

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)

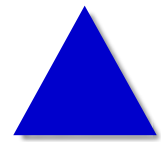
A close-up photograph of a field of purple daisies with bright yellow centers. The flowers are in various stages of bloom, and the background is a soft-focus green. A dark red vertical bar is visible on the left side of the image.

**Part 3. Drugs for Treatment of
Chronic Cardiac Dysfunction
(治疗慢性心功能不全药)**

Contents

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- I. Cardiac glycosides
- II. Diuretics and vasodilators
- III. Angiotensin I converting enzyme inhibitors(ACEIs) and relative receptor antagonists
- IV. Other drugs



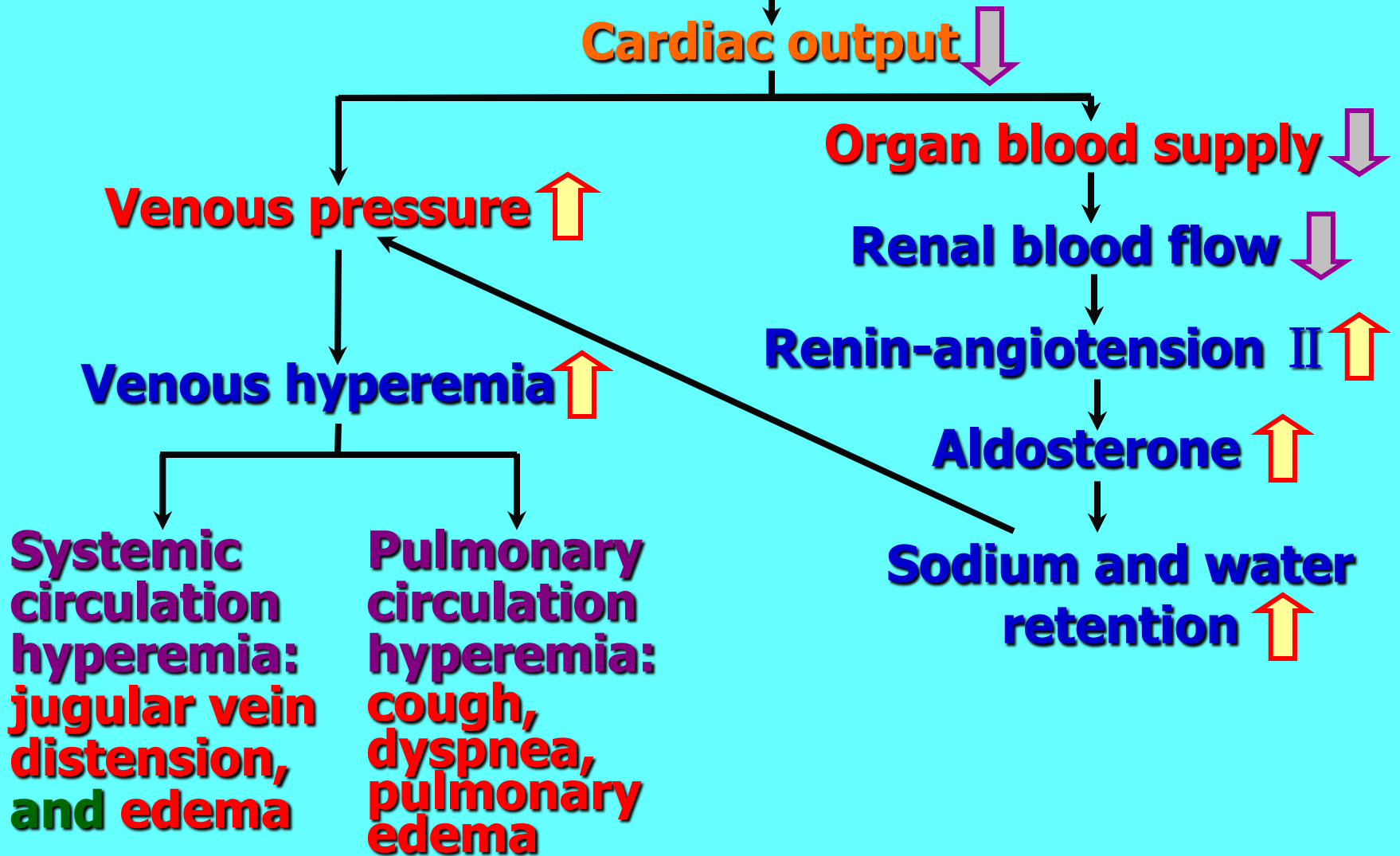
Overview

Chronic Cardiac Dysfunction
(慢性心功能不全)

Congestive Heart Failure(CHF)
(充血性心力衰竭, 简称心衰)

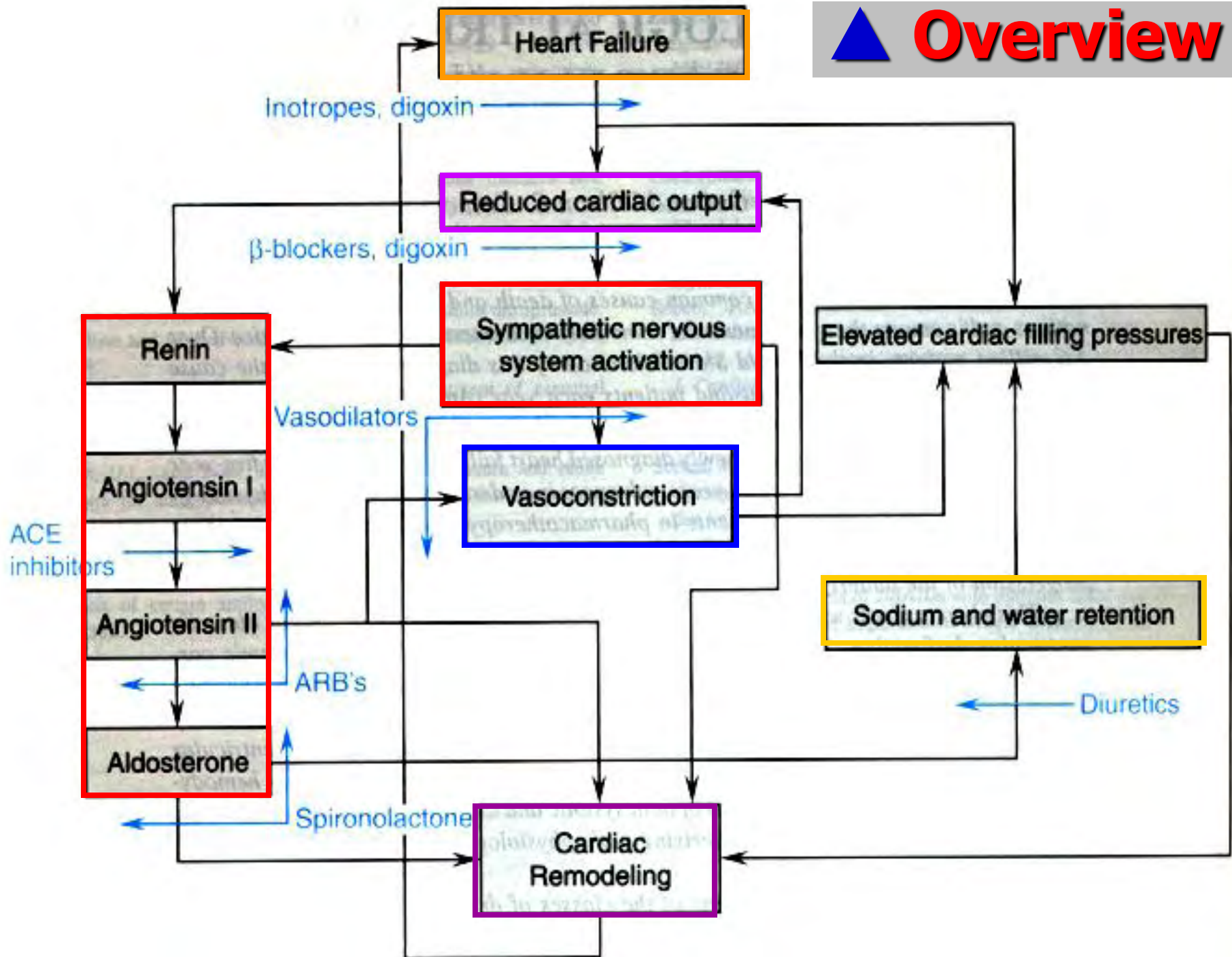
▲ Overview

Congestive Heart failure



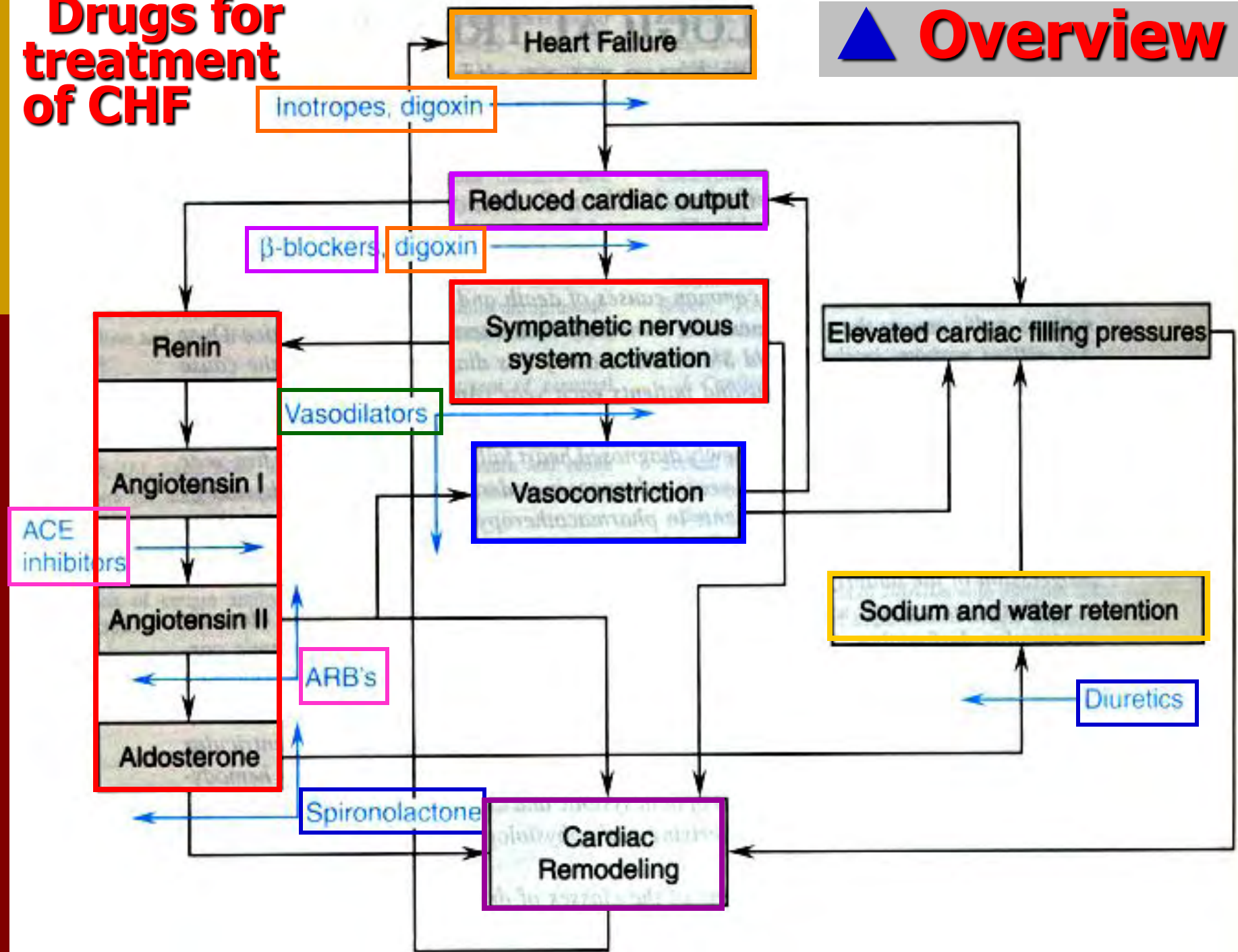
Changes of hemodynamics in CHF

▲ Overview



Drugs for treatment of CHF

▲ Overview



The drugs for treatment of CHF

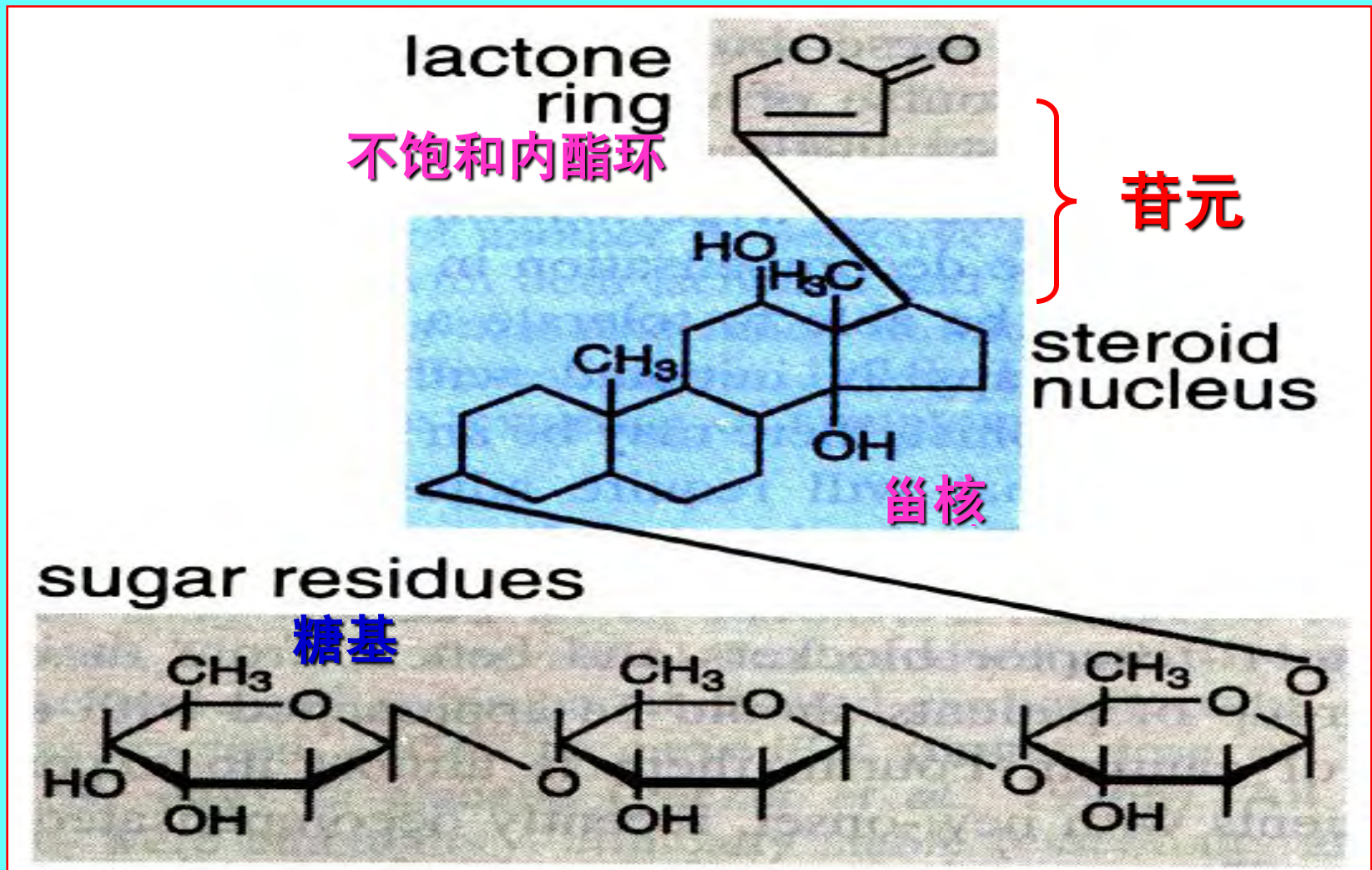
- I. **Cardiac glycosides(强心苷类)**
- II. **Diuretics and vasodilators(利尿药和血管扩张药)**
- III. **ACE inhibitors and relative receptor antagonists(血管紧张素 I 转换酶抑制药和相关受体拮抗药)**
- IV. **Other anti-CHF drugs(其他抗心衰药)**

I . Cardiac glycosides **(强心苷类)**

A kind of glucoside compounds which can selectively act on cardiac muscle, and increase cardiac contractility.

(是一类选择性地作用于心肌、有强心作用的苷类化合物)

I. Cardiac glycosides(强心苷类, — Digitalis, 洋地黄类)



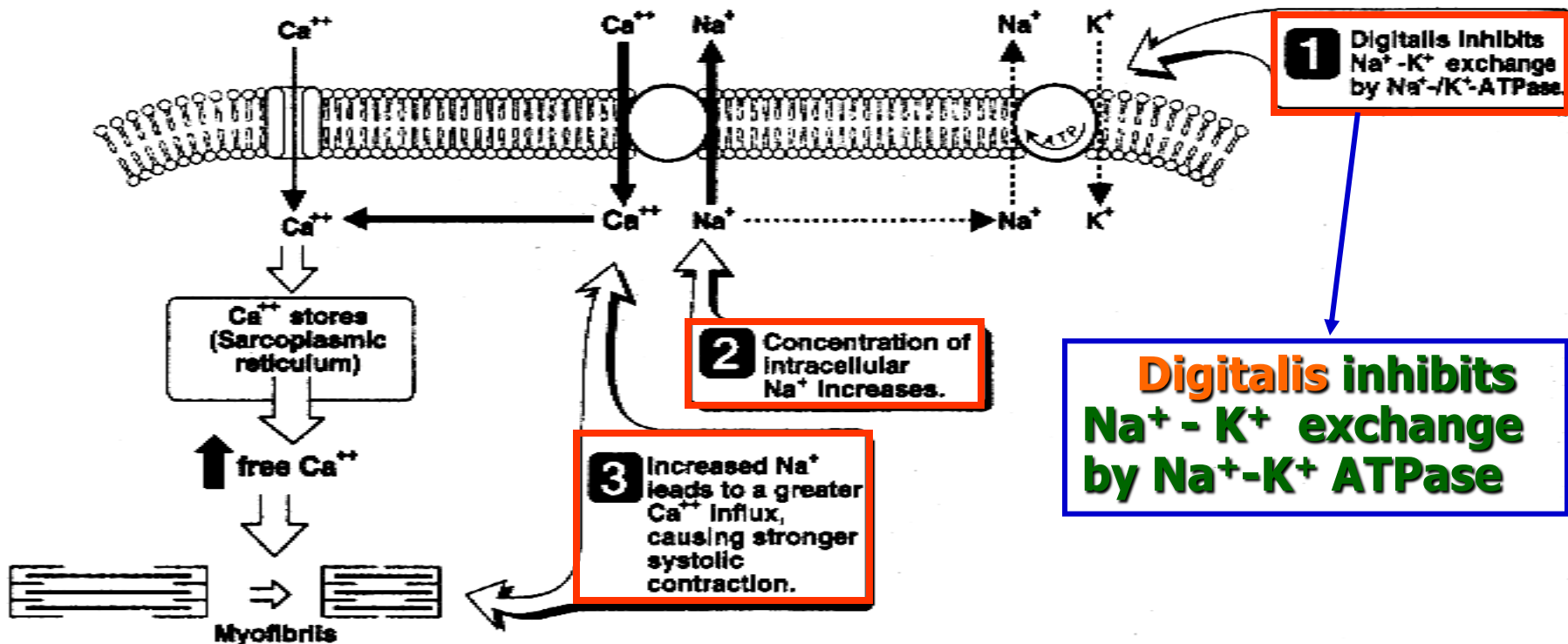
1. Pharmacological effects:

(1) Positive inotropic effects:

Digitalis can inhibit $\text{Na}^+ - \text{K}^+ - \text{ATPase}$

→ intracellular free $\text{Ca}^{2+} \uparrow$,

→ excitation-contraction coupling \uparrow :



Owing to **digitalis** inhibiting **Na⁺-K⁺ ATPase**,

- intracellular free **Ca²⁺** ↑,
- **excitation-contraction coupling** ↑,
- **myocardial contraction** ↑:

① **cardiac output** ↑:

- **organ blood supply** ↑.

② **V_{max}** ↑ → **diastolic duration** ↑:

- **venous return** ↑;
- **coronary blood supply** ↑.

③ **Cardiac oxygen consumption** ↓.

(2) Negative chronotropic effects:

① Reflexly inhibiting sympathetic activity.

Mechanisms:

Owing to positive inotropic effects

→ Cardiac output ↑,

→ Sympathetic activity ↓, and

→ Heart rate ↓.

② Increasing vagal activity directly.

(3) Electrophysiological effects:

- ① decreasing automaticity of sinoatrial node;
- ② slowing A-V node conduction;
- ③ increasing automaticity of *Purkinje* fibers;
- ④ shortening ERP of fast response cells.

When **overdose** of digitalis, intracellular $\text{Na}^+ \uparrow \uparrow$, $\text{K}^+ \downarrow \downarrow$, and $\text{Ca}^{2+} \uparrow \uparrow$:

→ ↓ size of MDP, & ↑ afterdepolarization
→ **arrhythmias !!**

(4) Other effects:

① **Blood vessel: directive contraction.**

② **Nervous system:**

Autonomic nervous system:

Sympathetic activity ↓;

Central nervous system:

Agonizing CTZ D₂ receptor → vomiting.

③ **Kidney:**

**Increasing blood flow of kidney →
diuretic effect;**

**Inhibiting Na⁺-K⁺ ATPase of renal
tubules → inhibiting Na⁺ resorption →
blood volume ↓.**

2. Clinical uses:

(1) CHF:

various CHF,
especially associated with atrial fibrillation and sinus tachycardia.

(2) Arrhythmias:

atrial fibrillation;
atrial flutter → atrial fibrillation;
paroxysmal supraventricular tachycardia.

3. Adverse effects:

(1) Gastrointestinal effects:
nausea, vomiting, etc.

(2) CNS effects:

① **alteration of color perception(色视),**
such as yellow vision(黄视), green vision
(绿视);

② **headache,**

③ **fatigue,**

④ **confusion, etc.**

(3) Cardiac toxicity:

Arrhythmias: premature beats, tachycardia, atrioventricular block, sinus bradycardia, *etc.*

Prevention:

Dose individualization;

Avoiding provocation factors: such as plasma K^+ ↓, and drug interactions, *etc.*

Treatment:

KCl, phenytoin sodium or lidocaine, *i.v.*

Atropine: A-V block, sinus bradycardia

Fab segment of digoxin antibody, *i.v.*

4. Administration:

- (1) Loading dose + maintaining dose full dose(digitalization) + maintaining dose daily for severe patients.**
- (2) Maintaining dose given daily reaching C_{ss} with 1 week(digoxin). for stable patients.**

5. Pharmacodynamic parameters of three digitalis drugs:

表 31-1 四种强心苷类药物的药动学参数

项 目	洋地黄毒苷	地高辛	毛花苷 C	毒毛花苷 K
口服吸收(%)	90~100	60~85	20~30	2~5
蛋白结合(%)	97	25	<20	
肝-肠循环(%)	27	7	少	少
代谢转化(%)	70	20	少	
原形经肾排出(%)	10	60~90	90~100	100
分布容积(L/kg)	0.6	5.1~8.1	4.4	—
半衰期(h)	5~7d	36	23	12~19
治疗血浆浓度(ng/ml)	10~35	0.5~2.0	—	
给药途径	口服	口服	静脉注射	静脉注射
起效时间(h)	2	1~2	10~30min	5~10min
T _{max} (h)	8~12	4~8	1~2	0.5~2
毒性消失时间(d)	3~10	1~2	1~1.5	6h
作用完全消失时间(d)	2~3周	5~7	4~5	1~3
全剂量(mg)	0.8~1.2	0.7~1.2	1~1.2	0.25~0.5
维持量(mg)	0.05~0.3	0.7~1.2	—	—

6. Properties of different digitalis drugs:

(1) Moderate-acting:

digoxin(地高辛)

maintaining dose daily.

(2) Long-acting:

digitoxin(洋地黄毒苷)

maintaining dose daily;

digitalization+maintaining dose daily.

(3) Short-acting:

deslanoside(毛花苷C, 西地兰)

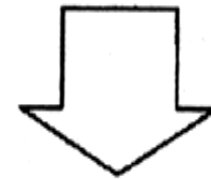
used for acute attack of CHF.

7. Drug Interaction:

**Drug interactions
that probably
induce digitalis
cardiotoxicity**

Increased digitalis
concentration may
occur during
concurrent therapy

Amlodarone
Erythromycin
Quinidine
Tetracycline
Verapamil



**Enhanced potential
for cardiotoxicity**



Decreased levels of
blood potassium

Corticosteroids
Thiazide diuretics
Loop diuretics

Let's take a rest !

II. Diuretics(利尿药) and vasodilators(血管扩张药)

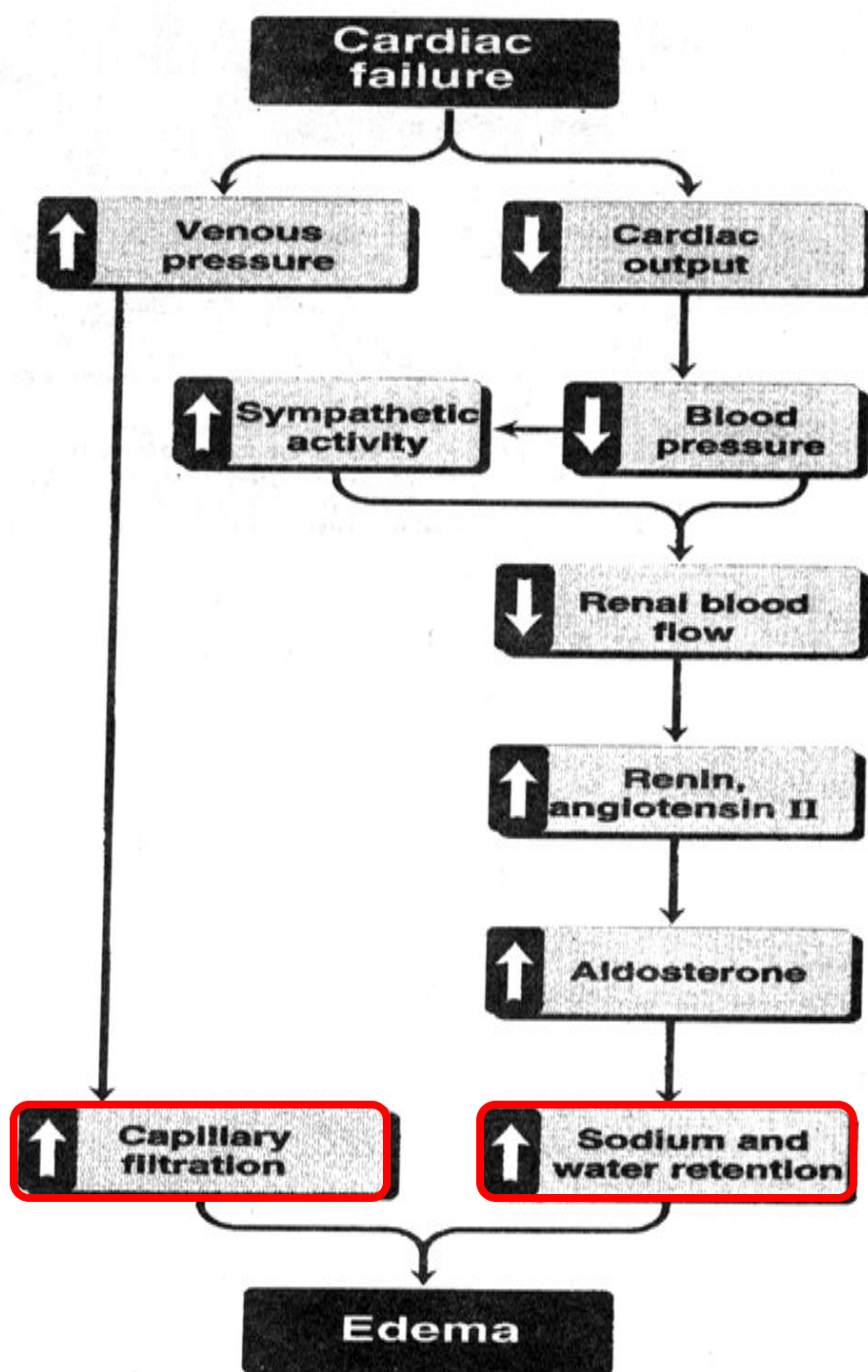
II. Diuretics & vasodilators

Diuretics

1. Pharmacological effects:

(1) Reduce plasma volume;

(2) Reduce Na^+ - Ca^{2+} exchange in vessel smooth muscle cells.



Therapeutic effects of diuretics in CHF

2. Clinical uses:

**CHF: grand I -IV (mainly used in II -III),
alone or combined with other drugs**

Edema, hypertension, etc.

Commonly used drugs:

Thiazide(噻嗪类):

hydrochlorothiazide(氢氯噻嗪)

Semide(塞米类):

furosemide(呋塞米)

Renone(螺内酯类):

spironolactone(螺内酯)

3. Adverse effects:

Thiazide(噻嗪类), Furoemide(呋塞米)
inducing hypokalemia

→ digitalis cardiotoxicity ↑

should replenish KCl.

II. Diuretics & vasodilators

Vasodilators

↓ Cardiac preload and afterload, →
↑ cardiac output.

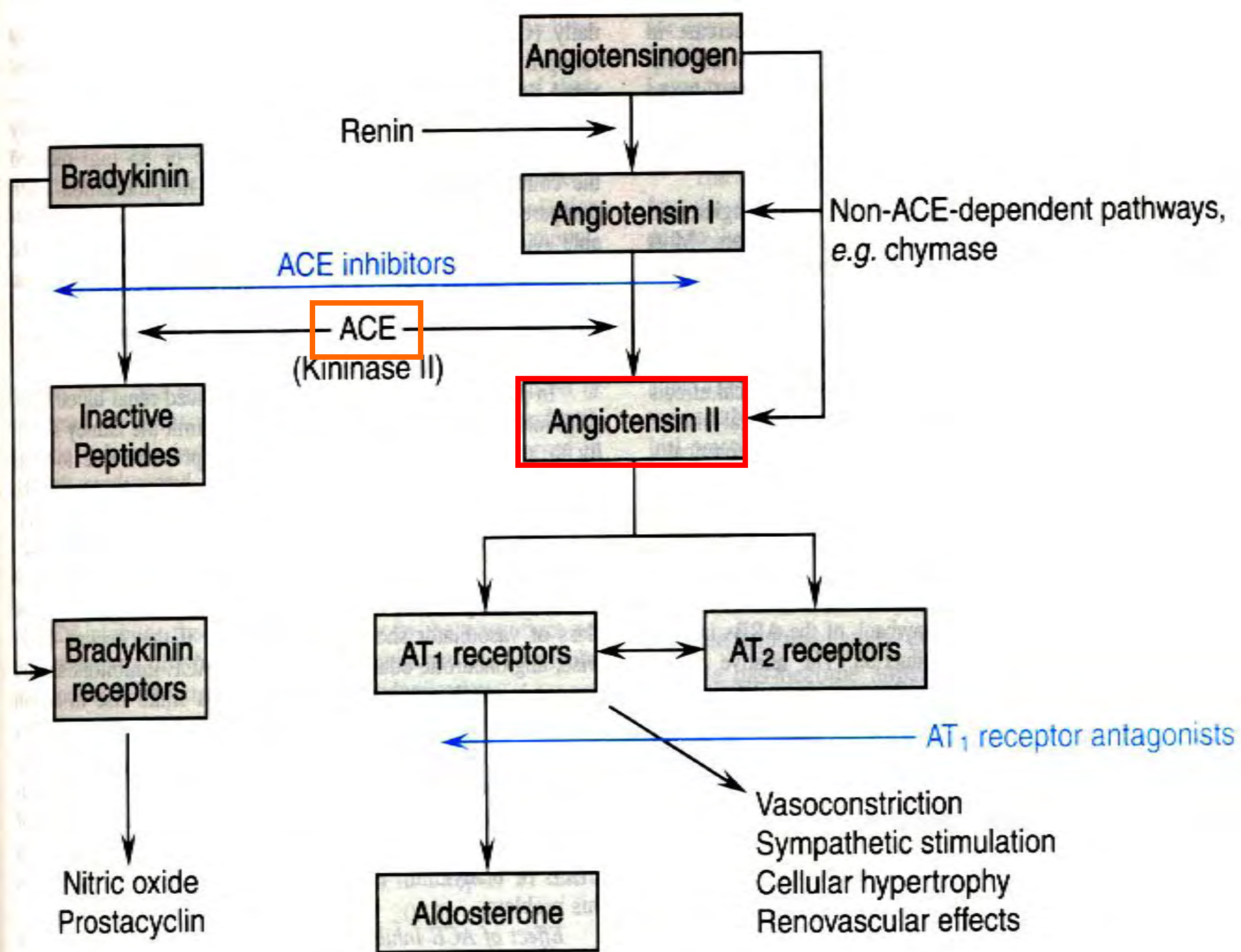
Nitroglycerin(硝酸甘油);

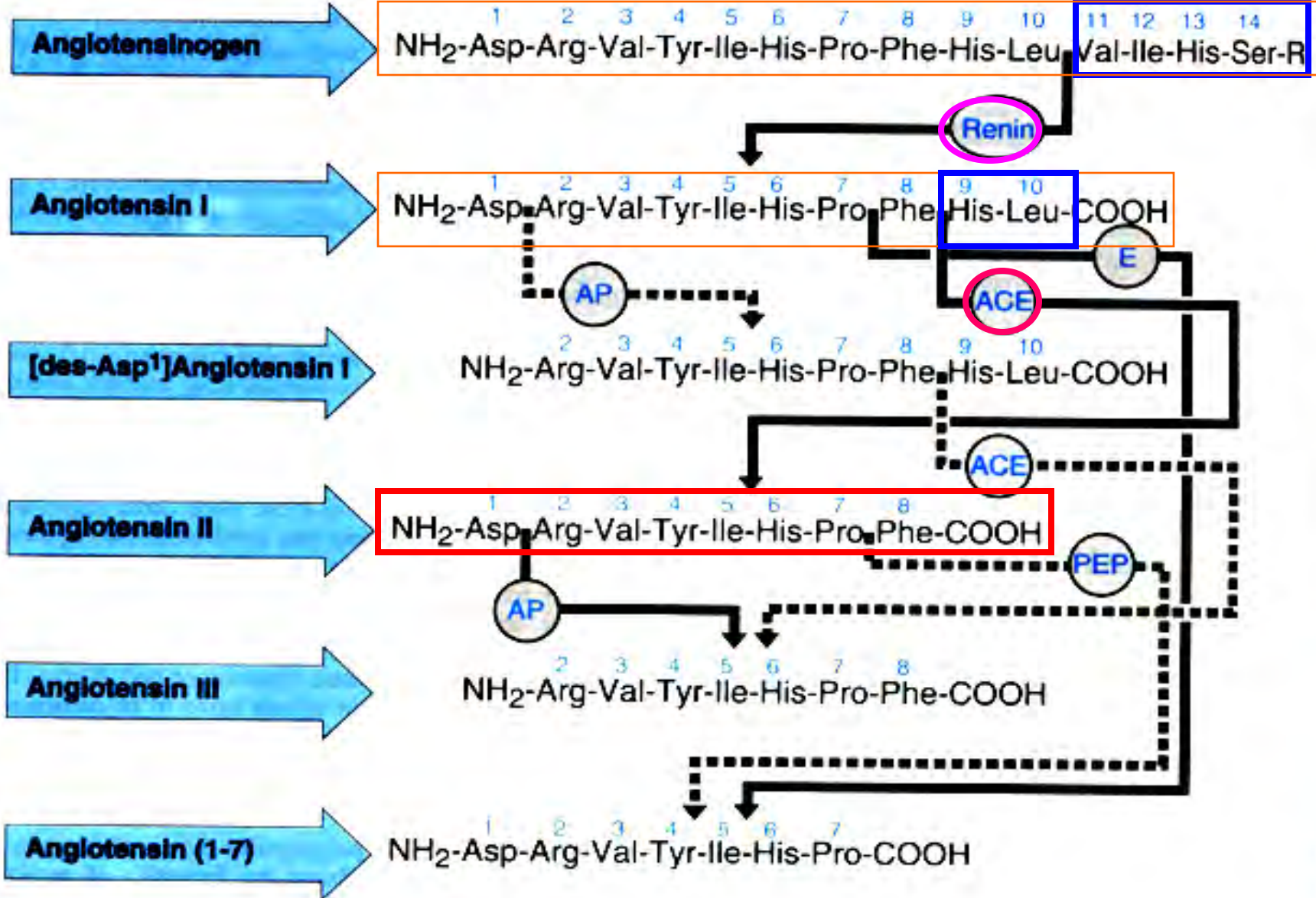
Nitroprusside sodium(硝普钠),

Hydralazine(肼屈嗪),

Prazosin(哌唑嗪), etc.

III. Angiotensin I converting enzyme inhibitors (ACEIs) and relative receptor antagonists(血管紧张素转换酶抑制剂和相关受体拮抗药)

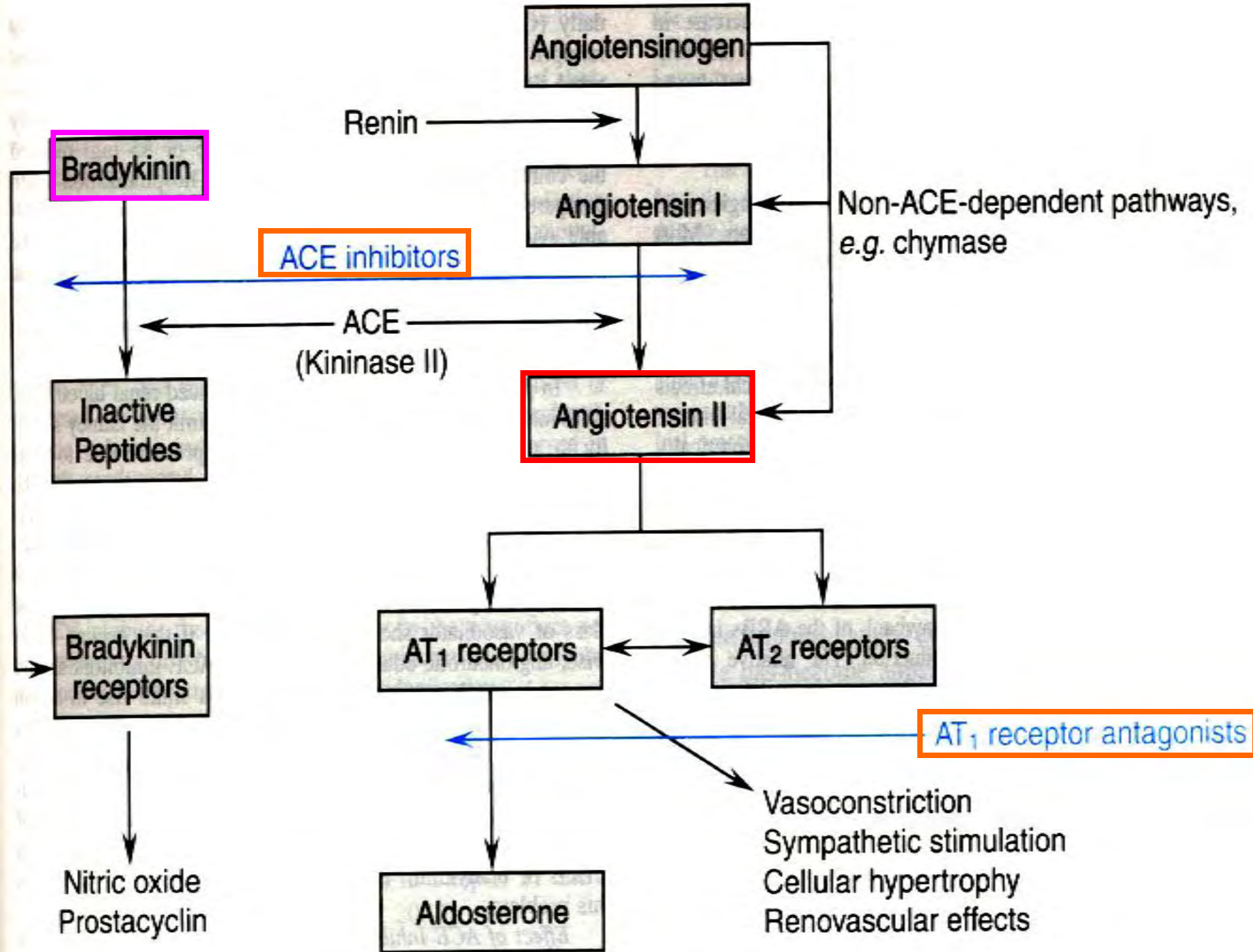




AP Aminopeptidase
 E Endopeptidases (24.15; 24.11; 24.26)
 ACE Angiotensin Converting Enzyme
 PEP Prolylcarboxypeptidase

Effects of angiotensin II (Ang II)

- ① constricting vessels directly, to increase peripheral resistance;**
- ② Increasing sympathetic tension by promoting release of sympathetic transmitter(NA);**
- ③ Stimulating release of aldosterone and return blood volume;**
- ④ Inducing the expression of *c-fos*, *c-myc*, *c-jun* rapidly, to promote cardiac remodeling.**



III. ACEI and relative receptor blockers

**Angiotensin I converting
enzyme inhibitor: ACEI**

Commonly used drugs:

Captopril(卡托普利)

Enalapril(依那普利)

1. Pharmacological effects:

- (1) Inhibiting the production of Ang II**
vasoconstriction ↓;
sodium retention ↓;
cardiac remodeling (myocardial hypertrophy) ↓.
- (2) Inhibiting the degradation of bradykinin**
vasodilatation ↑.
- (3) Scavenging free radicals**

★ Cardiovascular effects of ACEI:

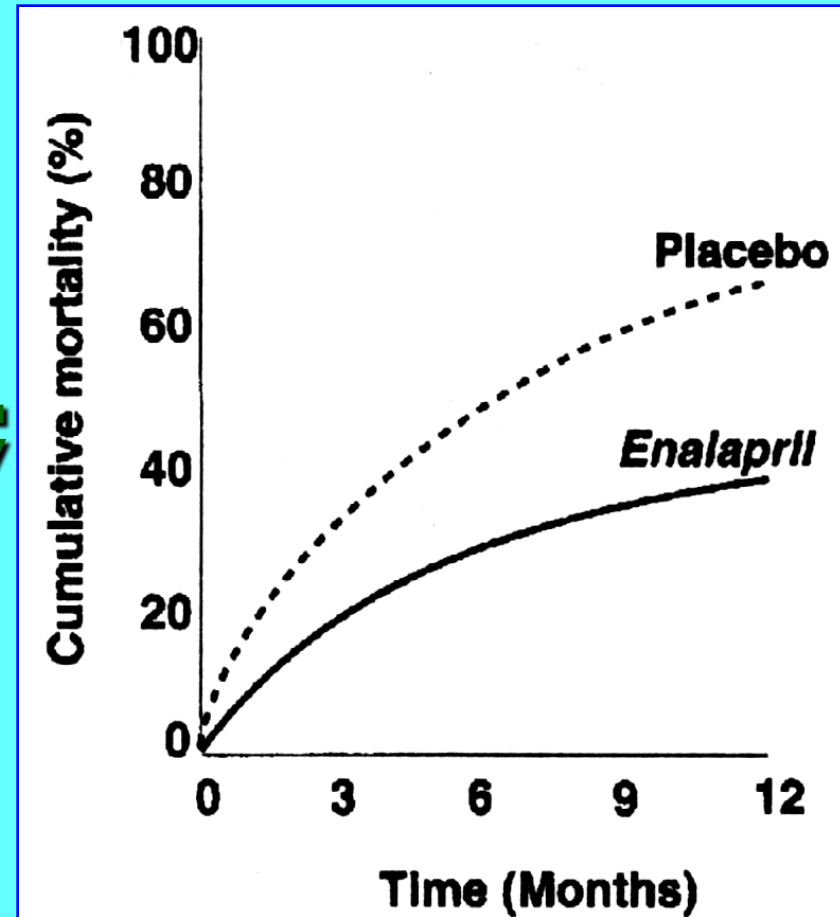
- ① **Decrease resistance of peripheral vessels.**
- ② **Dilating coronary artery, increasing blood supply of heart and kidney, to improve cardiac and renal function.**
- ③ **Reverse myocardial hypertrophy and ventricular remodeling.**

2. Clinical uses:

(1) CHF

↑ motor tolerance;
↓ mortality.

(2) Hypertension



3. Adverse effects:

Hypotension;

Dry cough and angioedema;

Hyperpotassemia.

Contraindications:

pregnancy;

stenosis of renal artery.

III. ACEI and relative receptor blockers

AT₁ receptor antagonists

Losartan(氯沙坦)
Irbesartan(伊白沙坦)

Compared with ACEI:

- (1) Blocking actions of ang II directly;
- (2) Not influencing bradykinin metabolism, no dry cough;
- (3) Protecting renal function;
- (4) Used for CHF with hypertension.

III. ACEI and relative receptor blockers

β receptor blockers

Main drugs:

Carvedilol(卡维地洛) and Labetalol(拉贝洛尔), *etc.*

β receptor blockers can inhibit cardiac function, but Carvedilol is a nonselective β receptor blockers and an α_1 -selective α receptor blockers.

In patients randomized to carvedilol there was a 65% reduction in all-cause mortality, which was independent of age, gender, and etiology of heart failure, *etc.*

IV. Other drugs

IV. Other drugs

1. Phosphodiesterase 3(PDE3) inhibitors:

**Amrinone(氨力农),
Milrinone(米力农),
Vesnarinone(维司力农),**

(1) Effects:

**increasing intracellular cAMP \uparrow , \rightarrow
positive inotropic effects.**

(2) Clinical uses: CHF

(3) ADRs:

**Hypotension,
Thrombocytopenia(Amrinone), *etc.***

IV. Other drugs

2. Calcium sensitizers:

Sulmazole(硫马唑), etc.

3. Calcium channel blockers:

Amlodipine(氨氯地平) ✓

4. β receptor agonists:

Dobutamine(多巴酚丁胺),

Xamoterol(扎莫特罗)

**positive inotropic drugs,
can cause arrhythmias, etc.**

Today's class is over !