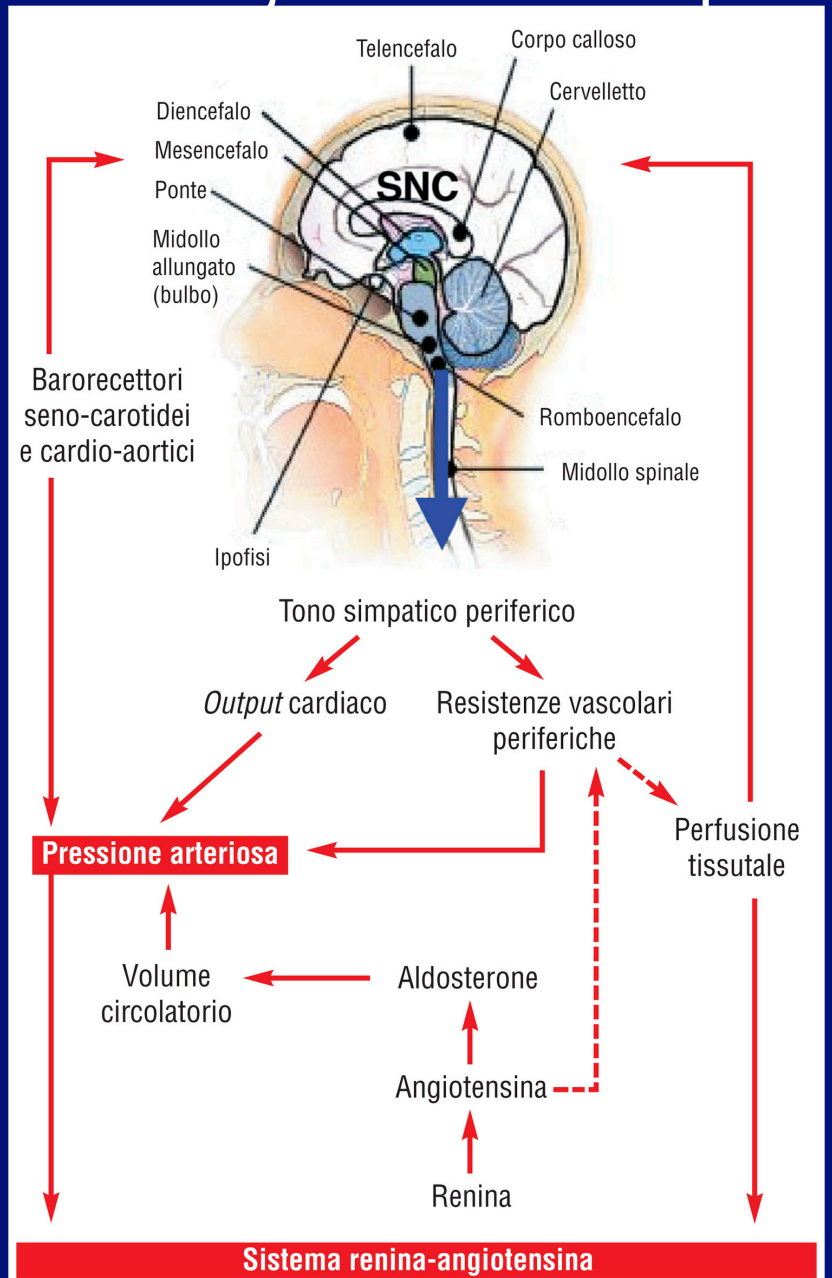
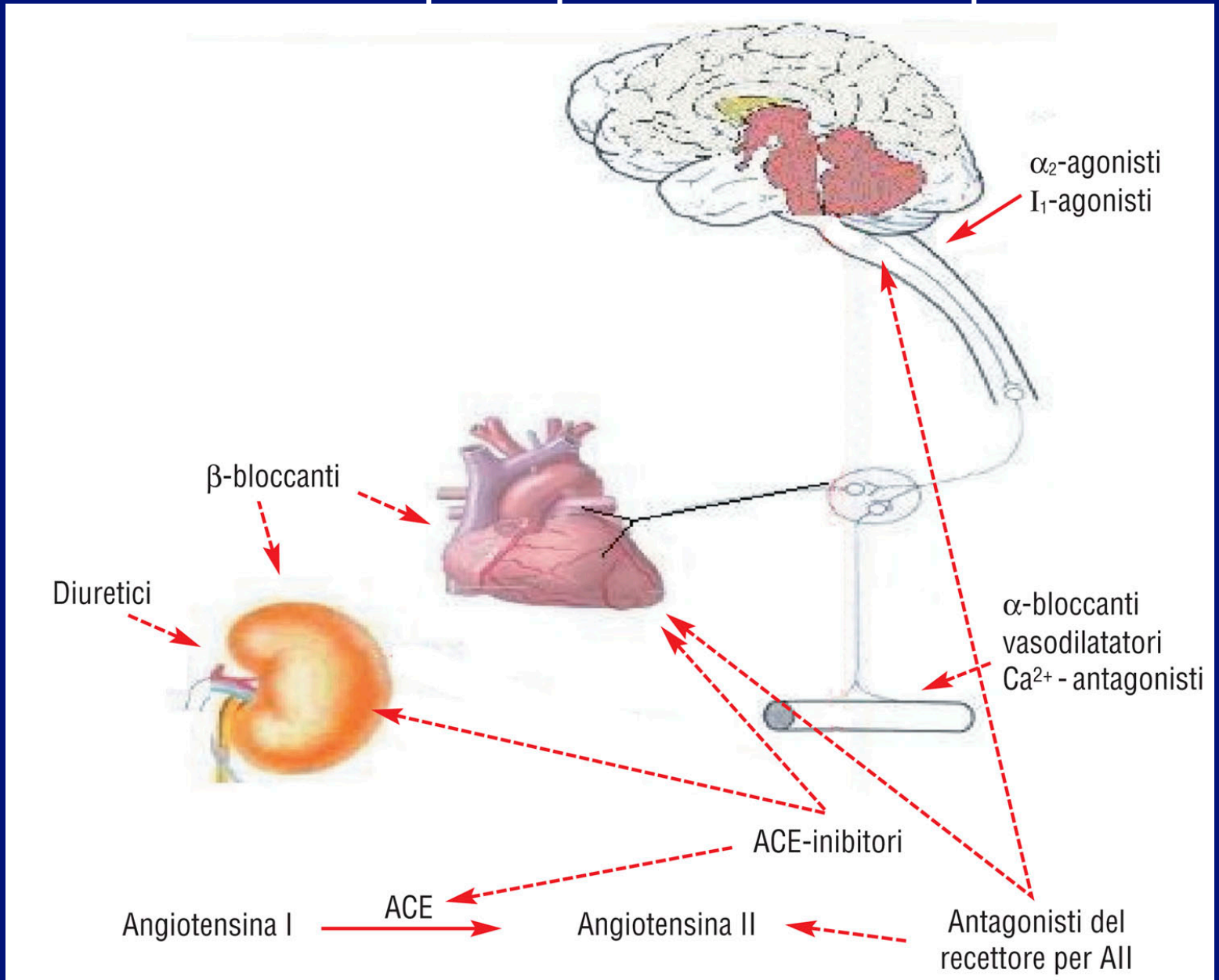
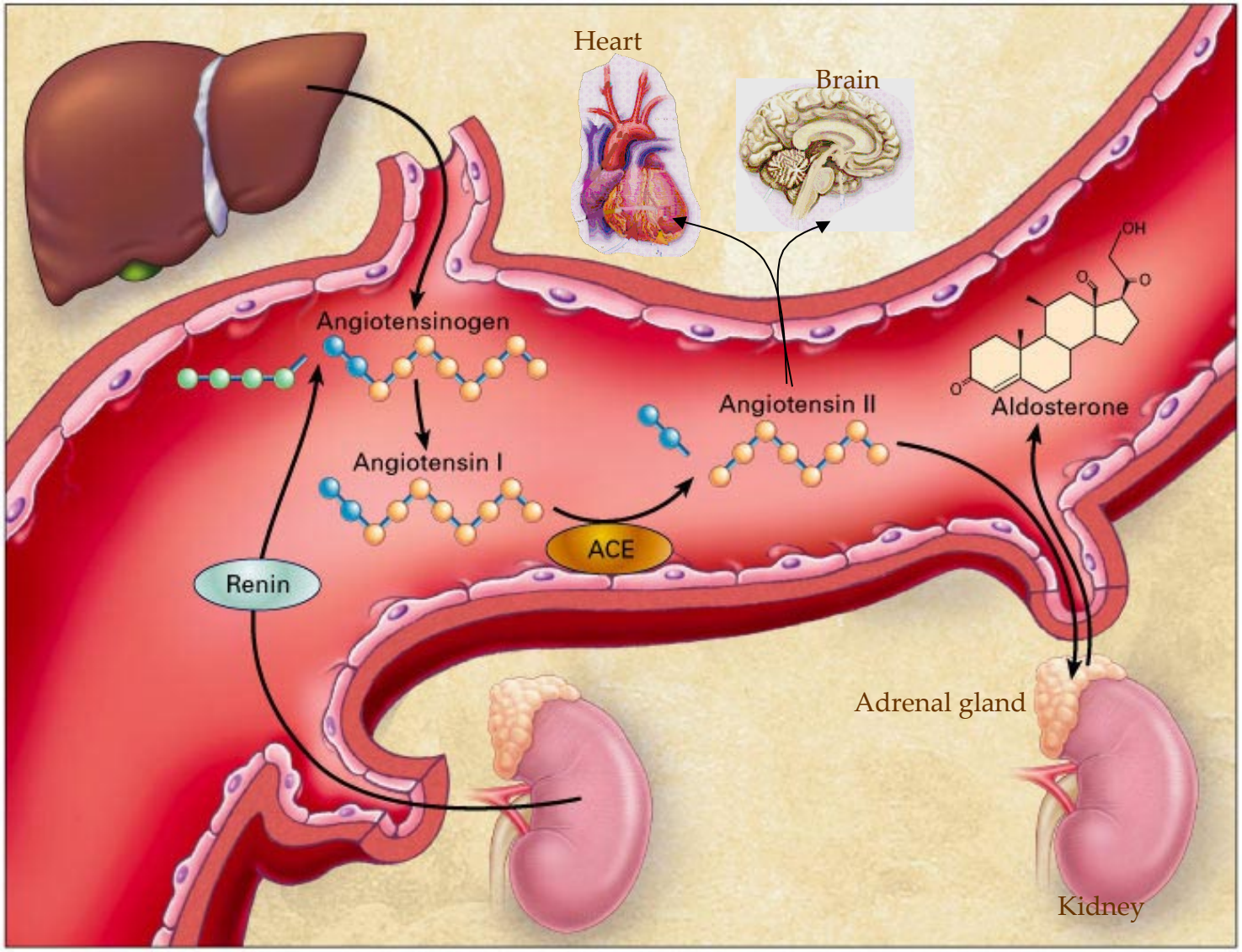
Fattori implicati nella regolazione della pressione arteriosa



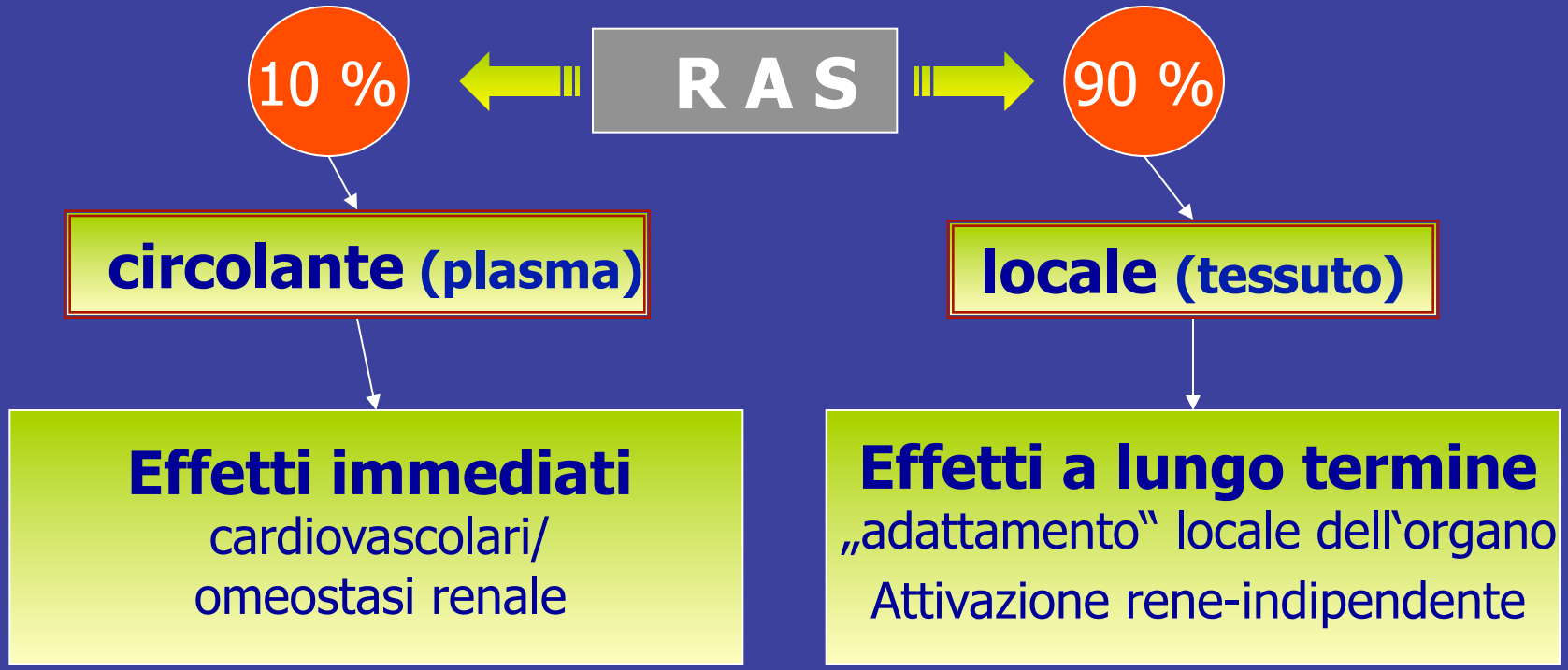
Siti di azione dei principali farmaci anti-ipertensivi



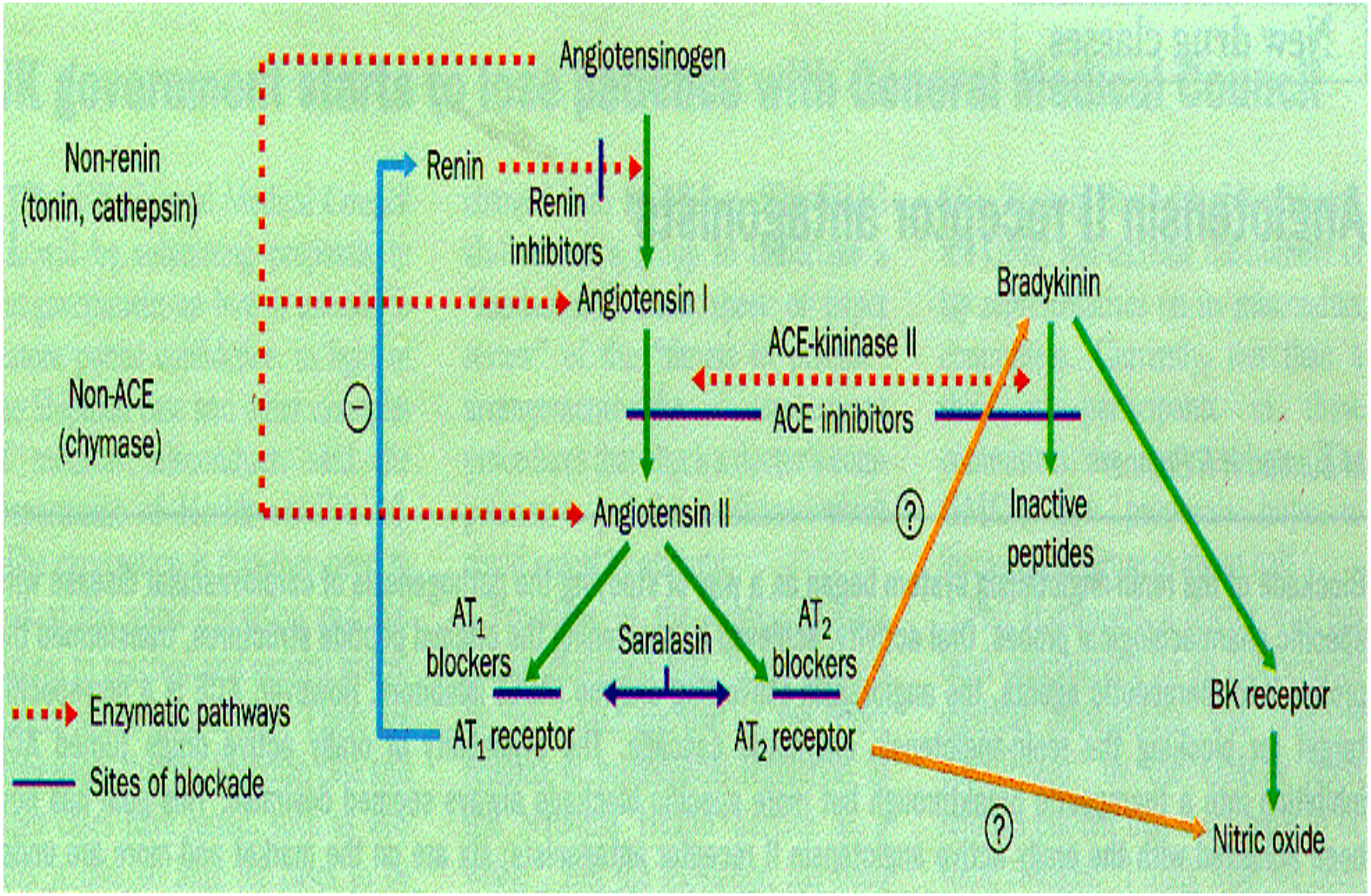

Heart
Brain
Angiotensinogen
Angiotensin I
Angiotensin II
ACE
Renin
Aldosterone
OH
O
O
O
Adrenal gland
Kidney

Sistema renina-angiotensina (RAS)

Ditribuzione dell‘ACE nell‘organismo:

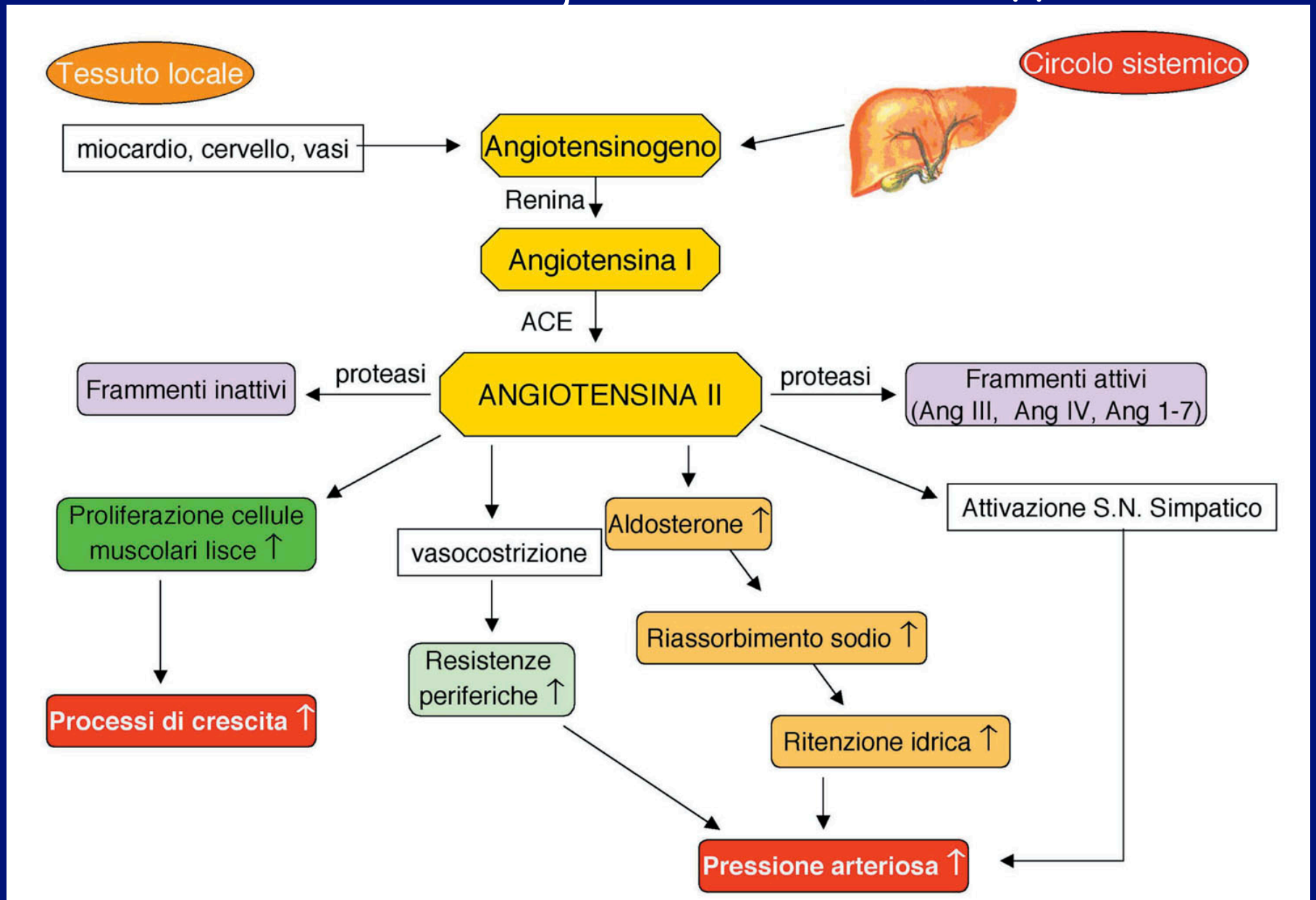


mod. sec Dzau V, Arch Intern Med 153 (1993)

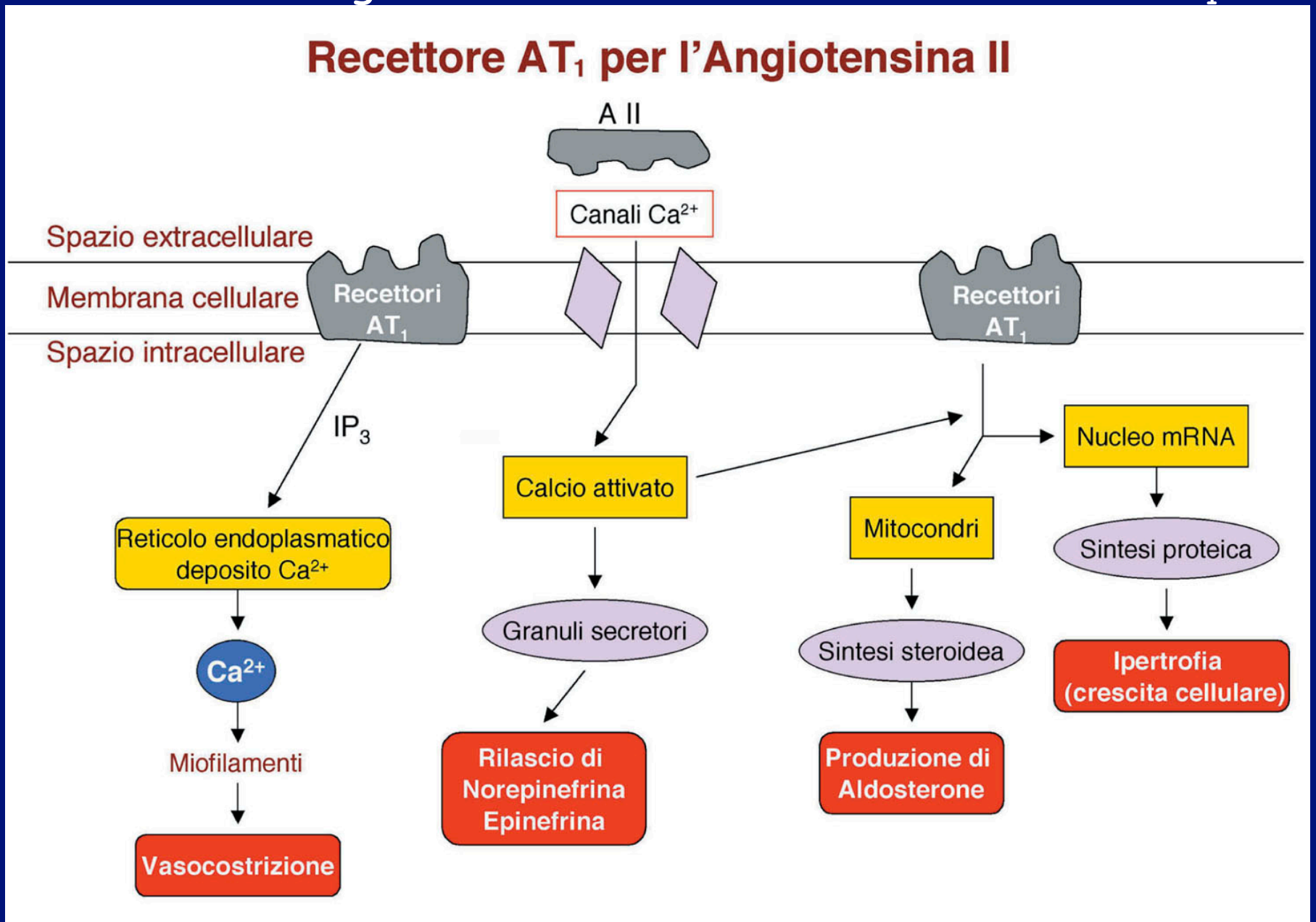


Angiotenin II receptor antagonists. Lancet 355, 637, 2000

Sintesi dell'angiotensina II e suoi effetti



Azioni dell'angiotensina II mediate dal recettore AT_1



ANGIOTENSIN II

Altered Peripheral Resistance

1. Direct Vasoconstriction
2. Enhancement of peripheral noradrenergic neurotransmission
3. Increased sympathetic discharge
4. Release of catecholamines from adrenal medulla

→ Rapid Pressor Response

Altered Renal Function

1. Direct increase of Na reasbsorption in prox tubule
2. Release of aldosterone from adrenal cortex
3. Altered hemodynamics:
   - vasoconstriction
   - Increased NA control on kidney

→ Slow Pressor Response

Altered Cardiovascular Structure

1. Non-hemodinamically mediated effects:

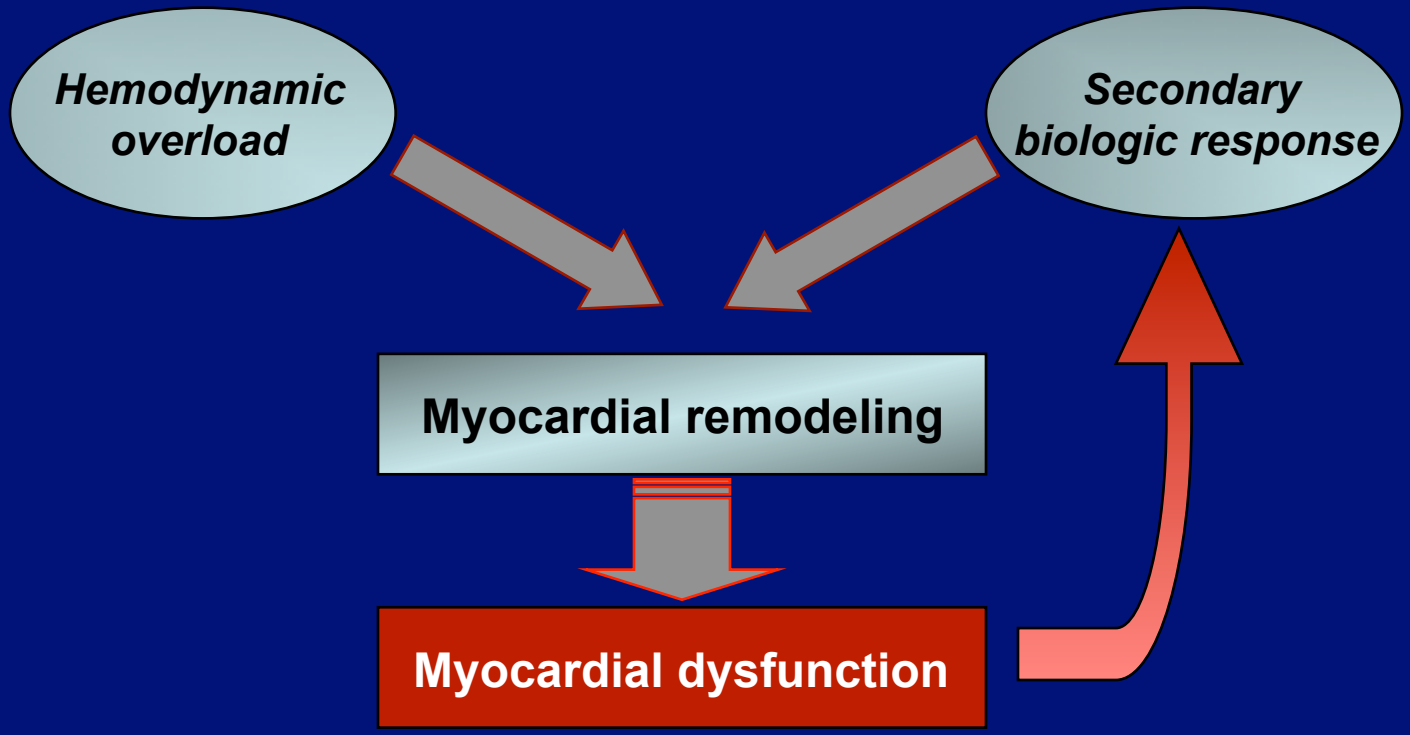
A. Expression of proto-oncogenes
B. Release of Growth Factors
C. Synthesis of extracellular matrix

2. Hemodinamically mediated effects:

A. Increased afterload
B. Increased preload

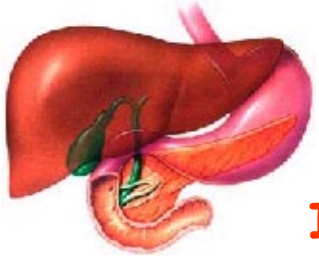
→ Vascular and cardiac hypertrophy and remodeling

Central role of myocardial remodeling in the pathophysiology of heart failure



Hemodynamic overload (e.g., due to myocardial injury) serves as the primary stimulus for myocardial remodeling. With the development of myocardial dysfunction, there is an activation of secondary biologic responses, including the stimulation of systemic neurohormonal systems (e.g., renin-angiotensin and sympathetic nervous systems) and expression of myocardial peptides (e.g., endothelin, angiotensin, inflammatory cytokines) that can act directly on the myocardium to cause further remodeling

FARMACI DEL SISTEMA RENINA-ANGIOTENSINA-ALDOSTERONE



Angiotensin Converting Enzyme -ACE

ACE-inibitori

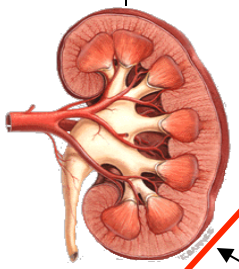
Inibitori della renina

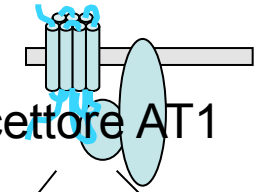
Angiotensinogeno → Angiotensina I → Angiotensina II

renina

Beta-bloccanti

AT1-antagonisti (Sartani)

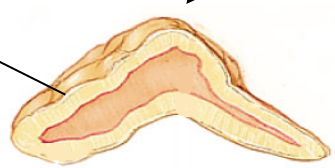


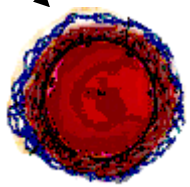


recettore AT1

Spironolattone
Canrenone

aldosterone





vasocostrizione

INIBITORI DELLA RENINA

Gli inibitori della renina sono molecole “modellate” sull’angiotensinogeno umano che bloccano l’azione della renina sul substrato legandosi in maniera competitiva al sito attivo della renina al quale rimangono legati senza subire alcun attacco enzimatico (falsi substrati).

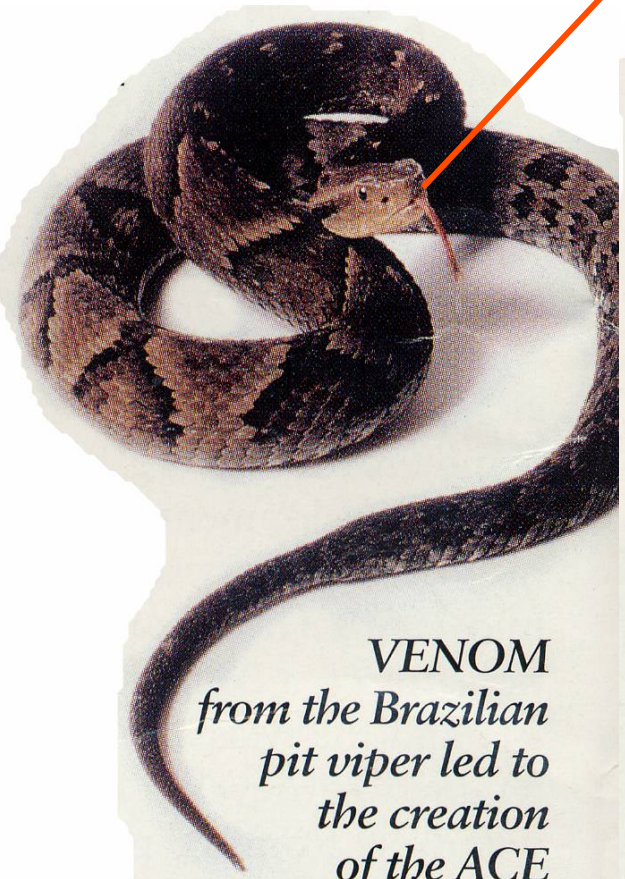
Enalkiren

Ramikiren

Aliskiren

Zankiren

TEPROTIDE – BRADYCHININ POTENTIATING FACTOR (Ferreira)



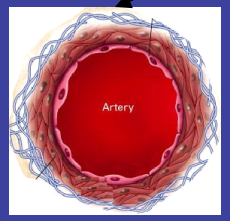
VENOM from the Brazilian pit viper led to the creation of the ACE inhibitor captopril.

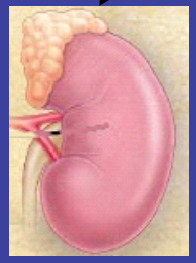
In the 1970s Squibb researchers Miguel A. Ondetti and David W. Cushman exploited this kind of information—with the help of the venom from the Brazilian pit viper. The toxin catastrophically lowers the blood pressure of its victims. A component of the venom blocks the action of angiotensin converting enzyme (ACE), which raises blood pressure by causing blood vessels to constrict. In part through crystallography, the researchers constructed a model of the active ACE site and created captopril, which blocks the site, thereby inhibiting ACE and bringing down the blood pressure.

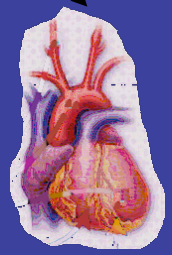
The 1998 National Medal of Technology, Scientific American, March 1999

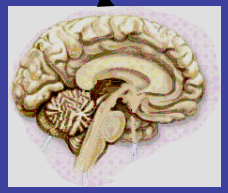
ACE-I

↓ ANG









Vascular wall

↑ VASODILATATION

Kidney
Adrenal gland

↓ ALDOSTERONE

↑ Na+ excretion

Heart

↓ INOTROPIC, CHRONOTROPIC ACTIONS

Brain

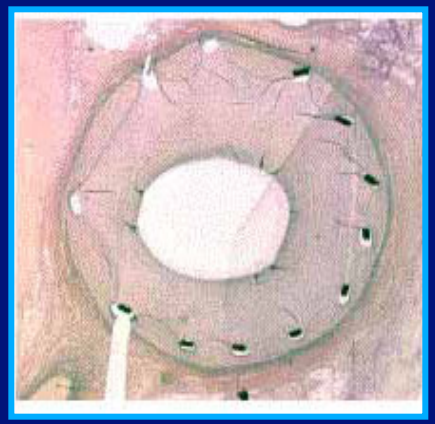
↓ SYMPATHETIC TONE

↓ BLOOD PRESSURE

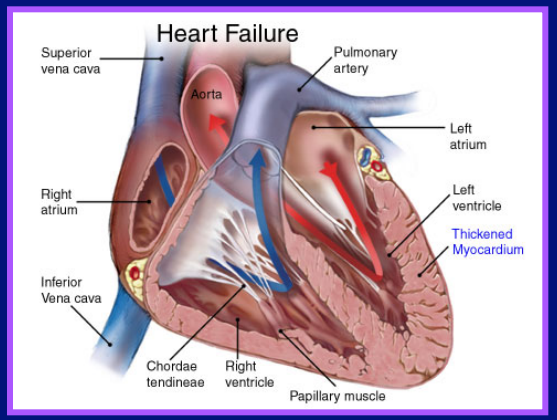
⬇ ANG II

ACE-I

⬇ RIMODELLAMENTO VASCOLARE



⬇ RIMODELLAMENTO CARDIACO



Effetti farmacodinamici degli ACE-I

Effetti ormonali

Diminuzione	Aumento
Angiotensina II plasmatica	Angiotensina I
Aldosterone plasmatico	Renina
Kallicreina urinaria	Kinine urinarie

Effetti emodinamici

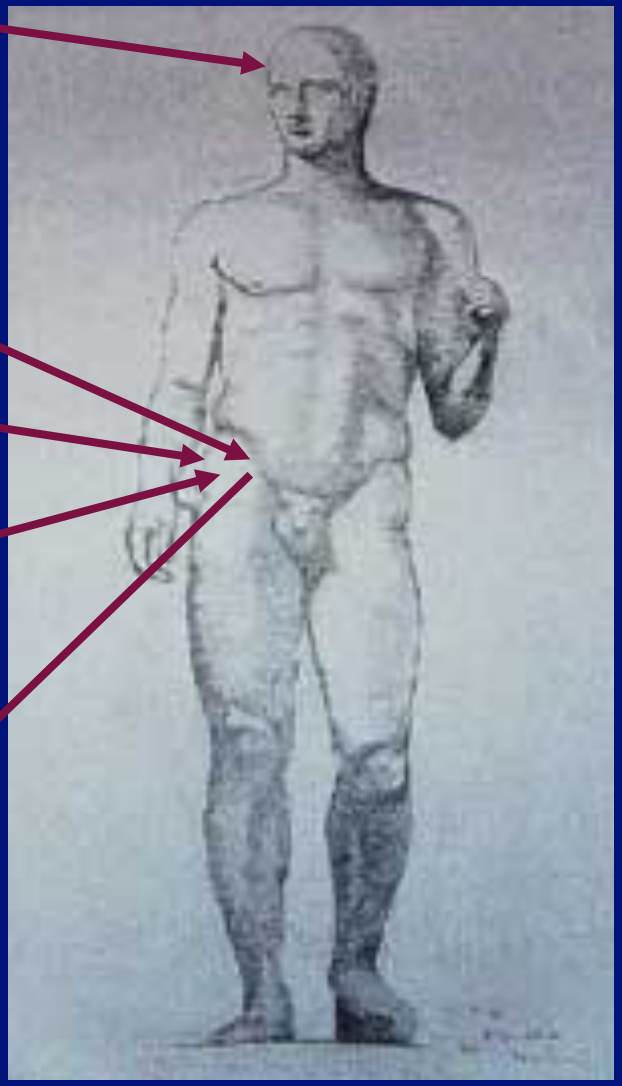
Diminuzione	Aumento
Resistenze periferiche	Gettata cardiaca
Pressione arteriosa	Flusso ematico regionale
	Flusso ematico renale

ACE-Inibitori ed ipertensione

ACE-I

- ⬇sistema adrenergico
- ⬇aldosterone
- ⬆bradichinina prostaglandine vasorilascianti
- dilatazione arteriole
- ⬇resistenze vascolari sistemiche

⬇ pressione arteriosa

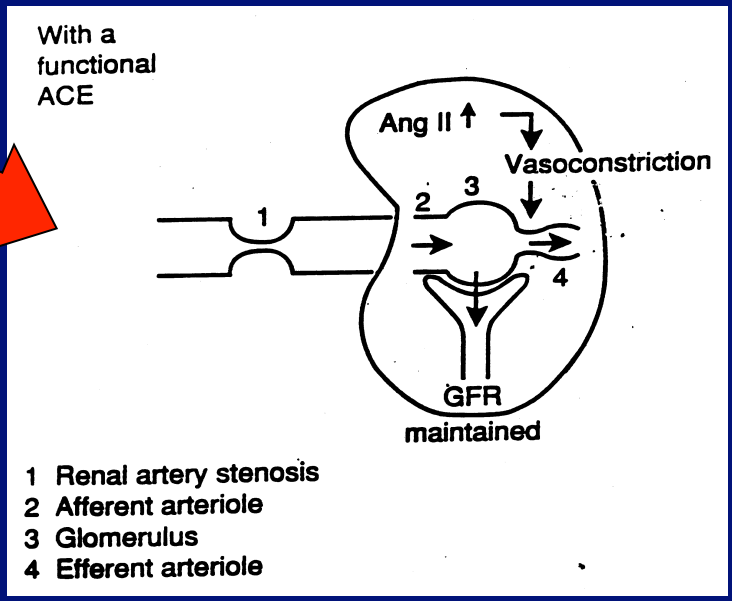


Principali indicazioni degli ACE-Inibitori

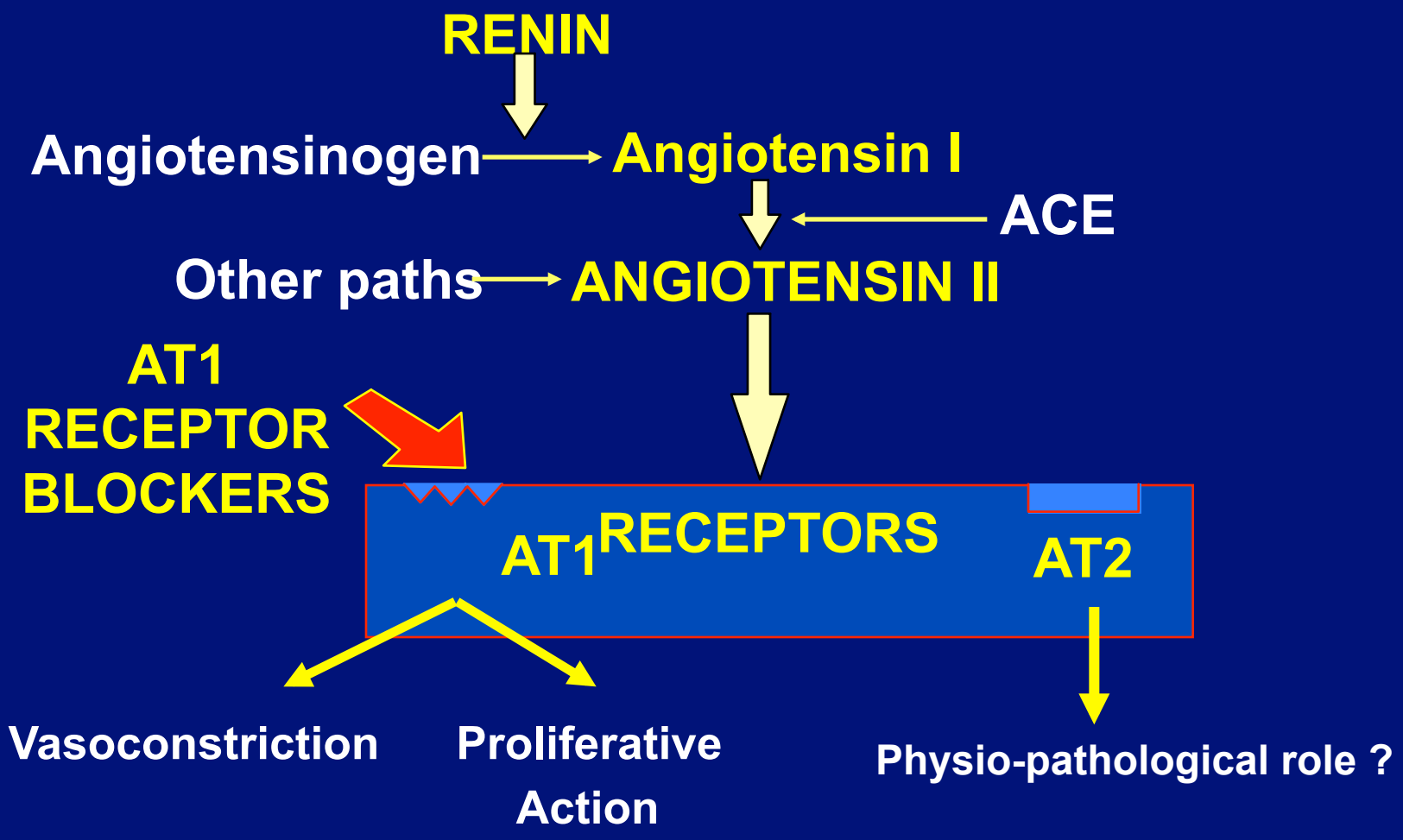
- ✓ **Ipertensione**
- ✓ **Scompenso cardiaco**
- ✓ **Post-infarto**
- ✓ **Nefropatia diabetica e ipertensiva**
- ✓(microalbuminuria)

ACE-I CONTRAINDICATIONS

- Renal artery stenosis
- Renal insufficiency
- Hyperkalemia
- Arterial hypotension
- Intolerance (due to side effects)



ANTAGONISTS OF AT-1 receptors
MECHANISM OF ACTION

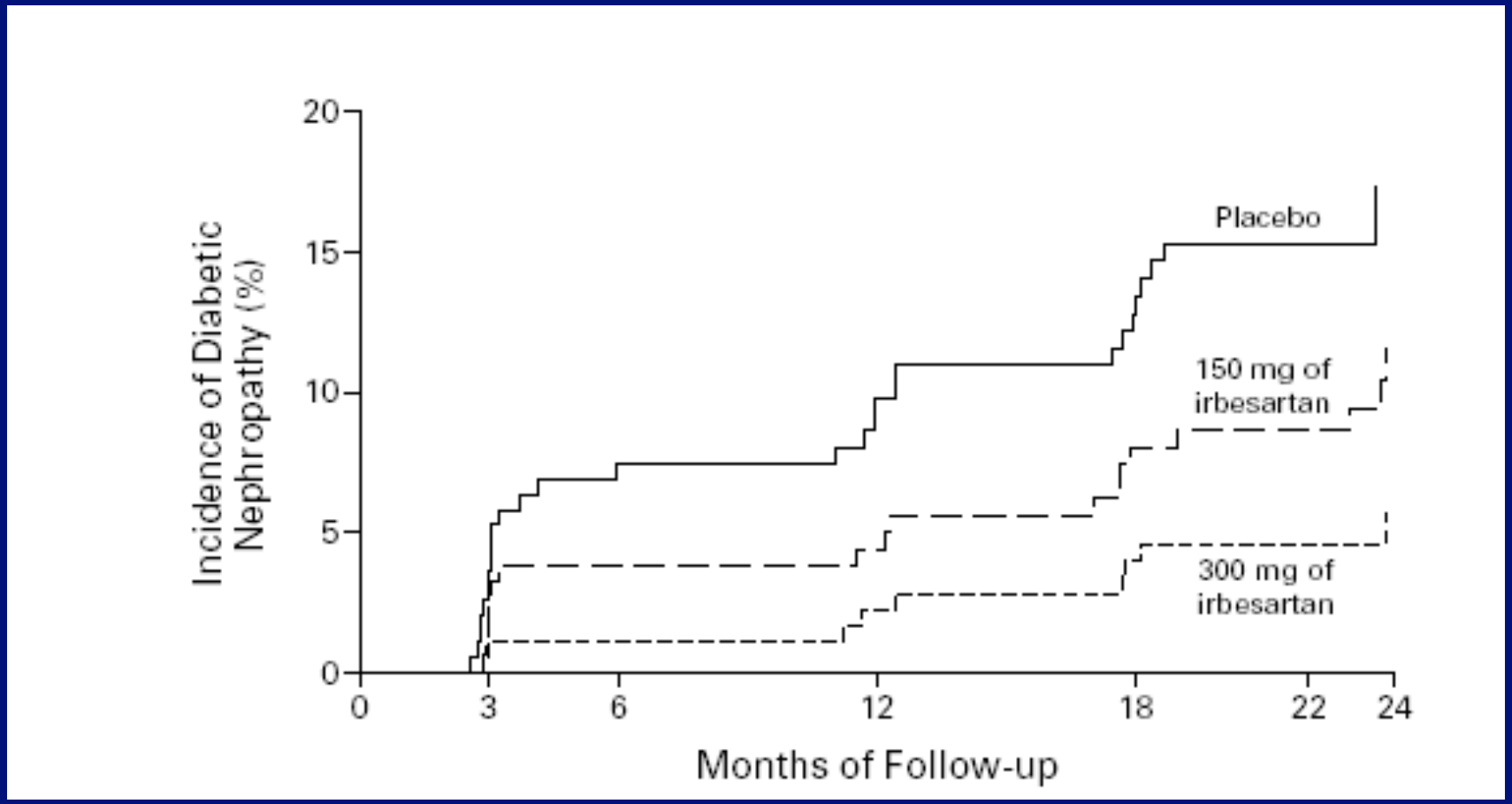


Antagonisti dei Recettori AT-1 dell'Angiotensina II
SARTANI

Antagonisti competitivi e selettivi dei recettori AT-1

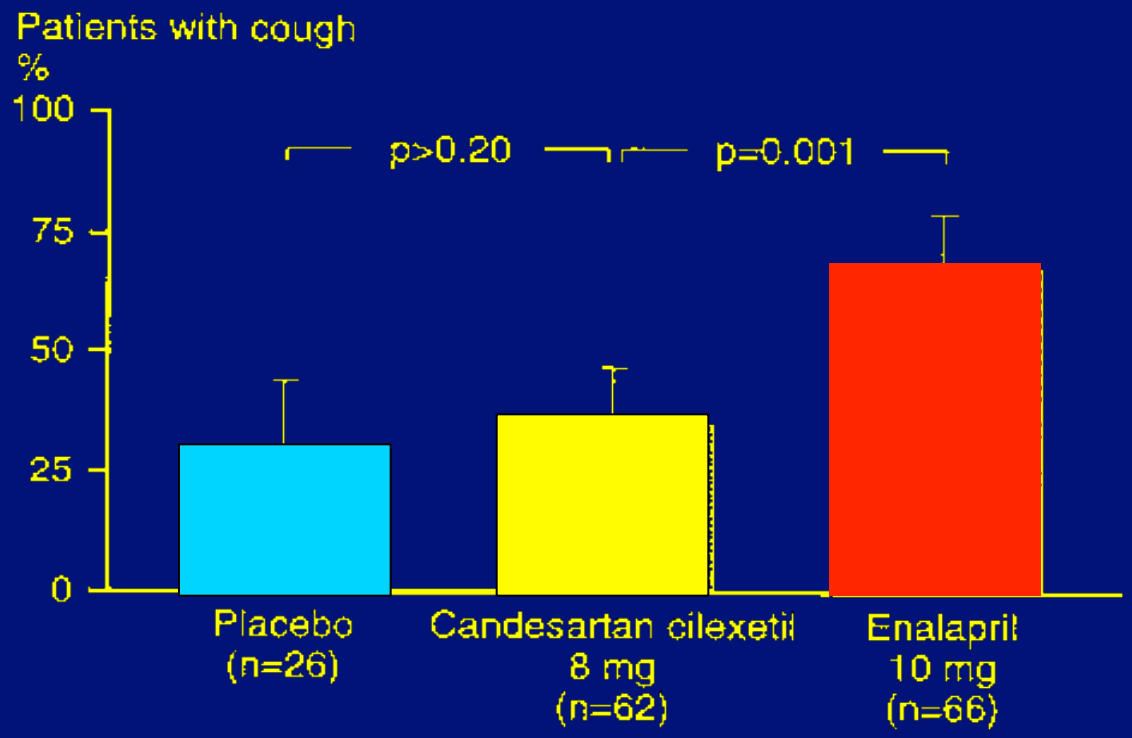
- Losartan
- Valsartan
- Irbesartan
- Eprosartan
- Candesartan cilexetil
- Olmesartan medoxomil

EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES



Parving et al., NEJM 345:870 2001

INCIDENZA DI TOSSE



Studio clinico in pazienti ipertesi con storia di tosse da ACE-inibitori
Am. J. Hypert. 13, 214, 2000