

# **Chapter 6.**

## **Drugs acting on cardiovascular system(CVS)**

**Part 1. Drugs Acting Ion Channels in CVS(作用心血管离子通道的药物)**


**Part 2. Antiarrhythmic Drugs(抗心律失常药)**

**Part 3. Drugs for Treatment of Chronic Cardiac Dysfunction**

**Part 4. Antianginal Drugs(抗心绞痛药)**

**Part 5. Antiatherosclerotic drugs(抗动脉粥样硬化药)**

**Part 6. Antihypertensive Drugs(抗高血压药)**



**Part 6.**  
**Antihypertensive Drugs**  
**(抗高血压药)**

# Contents

- I . Overview**
- II. Antihypertensive drugs most in use**
- III. Other antihypertensive drugs**
- IV. Rational application of anti-hypertensive drugs**

# I . Overview

**高血压是冠心病、卒中、外周血管病、慢性心力衰竭和慢性肾功能衰竭的主要危险因素。**

# I. Overview

我国饮食结构从20世纪50~70年代的以粮食和蔬菜为主, 油、鸡蛋、鱼、肉等的定量供给, 转变成现在的高脂肪、高蛋白、高热量的三高饮食, 人们的运动减少, 超重和肥胖的比例显著增加. 存在与生活方式有关的心血管危险因素的人群急剧增加, 这些危险因素直接导致了上述我国心脑血管疾病的严峻形势.

## 高血压的患病率:

20世纪70年代, 7.73%;

1991年调查为, 11.88%;

目前比1991年又上升31%, 达15.56%.

# I . Overview

**Hypertension** can be divided into:

Essential hypertension: 90~95%

Secondary hypertension: 5~10%

**Normal blood pressure(BP), 2004:**

Diastolic BP  $\leq$  80 mmHg

Systolic BP  $\leq$  120 mmHg

**Criterion of hypertension:**

Diastolic BP  $\geq$  90 mmHg

Systolic BP  $\geq$  140 mmHg

## 2004 《中国高血压防治指南》

与1999年的指南相比, 一个重要的区别是将正常血压确定为 $<120/80\text{mmHg}$ (1999年指南为 $130/85\text{mmHg}$ ). 这种改变的依据来自国内外心血管流行病学调查资料.

国内的资料显示, 当血压 $>115/75\text{mmHg}$ 时, 随着血压增加, 心血管危险显著增加. 每升高 $20/10\text{mmHg}$ , 因心血管疾病死亡的危险都将增加1倍. 而降低血压可以降低与高血压相关的心血管疾病的危险.



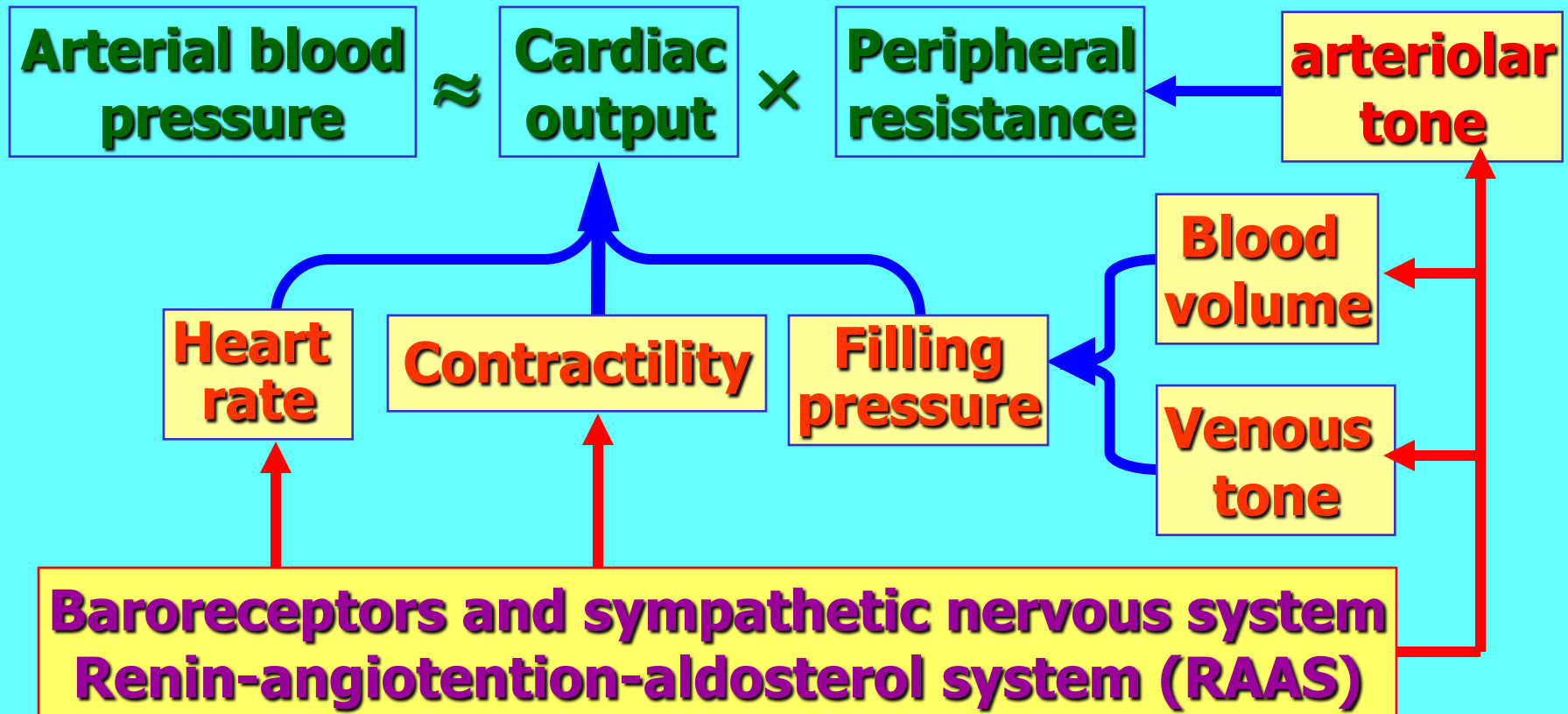
# I. Overview

将正常血压定在**120/80mmHg**这个水平,并不是要求降压治疗一定要达到这个水平,指南确定的正常血压水平与降压治疗的目标目前还有一定距离.

美国高血压预防监测、评估和治疗委员会第7次报告(JNC7)提出,年龄**>18岁**普通人群的血压控制目标是**<140/90mmHg**,但糖尿病和高危病人应**<130/80mmHg**,肾功能衰竭和蛋白尿病人更应**<125/75 mmHg**.

# I. Overview

## Major factors influencing blood pressure:



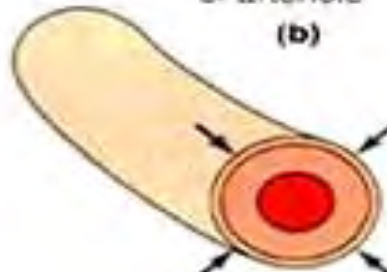
Normal arteriolar tone



Cross section of arteriole

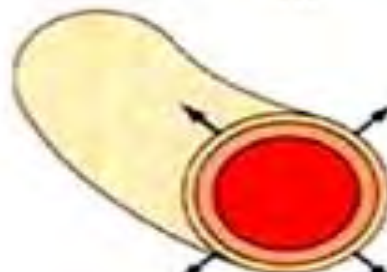
(b)

**Vasoconstriction**  
(increased contraction of circular smooth muscle in the arteriolar wall, which leads to increased resistance and decreased flow through the vessel)



(c)

**Vasodilation**  
(decreased contraction of circular smooth muscle in the arteriolar wall, which leads to decreased resistance and increased flow through the vessel)



(d)

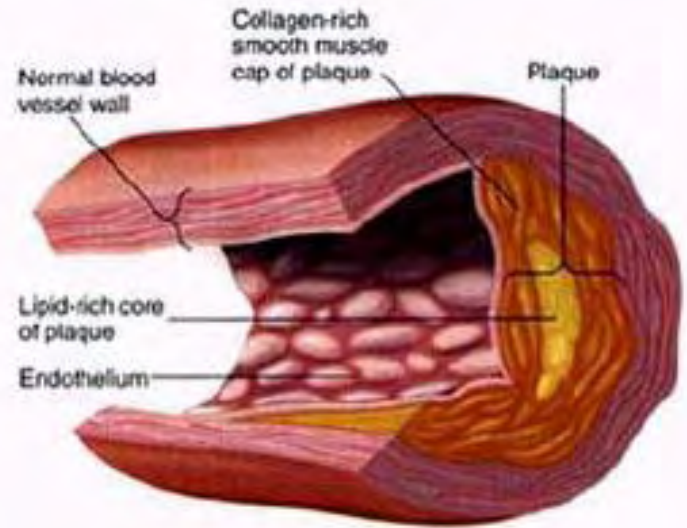
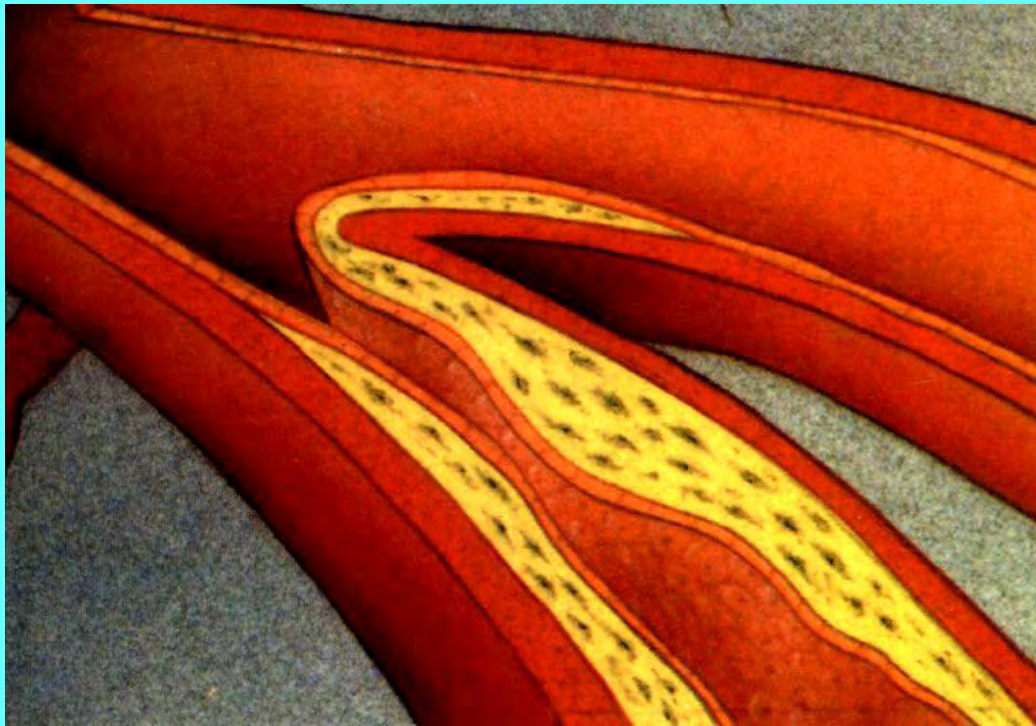
**Caused by:**

- ↓ Myogenic activity
- ↓ Oxygen ( $O_2$ )
- ↓ Carbon dioxide ( $CO_2$ ) and other metabolites
- ↓ Sympathetic stimulation
- ↓ Vasopressin; angiotensin II
- ↓ Cold

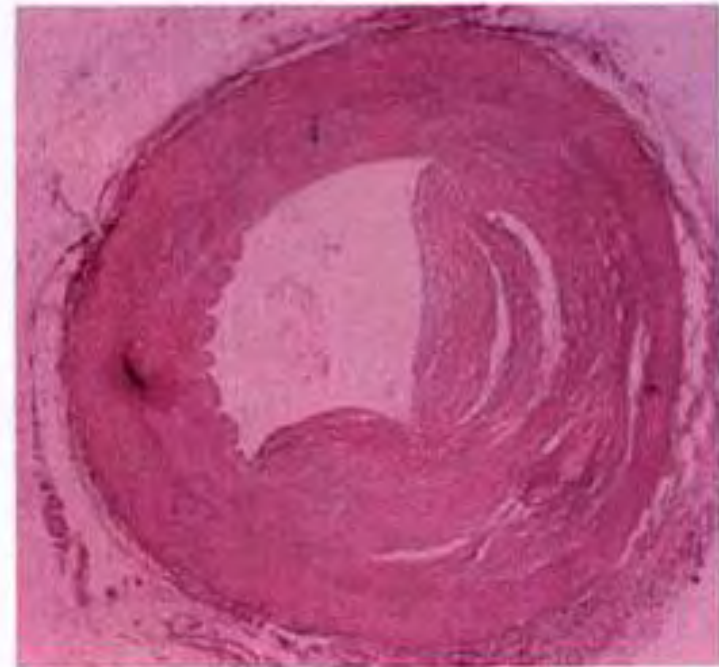
**Caused by:**

- ↓ Myogenic activity
- ↓  $O_2$
- ↓  $CO_2$  and other metabolites
- ↓ Sympathetic stimulation
- ↓ Histamine release
- ↓ Heat

**Peripheral resistance and vascular tone and elasticity**



(a)



**Arterial wall hypertrophy  
and sclerosis**

# Classification of Antihypertensive Drugs

## Diuretics

1. Thiazides and related agents (hydrochlorothiazide, chlorthalidone, etc.)
2. Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)
3. K<sup>+</sup>-sparing diuretics (amiloride, triamterene, spironolactone)

## Sympatholytic Drugs

1. Centrally acting agents (methyldopa, clonidine, guanabenz, guanfacine)
2. Adrenergic neuron blocking agents (guanadrel, reserpine)
3.  $\beta$ -Adrenergic antagonists (propranolol, metoprolol, etc.)
4.  $\alpha$ -Adrenergic antagonists (prazosin, terazosin, doxazosin, phenoxybenzamine, phentolamine)
5. Mixed adrenergic antagonists (labetalol, carvedilol)

## Vasodilators

1. Arterial (hydralazine, minoxidil, diazoxide, fenoldopam)
2. Arterial and venous (nitroprusside)

## Ca<sup>2+</sup>-Channel Blockers

(verapamil, diltiazem, nifedipine, nimodipine, felodipine, nicardipine, isradipine, amlodipine)

## Angiotensin Converting Enzyme Inhibitors

(captopril, enalapril, lisinopril, quinapril, ramipril, benazepril, fosinopril, moexipril, perindopril, trandolapril)

## Angiotensin II-Receptor Antagonists

(losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan)

# Classification of Drugs

## 1. Drugs most in use:

- (1) Diuretics
- (2) Adrenoceptor blockers
- (3) Calcium channel blockers
- (4) Regin-angiotensin system inhibitors

## 2. Other drugs:

- (1) Centrally-acting drugs
- (2) Ganglion blockers;
- (3) Noradrenergic nerve ending blockers;
- (4) Vasodilators

## **II . Antihypertensive drugs most in use**

## II. Drugs most in use(1)

### Diuretics

#### 1. Pharmacological effects:

(1) Reducing plasma volume →  
**cardiac output ↓;**

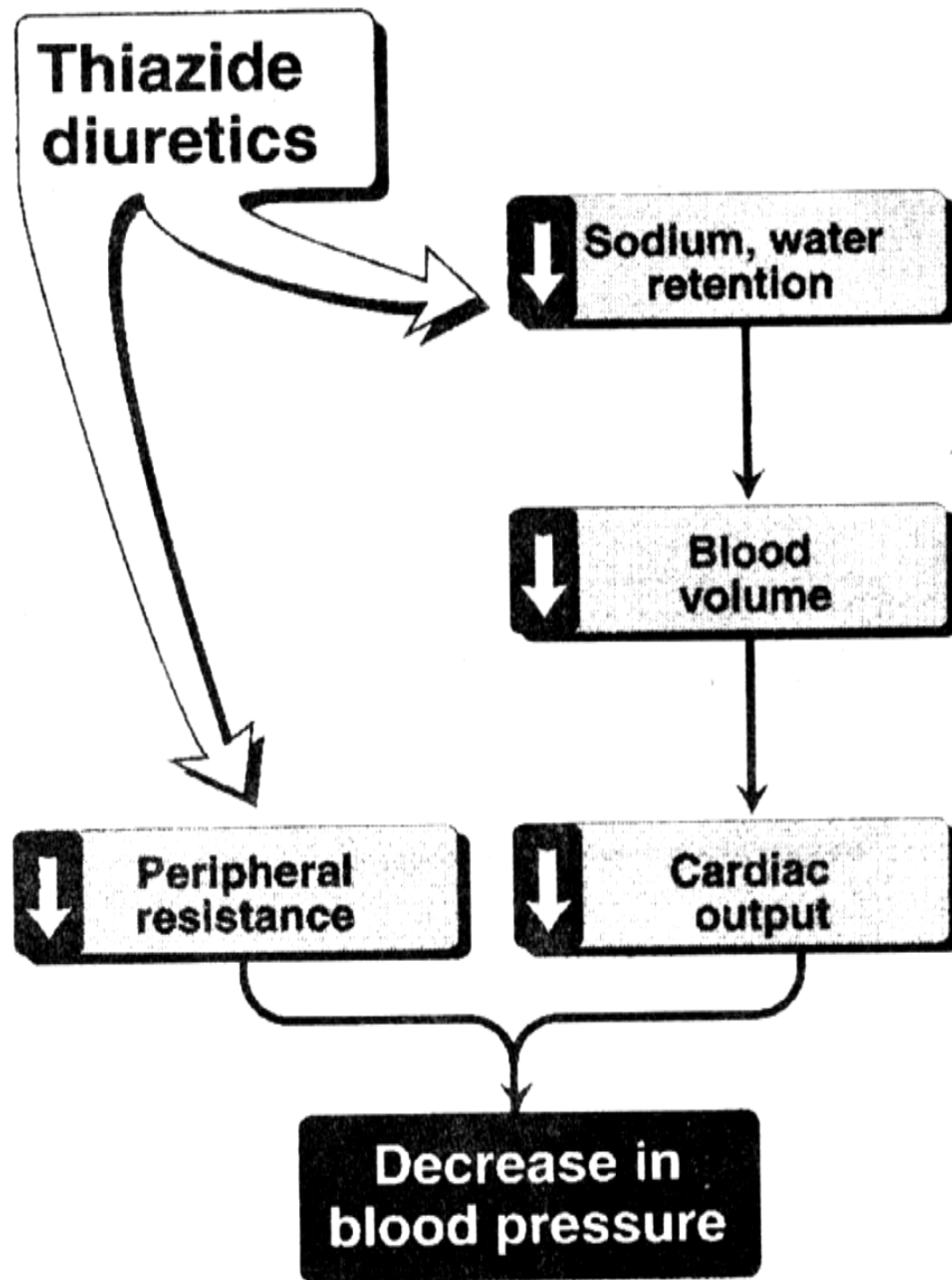
(2) Owing to excretion of  $\text{Na}^+$  ↑, →  
 $\text{Na}^+$ - $\text{Ca}^{2+}$  exchange ↑ in vascular  
smooth muscle cells,  $\text{Ca}^{2+}_i$  ↓, →  
**peripheral resistance ↓.**



**Mechanism  
of diuretics:**

① **blood volume** ↓;

② **Na<sup>+</sup>-Ca<sup>2+</sup> exchange** ↑,  
**↓Ca<sup>2+</sup>**; in va-  
scular smo-  
oth muscle  
cells



## 2. Clinical uses:

### (1) Hypertension:

**single or combined with other drugs;  
mild to moderate hypertension**  
particularly useful in the treatment of elderly patients, pure systolic hypertension, hypertension with heart failure.

### (2) Other uses:

**diuresis, anti-CHF, *etc.***

## 3. Adverse effects:

plasma levels of renin ↑

hypokalemia

hyperuricemia

hyperglycemia

hyperlipidemia

# Diuretics

## Hemodynamic Effects of Long-Term Administration of Antihypertensive Agents\*

	HEART RATE	CARDIAC OUTPUT	TOTAL PERIPHERAL RESISTANCE	PLASMA VOLUME	PLASMA RENIN ACTIVITY
Diuretics	↔	↔	↓	-↓	↑
Sympatholytic agents					
Centrally acting	-↓	-↓	↓	-↑	-↓
Adrenergic neuron blockers	-↓	↓	↓	↑	-↑
$\alpha$ -Adrenergic antagonists	-↑	-↑	↓	-↑	↔
$\beta$ -Adrenergic antagonists					
No ISA <sup>†</sup>	↓	↓	-↓	-↑	↓
ISA	↔	↔	↓	-↑	-↓
Arteriolar vasodilators	↑	↑	↓	↑	↑
Ca <sup>2+</sup> -channel blockers	↓ or ↑	↓ or ↑	↓	-↑	-↑
ACE inhibitors	↔	↔	↓	↔	↑
ATRA	↔	↔	↓	↔	↑

\*Changes are indicated as follows: ↑, increased; ↓, decreased; -↑, increased or no change; -↓, decreased or no change; ↔, unchanged.

<sup>†</sup>ISA, intrinsic sympathomimetic activity. ACE, angiotensin converting enzyme. ATRA, angiotensin II-receptor antagonists.

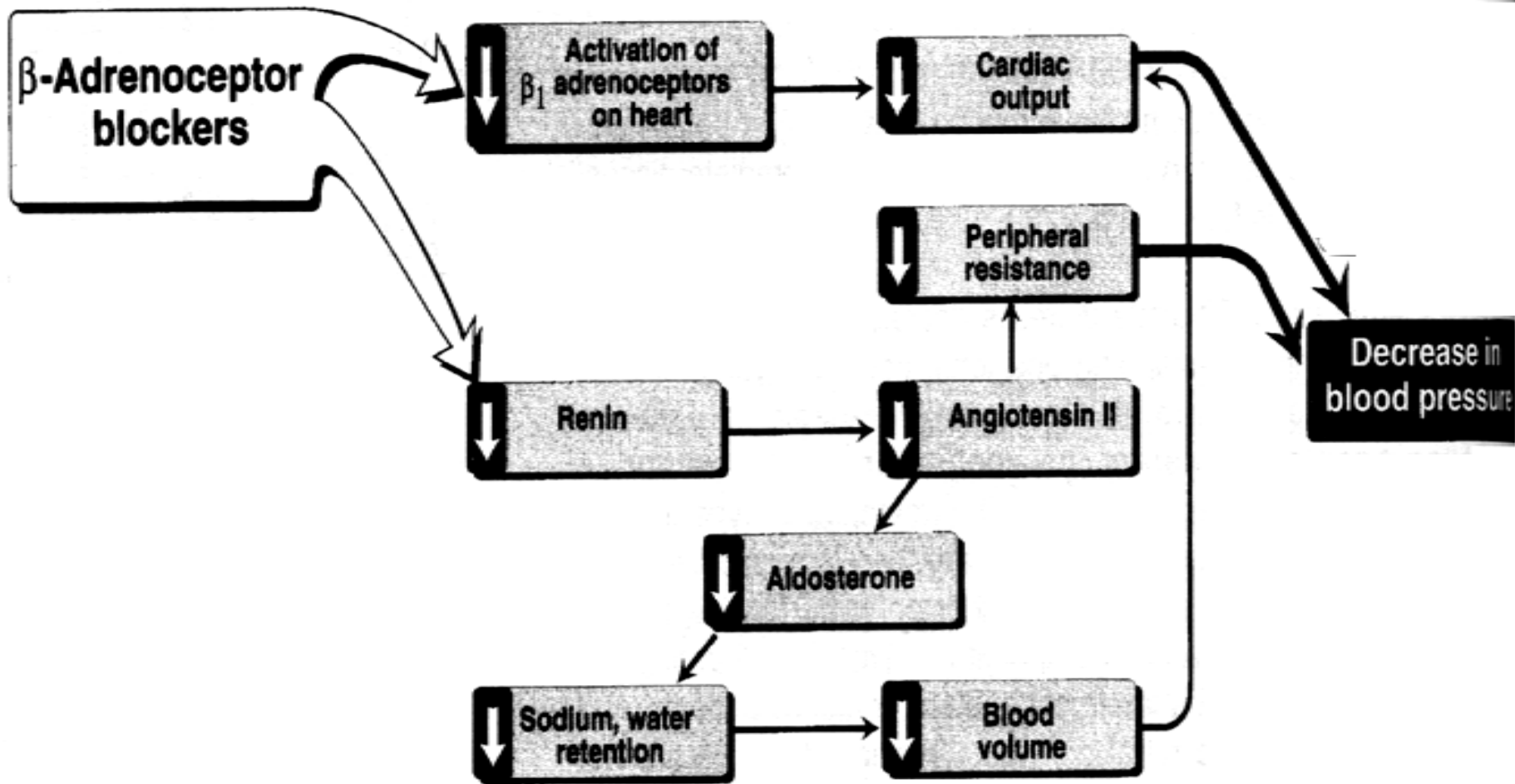
## **II. Drugs most in use(2)**

### **Adrenoreceptor blockers**

#### **$\beta$ Receptor blockers: propranolol**

#### **1. Pharmacological effects:**

- (1) Decreasing cardiac output;**
- (2) Inhibiting the release of renin from kidney (to inhibit formation of angiotension and secretion of aldosterone);**
- (3) Decreasing sympathetic outflow from CNS;**
- (4) Decreasing releasing of noradrenalin (NA) from peripheral nerve endings;**
- (5) Increasing production of PGs.**



**Main actions of  $\beta$  receptor antagonists on blood pressure**

## 3. Clinical uses:

### (1) Hypertension:

All kinds of hypertension, more effective in young patients than elderly.

Useful in treating coexisting conditions, such as supraventricular tachycardia, previous myocardial infarction, angina pectoris, glaucoma and migraine headache.

# $\beta$ Receptor blockers

**(2) Other uses:**

**angina pectoris; arrhythmias.**

**3. Adverse effects:**

**cardiac depression**

**drug withdrawal;**

**inducing attack of asthma, etc.**



# $\beta$ Receptor blockers

## Hemodynamic Effects of Long-Term Administration of Antihypertensive Agents\*

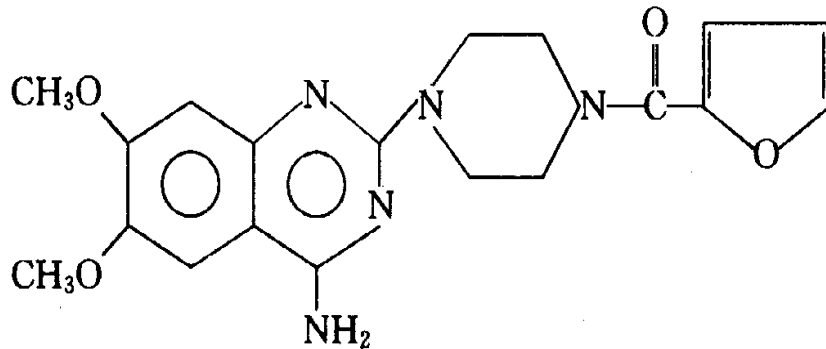
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Adrenergic neuron blockers	-↓	↓	↓	↑	-↑
$\alpha$ -Adrenergic antagonists	-↑	-↑	↓	-↑	↔
$\beta$ -Adrenergic antagonists					
No ISA <sup>†</sup>	↓	↓	-↓	-↑	↓
ISA	↔	↔	↓	-↑	-↓
Arteriolar vasodilators	↑	↑	↓	↑	↑
Ca <sup>2+</sup> -channel blockers	↓ or ↑	↓ or ↑	↓	-↑	-↑
ACE inhibitors	↔	↔	↓	↔	↑
ATRA	↔	↔	↓	↔	↑

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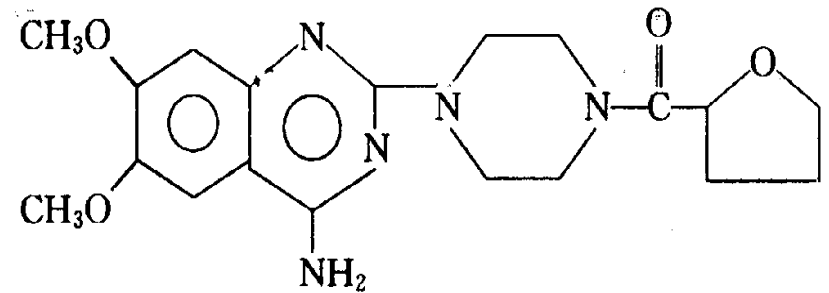
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# II. Drugs most in use(2)

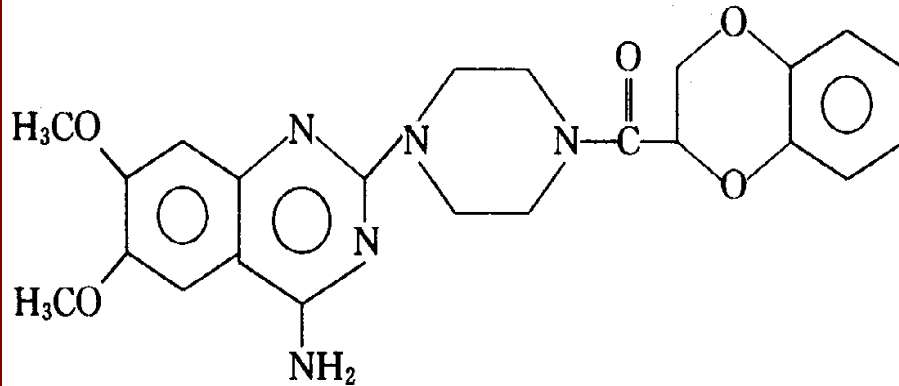
## $\alpha_1$ Receptor blockers



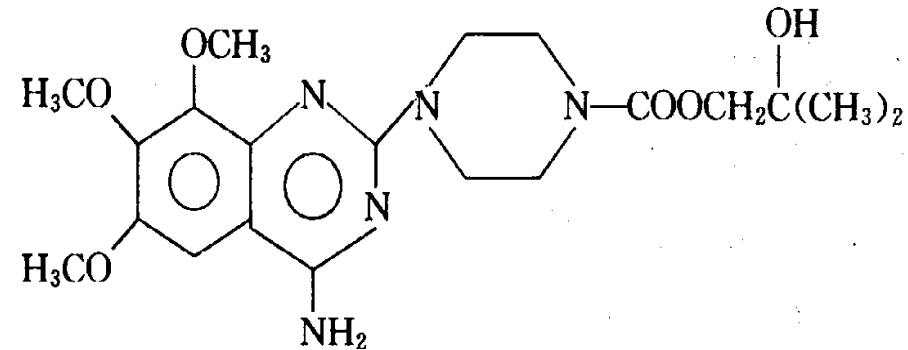
**Prazosin(哌唑嗪)**



**Terazosin(特拉唑嗪)**



**Doxazosin(多沙唑嗪)**



**Trimazosin(曲马唑嗪)**

## Prazosin(哌唑嗪)

### 1. Pharmacological effects:

- (1) Blocking  $\alpha_1$ -receptor of blood smooth muscles and relaxing small artery and vein;
- (2) Decreasing peripheral resistance.

# $\alpha_1$ Receptor blockers

## Prazosin

### 2. Clinical uses:

#### Hypertension:

mild to moderate(single);  
severe hypertension(combined with diuretics and  $\beta$  blockers).

minimal changes in renal blood flow, glomerular filtration, and renin release.

### 3. Adverse effects:

first dose phenomenon(postural hypotension);

water and sodium retention.

# $\alpha_1$ Receptor blockers

## Hemodynamic Effects of Long-Term Administration of Antihypertensive Agents\*

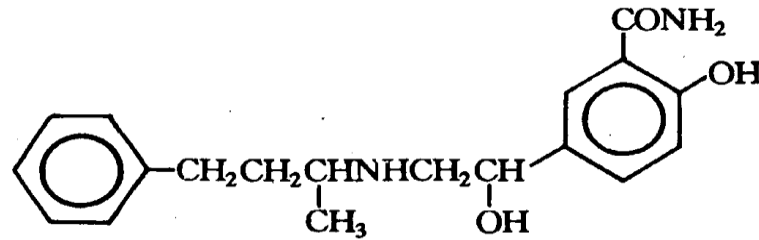
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Sympatholytic agents					
Centrally acting	-↓	-↓	↓	-↑	-↓
Adrenergic neuron blockers	-↓	↓	↓	↑	-↑
$\alpha$ -Adrenergic antagonists	-↑	-↑	↓	-↑	↔
$\beta$ -Adrenergic antagonists					
No ISA†	↓	↓	-↓	-↑	↓
ISA	↔	↔	↓	-↑	-↓
Arteriolar vasodilators	↑	↑	↓	↑	↑
Ca <sup>2+</sup> -channel blockers	↓ or ↑	↓ or ↑	↓	-↑	-↑
ACE inhibitors	↔	↔	↓	↔	↑
ATRA	↔	↔	↓	↔	↑

\*Changes are indicated as follows: ↑, increased; ↓, decreased; -↑, increased or no change; -↓, decreased or no change; ↔, unchanged.

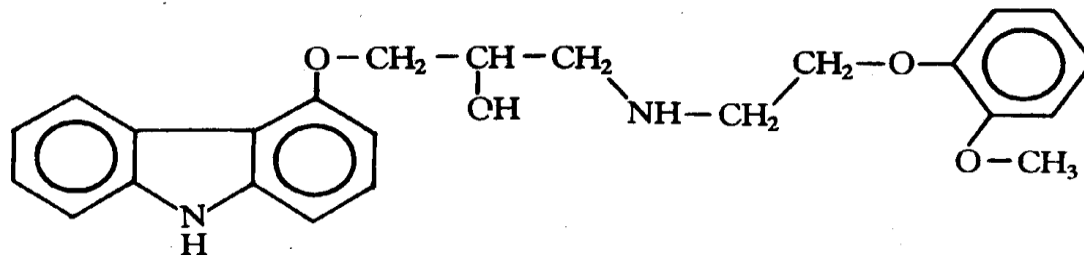
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# II. Drugs most in use(2)

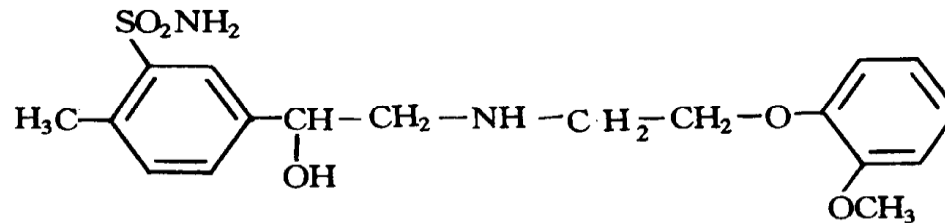
## $\beta$ and $\alpha_1$ Receptor blockers



**Labetalol(拉贝洛尔)**



**Carvedilol(卡维地洛)**



**Amosulalol(氨磺洛尔)**

# $\beta$ and $\alpha_1$ Receptor blockers

## Characteristics of $\beta$ and $\alpha_1$ Receptor blockers:

- (1)  $\downarrow$  blood pressure moderately;
- (2) Minimal changes in cardiac output and heart rate;
- (3) Used for all kinds of hypertension, including hypertensive emergency;
- (4) Less adverse effects.

**Let's take a rest !**



## **II. Drugs most in use(3)**

### **Calcium channel blockers**

#### **Nifedipine(硝苯地平)**

- 1. Pharmacological effects:**  
**Relaxing vascular smooth muscles.**
- 2. Clinical uses:**  
**Mild to severe hypertension.**

# Calcium channel blockers

## 3. Adverse effects:

**Peripheral edema;**

**Reflex sympathetic activation;**

**Renin activity ↑.**

## Other calcium channel blockers:

**Amlodipine(氨氯地平), *etc.***

# Calcium channel blockers

## Hemodynamic Effects of Long-Term Administration of Antihypertensive Agents\*

	HEART RATE	CARDIAC OUTPUT	TOTAL PERIPHERAL RESISTANCE	PLASMA VOLUME	PLASMA RENIN ACTIVITY
Diuretics	↔	↔	↓	-↓	↑
Sympatholytic agents					
Centrally acting	-↓	-↓	↓	-↑	-↓
Adrenergic neuron blockers	-↓	↓	↓	↑	-↑
$\alpha$ -Adrenergic antagonists	-↑	-↑	↓	-↑	↔
$\beta$ -Adrenergic antagonists					
No ISA <sup>†</sup>	↓	↓	-↓	-↑	↓
ISA	↔	↔	↓	-↑	-↓
Arteriolar vasodilators	↑	↑	↓	↑	↑
Ca <sup>2+</sup> -channel blockers	↓ or ↑	↓ or ↑	↓	-↑	-↑
ACE inhibitors	↔	↔	↓	↔	↑
ATRA	↔	↔	↓	↔	↑

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## II. Drugs most in use(4)

### Renin-angiotensin system inhibitors

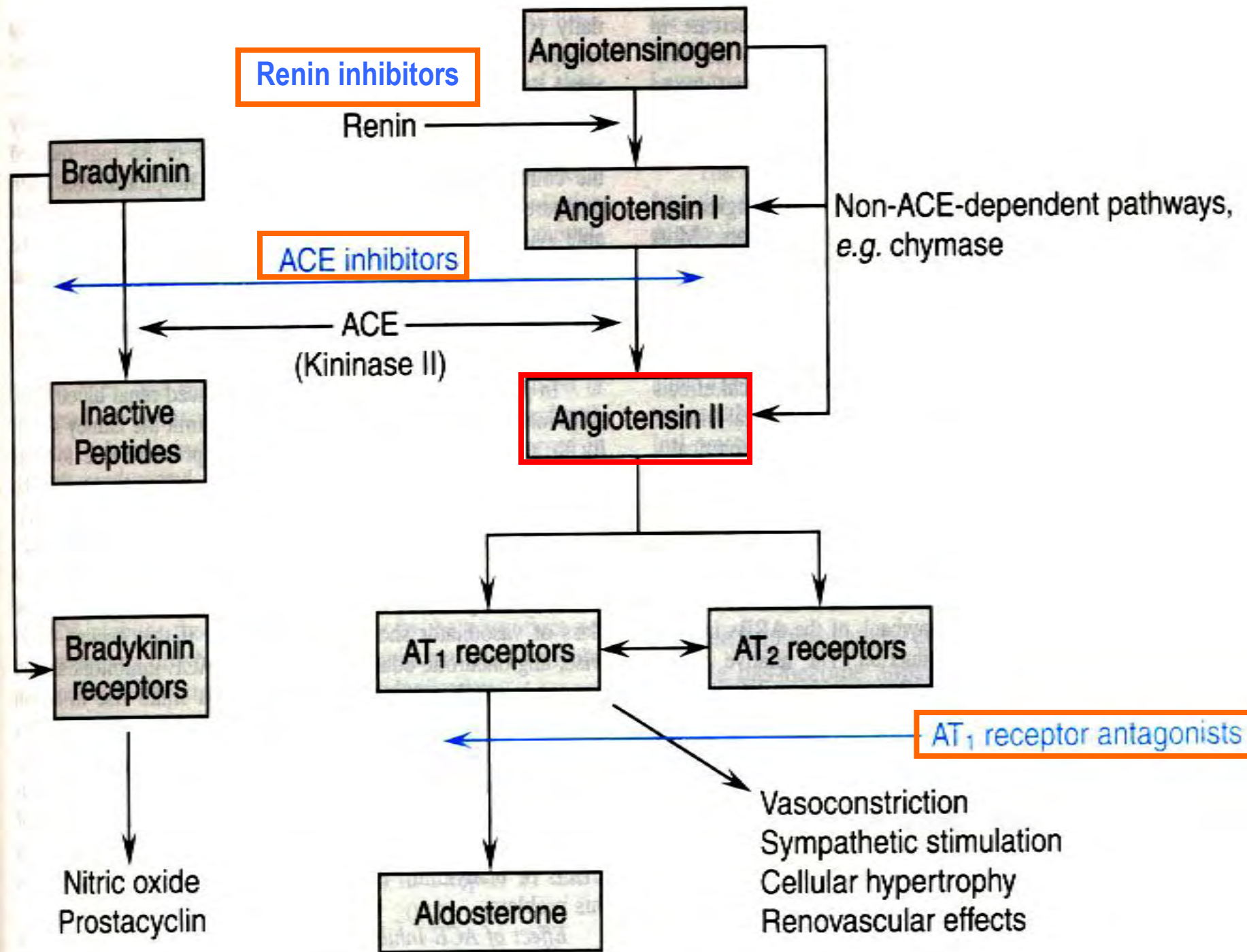
#### ACEI:

captopril (卡托普利),  
enalapril (依那普利)

AT<sub>1</sub> receptor antagonists:  
losartan (氯沙坦)

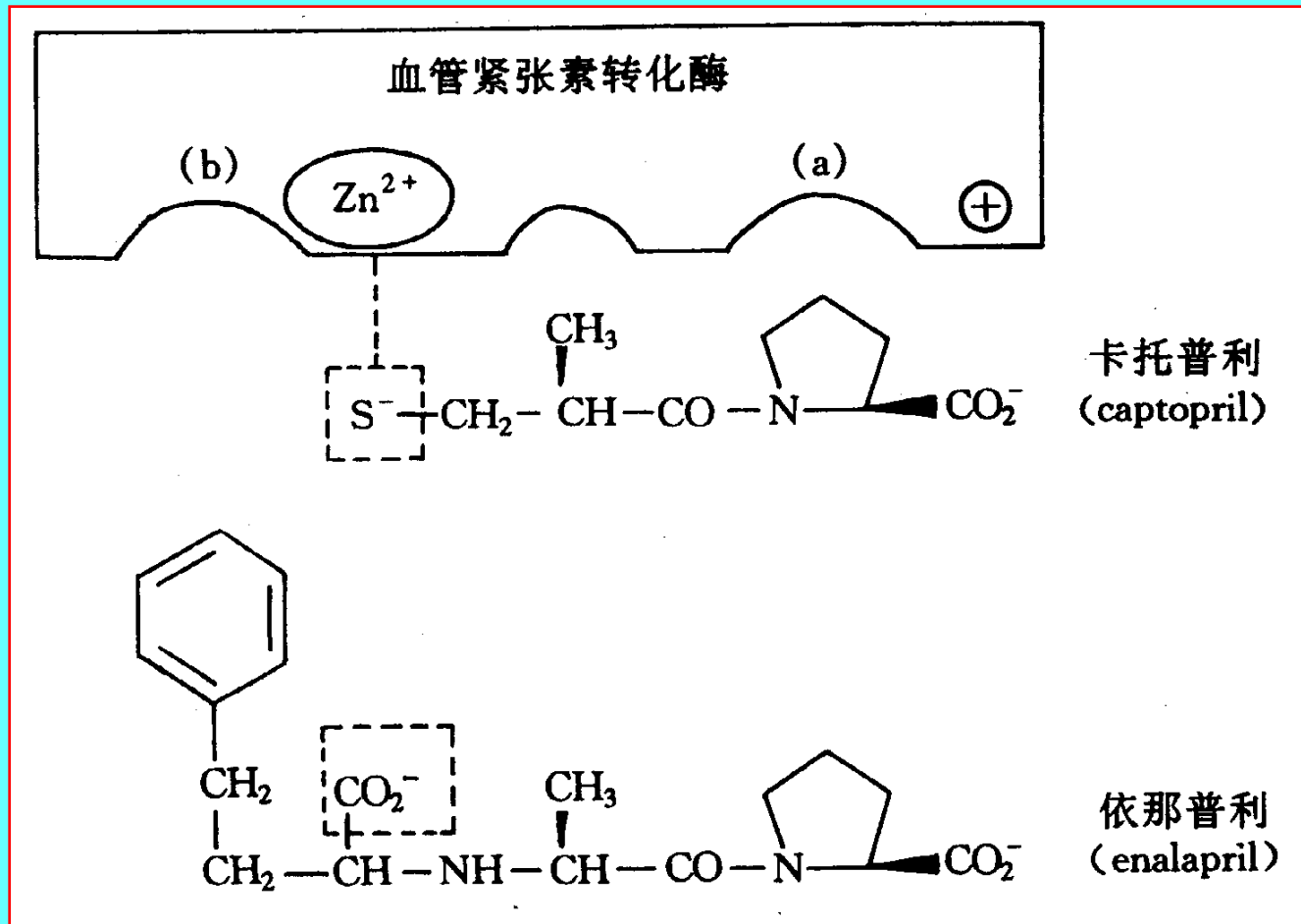
#### Renin inhibitors:

enalaprilat (依那吉仑)



## II. Drugs most in use(4)

# angiotensin converting enzyme inhibitors(ACEI)



# **1. Pharmacological effects:**

- (1) Inhibiting the production of Ang II ;**
- (2) Inhibiting the degradation of bradykinin, to vasodilatation;**
- (3) Decreasing the activity of sympathetic system;**
- (4) Inhibiting ventricular remodeling;**
- (5) decreasing aldosterone.**

## 2. Clinical uses:

### Hypertension

**not reflexly increasing the activity of sympathetic system;**

**effective in the patients with CHF, diabetes and ischemic heart disease also.**



### **3. Adverse effects:**

**hypotension (first dose phenomenon)**

**renal injury**

**dry cough**

**hyperkalemia**

**angioneuroedema**

**rashes and altered tastes**

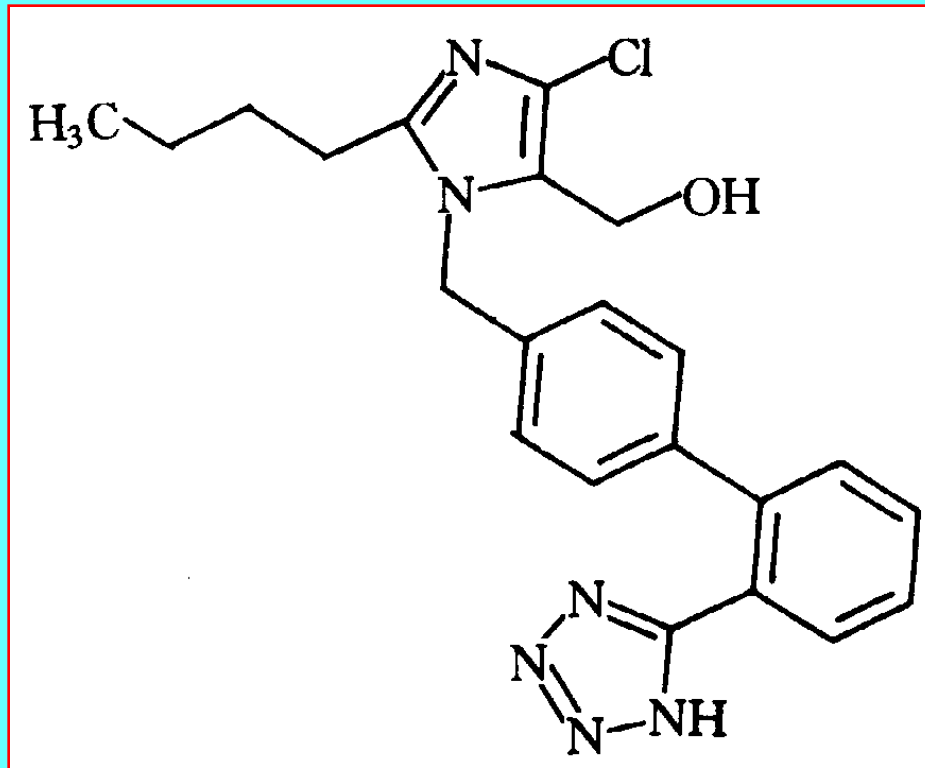
### **Contraindications:**

**renal artery stenosis, pregnant  
and lactational women.**

## II. Drugs most in use(4)

### AT<sub>1</sub> antagonists

### Losartan(氯沙坦)



## Compared with ACEI:

- (1) Block actions of angiotensin II directly;**
- (2) Not influence bradykinin metabolism;**
- (3) Protect renal function;**
- (4) Used for mild to moderate hypertension;**
- (5) Less adverse effects.**

## **II. Drugs most in use(4)**

### **Renin inhibitors**

**Enakiren(依那吉仑)**

**Remikiren(瑞米吉仑)**

**peptide or nonpeptide renin inhibitors.**

**They inhibit whole RAAS**

**Other drugs: renin antibody.**

# ACEI & AT<sub>1</sub> antagonists

## Hemodynamic Effects of Long-Term Administration of Antihypertensive Agents\*

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Sympatholytic agents					
Centrally acting	-↓	-↓	↓	-↑	-↓
Adrenergic neuron blockers	-↓	↓	↓	↑	-↑
$\alpha$ -Adrenergic antagonists	-↑	-↑	↓	-↑	↔
$\beta$ -Adrenergic antagonists					
No ISA <sup>†</sup>	↓	↓	-↓	-↑	↓
ISA	↔	↔	↓	-↑	-↓
Arteriolar vasodilators	↑	↑	↓	↑	↑
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ACE inhibitors	↔	↔	↓	↔	↑
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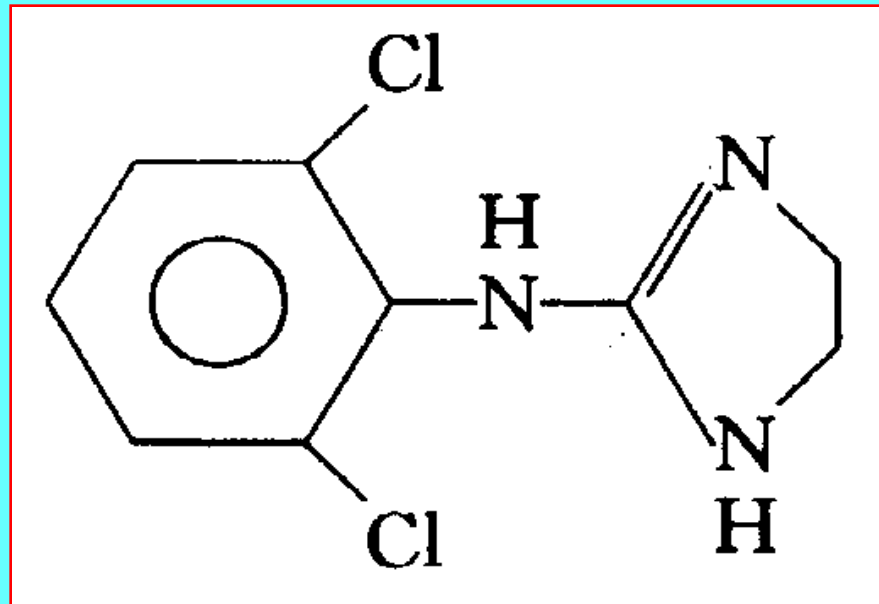
<sup>†</sup>ISA, intrinsic sympathomimetic activity. ACE, angiotensin converting enzyme. ATRA, angiotensin II-receptor antagonists.

## **III. Other anti-hypertensive drugs**

### III. Other Drugs(1)

Centrally-acting drugs:

**Clonidine(可乐定)**



# Centrally-acting drugs

## Clonidine

### 1. Pharmacological effects:

Diminishing central adrenergic outflow;  
Activating  $\alpha_2$  and  $I_1$  receptor in medulla.

### 2. Clinical uses:

**Hypertension:** mild to moderate hypertension that has not responded adequately to treatment with diuretics alone.

minimal changes in renal blood flow and glomerular filtration inhibit gastrointestinal secretion and mobility.



### **3. Adverse effects:**

**(1) Central and atropine-like side effects;**

**(2) long-term uses:  
water and sodium retention;  
rebound phenomenon.**

## III. Other Drugs(2)

**Ganglionic blockers:**

**Trimetaphan(米噻芬)**

**Mecamylamine(美卡拉明)**

**Short-acting;**

**Tolerance;**

**For controlling hypotension.**

## III. Other Drugs(3)

### Noradrenergic nerve ending blockers

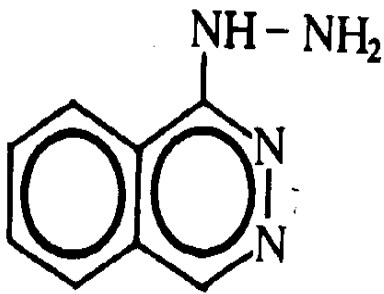
Reserpine(利舍平, 利血平)

Guanethidine(胍乙啶)

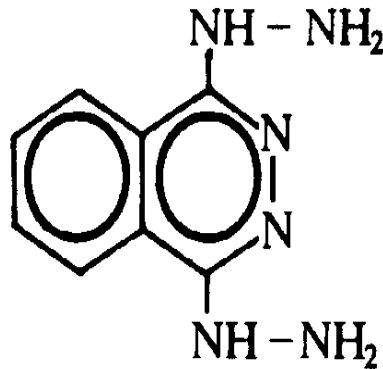
- (1) Decreasing NA storage in noradrenergic nerve endings;
- (2) Slow and lasting effects;
- (3) Central depression.

# III. Other Drugs(4)

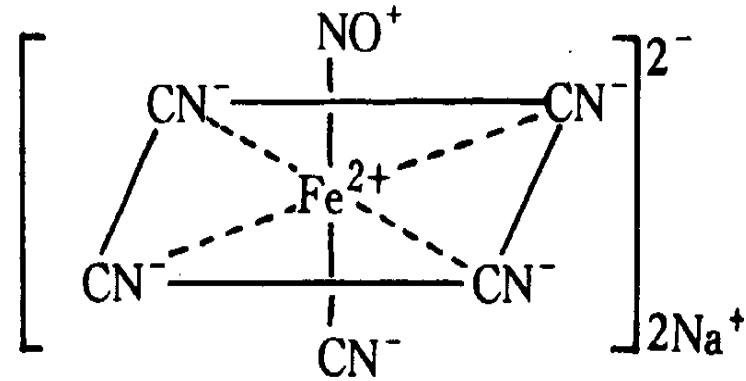
## Vasodilators (Peripheral vasodilators)



**Hydralazine**  
(肼屈嗪)



**Dihydralazine**  
(双肼屈嗪)



**Sodium Nitroprusside**  
(硝普钠)

## III. Other Drugs(4)

### Vasodilators

#### Hydralazine(肼屈嗪)

- (1) Dilating arteries and arterioles;
- (2) Decreasing peripheral resistance;
- (3) Reflexly elevating heart rate, cardiac output and renin release.

Combined with  $\beta$  blockers and diuretics.

#### Adverse effects:

due to vasodilation;  
and lupus-like syndrome.

## III. Other Drugs(4)

### Vasodilators

#### Nitroprusside sodium(硝普钠)

Dilating small arteries and veins.

#### Clinical Uses:

- (1) emergency hypertension;
- (2) hypertension with CHF and obstinate CHF;
- (3) controlled blood pressure in surgical operation.

#### Adverse effects:

due to hypotension in excess;  
and sulfocyanate(硫氰化物) poisoning.

### III. Other Drugs(4)

#### Potassium channel openers

Including: minoxidil(米诺地尔), nicorandil(尼可地尔), diazoxide(二氮嗪), *etc.*

- (1) Dilating arteries ( $\text{Ca}^{2+}$  influx ↓);
- (2) Reflexly elevating heart rate, cardiac output and renin release.

Used for treatment of obstinate(顽固性) and severe hypertension

#### Adverse effects:

include sodium retention, palpitation, *etc.*

## **IV. Rational application of antihypertensive drugs**



# IV. Rational application of antihypertensive drugs

## 1. Prescription according to the degree of hypertension:

### (1) Mild:

**single drug: diuretics,  $\beta$  blockers, ACEI, calcium channel blockers,  $\alpha_1$  blockers, or  $AT_1$  blockers.**

### (2) Moderate:

**combined with two above drugs.**

### (3) Severe:

**adding centrally acting drugs or vasodilators to the two combined drugs.**

# IV. Rational application of antihypertensive drugs

## 2. Prescription according to complications:

	indicated	contraindicated
<b>CHF and/or COPD, Asthma</b>	<b>Diuretics, ACEI, Prazosin</b>	<b><math>\beta</math> Blockers</b>
<b>Renal failure</b>	<b>ACEI, Methyldopa</b>	
<b>Tachycardia</b>	<b><math>\beta</math> Blockers</b>	
<b>GI ulcer</b>	<b>Clonidine</b>	<b>Reserpine</b>
<b>Diabetes and gout(痛风)</b>	<b>ACEI, prazosin</b>	<b>Thiazides</b>

## **IV. Rational application of antihypertensive drugs**

**(1) Hypertensive emergency:**

**vasodilators (nitroprusside sodium, diazoxide), labetalol, loop diuretics.**

**(2) Elderly patients:**

**avoiding drugs that could induce postural hypotension (eg.  $\alpha_1$  blockers) and influence the cognizant ability. (clonidine, methyldopa).**

**(3) Cardiac ischemia:**

**avoiding (peripheral) vasodilators.**

# **IV. Rational application of antihypertensive drugs**

**3. Combination of drugs;**

**4. Avoid blood pressure to decrease too rapidly and excessively;**

**5. Individual therapy.**

**The class is over !**