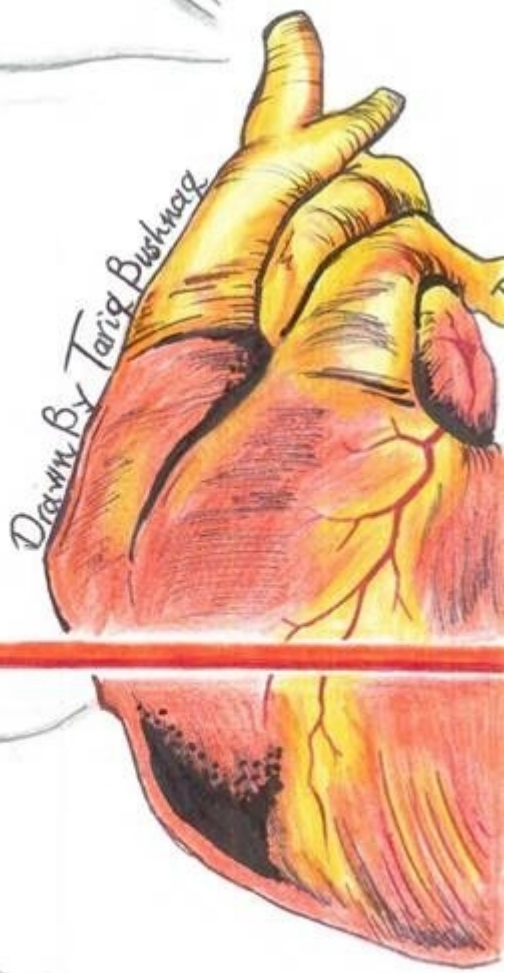
The Cardio-VASCULAR System

- ○ Anatomy
- ○ Histology
- ○ Pathology
- ● Pharmacology
- ○ Physiology
- ○ Microbiology

#: 1

Dr. Name: **Malik Zihlif**

- ○ Handout
- ○ Sheet
- ● Slide



ILOs

Antihypertensive mechanisms: Diuretics, ACE inhibitors, ARBs, Beta-blockers, alpha-blockers, CCBs, Vasodilators and central sympatholytics

Present status of above mentioned group of Drugs

Common Adverse effects of above groups of Drugs

Pharmacotherapy of Hypertension

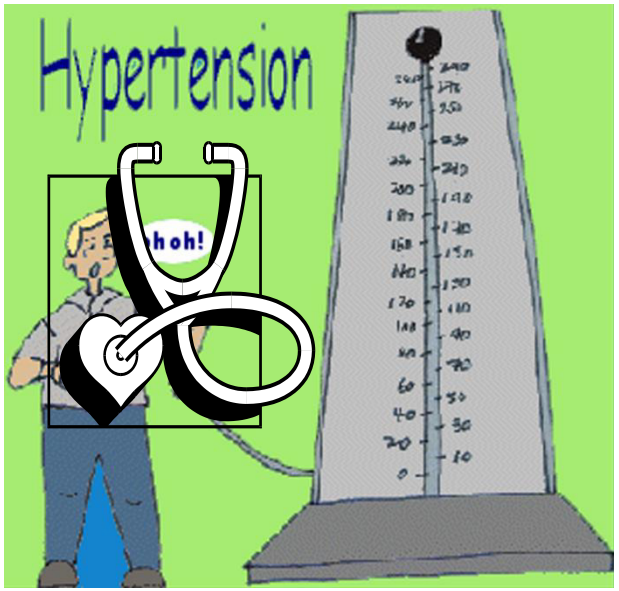
Pharmacotherapy of hypertensive emergencies

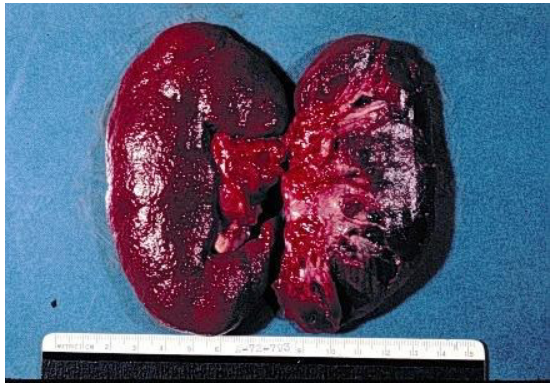
Preparation and dosage of commonly used drugs of above mentioned groups

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!

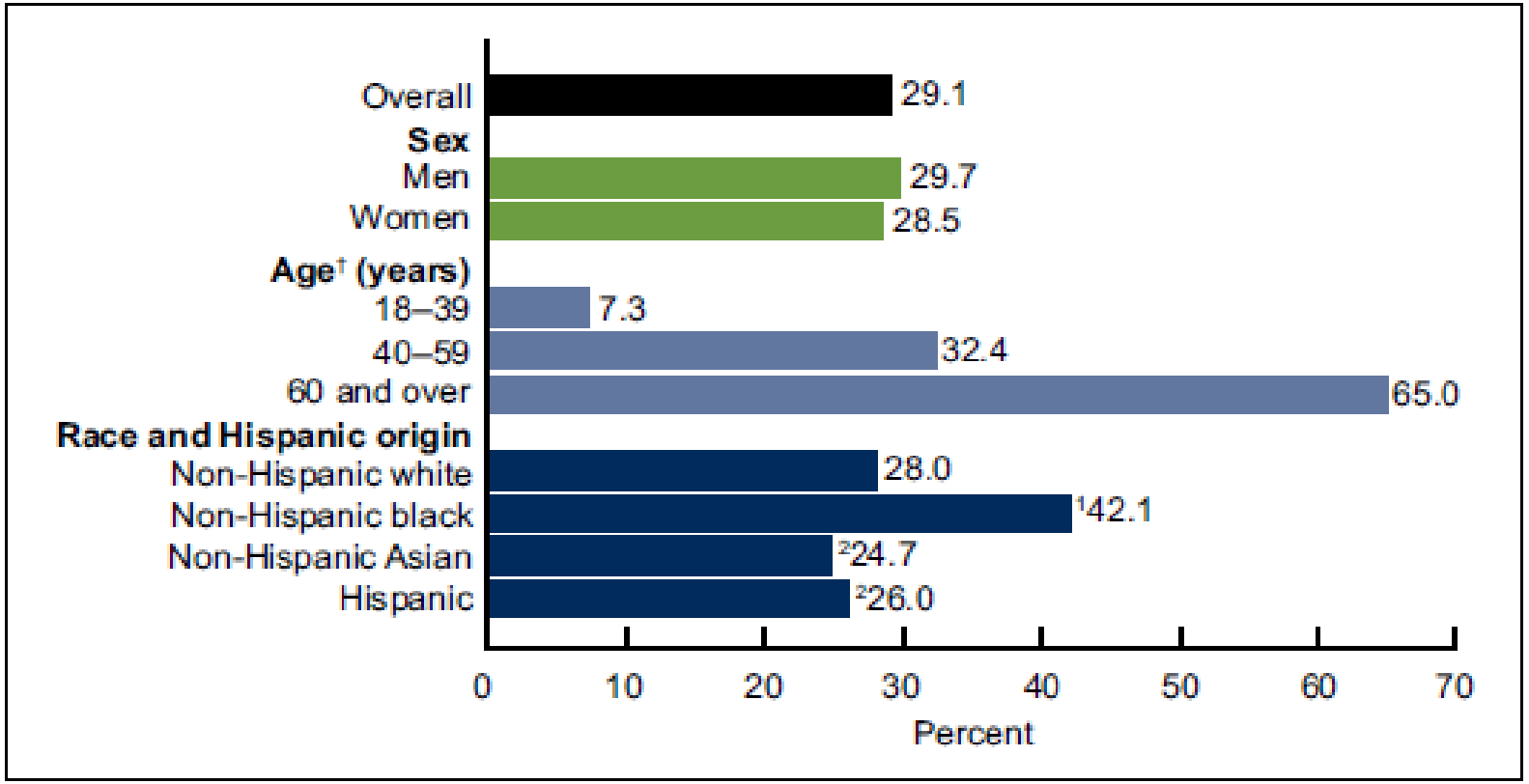
Hypertension- asymptomatic

Morbidity and mortality due to end organ damage

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

Hypertension in the U.S.

Figure 1. Age-specific and age-adjusted prevalence of hypertension among adults aged 18 and over: United States, 2011–2012



Source:CDC/NHNS, National Health and Nutrition Examination Survey, 2011-2012

JNC-8 Recommendations

- **In patients ≥60 years of age, start medications at blood pressure of ≥150/90mm Hg and treat to goal of <150/90mm Hg**

- **In patients ≤60 years of age, start medications at blood pressure of ≥140/90mm Hg and treat to goal of <140/90mm Hg**

- **In all adult patients with diabetes or chronic kidney disease, start medications at blood pressure of ≥140/90mm Hg and treat to goal of <140/90mm Hg**

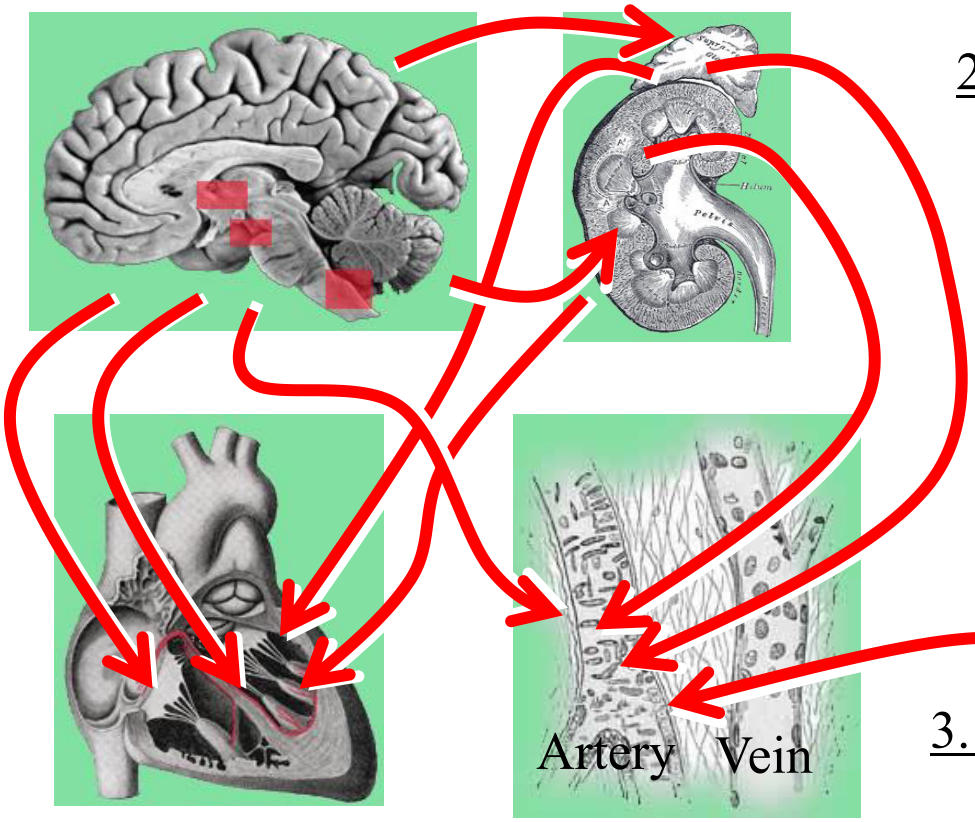
Lifestyle Modification

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

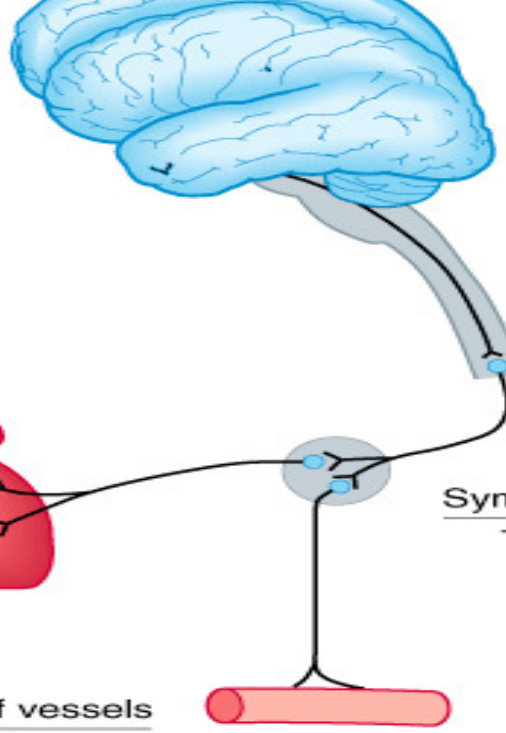
Mechanisms Controlling CO and TPR

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

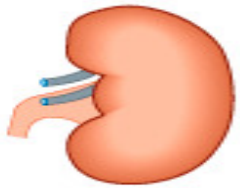
β-Receptors of heart
Propranolol and other β-blockers

Angiotensin receptors of vessels
Losartan and other angiotensin receptor blockers

α-Receptors of vessels
Prazosin and other α_1-blockers

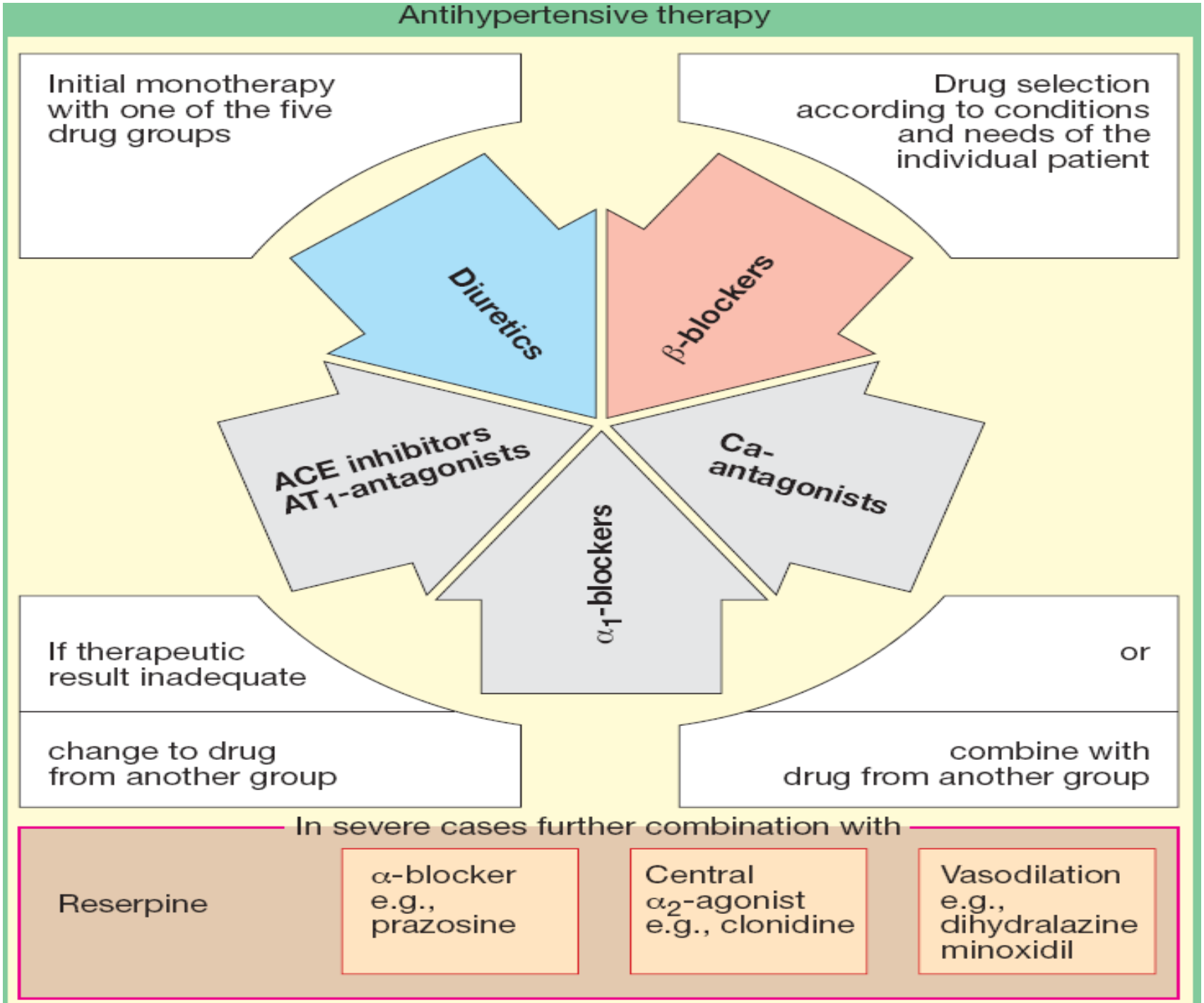
Vascular smooth muscle
Hydralazine
Minoxidil
Nitroprusside
Diazoxide
Verapamil and other calcium channel blockers
Fenoldopam

Kidney tubules
Thiazides, etc



β-Receptors of juxtaglomerular cells that release renin
Propranolol and other β-blockers

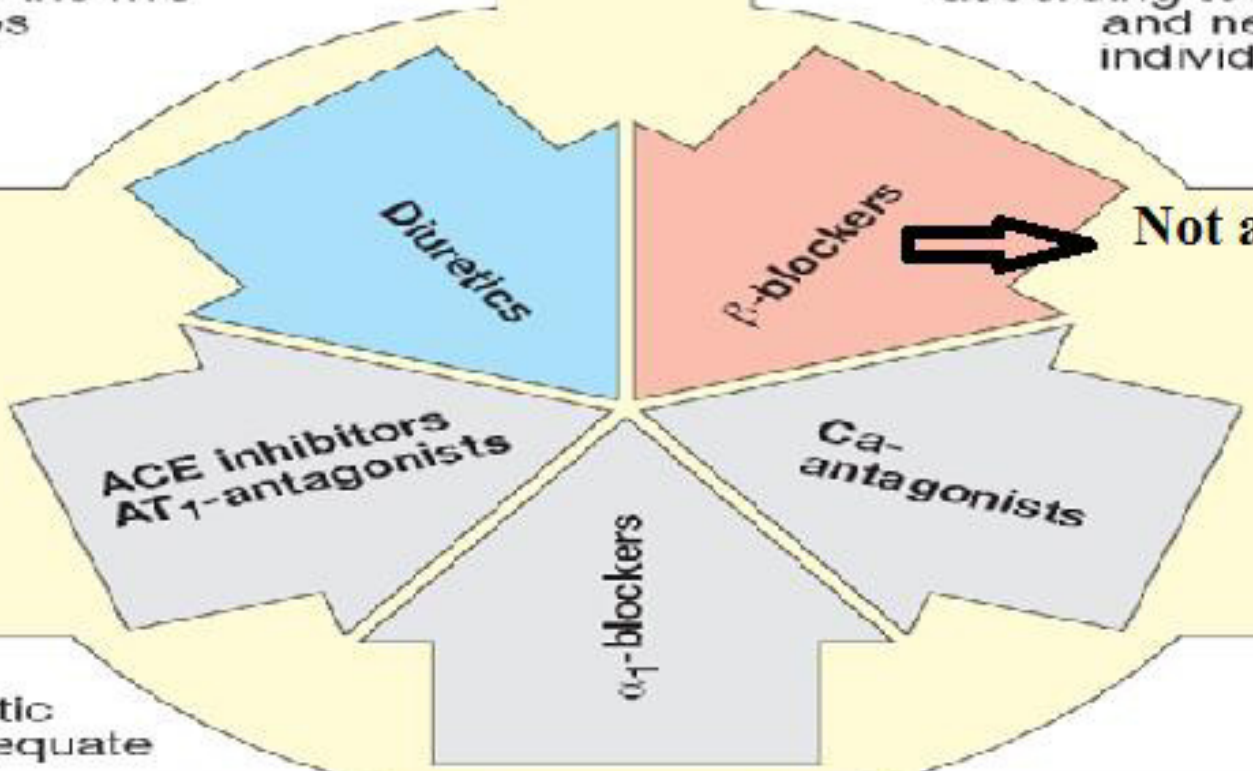
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com


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

Antihypertensive therapy

Initial monotherapy with one of the five drug groups

Drug selection according to conditions and needs of the individual patient



If therapeutic result inadequate

or

change to drug from another group

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In severe cases further combination with

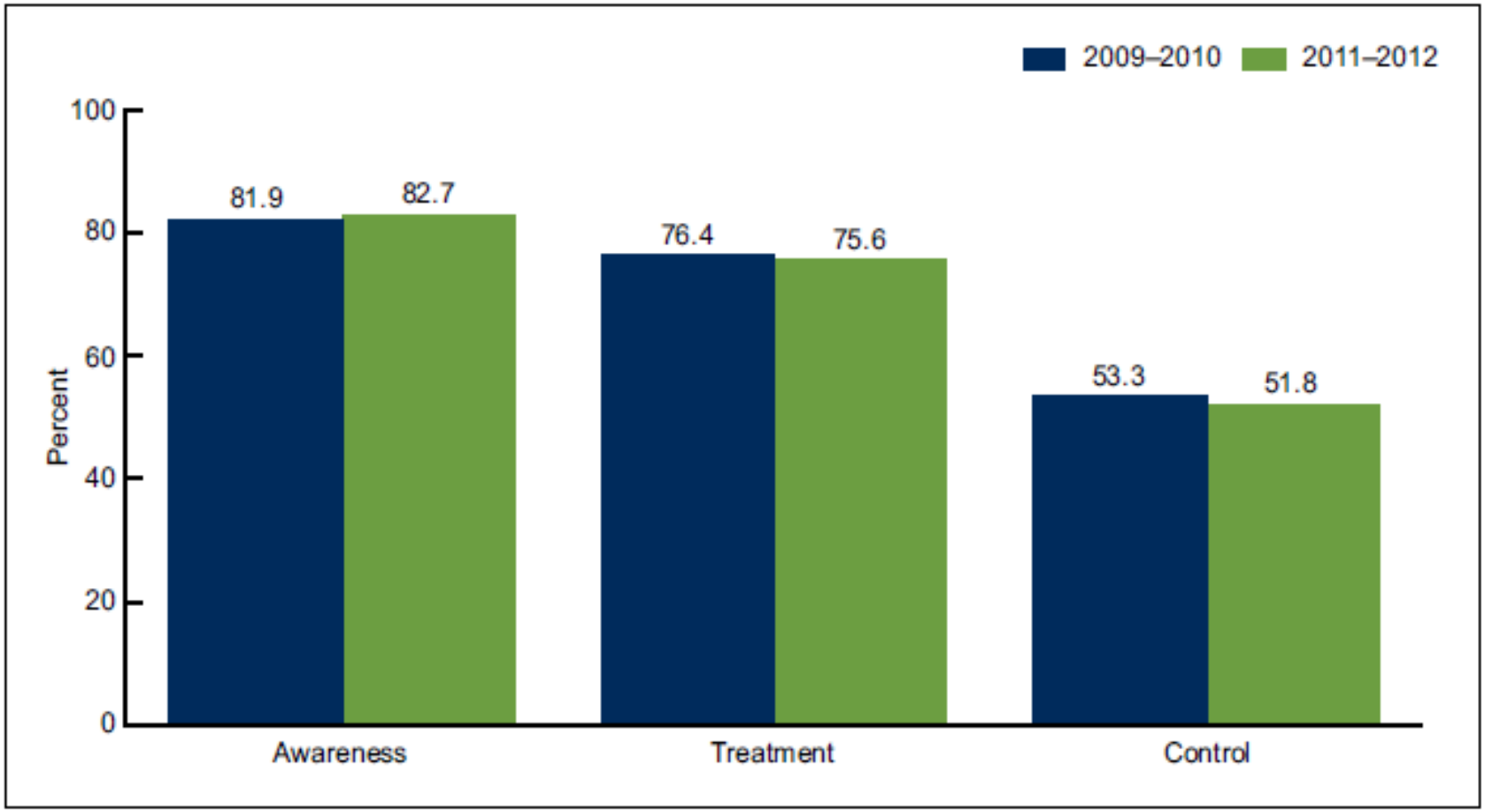
Reserpine	α-blocker e.g., prazosine	Central α2-agonist e.g., clonidine	Vasodilation e.g., dihydralazine minoxidil

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).

Hypertension in the U.S.



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

What to choose first?

JNC-8

- **For the non-black population (including diabetes), initial antihypertensive treatment may include a thiazide, ACEI, ARB, or CCB**

- **For the black population (including diabetes), initial antihypertensive treatment should include a thiazide or CCB**

- **For all patients with CKD, initial (or add-on) therapy for hypertension should include an ACEI or ARB**

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

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.**

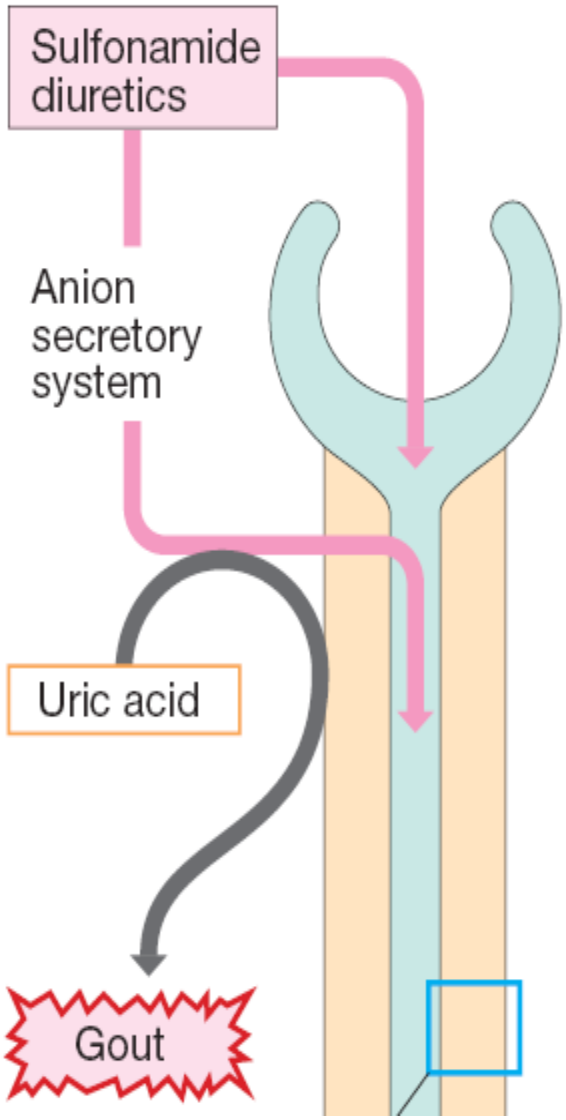
- **There are many analogs, but the most important prototypes are:**

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

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

Thiazide diuretics

- - Adverse Effects:
  - Hypokalaemia – muscle pain and fatigue
  - Hyperglycemia: Inhibition of insulin release due to K+ depletion (proinsulin to insulin) – precipitation of diabetes
  - Hyperlipidemia: rise in total LDL level – risk of stroke
  - Hyperurecaemia: inhibition of urate excretion
  - All the above metabolic side effects – higher doses (50 – 100 mg per day)
  - But, its observed that these adverse effects are minimal with low doses (12.5 to 25 mg) - Average fall in BP is 10 mm of Hg



Side effect

- 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**

actions of Angiotensin-II

1. Powerful vasoconstrictor particularly arteriolar – direct action and release of Adr/NA release
   - Promotes movement of fluid from vascular to extravascular
   - More potent vasopressor agent than NA – promotes Na+ and water reabsorption
   - It increases myocardial force of contraction (CA++ influx promotion) and increases heart rate by sympathetic activity, but reflex bradycardia occurs
   - Cardiac output is reduced and cardiac work increases
2. Aldosterone secretion stimulation – retention of Na++ in body
3. Vasoconstriction of renal arterioles – rise in IGP – glomerular damage
4. Decreases NO release
5. Decreases Fibrinolysis in blood
6. Induces drinking behaviour and ADH release by acting in CNS – increase thirst
7. Mitogenic effect – cell proliferation

ACE Inhibitors

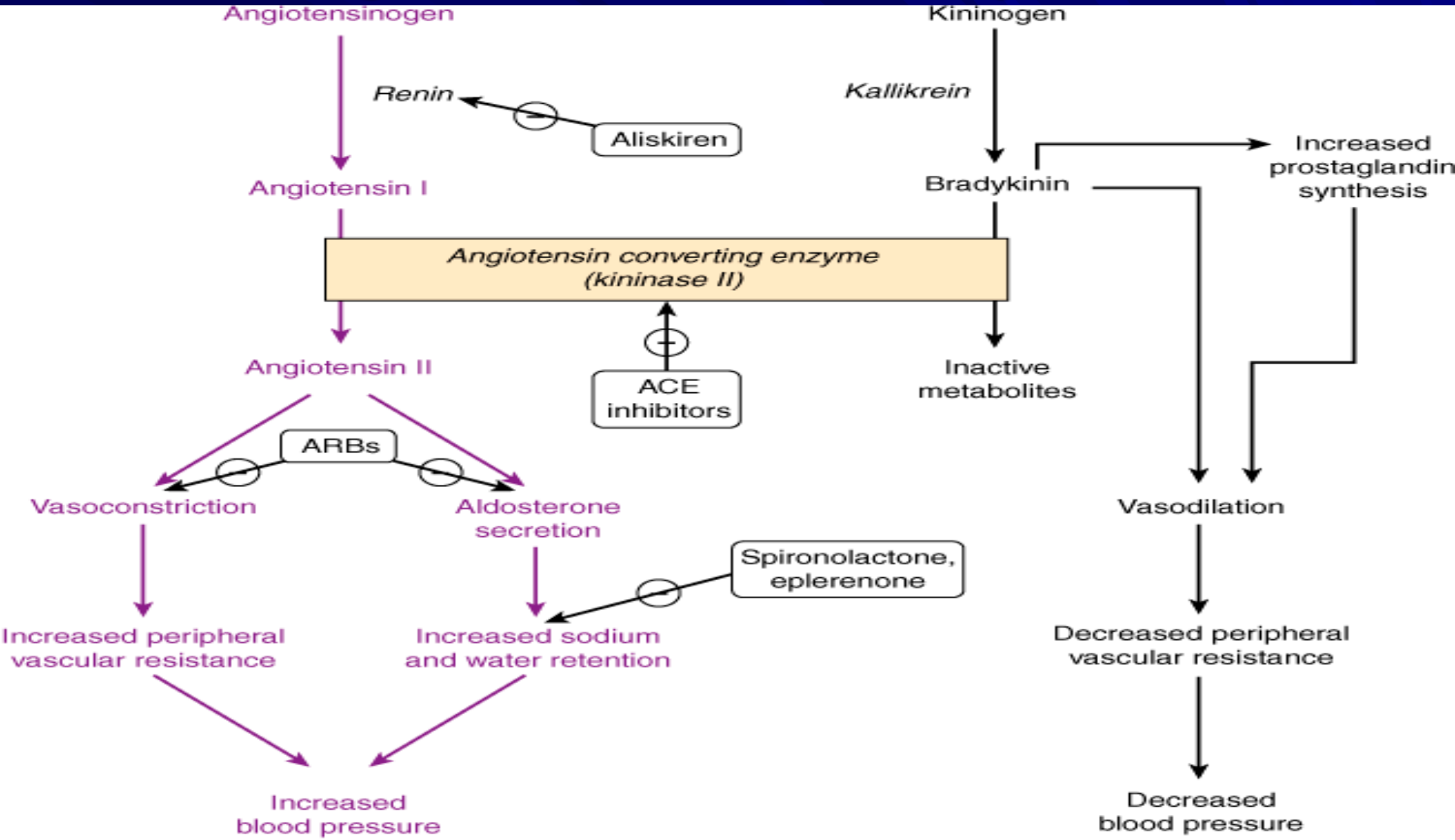
- **ACE Inhibitors, such as Enalapril, Lisinopril, and Captopril are recommended when the preferred first line agents (diuretics or β blockers) are contraindicated or ineffective.**

- **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

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- **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

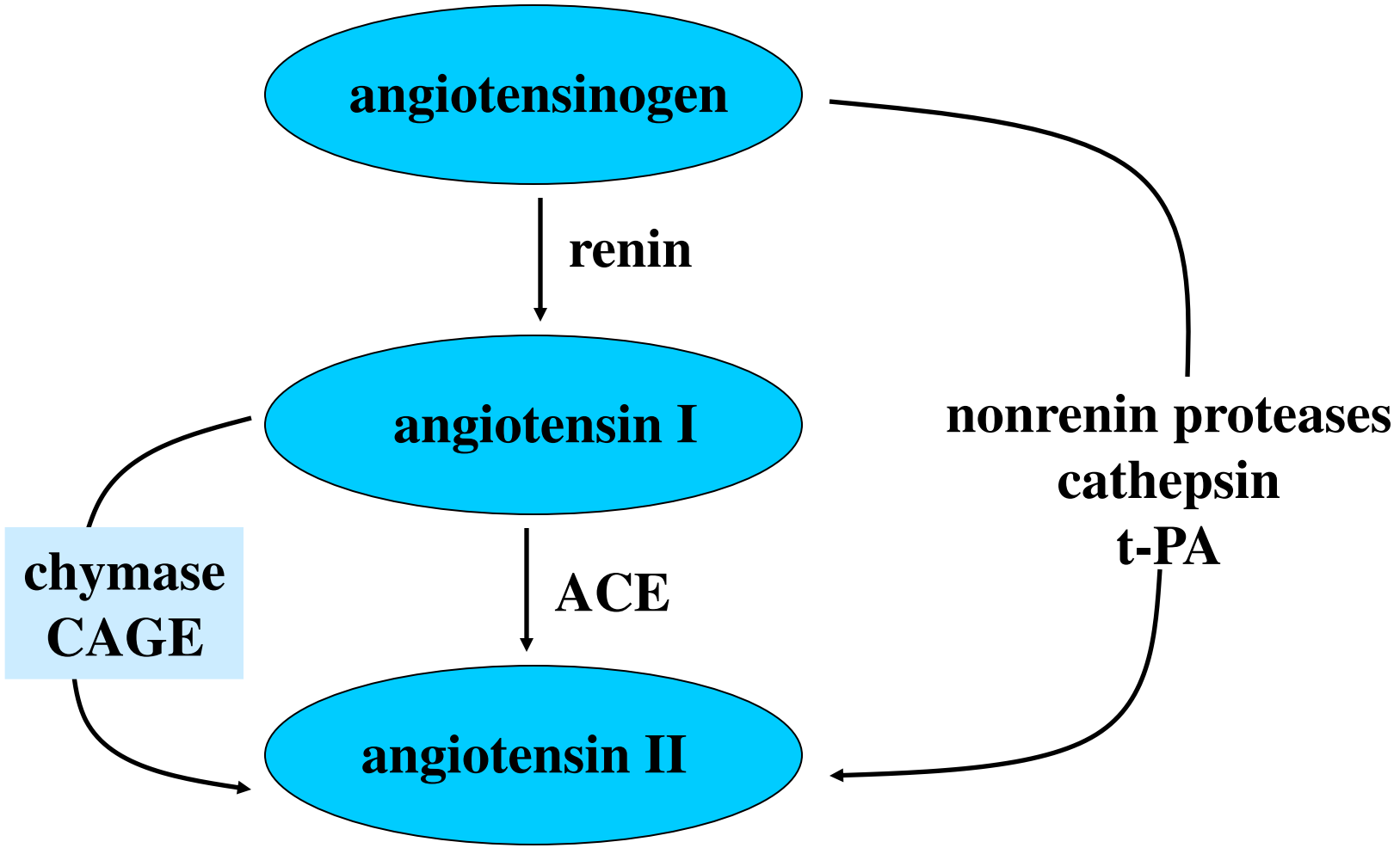
- These agents are alternatives to the ACE Inhibitors, and can be used in patient who cannot tolerate ACE Inhibitors. **Losartan** being the prototype.

- 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

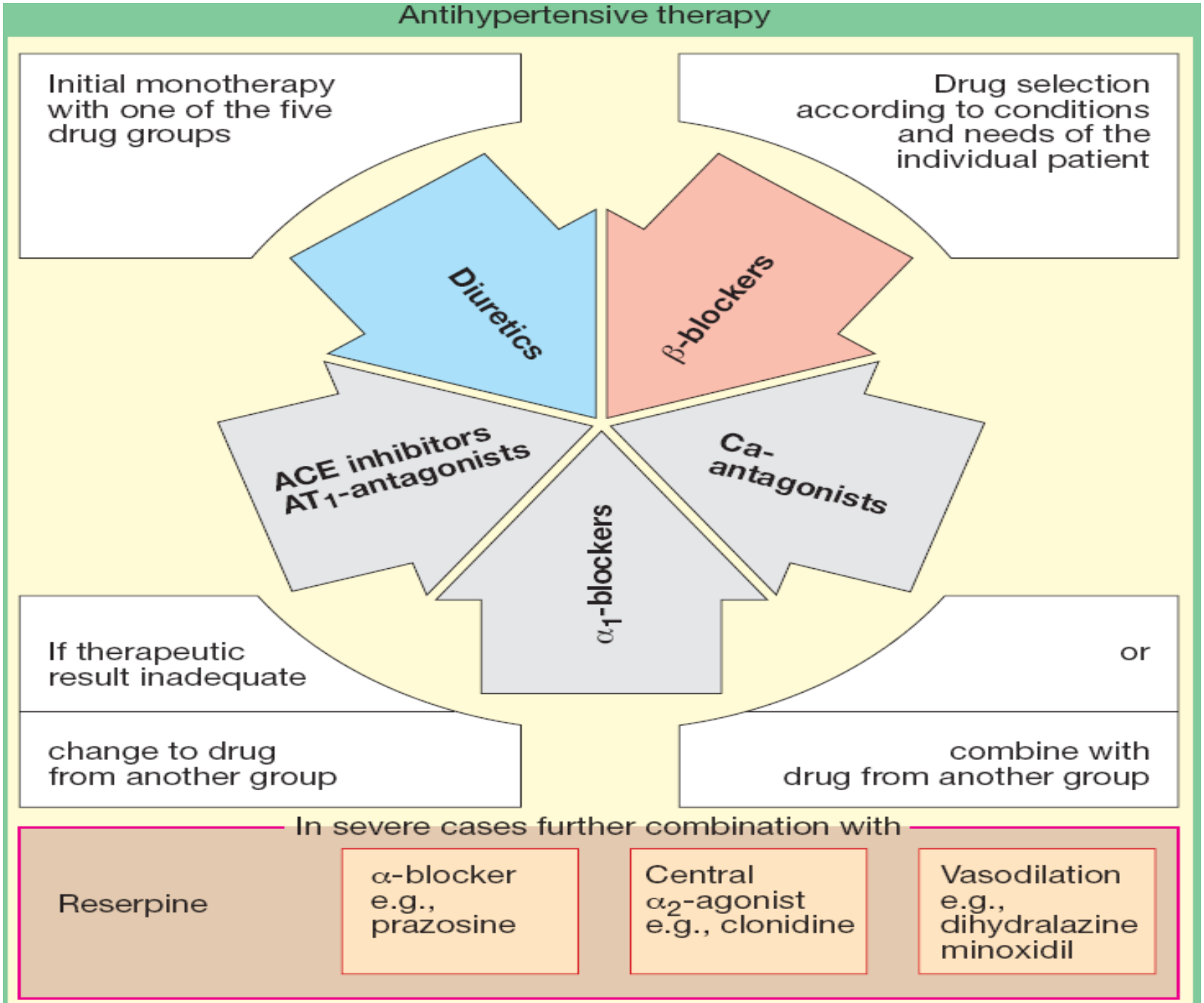
↑ = increase

↔ = 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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In severe cases further combination with
Reserpine
α-blocker e.g., prazosine
Central α2-agonist e.g., clonidine
Vasodilation e.g., dihydralazine minoxidil

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**

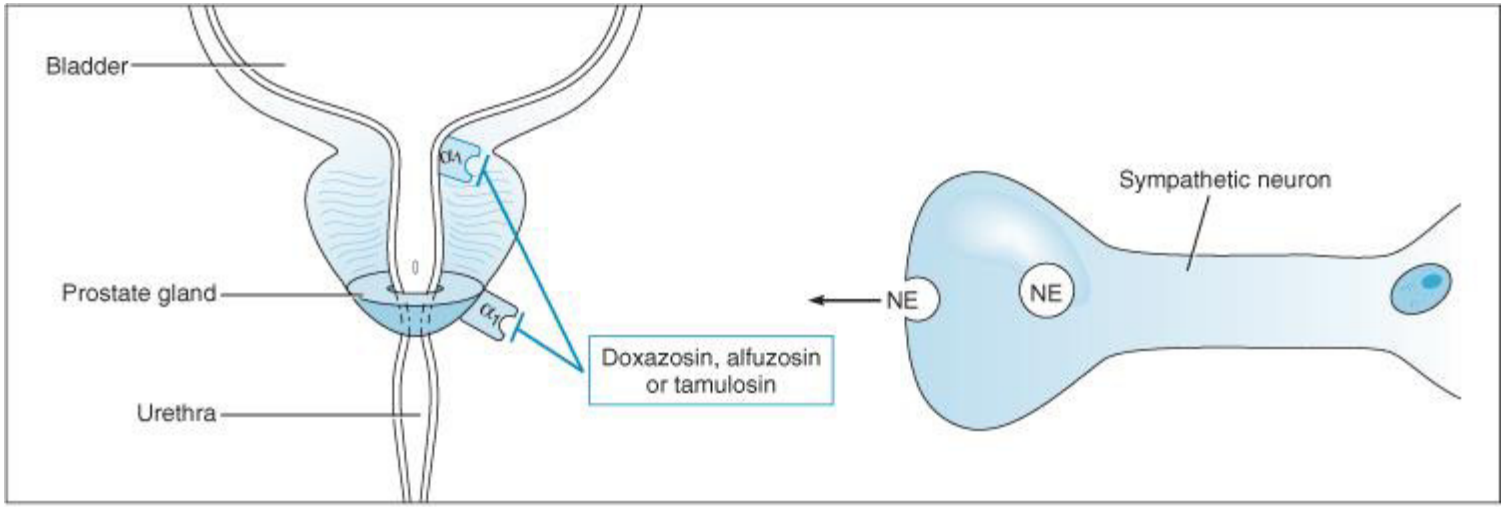
Selective α_1-blockers

- 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

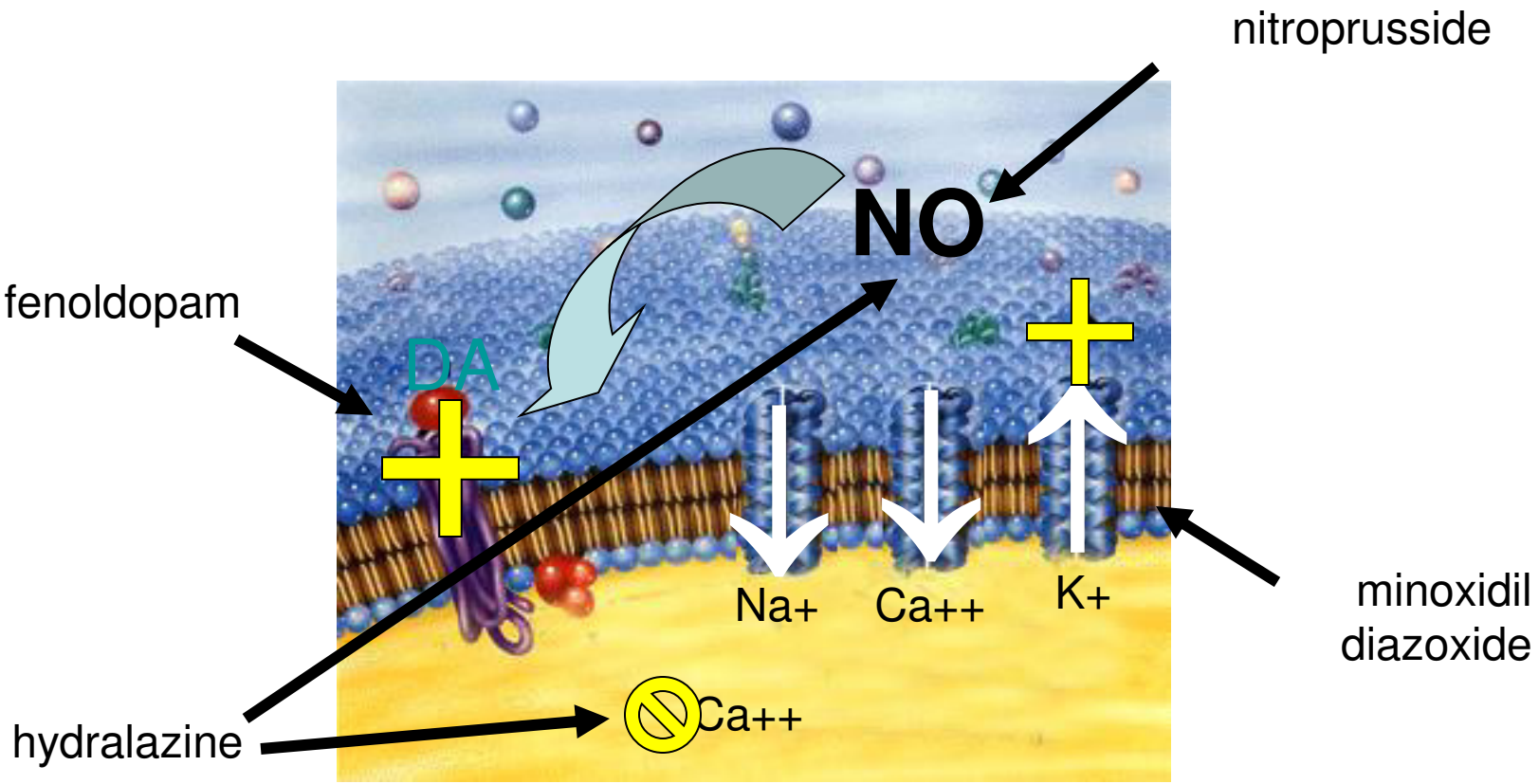
- **α2 agonist that converted to methylnorepinihrine centrally to diminish the adrenergic outflow from the CNS,**
- **Which lead to reduced the peripheral resistance and decreased blood pressure.**
- **Cardiac output is not decreased, and so the blood supply to the vital organs, such as kidney, which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

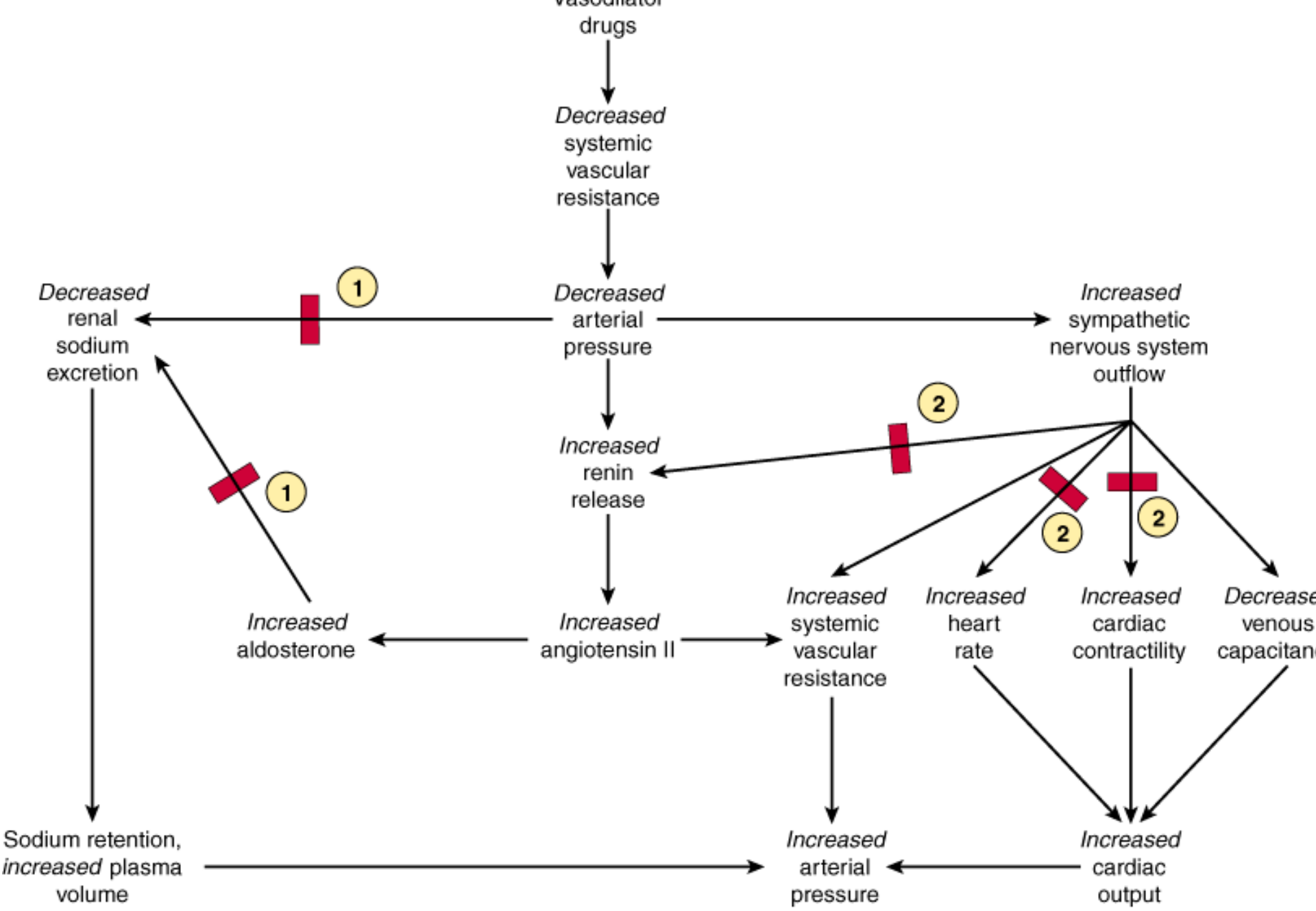
Vasodilator

- 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.

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).