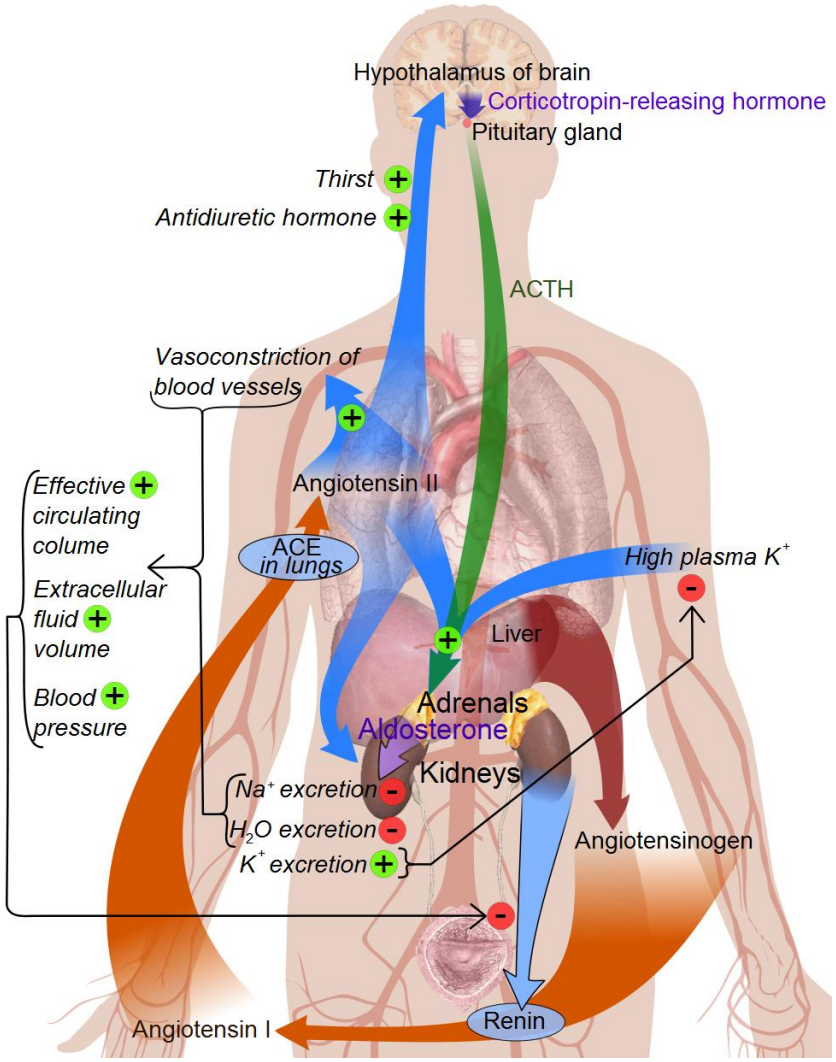
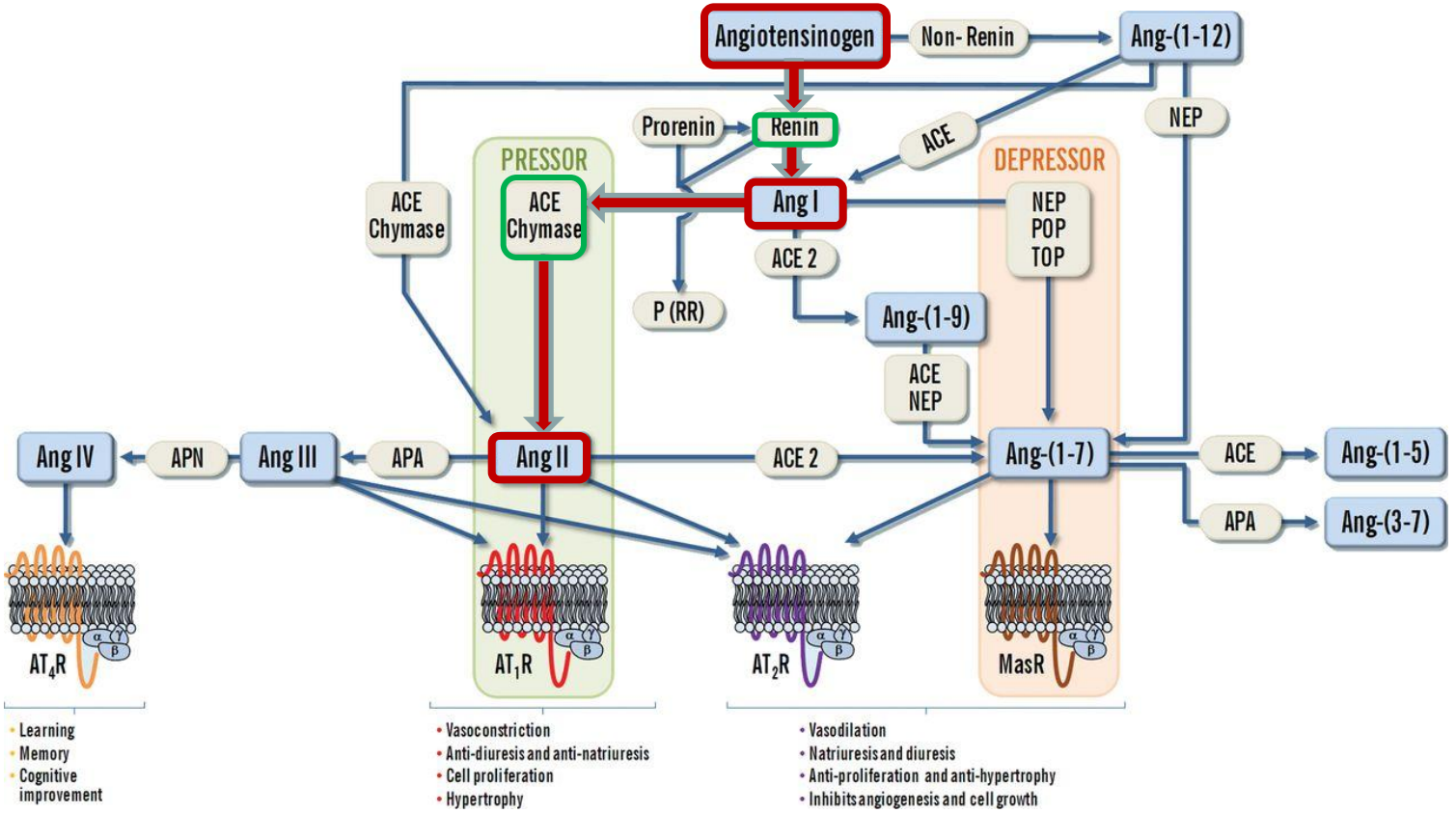
# THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

• The **renin–angiotensin system** (**RAS**) or the **renin–angiotensin–aldosterone system** (**RAAS**) is a hormone system that is involved in the regulation of the plasma sodium concentration and arterial blood pressure.



# ANGIOTENSIN II

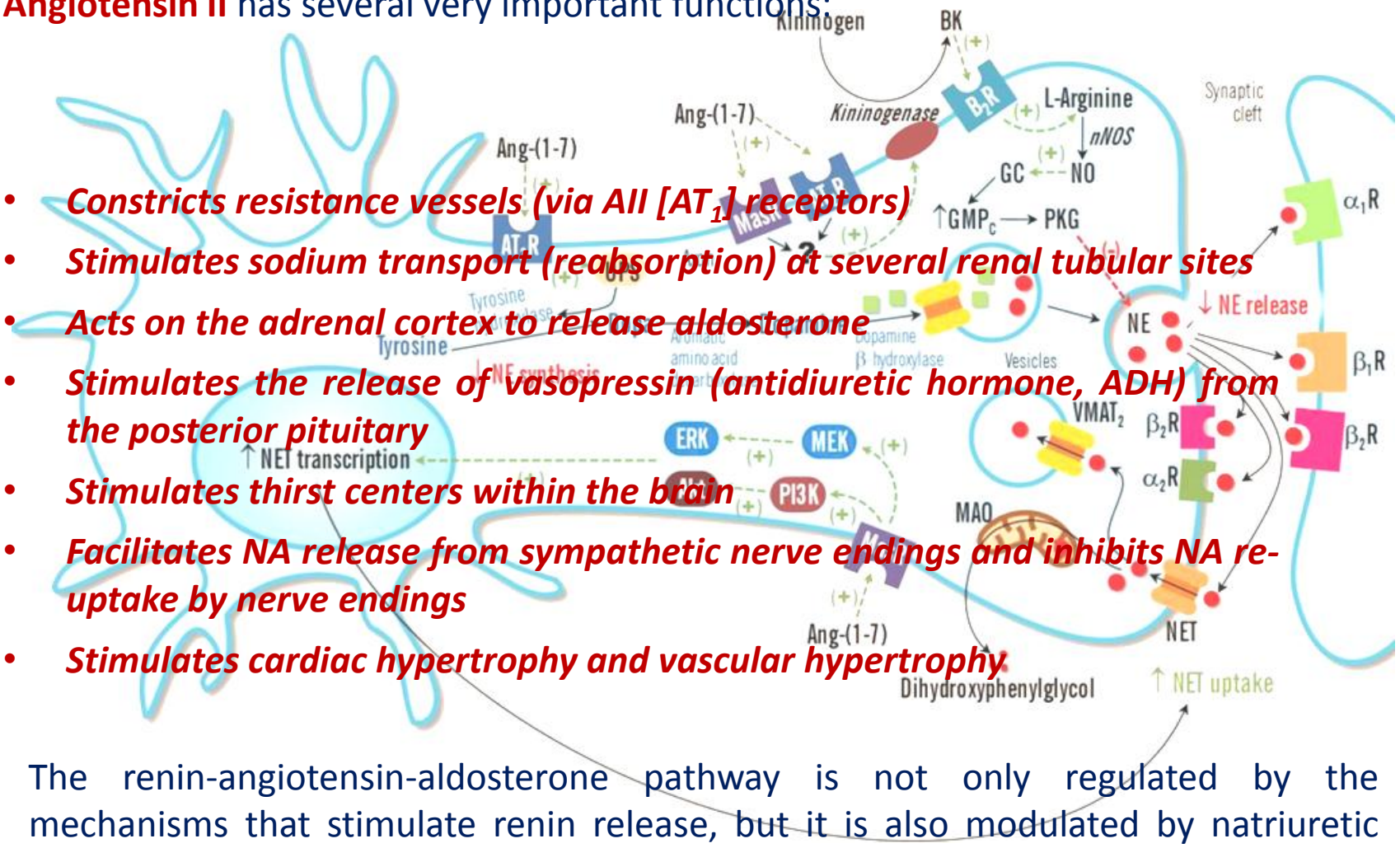
When renin is released into the blood, it acts upon a circulating substrate, **angiotensinogen**, that undergoes proteolytic cleavage to form the decapeptide **angiotensin I**. Vascular endothelium, particularly in the lungs, has an enzyme, **angiotensin converting enzyme (ACE)**, that cleaves off two amino acids to form the octapeptide, **angiotensin II** (AII), although many other tissues in the body (heart, brain, vascular) also can form AII.



# ANGIOTENSIN II

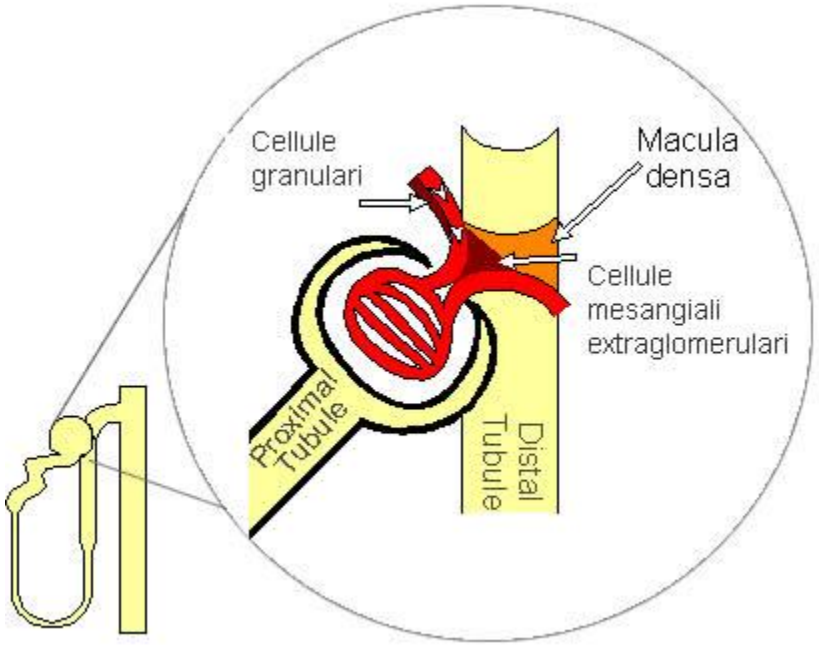
**Angiotensin II** has several very important functions:

- ***Constricts resistance vessels (via AII [$AT_1$] receptors)***
- ***Stimulates sodium transport (reabsorption) at several renal tubular sites***
- ***Acts on the adrenal cortex to release aldosterone***
- ***Stimulates the release of vasopressin (antidiuretic hormone, ADH) from the posterior pituitary***
- ***Stimulates thirst centers within the brain***
- ***Facilitates NA release from sympathetic nerve endings and inhibits NA re-uptake by nerve endings***
- ***Stimulates cardiac hypertrophy and vascular hypertrophy***

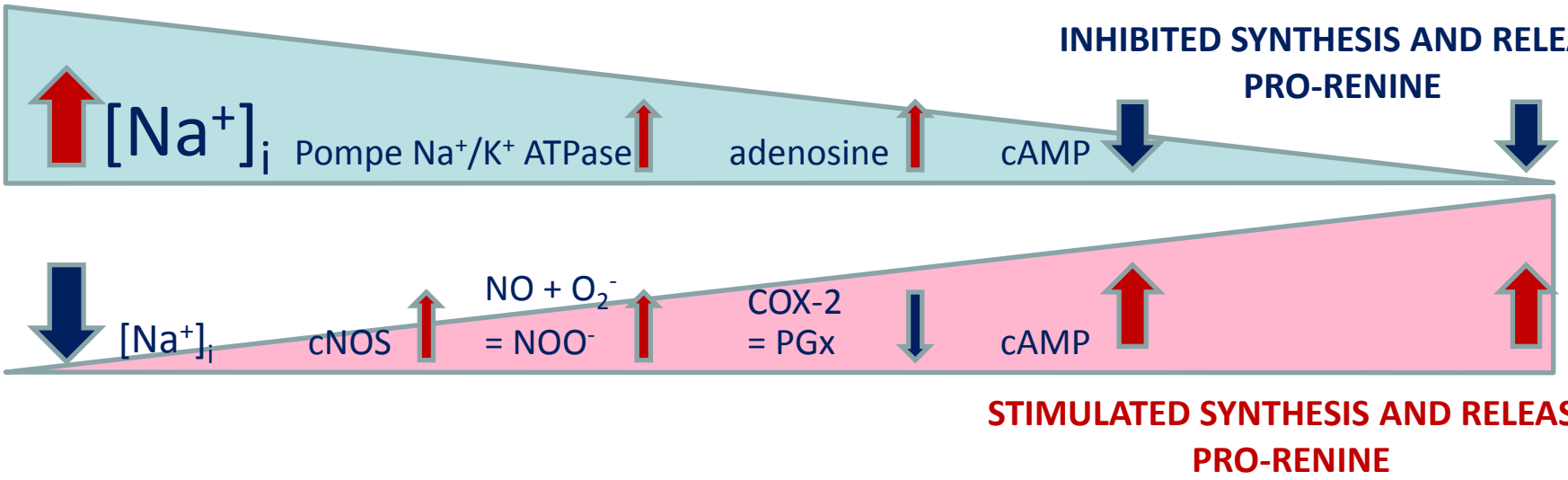



The renin-angiotensin-aldosterone pathway is not only regulated by the mechanisms that stimulate renin release, but it is also modulated by natriuretic peptides (ANP and BNP) released by the heart. These natriuretic peptides acts as an important counter-regulatory system.

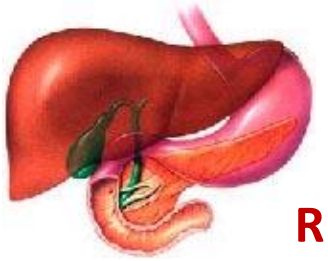
# FEED-BACK of RENIN-ANGIOTENSIN regulation




- Renin release is activated by a reduced systemic resistance and low volemia (low-salt diet, diuretics, hemorragic state, heart failure, cyrrhosis, nephrotic syndrome )
- This last condition (more appropriately, changes in the saline load), is directly responsible for iunxtaglomerular regulation with opposite effects on renin release



# DRUGS OF THE RAAS SYSTEM



Angiotensin Converting Enzyme -ACE

**ACE-INHIBITORS**

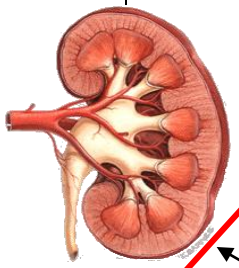
**RENIN INHIBITORS**

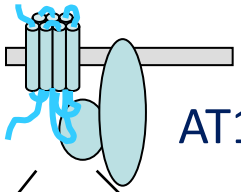
Angiotensinogen → Angiotensin I → Angiotensin II

renin

**BETA BLOCKERS**

**AT1-ANTAGONISTS (ARBs)**

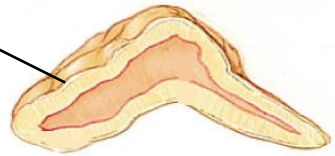


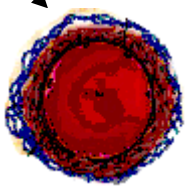


AT1 receptor

aldosterone

**DIURETICS anti-aldosterone**



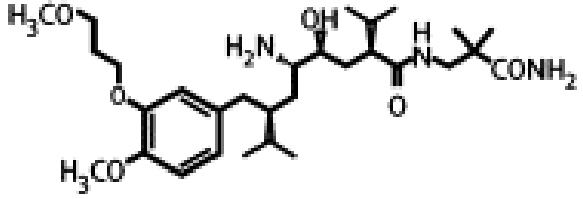


vasoconstriction

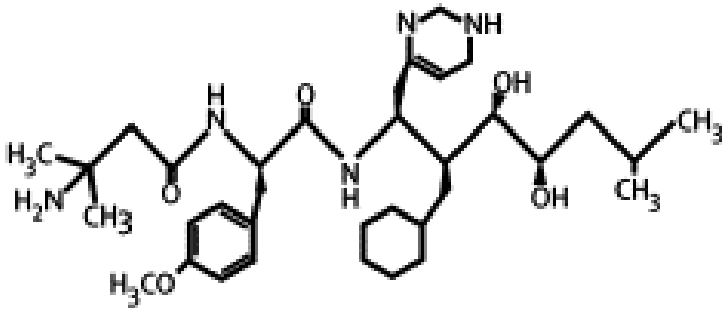
# • RENIN INHIBITORS

These drugs are molecules resembling angiotensinogen (act as false substrates), competitively binding renin enzyme at the catalytic active site. This binding is more stable than the physiological one. Therefore, by sequestering renin, renin inhibitors slow down the enzymatic reaction converting angiotensinogen to angiotensin I

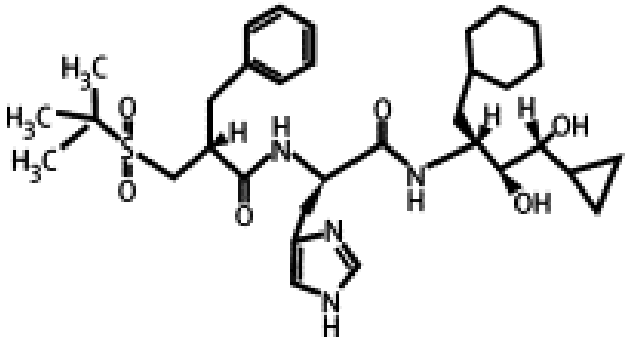
## Aliskiren



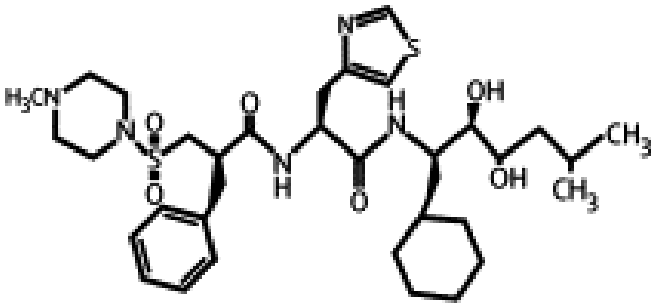
## Enalkiren



## Remikiren



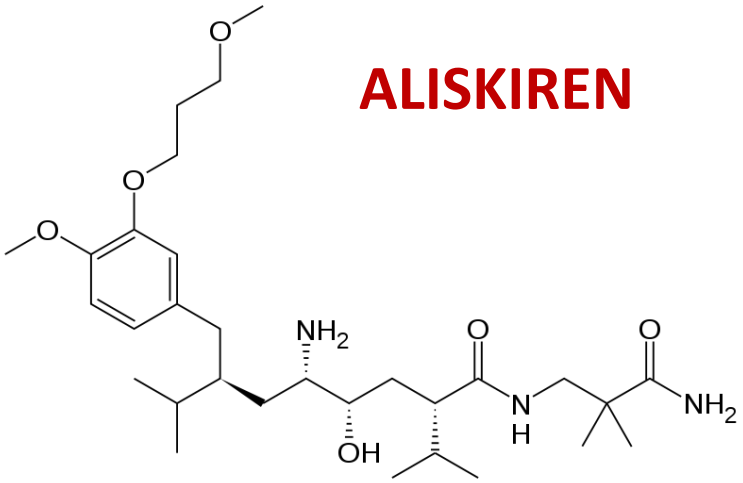
## Zankiren



J Clin Pharmacol 1994, 34: 873

Lancet 2006, 368, 9545: 1449

# ALISKIREN




| | |
|---|---|
| Bioavailability | low (approx 2.5%) |
| Metabolism | Liver, CYP3A4-mediated |
| Half-life | 24 hours |
| Disposal | Renal |

**MECHANISM of ACTION:** Aliskiren binds renin on S3bp position at the catalytic site.

**MEDICAL USE:** In 2007, FDA approved aliskiren for the treatment of essential hypertension

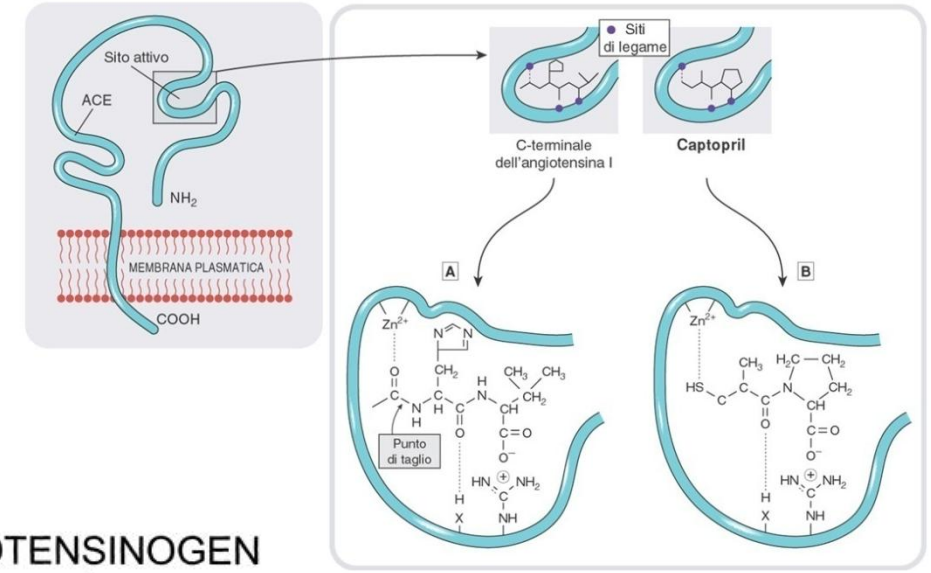
Aliskiren (300 mg/die) co-administered with losartan has been demonstrated to significantly reduce albuminuria levels in patients with hypertension and diabetes (NEJM, 2008;358:2433-46).

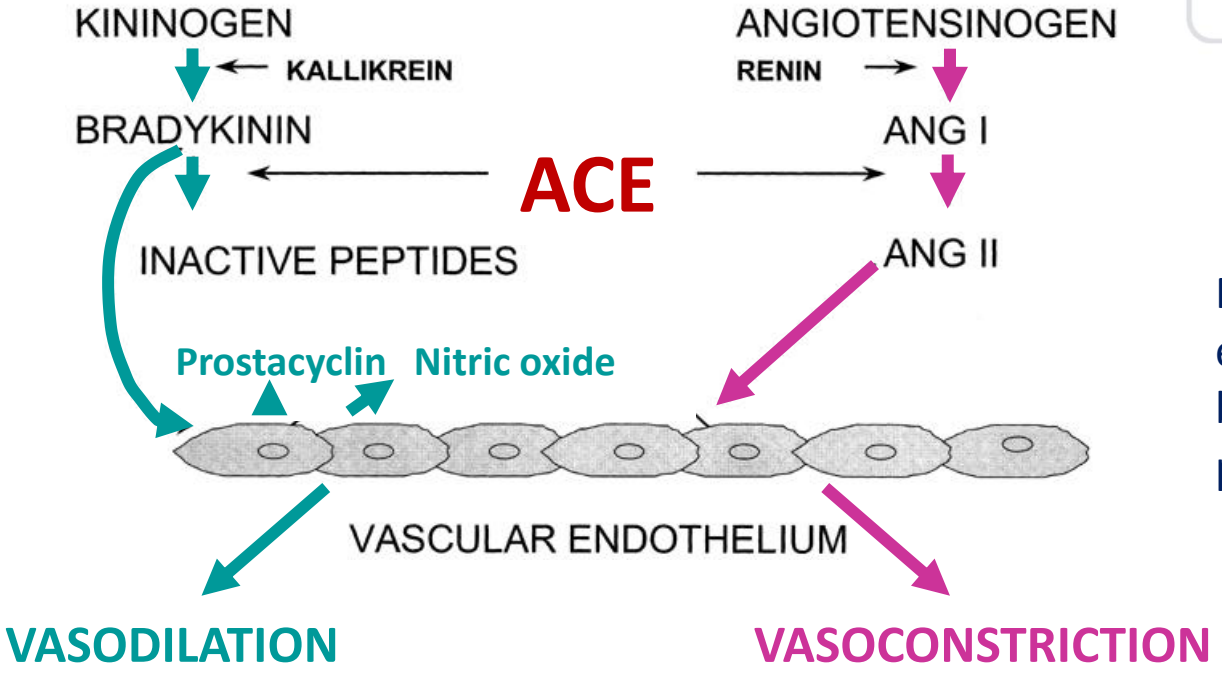
**SIDE EFFECTS**

hypotension, iperkaliemia (mainly if associated to ACE-I)
diarrea and gastro-intestinal discomfort
rash, angioedema

# ANGIOTENSIN-CONVERTING ENZYME

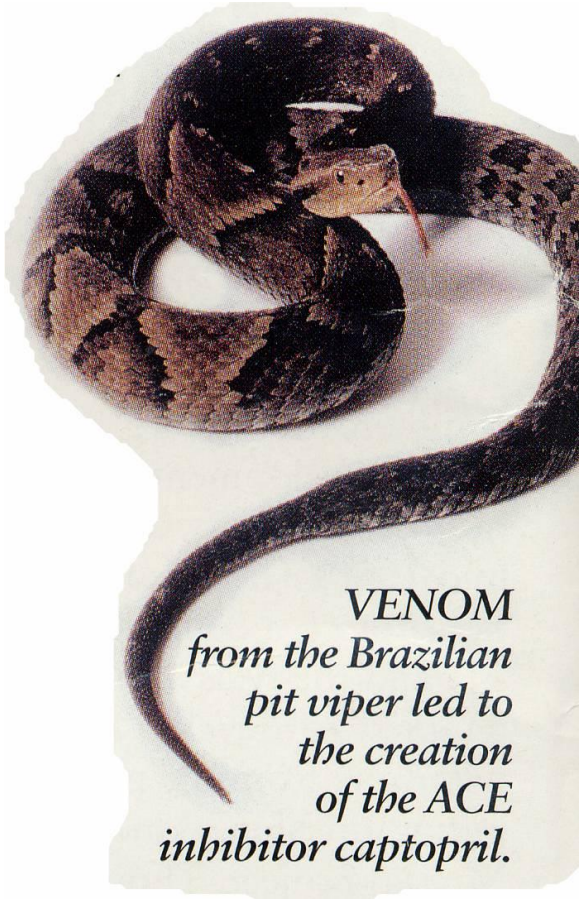
This transmembrane carboxypeptidase mediates several catalytic reactions




For example, the enzyme transforms bradykinin to inactive peptides

# • ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE-I)




• in 1965 brasilian Dr Sergio Ferreira reported a 'bradykinin potentiating factor (BPFs) TEPROTIDE" among components of the venom from *bothrops jararaca*, a South American snake (Brit J Pharmacol & Chemother 1965).

• this toxin is responsible for a drastic drop of systemic blood pressure in snake victims.

• in the '70s, Dr Ondetti and Cushman were able to isolate and characterize a venom component blocking ACE activity (Biochemistry 1971, 10:4033)

• in the next years, the first orally available ACE-inhibitor was released (Science 1977; 196: 441) and approved by FDA (1981).

# ACE-INHIBITORs

ACE-Inhibitors are grouped according to their chemical structure:

1- oligopeptides from snake venom and analogues (easily degraded, no use).

2- non peptydic inhibitors, bind to Zinc atom of the ACE catalytic site.

**OLIGOPEPTIDES**

- **Teprotide (SQ20881)**
- **BPP5a**

**NON PEPTIDES**

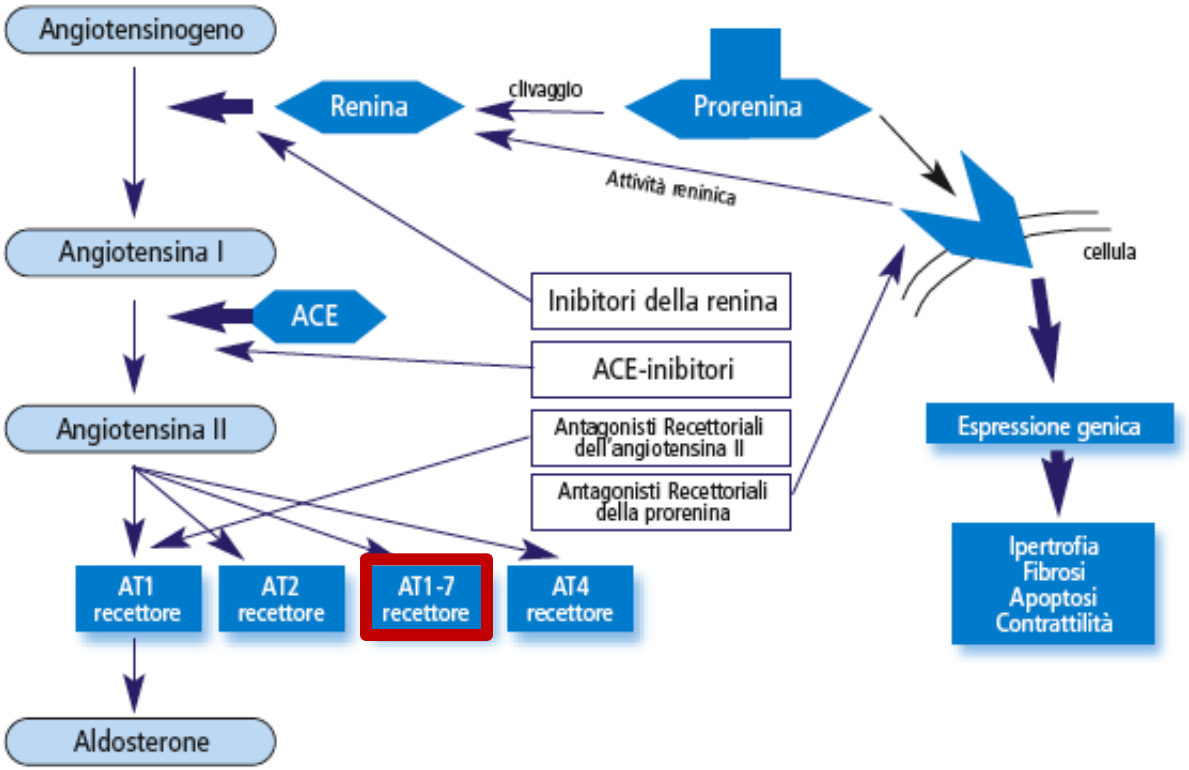
- **Captopril**
- **Alacepril**
- **Benazepril**
- **Delapril**
- **Enalapril**
- **Fosinopril**
- **Lisinopril**
- **Perindopril**
- **Quinapril**
- **Ramipril**

# PEPTIDES OTHER THAN Ang II

- at least in part, beneficial effects of ACE-inibitors may depend on increased production of **Ang (1-7),** subsequent to high availability of Ang I under ACE inhibition

- on these conditions, a substantial amount of accumulating Angiotensin (1-9) is converted to Ang (1-7) by the carboxypeptidase ACE2.

- although previously considered an inactive derivative of Ang II, **Ang (1-7)** is able to increase vasodilation by facilitating NO and prostacyclin release from endothelial cells, thus counteracting pro-mitogenic and sodium-retention properties of Ang II.



# MAIN PK FEATURES of ACE-Inhibitors

| | Captopril | Enalapril | Lisinopril | Ramipril | Quinapril | Fosinopril |
|---|---|---|---|---|---|---|
| Binding residues | **-SH** | **-COOH** | **-COOH** | **-COOH** | **-COOH** | **-POOH** |
| Prodrug | **NO** | YES | **NO** | YES | YES | YES |
| Protein binding % | 25 | 50 | 10 | 56 | 97 | 96 |
| Disposal (kidney) | GF/TS | GF/TS | GF | GF/TS | GF/TS | GF/TS |
| Dose | 50-150 | 5-40 | 5-40 | 5-20 | 5-40 | 10-40 |
| $t_{max}$ (h) | 0.5-1.5 | 3-4 | 6-7 | 1.5-3 | 1.5-2 | 3 |
| $t_{slow}$ (h) | - | 30-50 | 30 | 110 | - | 12 |
| Peak (h) | 0.25-0.5 | 1-4 | 1-2 | 0.5-2 | 1-2 | 1-2 |
| Duration | **3-12** | **12-30** | **18-30** | **≥24** | **≤24** | **24** |

**Almost all ACE-I are PRODRUGS**

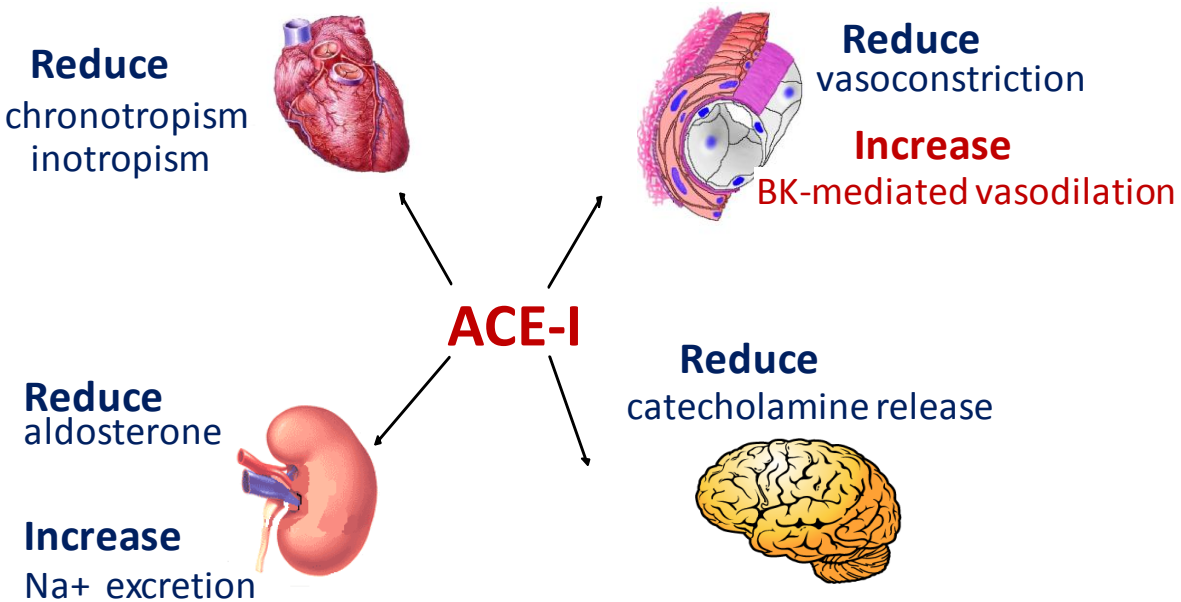
# MEDICAL USE FOR ACE-Inhibitors

## • HYPERTENSION

ACE inhibitors are effective in the treatment of **primary hypertension** and **hypertension caused by renal artery stenosis**, which causes renin-dependent hypertension owing to the increased release of renin by the kidneys.

Reducing angiotensin II formation leads to arterial and venous dilation, which reduces arterial and venous pressures.

By reducing the effects of angiotensin II on the kidney, ACE inhibitors cause natriuresis and diuresis, which decreases blood volume and cardiac output, thereby lowering arterial pressure

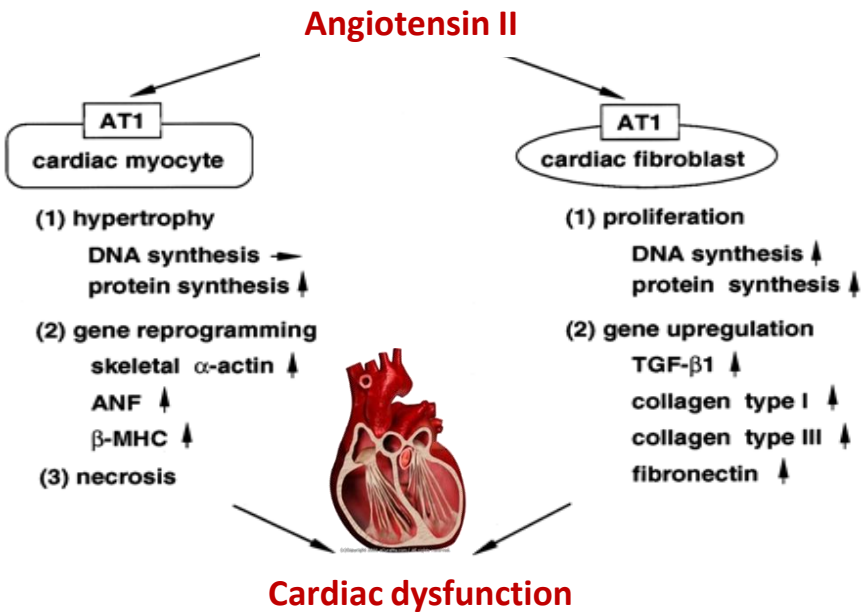


# MEDICAL USE FOR ACE-Inhibitors

## • HEART FAILURE

ACE inhibitors have proven to be very effective in the treatment of heart failure caused by systolic dysfunction (e.g., dilated cardiomyopathy) because of:

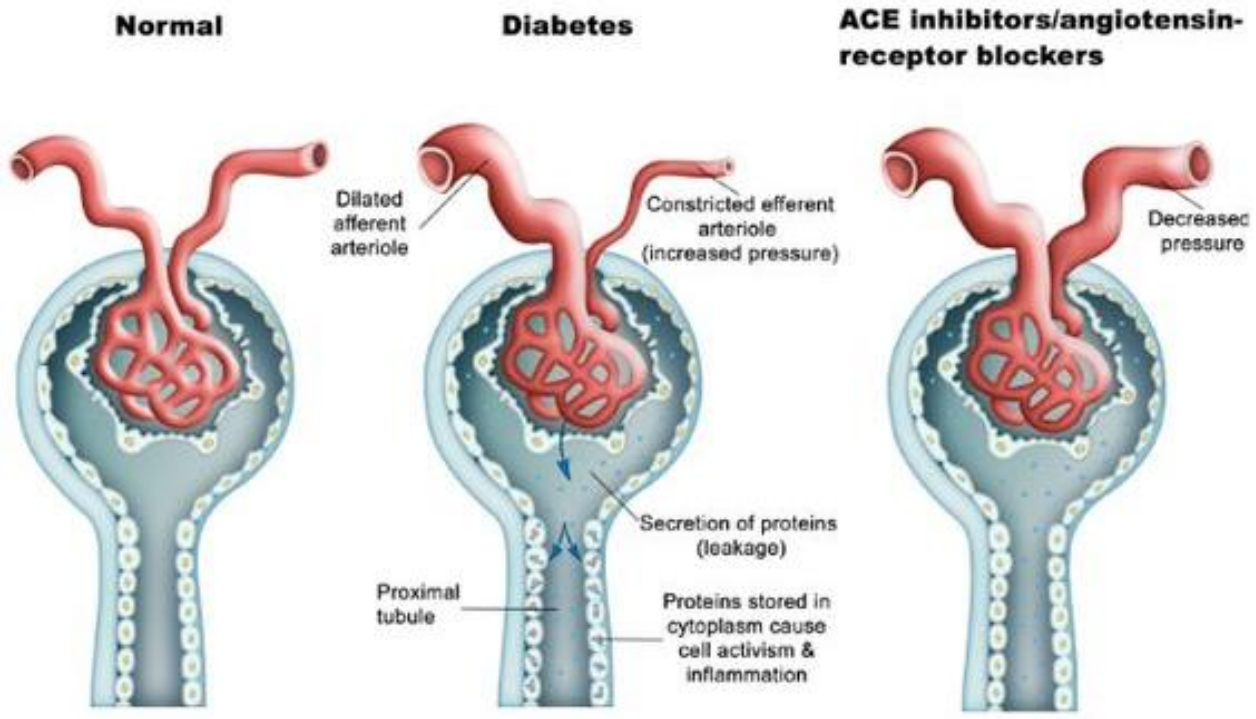
- **Reduced afterload**, which enhances ventricular stroke volume and improves ejection fraction.
- **Reduced preload**, which decreases pulmonary and systemic congestion and edema.
- **Reduced sympathetic activation**, which has been shown to be deleterious in heart failure.
- **Improving the oxygen supply/demand ratio** primarily by decreasing demand through the reductions in afterload and preload.
- **Prevents** angiotensin II from triggering deleterious **cardiac remodeling**.



# MEDICAL USE FOR ACE-Inhibitors

- **NEPHROPATHY by HYPERTENSION or DIABETES**

ACE- I are effective in slowering renal disease by diabetes or hypertension because they reduce the vasoconstriction in the efferent renal artery. In this way less protein crosses the glomerular filter into the tubule of nephron



# SIDE EFFECTS of ACE-INHIBITORS

- First-Dose Hypotension
  - Usually occurs with initial dose.
  - Worse in patients with severe hypertension, or are on diuretics, or are sodium or volume depleted.
- Cough
  - "Persistent, dry, irritating, nonproductive cough can develop with all ACE inhibitors." (Lehne, 2007, pg. 466)
  - Due to rise in bradykinin which occurs due to inhibition of kinase II.
- Hyperkalemia
  - Potassium levels rise due to the inhibition of aldosterone, which causes potassium to be retained by the kidneys.
- Renal Failure
  - Can cause renal insufficiency in people who have bilateral renal artery stenosis, because dropping the pressure in the renal arteries in these patients can cause glomerular filtration to fail.
- Fetal Injury
  - In the second and third trimesters a fetus can experience hypotension, hyperkalemia, skull hypoplasia, renal failure, and death.

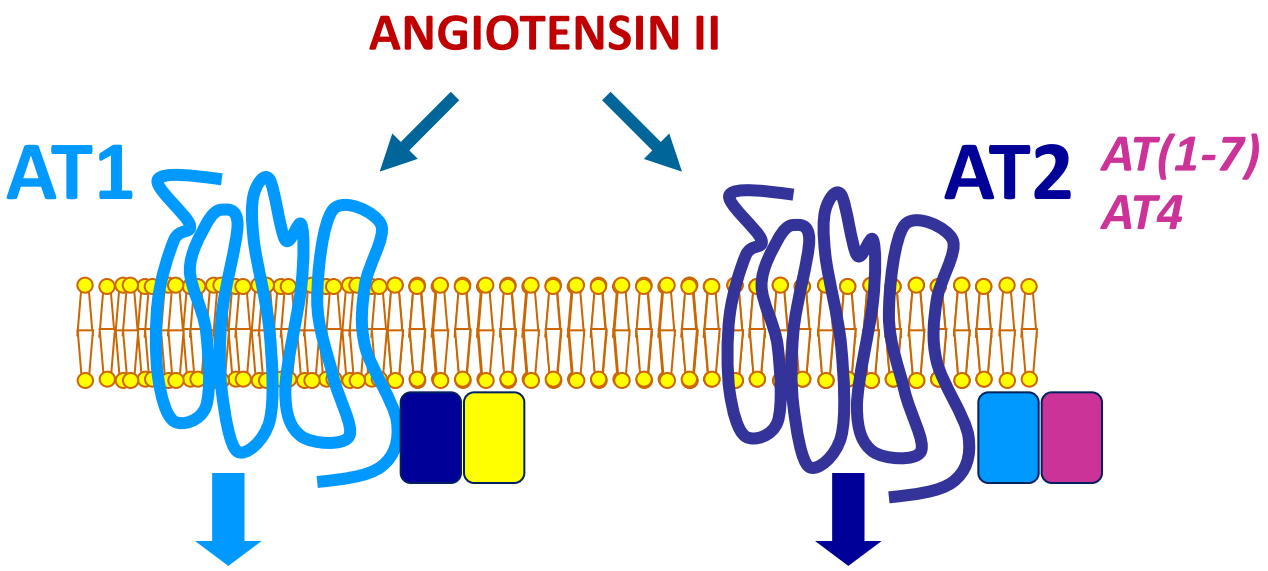
CONTRAINDICATIONS

# SIDE EFFECTS of ACE-INHIBITORS *cont'd*

**CAPTOPRIL:**

- **C**ough / **C**1 esterase deficiency *contraindication*
- **A**ngioedema / **A**granulocytosis
- **P**roteinuria / **P**otassium excess (hyperkalemia)
- **T**aste change
- **O**rthostatic hypotension
- **P**regnancy *contraindication* (fetal renal damage)
- **R**enal artery stenosis *contraindication*
- **I**ncreases renin
- **L**eukopenia/**L**iver toxicity

# • AT1 RECEPTOR ANTAGONISTS (ARBs)



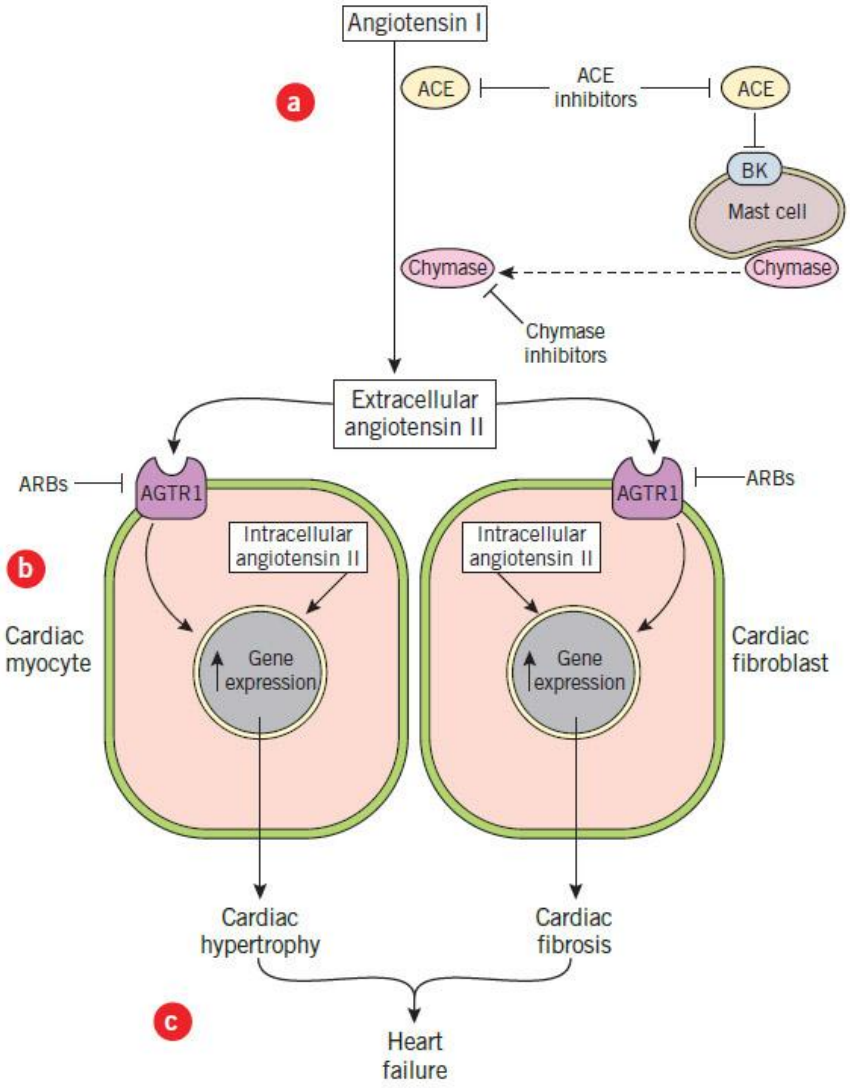

- vasoconstriction
- aldosterone release
- oxidative stress
- vasopressin release
- sympathetic enhancement
- renin release inhibition
- renal Na and H2O reabsorption
- cellular proliferation

- vasodilation
- anti-proliferative effects
- apoptosis
- antidiuretic/antinatriuretic effects
- BK production
- NO release

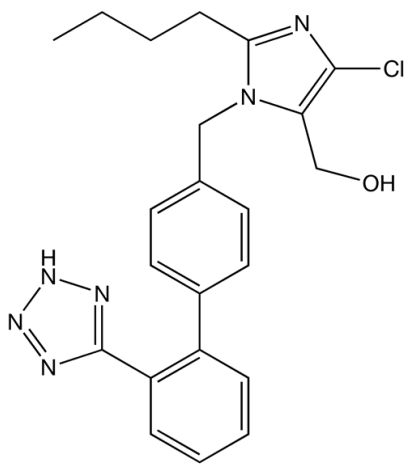
# • AT1 RECEPTOR ANTAGONISTS (ARBs)

• ACE inhibitor escape occurs when the drugs induce increased extracellular levels of bradykinin (BK), which binds its receptor on cardiac mast cells and triggers release of chymase. Chymase is a protease that generates angiotensin II even when ACE is blocked. Thus, chymase inhibitors in combination with ACE inhibitors should block angiotensin II production better than ACE inhibitors alone.

• Along with ACE inhibitors, angiotensin receptor blockers (ARBs), which target AGTR1 on cardiac and vascular cells, are marketed to treat hypertension and heart failure.



# • AT1 RECEPTOR ANTAGONISTS (ARBs)



Losartan

**SARTANs**

- LOSARTAN
- VALSARTAN
- IRBESARTAN
- EPROSARTAN
- CANDESARTAN CILEXETIL
- OLMESARTAN MEDOXOMIL

**ARBS OR THEIR ACTIVE METABOLITES BIND THE AT1-RECEPTOR IN A MANNER WHICH IS COMPETITIVE BUT SLOWLY SURMOUNTABLE, SO THAT DURATION OF ACTION IS PROLONGED**

# MAIN PK FEATURES of ARBs

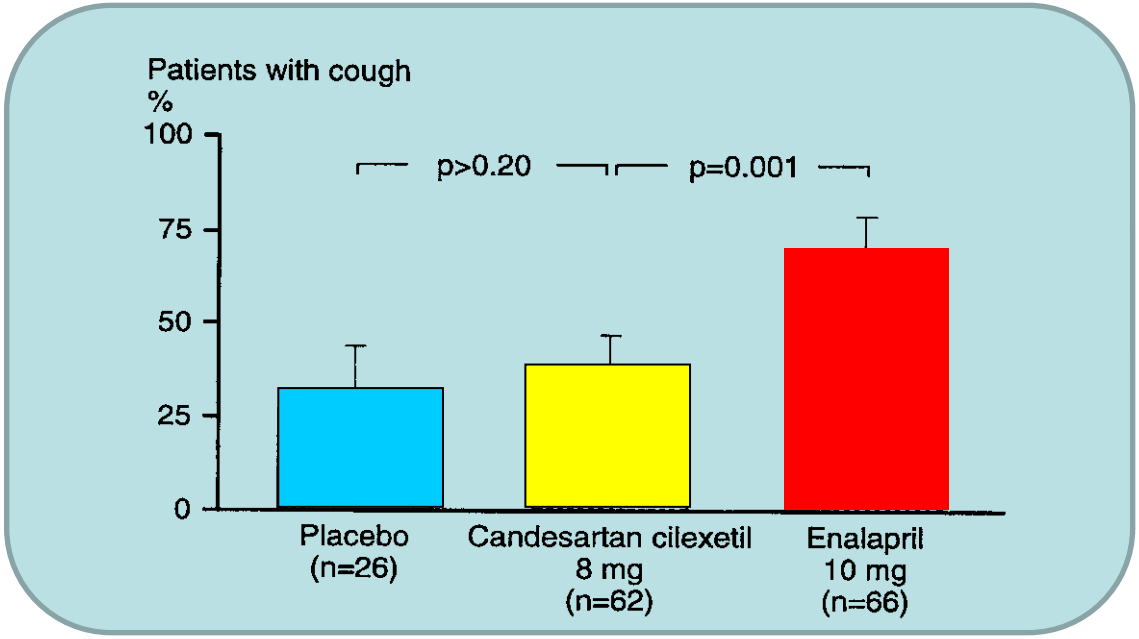
| | LOSARTAN | VALSARTAN | IRBESARTAN | EPROSARTAN | CANDESARTAN *CILEXETIL* |
|---|---|---|---|---|---|
| RECEPTOR AFFINITY | **Ki 10 nM** | | ++ | | +++ |
| DOSE (mg) | 50-100 | 80-160 | 75-300 | 600-800 | 8-16 |
| $T_{MAX}$ (H) | 6-9 | 9 | 13-17 | 5-9 | 8 |
| ORAL AVAILABILITY (%) | 33 | 23 | 82 | 13 | 14 |
| ACTIVE METABOLITES | EXP 3174 * | | | | Prodrug |
| ELIMINATION ROUTE | Renal, Biliary tract | 70% liver | 20% renal 80% liver | Renal, liver | 33% renal 67% liver |

**Almost all ARBs undergo liver metabolism and are eliminated by bile duct**

# MEDICAL USE FOR ARBs

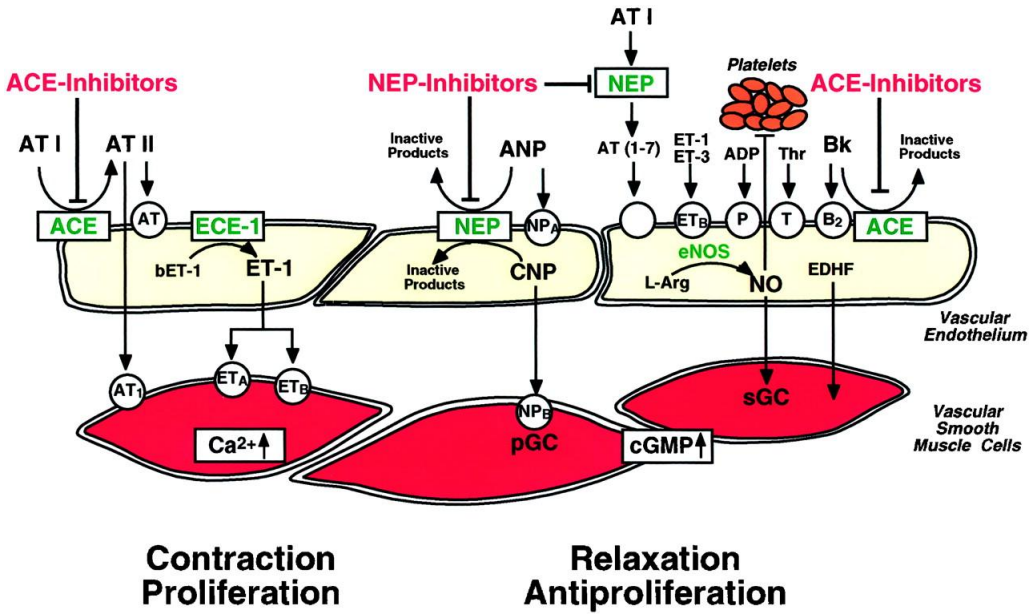
## ACE-I and ARBs overlapping medical uses

| | ACE inhibitor | ARB |
|---|---|---|
| Cough | yes | no |
| Hypertension | yes | yes |
| CCF | yes | yes |
| Microalbuminuria | type 1 | type 2 |
| Macroalbuminuria | type 1 | type 2 |
| Cardioprotection | yes | no evidence |



# DUAL VASOPEPTIDASE INHIBITORS

The proposed synergistic effect of **neutral endopeptidases (NEP) and ACE inhibition** is based on similar modes of action, including blockade of ang synthesis and simultaneous potentiation of peptides such as ANP, BNP, and bradykinin (by preventing their degradation), resulting in vasodilatation and diuresis and improved myocardial function.




| Enzyme | Omapatrilat $IC_{50}$ (nM) | Fasidotrilat $IC_{50}$ (nM) | Sampatrilat $IC_{50}$ (nM) |
|---|---|---|---|
| Neutral endopeptidase | 8.9 | 5.1 | 8.0 |
| Angiotensin-converting enzyme | 0.5 | 9.8 | 1.2 |

The earliest dual metalloprotease inhibitors had limitations because of low potency, short duration of action, or limited oral bioavailability. The new vasopeptidase inhibitors exhibit long-lasting and potent effects in the cardiovascular system.