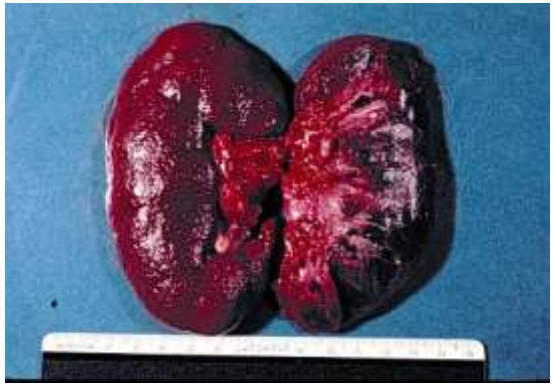
Hypertension as a disease

- **Hypertension affecting approximately 15% of the USA population (60 million).**
- **Hypertension defined**
  - **as either a sustained systolic blood pressure (SBP) of greater than 140 mm Hg**
  - **or sustained diastolic blood pressure (DSP) of greater than 90 mm Hg.**
- **Hypertension results from increased peripheral vascular smooth muscle tone, which leads to increase arteriole resistance and reduce the capacitance of the venous system.**

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!

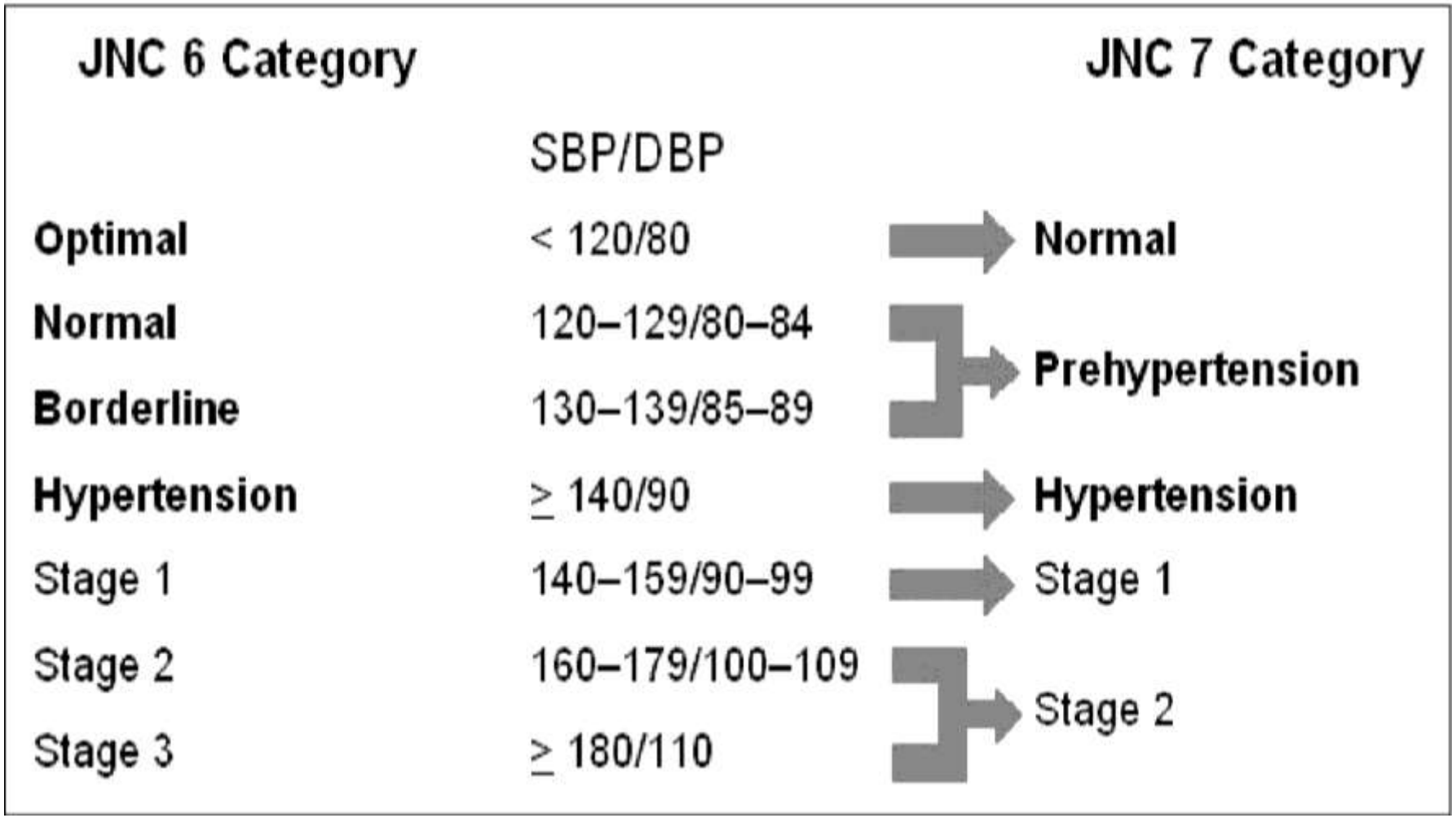
Hypertension– asymptomatic

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:**



Causal Factors for Hypertension

- Excess body weight
  - 122 million Americans are overweight or obese
  - **How about the Jordanians?????**
- Excess dietary sodium
  - Mean intake: Men 4100 mg; Women 2750 mg
  - 75% from processed foods
- Reduced physical activity.
- Excess(why is this) alcohol consumption

Hypertension 2003;289:2560-2572.

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

Mechanism of controlling the blood pressure

A. Baroreceptors and sympathetic nervous system

Responsible for rapid, moment-to-moment regulation of blood pressure.

For example a fall in the blood pressure causes pressure sensitive neurons to send impulses to the cardiovascular centre in the spinal cord.

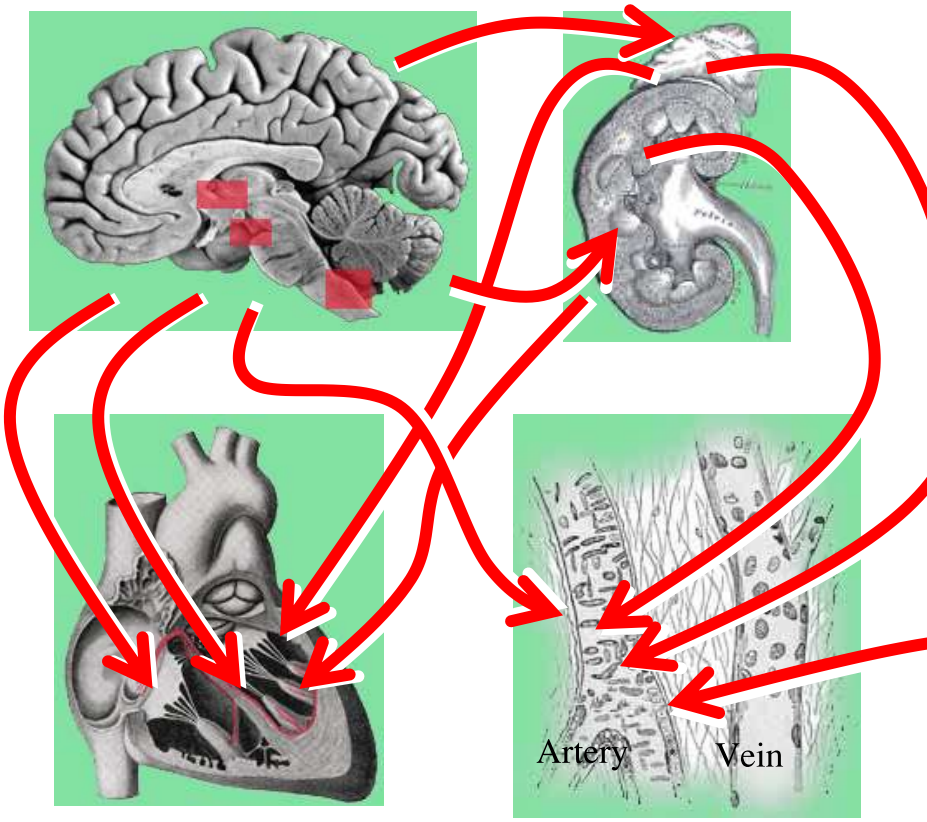
This activate a reflex response of increase the sympathetic and decrease the parasympathetic output to the heart and the vasculature system. (What is called Baroreflexe).

Mechanisms Controlling CO and TPR

1. Neural

SymNS

PSNS



2. Hormonal

Renal

Ang II

Adrenal

Catecholamines

Aldosterone

3. Local Factors

Mechanism of controlling the blood pressure

B. Renin-angiotensin-aldesterone system

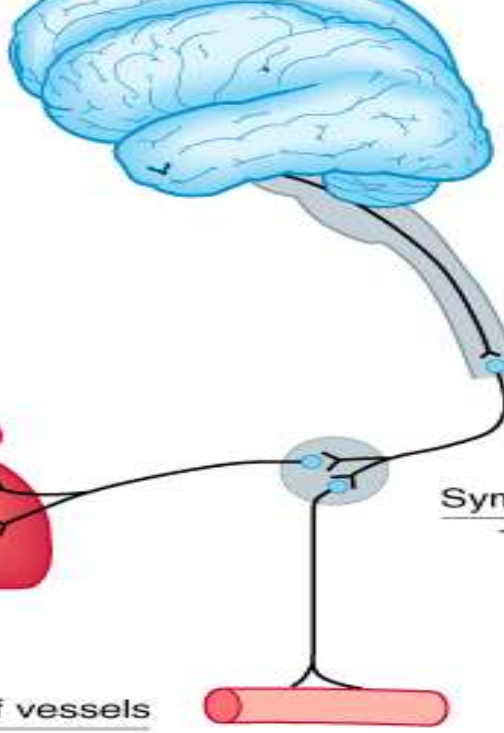
-the kidney provides for the long-term control of blood pressure by altering the blood volume.

-baroreceptors in the kidney respond to reduce arterial pressure by releasing the enzyme renin.

-renin activate the conversion of angiotensinogen to angiotensin I, which concerted in turn to angiotensin II in the presence of angiotensin-concerting enzyme (ACE).

-angiotensin II is most potent vasoconstructor in the blood, causing an increase in the blood pressure.

-angiotensin II also stimulates aldesterone secrestion, leading to increased renal sodium reabsorption and increase blood volume, which will contribute to further increase in blood pressure



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

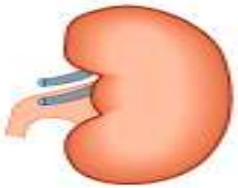
Hydralazine
Minoxidil
Nitroprusside
Diazoxide
Verapamil and other calcium channel blockers
Fenoldopam

Kidney tubules

Thiazides, etc

β-Receptors of juxtaglomerular cells that release renin

Propranolol and other β-blockers

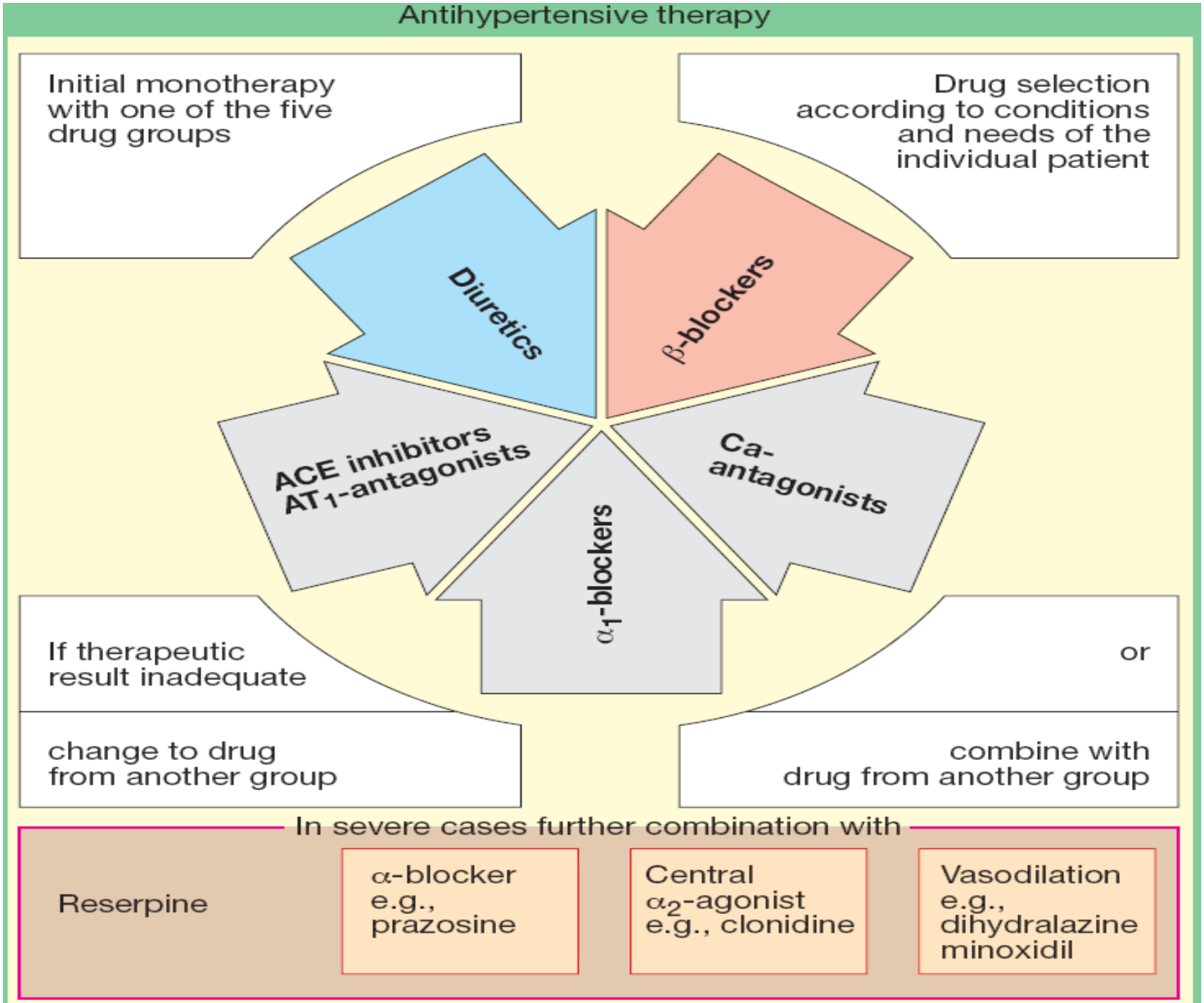


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

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).


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

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.

Diuretics

- The sites of action within the kidney and the pharmacokinetics of various diuretic drugs are different.

- Thiazide diuretics are appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function.

- More powerful diuretics (eg, those acting on the loop of Henle) such as furosemide are necessary in severe hypertension, when multiple drugs with sodium-retaining properties are used; in renal insufficiency, when glomerular filtration rate is less than 30 or 40 mL/min; and in cardiac failure or cirrhosis, in which sodium retention is marked.

Diuretics

- **They are currently recommended as a first line therapy for hypertension unless there are convincing reason to chose another agent.**

- **A low dose diuretic therapy is safe and effective in preventing stroke, myocardial infarction, and congestive heart failure.**

A. Thiazide diuretics

They are the most frequently used diuretics, their early hypotension effect is related to a reduction in blood volume, their long-term effect is related to a reduction in peripheral vascular resistance.

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,

Diuretics

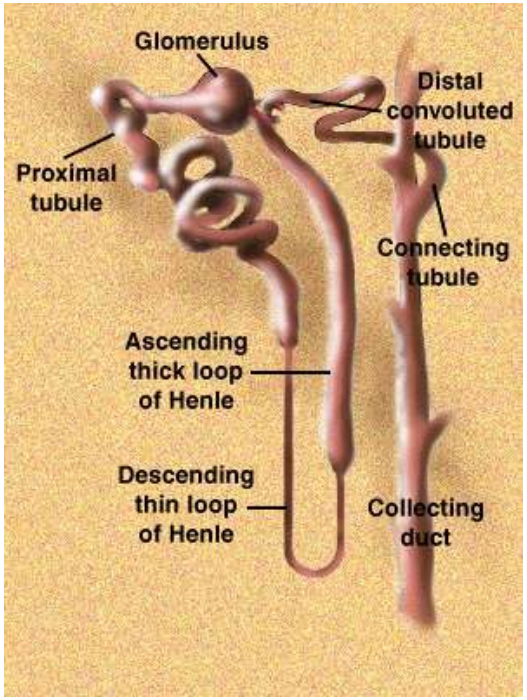
2. Mechanism of Action

↑ 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.**

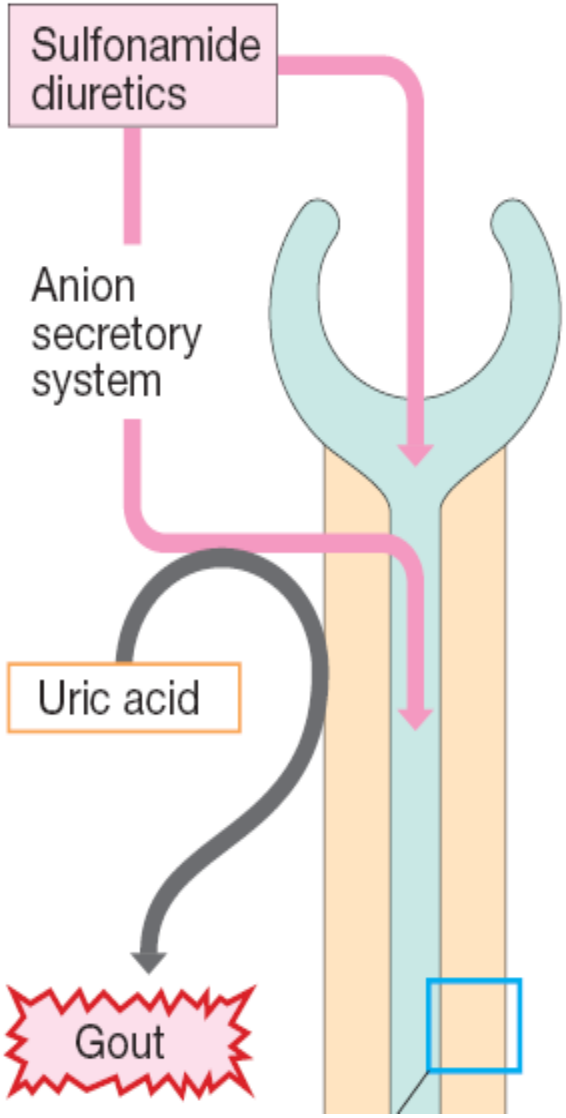
Thiazide diuretics

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 drugs which block β-receptors are very widely used in therapeutics, mostly for their antihypertensive effect.**

- **These agents are useful alone and in combination with other agents.**

- **Their mechanism of action in hypertension exactly has never been clarified.**

- **But several consequences of β-adrenergic blockade probably play a role, for example:**
  - **A. The β blocker reduce cardiac output.**
  - **B. they also inhibit renin secretion.**

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 ecause 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
- Postural orthostatic tachycardia syndrome
- 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

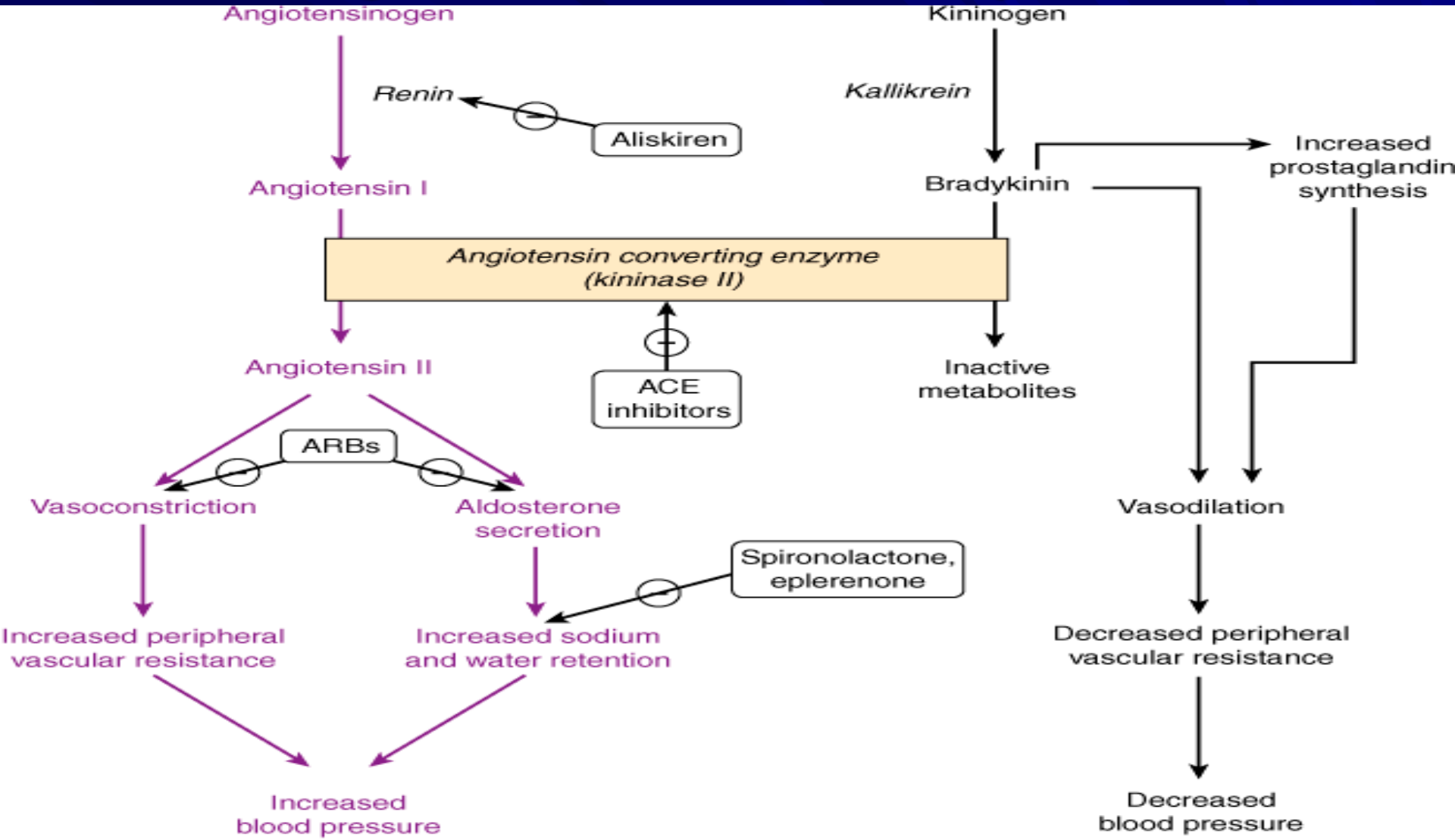
- **ACE Inhibitors, such as Enalapril, Lisinopril, and Captopril are recommended when the preferred first line agents (diuretics or β blockers) are contraindicated or ineffective.**

- **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

- **So the vasodilation occurs as a result of the combination effects of**

(1) lower vasconstruction effect because of the diminishing of angiotensin II and

(2) potent vasodilation effect of bradykinin.

- **ACE Inhibitors also decrease the secretion of aldesterone, resulting in decreased sodium and water retention.**

.

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**

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.

- Most of them have short half-lives (treatments is require three times a day).

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.

Calcium channel blockers

- Diphenylalkylamines,
  - Varapamil (prototype) is the least selective of any calcium channel blockers.
  - Has a significant effect on both cardiac and vascular smooth muscles.
  - It is also used to treat angina, superventiclar tachycardia, and migraine headache.
  - Should be avoided with patient with a congestive heart failure due to its negative inotropic effect on the heart.
  - Should not be used with β blockers, because it Depresses conductivity of the AV node

Calcium channel blockers

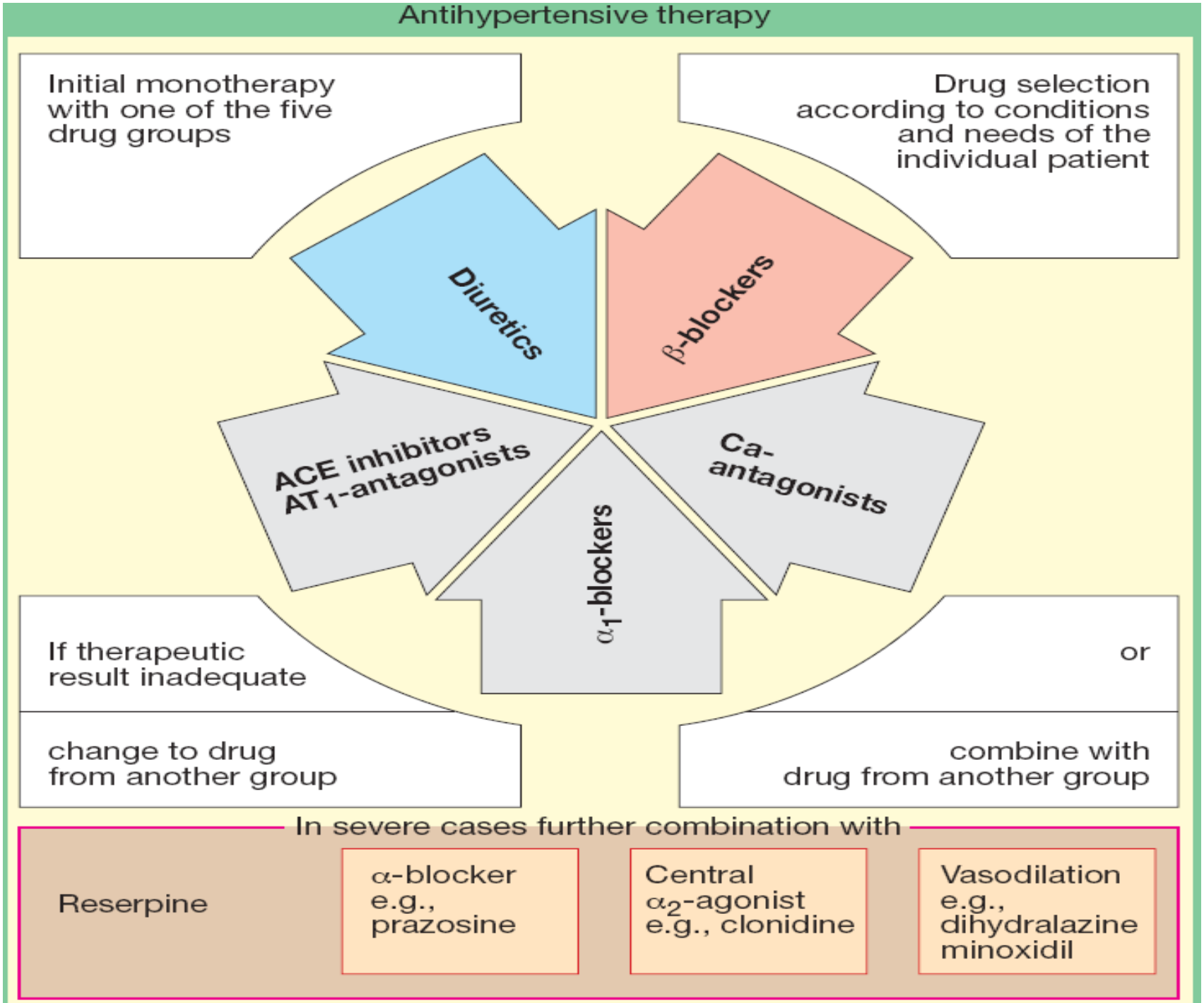
- Benzothiazepines,
  - Diltiazem (prototype) also effect both cardiac and vascular smooth muscles.
  - However, it has less inotropic effect on the heart than Varapamil.
  - It has Depression effect on the conductivity of the AV node, but to a lesser extent in comparison with Varapamil.

Calcium channel blockers

- Dihydropyridines, they include:
  a. Nifedipine (first generation).
  b. Amlodipine, Felodipine, Isradipine, Nacridine, Nisoldipine (second generation).

- The second generation differ in pharmacokinetics, uses, and drug interaction.

- All Dihydropyridines have a much greater affinity to vascular calcium channel blockers than the hearts ones.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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

α- Adrenoreceptor Blocking agents

- Prozasin, doxazosin, and terazosin produce a competitive block of α1, which result in the reduction in the peripheral vascular resistance and lower blood pressure.

- Produce minimal changes in cardiac output and renal blood flow.

- The drug of choice for men with hypertension and prostate enlargement.
- Prozasin is used to treat mild to moderate hypertension and prescribed in combination with Propanalol or a diuretics for additive effect.
- Reflex tachycardia and first dose syncope are common side effect for these agents.

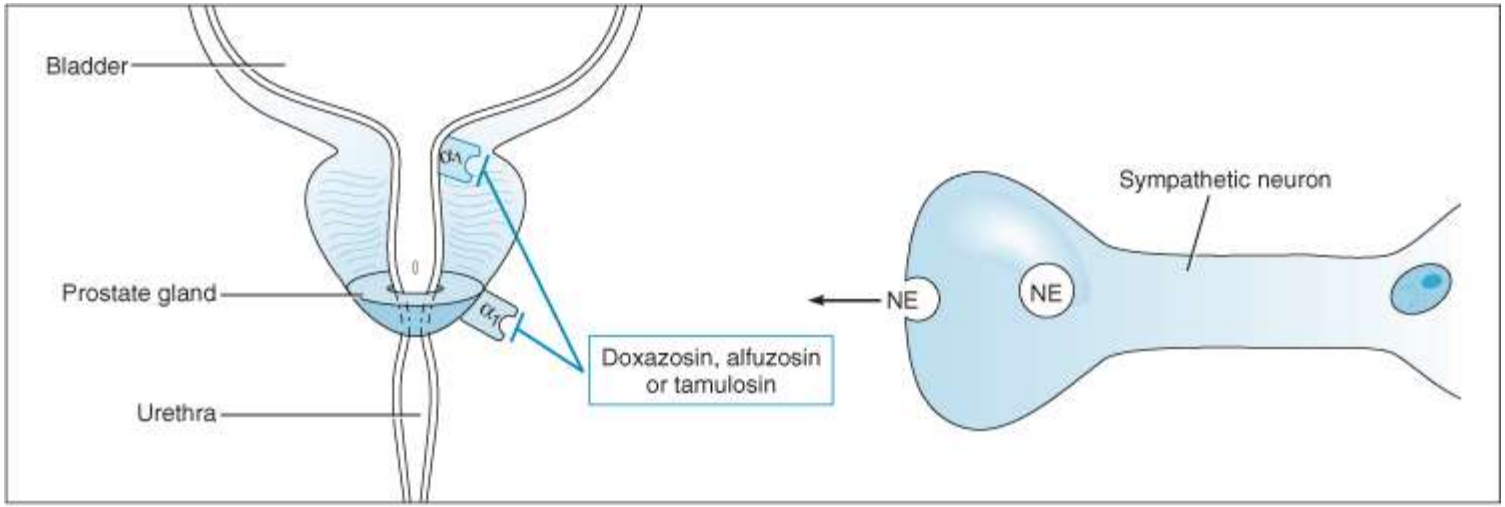
Selective α_1-blockers

- 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

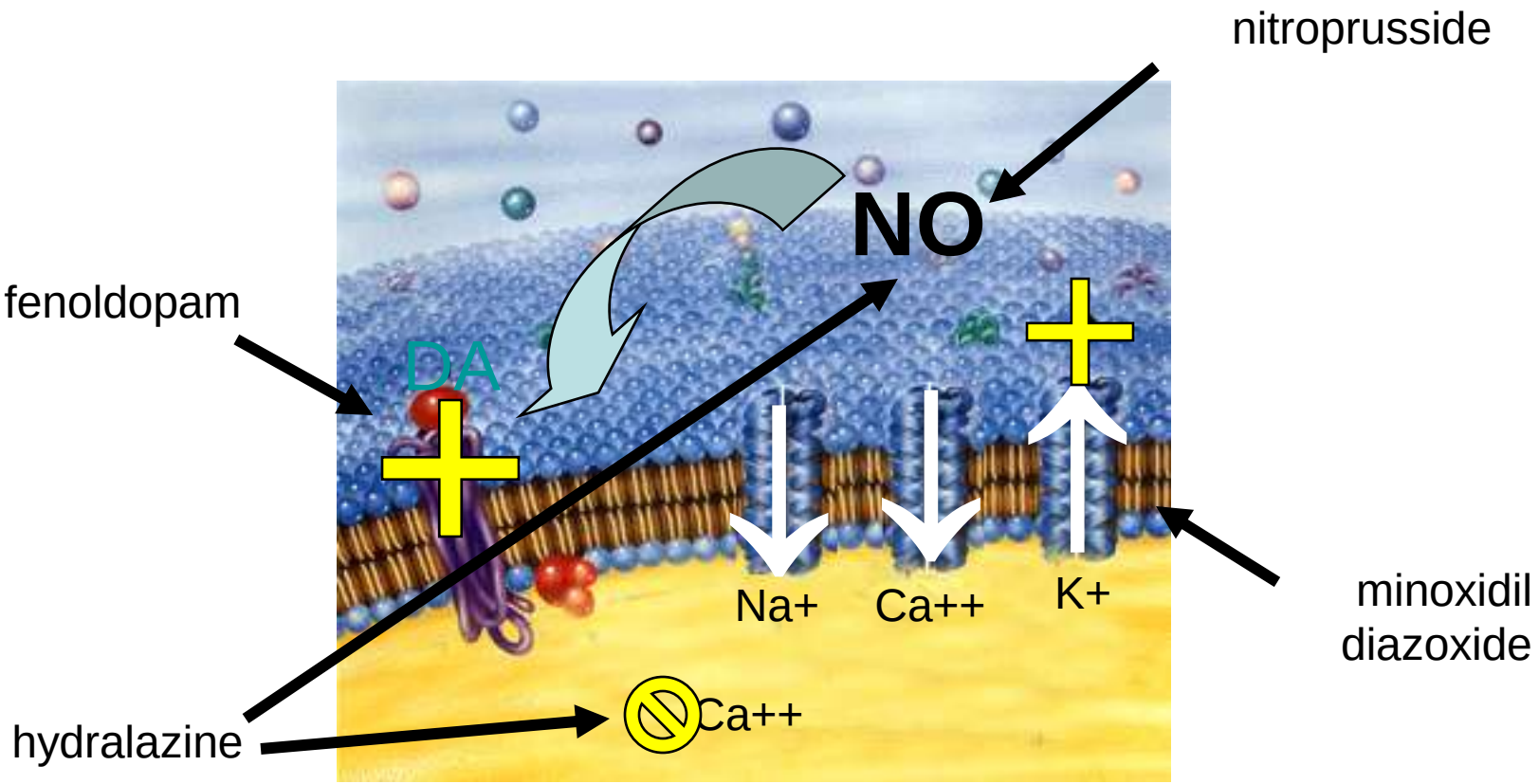
- **α2 agonist that converted to methylnorepinihrine centrally to diminish the adrenergic outflow from the CNS,**
- **Which lead to reduced the peripheral resistance and decreased blood pressure.**
- **Cardiac output is not decreased, and so the blood supply to the vital organs, such as kidney, which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

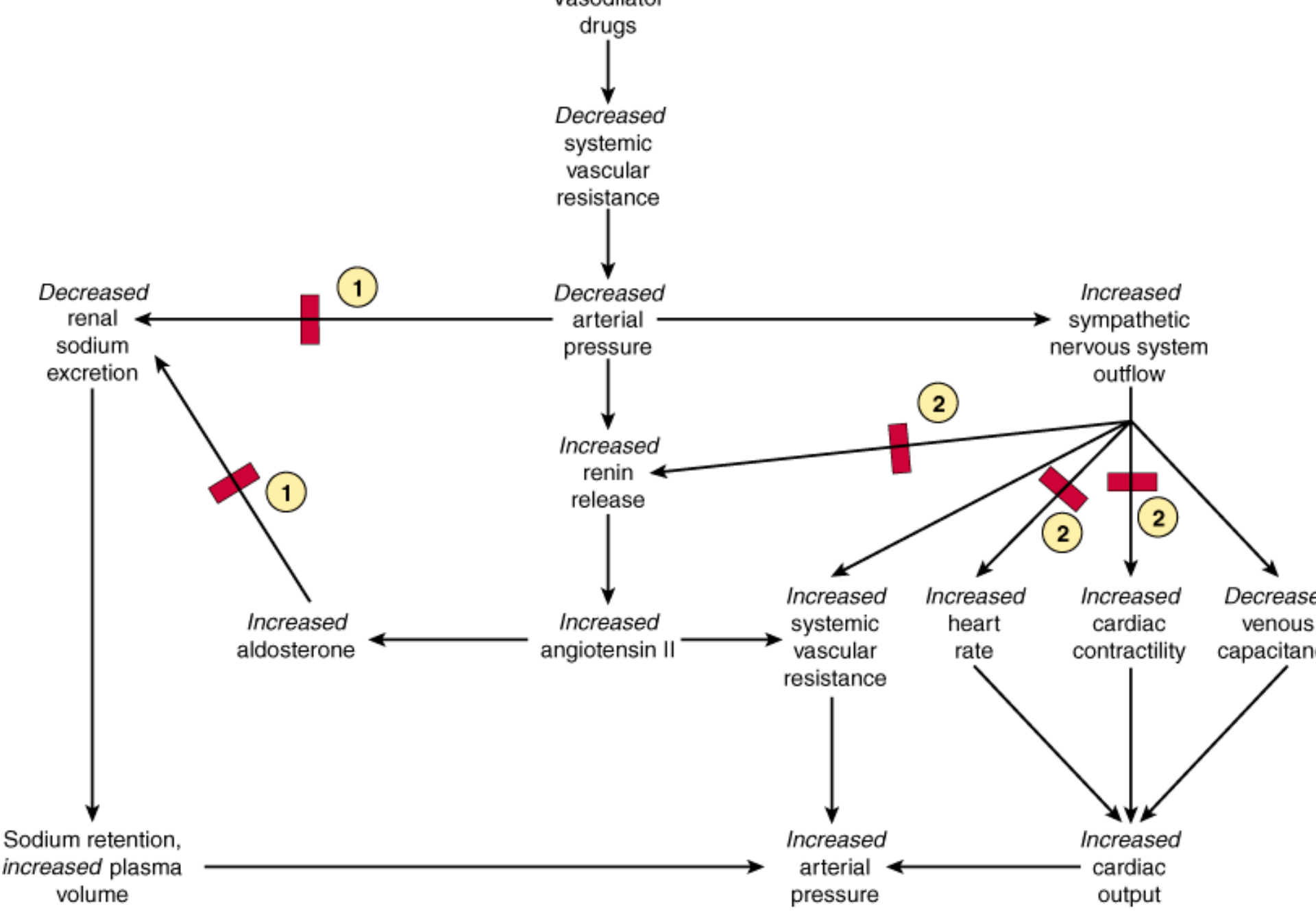
Vasodilator

- 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.**

Minoxidil

- **Used in treatment of severe hypertension that is refractory to other drugs.**
- **Importantly, this agent causes hyertrichosis (growth of the body hear), now used topically to treat pattern baldness.**

Monoxidil and hydralazin

- The most common adverse effects of hydralazine are headache, nausea, anorexia, palpitations, sweating, and flushing.

- Monoxidil Tachycardia, palpitations, angina, and edema are observed when doses of blockers and diuretics are inadequate.

- Headache, sweating, and hypertrichosis, which is particularly bothersome in women, are relatively common.

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).

- **Nicaridine** (onset 5-10 min) (Calcium channel blockers) also can be used (intravenous infusion).

it show little interaction with other cardiovascular drugs, such as Digoxin, Warfarin.

RAPID BP REDUCTION

Acute myocardial ischemia:	**IV NTG,b-blockers,ACE inhibitors**
CHF with pulmonary edema:	**iv NTG,furosemide,morphine**
Acute aortic dissection:	**iv nitroprusside+b-blockers or iv trimethaphan+b-blockers**
Hypertensive encephalopathy or sub-arachnoid hemorrhage:	**iv nitroprusside,labetalol**

VASODILATORS

DRUG	DOSAGE	ONSET/DUR	ADV.EFFE
Nitroprusside	0.25-10mcg/kg/min	Instant/1-2min.	Thiocyanate,cyanide poisoning
Nitroglycerine	5-100mcg/min	1-5min/3-5min	Flushing,headache,methemoglobin
Nicardipine	5-15mg/hr	5-10min/1-4hr	Tachycardia,flushing.avoid-heart failure
Hydralazine	10-20mg	5-15min/3-8hr	Flushing,tachy,avoid-A.diss,MI
Enalapril	10-40mg IM,1.25-5MG1Vq6hr	20-30min/6hr	Hypotension,renal failure,hyperkalemia
Fenoldopam	0.1-0.3mcg/kg/min	5min/10-15min	Flushing,headache,tachy

ADRENERGIC INHIBITORS

DRUG	DOSAGE	ONSET/DUR	ADV.EFF
Labetalol (a+b blocker)	20-80mgiv bolus every 10 min,2mg.min iv infusion	5-10min/3-6hrs	Heart block,ortho hypotension.avoid-heart failure,asthma
Esmolol (b-1 selective blocker)	200-500 mcg/kg/min for 4min,then 150-300mcg/kg/min	1-2min/10-20min	Hypotension,avoid-heart failure,asthma
Phentolamine (a1 blocker)	5-15mg iv	1-2min/3-10min	Tachycardia,flushing ,headache