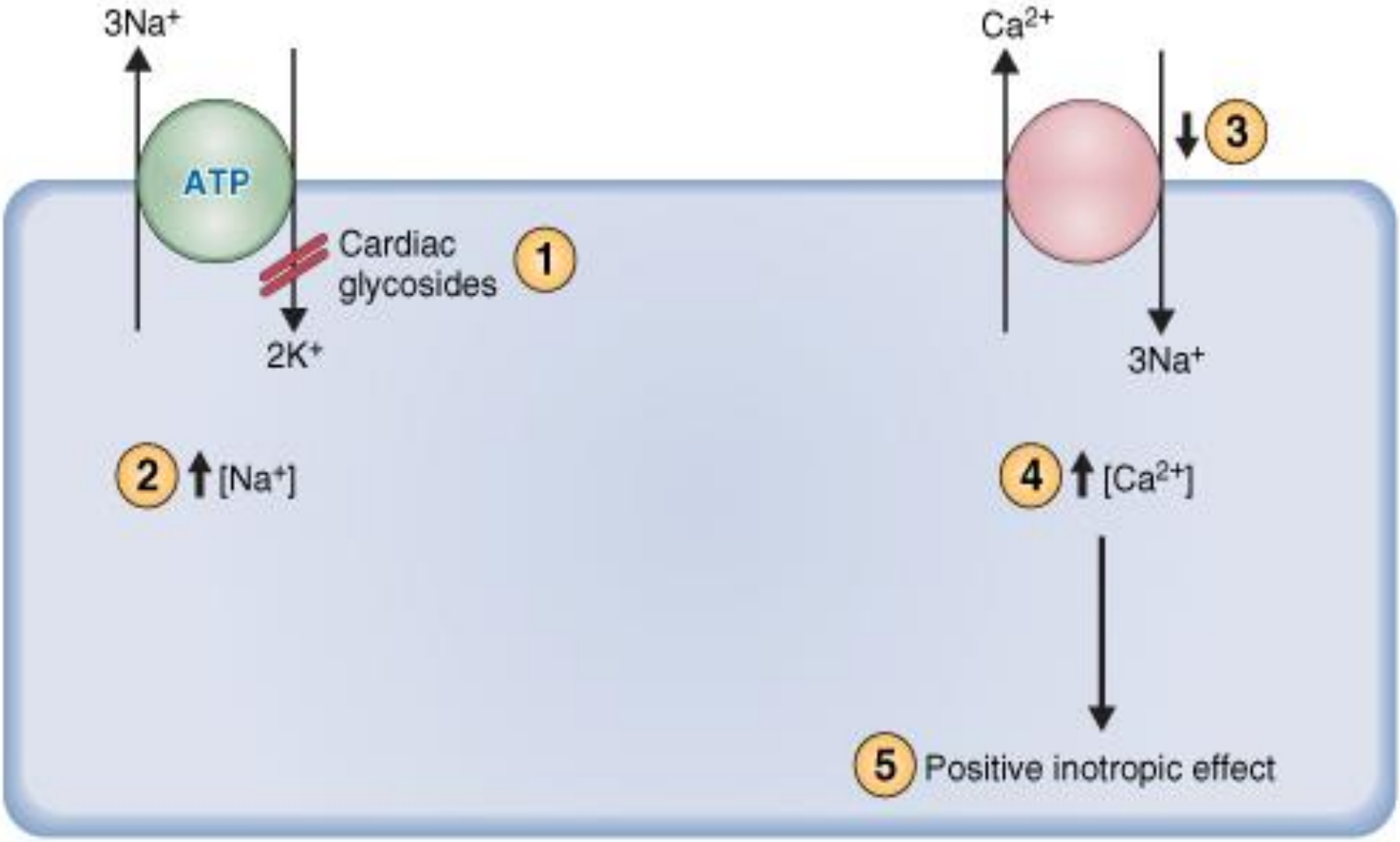
Inotropic drugs (Digitalis)

- **Increase the contractibility of heart muscles, and therefore are widely used in treatments of HF, causing the cardiac output to more closely resemble that of the normal heart. (The most widely used is digoxin).**

- **Influence the sodium and calcium ions flows in cardiac muscle, thereby increasing contraction of the atrial and ventricular myocardium (positive inotropic action).**

- **The digitalis glycoside show only a small difference between a therapeutically effective dose and doses that are toxic or fetal. So these agents have a low therapeutic index or window.**

POSITIVE INOTROPIC EFFECT OF CARDIAC GLYCOSIDES



Digoxin

- **Digoxin is indicated with severe left-ventricular systolic failure after initiation of ACE inhibitors, diuretics, and β Blocker.**

- **Patient with mild to moderate HF will usually respond to ACE inhibitors and diuretics, and do not need digoxin.**

- **No good oral inotropic agents exist other than digoxin.**

- **Digoxin also has a rapid onset of action, making it useful in emergency condition, in which the drug in given intravenously, and the onset of action will be within 5-30 minutes.**

Digoxin

- **Adverse effects:**

  digoxin have a low margin of safety (narrow therapeutic index) and intoxication from excess of both drug is common.

  intoxication is frequently precipitated by depletion of serum K^+ due to diuretic therapy.

  It also may happened because of the accumulation over a long period of time.

  as the signs of systemic intoxication appear, the therapy must be discontinued.

Digoxin

these signs includes:

1. **Anorexia, nausea and vomiting and diarrhea.**
2. **Vision changes (xanthopsia), fatigue and headache.**
3. **cardiac effects that include: premature ventricular contraction, and ventricular tachycardia and fibrillation. Arrhythmia and atrial tachycardia.**

Digoxin interaction:

Quinidine, varapamil, and amiodarone can cause digoxin intoxication, both by replacing digoxin from tissue protein binding sites, and by competing with digoxin for renal secretion.

Macrolide and tetracycline antibiotics should be avoided because they elevate digoxin serum concentration and enhance the risk for digoxin toxicity

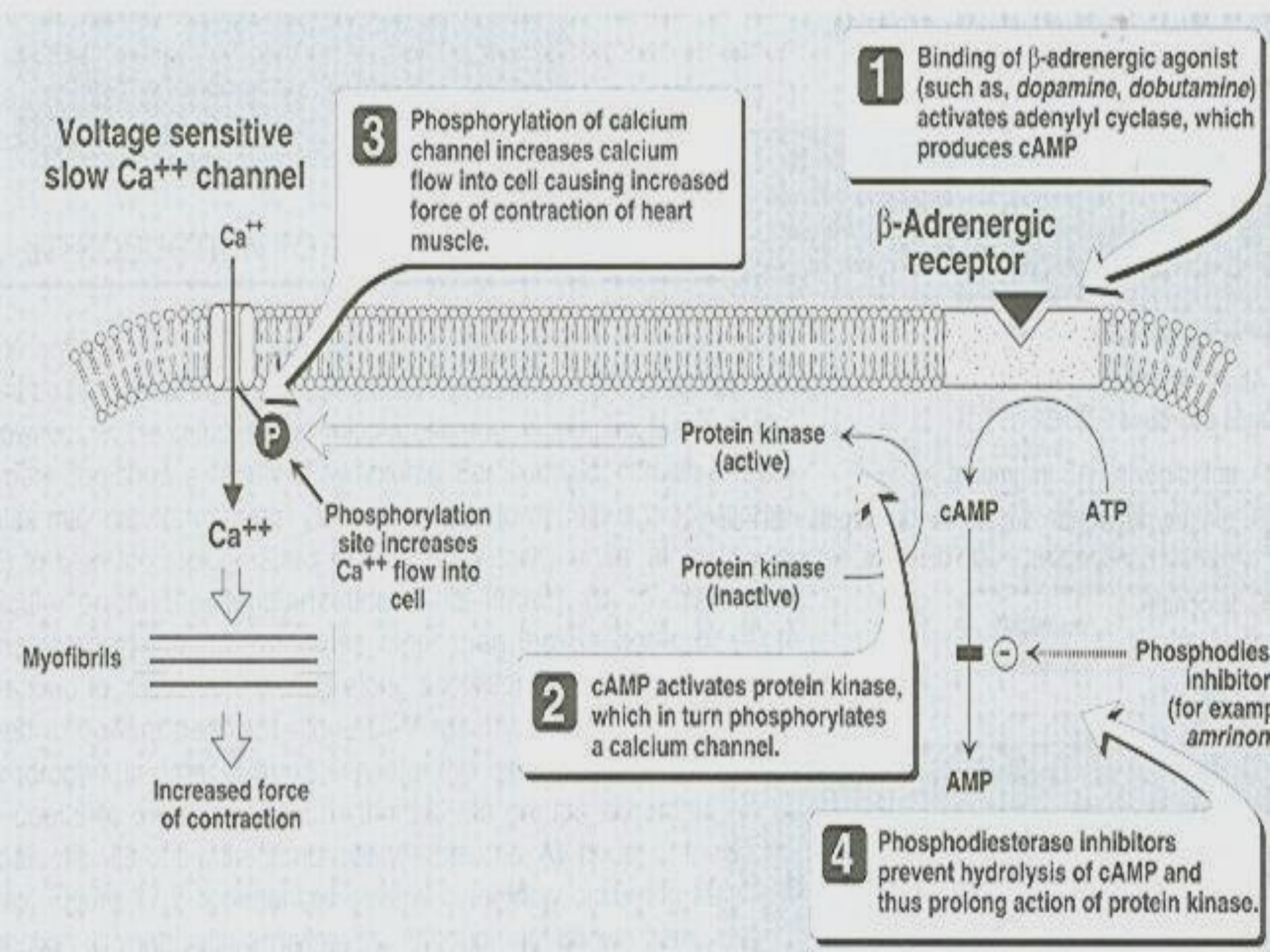
β-adrenergic agonist and Amrinone

- Dobutamine is a B1 adrenergic agonist that has positive inotropic effect and is the most used inotropc agent after digoxin.

- As mentioned, must be given by intravenous infusion and is used in the treatment of acute HF in a hospital setting.

- Amrinone Have a positive inotropic effect and increase systemic vasodilation.

- Amrinone used in short term therapy of HF that is refractory to other agents.


Voltage sensitive slow Ca++ channel
Ca++
3 Phosphorylation of calcium channel increases calcium flow into cell causing increased force of contraction of heart muscle.
1 Binding of β-adrenergic agonist (such as, dopamine, dobutamine) activates adenylyl cyclase, which produces cAMP
β-Adrenergic receptor
P
Protein kinase (active)
Protein kinase (inactive)
cAMP
ATP
Ca++
Phosphorylation site increases Ca++ flow into cell
Myofibrils
2 cAMP activates protein kinase, which in turn phosphorylates a calcium channel.
Phosphodies
inhibitor
(for examp
amrinon
AMP
Increased force of contraction
4 Phosphodiesterase inhibitors prevent hydrolysis of cAMP and thus prolong action of protein kinase.

Stage C Therapy
(Reduced LVEF with Symptoms)

Hydralazine and Isosorbide Dinitrate

The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms.

A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency.

- **African-American patients with advanced heart failure due to left ventricular systolic dysfunction should be considered for treatment with hydralazine and isosorbide dinitrate in addition to standard therapy.**

Charles Cullen

- admitted in 2003 to killing as many as 40 hospital patients with overdoses of heart medication—usually digoxin—at hospitals in New Jersey and Pennsylvania over his 16-year career as a nurse.

- On March 10, 2006 he was sentenced to 18 consecutive life sentences and is not eligible for parole.